



Volume 5 Issue 1 January 2019

e-ISSN: 2149-3189

# The European Research Journal





# The European Research Journal

## Aim and Scope

The European Research Journal (EuRJ) is an international, independent, double-blind peer reviewed, Open Access and online publishing journal, which aims to publish papers on all the related areas of basic and clinical medicine.

Editorial Board of the European Research Journal complies with the criteria of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), and Committee on Publication Ethics (COPE).

The journal publishes a variety of manuscripts including original research, case reports, invited review articles, technical reports, how-to-do it, interesting images and letters to the editor. The European Research Journal has signed the declaration of the Budapest Open Access Initiative. All articles are detected for similarity or plagiarism. Publication language is English. The journal does not charge any article submission or processing charges.

EuRJ recommends that all of our authors obtain their own ORCID identifier which will be included on their article.

The journal is published bimonthly (January, March, May, July, September, and November).

## Abstracting and Indexing

The journal is abstracted and indexed with the following: TR Index (ULAKBİM TR Dizin), Google Scholar, Index Copernicus (ICV 2017: 100), ProQuest Central, ROAD, EMBASE (Pending), SciLit, MIAR, J-Gate, SHERPA/RoMEO, BASE, EZB, CrossRef, JournalTOCs, WorldCat, TURK MEDLINE, Türkiye Atıf Dizini.

## Publisher

The European Research Journal (EuRJ)  
The Association of Health Research & Strategy  
Kırcaali Mah. Fevziçakmak Cd. Göktaş İş Mrk. Kat:3 No:62/12  
Osmangazi/BURSA-TURKEY  
[www.dergipark.gov.tr/eurj/](http://www.dergipark.gov.tr/eurj/)

**e-ISSN: 2149-3189**

The European Research Journal, hosted by Turkish JournalPark ACADEMIC, is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.



# Editorial Board

## FOUNDER EDITOR

Rustem ASKIN, MD,  
Professor,  
University of Health Sciences, Department of Psychiatry, Istanbul, Turkey  
Head of the Association of Health Research & Strategy, Bursa, Turkey

## EDITOR-IN-CHIEF

Senol YAVUZ, MD,  
Professor,  
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,  
Department of Cardiovascular Surgery, Bursa, Turkey,

## EDITORS

Davut AKDUMAN, MD,  
Associate Professor,  
Duzce University School of Medicine,  
Department of Otorhinolaryngology, Duzce, Turkey

Nizameddin KOCA, MD,  
Assistant Professor,  
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,  
Department of Internal Medicine, Bursa, Turkey

## ASSOCIATE EDITORS

Soner CANDER, MD,  
Associate Professor,  
Uludag University School of Medicine,  
Department of Endocrinology and Metabolism, Bursa, Turkey

Omer SENORMANCI, MD  
Associate Professor,  
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,  
Department of Psychiatry, Bursa, Turkey

Evren DILEKTASLI, MD,  
Associate Professor,  
Hayat Hospital  
Department of General Surgery, Bursa, Turkey

Rahmi DUMAN, MD,  
Associate Professor,  
LIV Hospital  
Department of Ophthalmology, Ankara, Turkey

Ali ASAN, MD  
Assistant Professor,  
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,  
Department of Infectious Disease Bursa, Turkey

Meliha KASAPOGLU AKSOY, MD  
Assistant Professor,  
University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital,  
Department of Physical Therapy and Rehabilitation, Bursa, Turkey

## STATISTICS EDITOR

Gokhan OCAKOGLU, PhD,  
Associate Professor,  
Uludag University School of Medicine,  
Department of Biostatistics, Bursa, Turkey

## LANGUAGE EDITOR

Nazmi ZENGIN, MD,  
Professor,  
Necmettin Erbakan University School of Medicine, Konya, Turkey

## EDITORIAL ASSISTANT

Ugur BOLUKBAS

# INTERNATIONAL EDITORIAL BOARD MEMBERS

Ahmet KIZILAY, MD

Professor, İnönü University School of Medicine, Department of Otorhinolaryngology, Malatya, Turkey

Alparslan ERSOY, MD

Professor, Uludag University School of Medicine, Department of Nephrology & Transplantation, Bursa, Turkey

Alparslan OZTURK

Professor, University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital, Department of Orthopedics & Traumatology, Bursa, Turkey

Ayşe TOPCU AKDUMAN, MD

Ataturk State Hospital, Department of Obstetrics & Gynecology, Duzce, Turkey

Aron Frederik POPOV, MD

Professor, University of Frankfurt, Department of Cardiothoracic Surgery, Frankfurt, Germany

Canan CELIK, MD

Professor, Giresun University School of Medicine, Department of Physical Medicine & Rehabilitation, Giresun, Turkey

Cristina Florescu, MD

Associate Professor, University of Craiova, Department of Medicine & Pharmacy, Romania

Cuma Bulent GUL, MD

Associate Professor, University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital, Department of Nephrology & Transplantation, Bursa, Turkey

Demet CANSARAN DUMAN, PhD

Associate Professor, Ankara University, Department of Biology, Ankara, Turkey

Elif Ekinci, MD

MBBS, FRACP, PhD, University of Melbourne, Department of Medicine, Melbourne, Australia

Emel YILMAZ, MD

Professor, Uludag University School of Medicine, Department of Infectious Disease, Bursa, Turkey

Emin USTUNYURT, MD

Associate Professor, University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital, Department of Obstetrics & Gynecology, Bursa, Turkey

Ender GUCLU, MD

Professor, Medipol University School of Medicine, Department of Otorhinolaryngology, Istanbul, Turkey

Erdem CUBUKCU, MD

Associate Professor, Uludag University School of Medicine, Department of Medical Oncology, Bursa, Turkey

Essam M MAHFOUZ, MD

Professor, University of Mansoura School of Medicine, Department of Cardiology, Mansoura, Egypt

Francesco CARELLI, MD

Professor, University of Milan School of Medicine, Department of Family Medicine, Milan, Italy

Gary TSE, MD, PhD

Assistant Professor, The Chinese University of Hong Kong, Department of Medicine and Therapeutics, Hong Kong, China

Haci Murat CAYCI, MD,

Associate Professor, University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital, Department of Gastrointestinal Surgery, Bursa, Turkey

Hasan ARI, MD,

Associate Professor, University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital, Department of Cardiology, Bursa, Turkey

Ibrahim TAYMUR, MD,

Associate Professor, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Department of Psychiatry, Bursa, Turkey

Kendra J. Grubb, MD, MHA, FACC

Assistant Professor, Emory University School of Medicine, Department of Cardiovascular Surgery, Atlanta, GA, USA

Koray AYAR, MD

Assistant Professor, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Department of Rheumatology, Bursa, Turkey

Metin GUCLU, MD

Associate Professor, University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital, Department of Endocrinology & Metabolism, Bursa, Turkey

Muhammet GUZELSOY, MD

Associate Professor, University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital, Department of Urology, Bursa, Turkey

Muzaffer DEMIR, MD

Professor, Trakya University School of Medicine, Department of Hematology, Edirne, Turkey

Nader D NADER, MD

Professor, University of Buffalo School of Medicine, Department of Anesthesiology, NY, USA

Nesrin COBANOGLU, MD

Professor, Gazi University School of Medicine, Department of Medical Ethics and History, Ankara, Turkey

Omer Fatih OLMEZ, MD

Associate Professor, Medipol University School of Medicine, Department of Medical Oncology, Istanbul, Turkey

Omer YALCIN, MD

Associate Professor, University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital, Department of Pathology, Bursa, Turkey

Ozen OZ GUL, MD

Associate Professor, Uludag University School of Medicine, Department of Endocrinology and Metabolism, Bursa, Turkey

Ozkan KANAT, MD,

Professor, Uludag University School of Medicine, Department of Medical Oncology, Bursa, Turkey

Safa KAPICIOGLU, MD

Professor, Yildirim Bayezid University School of Medicine, Department of Orthopedics & Traumatology, Ankara, Turkey

Sait Ait BenAli, MD

Professor, Cadi Ayyad University School of Medicine, Department of Neurosurgery, Marrakech, Morocco

Sedat ALTIN, MD

Professor, University of Health Sciences, Yedikule Training & Research Hospital, Department of Chest Diseases, Istanbul, Turkey

Semih HALEZEROGLU, MD, FETCS

Professor, Acibadem University School of Medicine, Department of Thoracic Surgery, Istanbul, Turkey

Veysel Tahan, MD, FACP, FACP, FESBGH

Assistant Professor, University of Missouri, Division of Gastroenterology and Hepatology, Columbia, Missouri, USA

YYenal DUNDAR, MD

University of Liverpool School of Medicine, Department of Psychiatry, Liverpool, UK

# Table of Contents

## Original Articles

- Childhood nasal obstruction and sleep-disordered breathing during clinical setting: Myth or reality? 1-7  
Marco Zaffanello, Giuseppe Lippi, Laura Tenero, Michele Piazza, Luca Sacchetto, Luana Nosetti, Emma Gasperi, Giorgio Piacentini
- A virtual pathway reduced the need for physical review in patients with a suspected scaphoid fracture 8-13  
Paul J Jenkins, Stephen Boyce, Pauline Garvey, Kevin Bee, David Shields, Lech A Rymaszewski
- The relationship between atrial natriuretic peptide and microvascular complications of diabetes 14-19  
Pınar Karakaya, Bahar Özdemir, Meral Mert, Hakan Koçoğlu, Abdulkaki Kumbasar
- The relationship between psychopathology, psychosocial adjustment, social support and quality of life in multiple sclerosis 20-28  
Vahap Ozan Kotan, Zeynep Kotan, Birgül Aydın, Özlem Taşkapılıoğlu, Berna Alkan, Güven Özkaya, Aslı Sarandöl, Ömer Faruk Turan, Selçuk Kırılı
- Beyond weight loss after sleeve gastrectomy: improvement in health-related quality of life 29-35  
Evren Dilektaşlı
- Improvement of the cardiorespiratory endurance, perception of the effort and walking performance of the old people of the hospice Saint Marc of Kingasani by the practice of the adapted physical activities 36-41  
Teddy Bofosa, Eric Kam, Betty Miangindula, François Njimbu, Constant Nkiama
- Preoperative hemogram-related parameters to distinguish renal cell carcinoma from benign kidney masses: HERR score 42-49  
Ali Rıza Türkoğlu, Yasemin Üstündağ
- Local resection for placenta accreta spectrum: a conservative uterus sparing technique for anterior placenta accreta 50-57  
Gülsüm Uysal, Nefise Tanrıdan Okçu, Eda Eskimez, Esra Saygılı Yılmaz
- Assessment of cyber abuse in sexually abused children and adolescents 58-67  
Merve Çıkılı Uytun, Sevgi Özmen, Esra Demirci
- Effectiveness of kinesiotaping on diaphragm thickness, diaphragmatic thickening fraction, and intercostal muscle thickness in patients undergoing mechanical ventilation: a pilot study 68-76  
Burcu Metin Ökmen, Korgün Ökmen
- The incidence of polyneuropathy and its relation with disease parameters in chronic obstructive pulmonary disease 77-82  
Nalan Ogan, Refah Sayın, Ayşe Baha, Evrim Eylem Akpınar, Meral Gülhan
- The association of carotid intima-media thickness with body mass index and cortisol level in fibromyalgia syndrome 83-87  
Tuba Tülay Koca, Ayla Çimen

Do antiepileptics have any potential to induce insulin resistance? A comparison between levetiracetam and valproic acid Gökhan Özer	88-93
Neurological findings in autosomal dominant polycystic kidney disease Demet Yıldız, Abdülmecit Yıldız	94-97
The importance of red cell distribution width and neutrophil-lymphocyte ratio as a new biomarker in rheumatoid arthritis Tuba Tülay Koca, Aydın Arslan, Filiz Çiledağ Özdemir, Ejder Berk	98-103
Association between serum uric acid and inflammation markers in ankylosing spondylitis patients treated with tumor necrosis factor- $\alpha$ or nonsteroidal anti-inflammatory drugs Betül Sargin, Gülcan Gürer, Gülnur Taşcı Bozbaş, Hakan Öztürk	104-108
Foam sclerotherapy combined with saphenofemoral ligation procedure: long-term results Lütfi Soylu, Oğuz Uğur Aydın	109-113
Evaluation of nursing students' diagnoses using the Omaha System Elif Ateş, Bahire Ulus	114-121
Evaluation of the relationship between perception of tobacco packaging pictorial warnings and the nicotine addiction levels of smokers who admitted to smoking cessation clinic in Malatya, Turkey Seda Beyhan Sağmen, Mikail Özdemir	122-127
Needlestick and sharps injuries among nurses at Atatürk university research hospital and their practices after injury Elif Okşan Çalıköğlü, Banu Bedir, Hilal Betül Akçay, Ali Gümüş	128-133
Emotional and behavioral problems in infants and preschool children: prevalence and sociodemographic risk factors Çağatay Uğur, Esra Yürümez, Yasemin Yılmaz	134-141
Wrongs known as right in thyroid scintigraphy and uptake study Serdar Savaş Gül	142-147
Comparison of effects of melatonin, pentoxifylline and dimethyl sulfoxide in experimental liver ischemia-reperfusion injury by three different methods Zeliha Türkyılmaz, Ahmet Hatipoğlu, Mahmut Yüksel, Nurettin Aydoğdu, Gülara Hüseyinova	148-158
Effect of lipid parameters on carotid artery disease progression in patients undergoing carotid endarterectomy and unoperated patients with non-severe carotid artery stenosis Kadir Kaan Özsin, Umut Serhat Sanrı, Faruk Toktaş, İbrahim Burak Şeker, Şenol Yavuz	159-165

## Reviews

Coenzyme Q10 deficiency in elderly: Can nutritional supplementation play a role? Mini review Angelo Michele Carella, Teresa Marinelli, Michele Di Pumpo, Giovanni Modola, Angelo Benvenuto	166-173
---	---------

## Case Report

Myocysticercosis: an unusual presentation in sternocleidomastoid muscle diagnosed by high frequency ultrasonography Mohd Ilyas, Arshad Bhat	174-177
Cornual heterotopic pregnancy after in vitro fertilization: management by laparoscopic repair Nur Dokuzeylül Güngör, Tuğba Gürbüz	178-182
Things to keep in mind after cardiopulmonary resuscitation: bilateral severe and widespread subcutaneous emphysema together with unilateral pneumothorax Timuçin Alar, İsmail Ertuğrul Gedik	183-185
Datura stramonium poisoning: a case report and review of the literature Muhammet Furkan Korkmaz, Muharrem Bostancı, Hatice Onur, Eren Çağan	186-188
An unusual cause of hemorrhagic shock: gastric Dieulafoy's lesion Ahmet Erdoğan, Murat Ferhat Ferhatoğlu, Hikmet Pehlevan, Osman Yıldırım, Kazım Şenol	189-192
Cecal diverticulitis mimicking acute appendicitis Cihan Bedel	193-195
Rectal resection for Schnitzler's metastasis in a patient presenting with severe rectal stenosis: case report and review of the literature Semra Doğan, Sezai Demirbaş, Elgun Samadov, Salih Erpulat Öziş, Hatim Yahya Uslu	196-201
Deep vein thrombosis and pulmonary embolism in a patient with acute type B aortic dissection: a case report Engin Akgül, Gülen Sezer Alptekin Erkul, Sinan Erkul, Ahmet Hakan Vural	202-205
Kikuchi-Fujimoto disease mimicking hematological malignancy: a case report Hakan Yarkıcı, Faruk Elyiğit, Ahmet Peker, Dudu Solakoğlu Kahraman, Nilgün Erbil, Harun Akar	206-208
A rare complication after inguinal hernia repair: testicular torsion Yusuf Önder Özsağır, Görkem Akça, Mustafa Ozan Horsanalı, Hüseyin Eren, Eyüp Dil	209-212
Pure spinal extradural arteriovenous malformation in the thoracolumbar region: a case report Fatih Yakar, Ümit Eroğlu, İhsan Doğan, Hasan Çağlar Uğur	213-216
Extensive cranial, spinal and abdominal involvement in brucellosis: a case with review of the literature Ali Murat Koç, Yaprak Ünsal, Hülya Mollamehmetoğlu, Özgür Esen, Rıfat Reha Bilgin	217-222
Treatment of the nevus of Ota with the 1064-nm Q-switched Nd:YAG laser Yeşim Akpınar Kara	223-225
Vibration related white finger disease: a case report Seher Kurtul, Meral Türk	226-229

## Letter to the Editor

- Bilateral sacroiliitis and left hip arthritis secondary to isotretinoin treatment 230-232  
Sevgi Kulaklı, Fazıl Kulaklı, İlker İlhanlı, Samet Tatlı, Canan Çelik
- Experience of thrombotic microangiopathy unresponsive to therapeutic apheresis 233-235  
Hilmi Erdem Sümbül, Onur Taktakoğlu



# Childhood nasal obstruction and sleep-disordered breathing during clinical setting: Myth or reality?

Marco Zaffanello<sup>1</sup>, Giuseppe Lippi<sup>2</sup>, Laura Tenero<sup>1</sup>, Michele Piazza<sup>1</sup>, Luca Sacchetto<sup>3</sup>, Luana Nosetti<sup>4</sup>, Emma Gasperi<sup>1</sup>, and Giorgio Piacentini<sup>1</sup>

<sup>1</sup>Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Division, University of Verona, Verona, Italy

<sup>2</sup>Department of Clinical Biochemistry, University of Verona, Verona, Italy

<sup>3</sup>Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Otorhinolaryngology Division, University of Verona, Verona, Italy

<sup>4</sup>Department of Pediatrics, University of Insubria, Varese, Italy

DOI: 10.18621/eurj.410657

## ABSTRACT

**Objectives:** The severity of sleep apneas largely depends on abnormal size of upper airway. Therefore, nasal examination is essential part of clinical evaluation of children with sleep-disordered breathing.

**Methods:** We performed a retrospective survey involving children aged 4 years and older which underwent in-laboratory overnight cardiorespiratory polygraph study between January 2016 and May 2017. Nasal obstruction test was used to score severity.

**Results:** Fifty-three children (62% males) with a median age of 6.1 (IQR 3.1) years were enrolled in this study. Linear regression analysis showed that nasal obstruction score was correlated with apnea-hypopnea index ( $\beta = 0.345$ ;  $p < 0.014$ ) and oxygen desaturation index ( $\beta = 0.328$ ;  $p < 0.022$ ), whilst no association was found with age, BMI z-score, snoring and phase angle. Correlation analysis also showed that nasal obstruction score was correlated with apnea-hypopnea index ( $r = 0.364$ ;  $p = 0.009$ ) and oxygen desaturation index ( $r = 0.350$ ;  $p = 0.012$ ) after adjustment for age and BMI z-score., but not with snoring time or phase angle degree.

**Conclusions:** Nasal obstruction test may be a useful, time saving assessment which aid exploring sleep disordered breathing in children. However, this test should not be used alone because it is plagued by objective consideration and at risk of under or overestimation.

**Keywords:** children, nasal obstruction, overnight respiratory polygraph, obstructive sleep apnea, sleep-disordered breathing

*Received: March 29, 2018; Accepted: May 17, 2018; Published Online: May 19, 2018*

Obstructive sleep apnea (OSA) consists of episodes of partial or complete closure of the upper airway that occur during sleep and lead to breathing cessation and oxygen desaturation [1, 2]. The severity of sleep apnea largely depends on abnormal size of the airway [3]. Turbulence of airflow, or nose, oropharynx, and hypopharynx resistance conventionally defines OSA severity. Hyperplasia of tonsils and adenoids [4] and craniofacial disharmony are the major contributors to high airway narrowing in children [5]. Some narrow regions such as nostrils, lips, palate and larynx limit the high airway



**Address for correspondence:** Marco Zaffanello, MD., University of Verona, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Division, Piazzale L.A. Scuro 10, 37134 Verona, Italy  
E-mail: marco.zaffanello@univr.it, Telephone: ++39 045 8127121, fax: ++39 045 8124790

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

patency [6].

Nasal difficulty decreases pharyngeal patency and nasal airway resistance may be explained by Starling resistance model. The Starling model describes upper airway as a hollow tube, with a partial obstacle at the inlet (nose), and a collapsible part downstream (oropharynx) [1]. Severe nasal block is then associated with a switch to oral breathing and an enhanced risk of sleep-disordered breathing (SDB) [7].

Albeit nasal examination is an essential part of clinical evaluation of children with SDB, there is still insufficient evidence to define whether or not nasal obstacle to respiration may be a risk factor for OSAS [1].

The aim of the present study was to evaluate the correlation between nasal difficulty severity and sleep respiratory actigraphy.

## METHODS

### Study population

The present study included compliant children aged 4 years and older, who were subjected to in-laboratory overnight polygraph study for SDB between January 2016 and May 2017, in our local Department (University Hospital of Verona, Verona, Italy). All children were referred to the local ambulatory, which belongs to a larger pediatric pneumology service. Medical records were accurately filled, including age, sex, body growth parameters, nasal patency assessment (as described below), and history for inhalant allergy. Children with allergic diseases were defined having disease history identified before the index date and lasting at least for three medical visits. Records review was carried out as previously described elsewhere [8]. The study was performed according to the Declaration of Helsinki and under the terms of relevant local legislation.

### Nasal barrier test

The assessment of nasal obstacle (ICD-9-CM 478.19) [9] was performed by alternatively closing the nostrils with a finger, accurately preventing to constrict the other nostril. The patient was then invited to breathe through the free nostril keeping the mouth closed. The test was then repeated closing the other

nostril. One-sided nasal block was classified according to the air flux recorded by the operator, as follows: 0 (open), 1 (mildly obstructed), 2 (severely obstructed) and 3 (obstructed). The score calculated for either nostril (i.e., right + left score) was then summed for all patients (minimum 0 -maximum 6). Three skilled blinded operators performed independently of the test and the final score was the mean of the three independent measurements. Nasal patency manoeuvre was performed the day of in-laboratory respiratory actigraphy study.

### Anthropometry

Height and weight were measured by the same skilled personnel, using standardized techniques. Body mass index [BMI: weight (kg) / height (m)<sup>2</sup>], BMI percentiles and BMI z-scores were calculated according to age and sex (<http://nccd.cdc.gov/dnpabmi/Calculator.aspx>).

### In-laboratory overnight respiratory polygraph

The in-laboratory overnight respiratory polygraph study (SOMNO screen <sup>TM</sup>PSG, SOMNO medics GmbH, Randersacker, Germany) was used to continuously record nasal airflow, chest and abdominal respiratory movements (thoracic and abdominal belts), arterial oxygen saturation (SaO<sub>2</sub>; digital pulse oximetry), heart rate (HR; finger probe), electrocardiogram (ECG; three chest electrodes), body position (mercury sensor) and tracheal sounds (microphone). Electroencephalography (EEG), eye movements (electrooculogram; EOG) and muscle activity or skeletal muscle activation (electromyogram; EMG) studies were not performed. The device was applied between 7:00 PM and 8:00 AM, and data were continuously recorded throughout the night. During the test, all children were monitored for ≥ 6 h in a quiet, properly prepared sleep room, in the presence of one of their parents [10]. The estimated total sleep time (TST) was calculated was the time between the child fell asleep and wake up, and was recorded in a nocturnal diary by the healthcare staff, which was also trained to promptly intervene, when needed. The nocturnal awakenings were identified considered from TST calculation and were then removed from final analysis.

The sleep analysis (DOMINO<sup>®</sup> software, Somnomedics v.2.6.0) of the valid recording session

was manually performed. Obstructive respiratory events were scored as previously reported [11]. In particular, the number of obstructive apneas (OA; n./hour) plus central apneas (CA; n./hour) plus hypopneas (H; n./hour) was divided by hours of TST and then expressed as apnea-hypopnea index (AHI, n./hour) [12].

All O<sub>2</sub> desaturations ( $\geq 3\%$ ; n./hour) from baseline, mean SpO<sub>2</sub> (%) and minimum SpO<sub>2</sub> (%) were quantified. The Oxygen Desaturation Index (ODI; n./hour) was measured as total number of desaturations divided by TST. Snoring (time% of the TST) was also regularly calculated [13].

Phase angle vector analysis is an index of thoracoabdominal asynchrony (TAA) and inspiratory airflow resistance. An increased value suggests compromised upper airway patency, leading to enhanced inspiratory work of breathing. Phase angle analysis and related thoracoabdominal asynchrony may be a useful parameter to detect upper airway obstacle [14, 15]. An increased inspiratory resistance as maintained during OA and H produces an asynchrony between rib cage and abdomen (no obstacle: phase angle close to 0 degrees; obstructive apnea: phase angle close to 180 degrees).

### Statistical Analysis

Statistical analysis was performed using SPSS

Statistics 22.0® software for Windows. Kolmogorov-Smirnov test for one sample was used to explore normal distribution of continuous variables. The demographic, clinical characteristics and actigraphy results, were presented as number and percentage for categorical variables, or as median and 95% confidence interval (CI) for continuous variables, respectively.

Linear regression (backward) analysis, in which nasal barrier score was entered as dependent variables, was carried out to explore potential associations with demographic, clinical and polygraphic variables (age, BMI z-score, snoring, phase angle, AHI or ODI). The value of statistical significance was set at  $p < 0.05$ .

Partial correlation analysis was performed between nasal barrier score and clinical and polygraphic results (AHI, ODI, snoring and phase angle), adjusted for age and BMI z-score. The value of statistical significance was set at  $p < 0.05$ .

## RESULTS

The final study population consisted of 53 children. A summary of demographic (sex, age), clinical (body growth parameters) and in-laboratory overnight polygraph results (AHI, ODI, snoring, phase angle) of the study population is shown in Table 1

**Table 1.** Summary of the demographic, clinical characteristics (Panel A) and overnight polygraph study (Panel B) of 53 consecutive children\*

	Median	IQR
<b>Panel A</b>		
Number (males %)	53 (62.3)	-
Age (years)	6.1	3.1
Weight (kg)	22	11
Height (cm)	116	15
BMI Percentiles	71.6	58.3
BMI z-score	0.6	1.8
<b>Panel B</b>		
eTST (hours)	9.0	1.4
AHI (events/h)	2.9	3.8
ODI (events/h)	0.6	0.9
Snoring (% time)	0.2	1.7
Phase angle (degrees)	57	32

\*Selection criteria were the absence of genetic and neurological conditions, and age range between 4 to 15 years. AHI = apnea-hypopnea index, BMI = body mass index, IQR = interquartile range, ODI = oxygen desaturation index, eTST = estimated total sleep time

**Table 2.** Linear regression (backward) analysis between nasal barrier test (score) and age, BMI Z-score, snoring, phase angle and apnea-hypopnea index (AHI; model 1) or oxygen desaturation index (ODI; model 2).

Dependent variable:	MODEL 1			MODEL 2		
	Nasal barrier test			Nasal barrier test		
STEP1	B	CI	p	B	CI	p
Age (years)	-0.121	-0.286÷0.114	0.393	-0.144	-0.302÷0.098	0.310
BMI z-score	-0.022	-0.335÷0.285	0.873	0.034	-0.276÷0.355	0.802
AHI (n./hr)	0.345	0.016÷0.133	0.014	-	-	-
ODI (n./hr)	-	-	-	0.328	0.014÷0.167	0.022
Snoring (% TST)	0.130	-0.046÷0.127	0.347	0.112	-0.053÷0.123	0.427
Phase angle (degrees)	0.061	-0.013÷0.020	0.660	0.061	-0.013÷0.021	0.665
Model Significance	0.104			0.138		
adj. R <sup>2</sup>	0.084			0.069		
STEP2						
Variable included	AHI			ODI		
Model Significance	0.005			0.009		
adj. R <sup>2</sup>	0.125			0.108		

AHI = apnea-hypopnea index, BMI = body mass index, ODI = oxygen desaturation index, TST = total sleep time

Panel A and B. Kolmogorov-Smirnov test for one sample showed that the variables in Table 1 (age, weight, height and BMI percentiles in Panel A; AHI, ODI and snoring in Panel B) are not normally distributed ( $p < 0.05$ ).

The linear regression (backward) analysis (Table 2, model 1 and model 2) showed that nasal barrier score was significantly associated with AHI ( $\beta = 0.377$ ;  $p = 0.005$ ) and ODI ( $\beta = 0.353$ ;  $p = 0.009$ ) variables. Age, BMI z-score, snoring and phase angle variables were excluded from the models.

Interestingly, with partial correlation analysis, nasal barrier score was associated with both AHI ( $r = 0.364$ ;  $p = 0.009$ ) and ODI ( $r = 0.350$ ;  $p = 0.012$ ), but not with snoring time ( $r = 0.170$ ;  $p = 0.232$ ) and phase angle ( $r = 0.49$ ;  $p = 0.734$ ) (Table 3).

Figure 1 shows the distribution of AHI values according to the different values of nasal barrier score.

## DISCUSSION

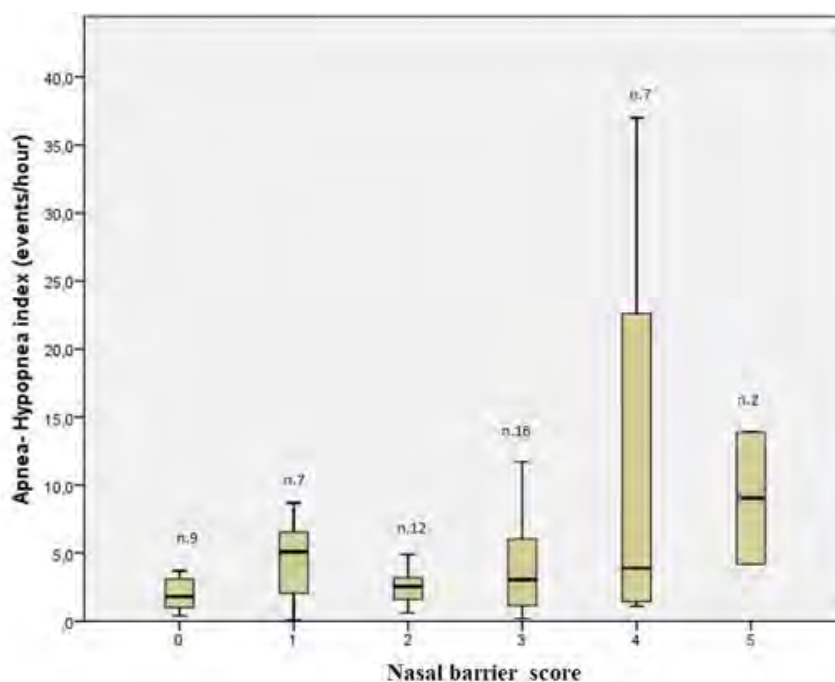
The potential contribution of the nose to the pathophysiology of OSAS remains a largely unexplored issue [1]. Daytime nasal difficulty was shown to be an independent risk factor for OSAS [16]. Nose difficulty strongly influences pharynx patency, since the inspiratory flow through the upper airway may promote its closure. The luminal pressure at which the airway begins to close is defined as critical closing pressure [17]. In the presence of nasal or upper airway congestion, oral breathing becomes prevalent.

Nasal difficulty and mouth breathing have been associated with adenotonsillar hypertrophy, which in turn is the leading cause of OSAS in children [18, 19]. In particular, enlarged adenoids dramatically influence the amount of air inhaled through the nose. Nasal difficulty and crowded oropharynx double the risk of

**Table 3.** Partial correlation analysis between nasal obstruction score, adjusted for age and BMI z-score, and apnea-hypopnea index (AHI) or oxygen desaturation index (ODI) or phase angle.

Adjusting variables:		Nasal barrier score	
		$r_{par}$	p
age (years) & BMI z-score	AHI (n./hr)	0.364	<b>0.009</b>
	ODI (n./hr)	0.350	<b>0.012</b>
	Snoring (% TST)	0.170	0.232
	Phase angle (degrees)	0.049	0.734

AHI = apnea-hypopnea index, BMI = body mass index, ODI = oxygen desaturation index, TST = total sleep time



**Figure 1.** Box plot of nasal barrier score and apnea-hypopnea index.

OSAS [9]. Nasal video-endoscopy is a useful tool to assess airway difficulty due to adenoid hypertrophy [29]. Medical treatments (nasal steroids and leukotriene receptor antagonists) or adeno(tonsillectomy) interventions are the most widely used medical measures for improving both symptoms and polysomnographic signs associated with adenoid hypertrophy [21, 22]. However, recent evidence has been provide that specific craniofacial characteristics may be commonplace in snoring children [2, 23]. Persistent allergy is another factor potentially involved in reducing air inhalation through the nose. Upper allergic persistent inflammation of both nasal mucosa and adenoid tissue are often causes of persistent nasal difficulty, even in children who underwent adenoidectomy [24].

The nasal examination is an important part of the ambulatory clinical assessment of children with SDB. A simple, straightforward and time wasting analysis can be useful to assess for SDB severity in cooperating children, before otorhinolaryngologic evaluation. In particular, the main finding of the present study was that nasal barrier score was significantly correlated with AHI and ODI. However, no correlation was found with snoring or with phase angle (i.e., thoracoabdominal asynchrony). Taken together, these findings would suggest that nasal barrier score and

AHI values may be at least partially coincident but not directly related to our population.

### Limitations

The main limitation of the present study is represented by subjective assessment of childhood nasaldifficulty. Other limitations include children collaboration, especially those very young, the challenge to perform cardiorespiratory analysis during the sleep (i.e., sleep stages could not be examined and sleep time was only deducted from healthcare staff observation, so that respiratory polygraph recordings [25] were only indicative of the pattern of the childhood respiration during the night).

### CONCLUSION

In conclusion, the nasal barrier test may be a useful, timewasting ambulatory assessment, that helps to assess the severity of SDB in children. However, this test should not be used alone because it is plagued by objective judgement and at risk of under or overestimation.

### Key Points

- Sleep-disordered breathing due to upper

airway difficulty is frequent in pediatric patients.

- Clinical evaluation of upper airway difficulty is needed in the ambulatory setting.
- Children with clinical evaluation suggesting sleep-disordered breathing need further assessment with sleep respiratory actigraphy or polysomnography.
- Assessment of nasal difficulty should be of clinical evaluation for sleep-breathing disorders.
- Nasal barrier test is a useful, timewasting ambulatory assessment, but poorly predicts sleep breathing disorders severity in children.
- Nasal barrier test should not be used alone since it is plagued by objective judgement, being sensitive to the risk of under or overestimation.

### Abbreviations

AHI = apnea-hypopnea index, OSA = obstructive sleep apnea, ODI = oxygen desaturation index, OSAS = obstructive sleep apnea syndrome, SDB = sleep disordered breathing.

### Contribution of each co-authors

Study conception and design: MZ, LN, GP; Acquisition of data: MZ, EG, LT, SB, LS; Analysis and interpretation of data: MZ, GL, LS, LT, LN, MP, SB; Drafting of the manuscript: MZ, GL, EG, LT, LN, MP, SB; Critical revision: GP, GL, LN, LS.

### Ethical approval

The study was approved by the Institutional Ethical Committee of Verona (University Integrated Hospital of Verona), and all parents signed the informed consent form.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

[1] Wilhelm CP, deShazo RD, Tamanna S, Ullah MI, Skipworth LB. The nose, upper airway, and obstructive sleep apnea. *Ann Allergy Asthma Immunol* 2015;115:96-102.  
 [2] Zaffanello M, Piacentini G, Gasperi E, Maffei C, Fava C, Bonafini

S, et al. Snoring in a cohort of obese children: Association with palate position and nocturnal desaturations. *J Pediatr Neonat Individual Med* 2016;5:e050134.  
 [3] White DP. The pathogenesis of obstructive sleep apnea: advances in the past 100 years. *Am J Respir Cell Mol Biol* 2006 ;34:1-6.  
 [4] Grime C, Tan HL. Sleep disordered breathing in children. *Indian J Pediatr* 2015;82:945-55.  
 [5] Tawfik KO, Sedaghat AR, Ishman SL. Trends in inpatient pediatric polysomnography for laryngomalacia and craniofacial anomalies. *Ann Otol Rhinol Laryngol* 2016;125:82-9.  
 [6] Strohl KP, Butler JP, Malhotra A. Mechanical properties of the upper airway. *Compr Physiol* 2012;2:1853-72.  
 [7] Rappai M, Collop N, Kemp S, deShazo R. The nose and sleep-disordered breathing: what we know and what we do not know. *Chest* 2003;124:2309-23.  
 [8] Sarkar S, Seshadri D. Conducting record review studies in clinical practice. *J Clin Diagn Res* 2014;8:JG01-4.  
 [9] Liistro G, Rombaux P, Belge C, Dury M, Aubert G, Rodenstein DO. High mallampati score and nasal obstruction are associated risk factors for obstructive sleep apnoea. *Eur Respir J* 2003;21:248-52.  
 [10] Tagetti A, Bonafini S, Zaffanello M, Benetti MV, Vedove FD, Gasperi E, et al. Sleep-disordered breathing is associated with blood pressure and carotid arterial stiffness in obese children. *J Hypertens* 2017;35:125-31.  
 [11] Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012;8:597-619.  
 [12] Villa MP, Pietropaoli N, Supino MC, Vitelli O, Rabasco J, Evangelisti M, et al. Diagnosis of pediatric obstructive sleep apnea syndrome in settings with limited resources. *JAMA Otolaryngol Head Neck Surg* 2015;141:990-6.  
 [13] Ross KR, Rosen CL. Sleep and respiratory physiology in children. *Clin Chest Med* 2014;35:457-67.  
 [14] Hammer J, Newth CJ. Assessment of thoraco-abdominal asynchrony. *Paediatr Respir Rev* 2009;10:75-80.  
 [15] Hammer J, Newth CJ, Deakers TW. Validation of the phase angle technique as an objective measure of upper airway obstruction. *Pediatr Pulmonol* 1995;19:167-73.  
 [16] Phillips BG, Kato M, Narkiewicz K, Choe I, Somers VK. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. *Am J Physiol Heart Circ Physiol* 2000;279:H234-7.  
 [17] Gold AR, Schwartz AR. The pharyngeal critical pressure. The whys and hows of using nasal continuous positive airway pressure diagnostically. *Chest* 1996;110:1077-88.  
 [18] Izu SC, Itamoto CH, Pradella-Hallinan M, Pizarro GU, Tufik S, Pignatari S, et al. Obstructive sleep apnea syndrome (OSAS) in mouth breathing children. *Braz J Otorhinolaryngol* 2010;76:552-6.  
 [19] Pacheco MC, Casagrande CF, Teixeira LP, Finck NS, de Araújo MT. Guidelines proposal for clinical recognition of mouth breathing children. *Dental Press J Orthod* 2015;20:39-44.  
 [20] Oliveira HF, Sampaio AL, Oliveira CA, Teixeira MC, Miranda LA, Miranda DA. Evaluation of airway obstruction by adenoid tissue: comparison of measures in the sitting and recumbent. *Int J Pediatr Otorhinolaryngol* 2012;76:1278-84.  
 [21] Cielo CM, Gungor A. Treatment options for pediatric obstructive sleep apnea. *Curr Probl Pediatr Adolesc Health Care* 2016;46:27-33.  
 [22] Venekamp RP, Hearne BJ, Chandrasekharan D, Blackshaw H, Lim J, Schilder AG. Tonsillectomy or adenotonsillectomy versus non-surgical management for obstructive sleep-disordered breathing in children. *Cochrane Database Syst Rev* 2015;10:CD011165.  
 [23] Zicari AM, Duse M, Occasi F, Luzzi V, Ortolani E, Bardanzellu F, et al. Cephalometric pattern and nasal patency in children with primary

snoring: the evidence of a direct correlation. PLoS One 2014;9:e111675.  
[24] Colavita L, Miraglia Del Giudice M, Stroschio G, Visalli C, Alterio T, Pidone C, et al. Allergic rhinitis and adenoid hypertrophy in children: is adenoidectomy always really useful? J Biol Regul Homeost Agents 2015;29(2 Suppl 1):58-63.

[25] Alonso-Álvarez ML, Terán-Santos J, Ordax Carbajo E, Cordero-Guevara JA, Navazo-Egüía AI, Kheirandish-Gozal L, et al. Reliability of home respiratory polygraphy for the diagnosis of sleep apnea in children. Chest 2015;147:1020-8.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# A virtual pathway reduced the need for physical review in patients with a suspected scaphoid fracture

Paul J Jenkins<sup>1</sup>, Stephen Boyce<sup>2</sup>, Pauline Garvey<sup>2</sup>, Kevin Bee<sup>3</sup>, David Shields<sup>1</sup>, Lech A Rymaszewski<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Glasgow Royal Infirmary, Glasgow, United Kingdom

<sup>2</sup>Department of Emergency Medicine, Glasgow Royal Infirmary, Glasgow, United Kingdom

<sup>3</sup>Department of, Dentistry & Nursing, University of Glasgow, School of Medicine, Glasgow, United Kingdom

DOI: 10.18621/eurj.411396

## ABSTRACT

**Objectives:** Suspected scaphoid fractures are a common reason for referral from the emergency department to fracture clinics. Few patients actually have a fracture. Cross sectional imaging has the potential to improve early diagnosis and reduce unnecessary immobilisation. The aim of this audit was to investigate the effectiveness of a virtual pathway, incorporating early magnetic resonance imaging (MRI) scan, for suspected scaphoid fractures. The secondary aim was to investigate whether the accuracy of other clinical signs, such as anatomical snuffbox pain on wrist ulnar deviation, was sufficient to reduce the number of patients requiring a MRI scan.

**Methods:** A prospective audit was undertaken of 123 patients in an emergency department and associated minor injuries unit. These patients were managed with an early MRI scan. Where no significant injury was found, they were discharged after a phone call from a virtual fracture clinic nurse.

**Results:** There were 16 (13%) true scaphoid fractures. MRI scanning showed other injuries including significant soft tissue injuries (13%), other carpal fractures (17%) and fractures of the distal radius (19.5%). The number of clinical appointments required was 0.42 per patient. Eighty patients did not have any face-to-face review. Other clinical examination techniques, such as anatomical snuff box pain on ulnar deviation of the wrist were not sufficiently sensitive or specific to reduce the need for MRI scanning or review.

**Conclusions:** A virtual fracture clinic pathway and early MRI scanning reduced face-to-face reviews and unnecessary immobilisation. Clinical examination techniques are not sufficiently sensitive to reduce the need for scanning.

**Keywords:** Scaphoid, fracture, virtual fracture clinic

*Received: March 31, 2018; Accepted: June 8, 2018; Published Online: July 10, 2018*

The incidence of scaphoid fracture has been reported as 29 per 100,000 [1]. The “suspected” scaphoid fracture is a common reason for referral to fracture clinic from the emergency department (ED). The prevalence of a true fracture, where clinical sus-

picion exists but x-rays are negative, ranges from 5% to 25% [2]. This reported variation arises from differences in clinical examination experience. The final outcome of this group is unclear. There is a fear that failure to identify and immobilise may lead to



**Address for correspondence:** David Shields, MBChB, MSc., MRSC., Glasgow Royal Infirmary, Department of Orthopaedic Surgery, 84 Castle Street, Glasgow, G4 0SF, United Kingdom  
E-mail: [dwshields@gmail.com](mailto:dwshields@gmail.com)

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>



nonunion and arthritis and missed scaphoid fractures are a cause for litigation [3, 4]. However, unnecessary immobilisation may lead to stiffness, time off work and avoidable healthcare utilisation.

Clinical diagnosis relies on the presence of anatomical snuffbox (ASB) pain on direct palpation. This sign, although sensitive, is not specific. Other signs, and combinations of signs, have been investigated to reduce the number of patients who require temporary immobilisation and advanced imaging. A recent study identified ASB pain on ulnar deviation of the wrist (within 72 hours of injury) and reported that no patient, without this sign, had a true scaphoid fracture [5]. Four factors were identified as predictive of actual fracture: male gender, sports injury, ASB pain on ulnar deviation of the wrist, and scaphoid tubercle tenderness. There have been a variety of clinical prediction rules suggested to improve diagnosis through examination [5-7]. Advocates of such signs and clinical predictions rules point to the potential overdiagnosis of clinical uncertain entities such as bone-bruising

and other soft-tissue injuries.

With increasing availability and reduced cost of advanced imaging, the cost-effectiveness of early magnetic resonance imaging (MRI) or computed tomography (CT) diagnosis has been revisited [8, 9] and found favourable. Our ED and fracture clinic has been an early adopter of universal use of MRI scanning to improve diagnosis and reduce unnecessary immobilisation. We have recently redesigned our fracture clinic service so that MRI scans were reviewed at Virtual Fracture Clinic (VFC) and patients only came to clinic if there was definite injury that required treatment. This protocol aimed to reduce healthcare utilisation and patient inconvenience.

The aim of this audit was to investigate the effectiveness of a virtual pathway, incorporating early MRI scan, for suspected scaphoid fractures. The secondary aim was to investigate whether the accuracy of other clinical signs, such as ASB pain on wrist ulnar deviation, was sufficient to reduce the number of patients requiring a MRI scan.

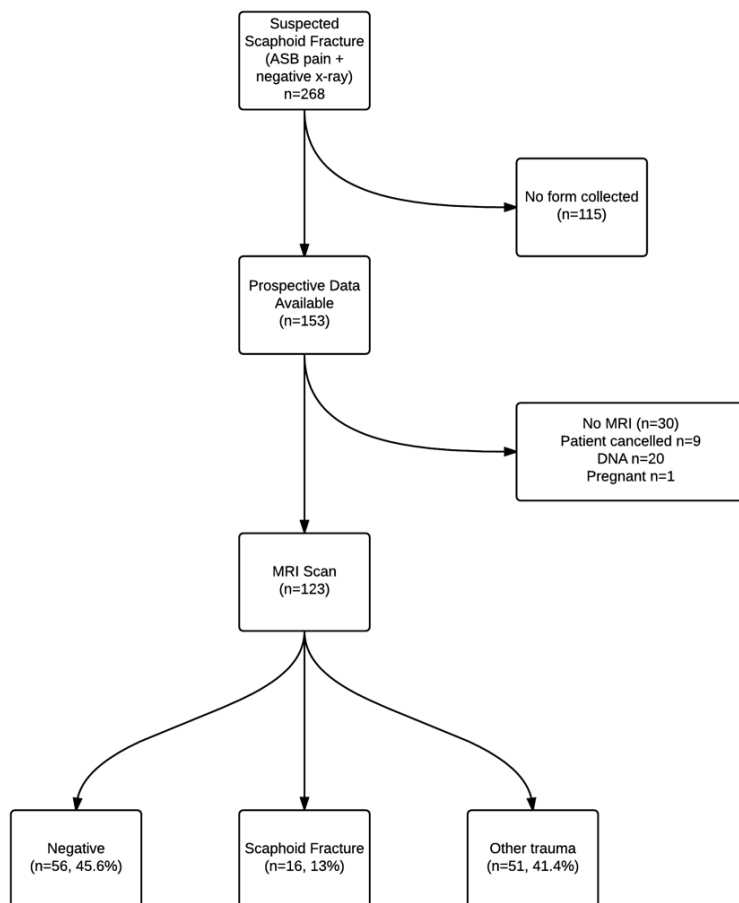


Figure 1. Flow chart of patients in study, along with clinical outcome

## METHODS

A prospective audit was performed at our institution's ED and its associated Minor Injuries Unit (MIU). Patients were included if they had suffered an injury to the wrist, had pain in the anatomical snuffbox, and did not have evidence of fracture on their initial radiographs. A standardised clinical examination was performed and recorded on an audit form. The use of this form was to support a full and effective clinical examination. This form recorded basic demographic details and the mechanism of injury. It also recorded the presence or absence pain on: thumb-index pinch, scaphoid tubercle tenderness, axial compression of the thumb, ASB pain on ulnar deviation and pronation, ASB pain on radial deviation and pronation. Patients were provided with a wrist splint without thumb extension (Promedics Beta Wrist Brace, Promedics, UK) and were referred for a MRI scan if they had no contraindications to scanning. The scans were performed on a Philips Achieve 1.5T scanner. The following protocols were used: (1) T1 D3 Vista Coronal, fov 82×82, tr 400, te21, voxel size 0.4×0.4×0.4 mm, 150 slices scan time 4.35 minutes and (2) T2 mSpir Drive Coronal, fov 80×80 tr3355, te 70, voxel size 0.3×0.4 mm, slice thickness 3 mm 16 slices scan time 3.11 min.

A virtual scaphoid pathway was implemented in the Orthopaedic Department. The results of pending MRI scans were regularly checked and reviewed at a VFC. If the scan was normal the patient received a phone call from a fracture clinic nurse. They were advised that they had a simple soft tissue injury of the wrist and were provided with advice regarding

mobilisation and splint removal. This was followed up with written information sent via post. Where there was an MRI abnormality, and ongoing symptoms, patients were offered review in a dedicated hand and wrist trauma clinic.

The audit took place from 1 February 2015 to 31 January 2016. A total of 268 patients met the inclusion criteria (Figure 1). There were 200 patients presenting to the ED and a further 68 to the MIU. There were audit forms completed for 108 (58%) patients in the ED and 45 (66.2%) in the MIU. Out of 153 patients with audit forms, a total of 123 underwent MRI scanning.

The median time from injury to assessment was 1 day (range 0 to 70, IQR 0 to 3.25, mean 4.1, SD 9.0). The mean time to from presentation to MRI scan was 19.4 days (0 to 56, IQR 12 to 27, SD 11.0). 115 presented within 3 days of injury. Of these, 94 underwent MRI scan.

## RESULTS

Out of 123 patients with a suspected scaphoid fracture there were 67 (54.4%) patient who had a traumatic lesion, of which 16 (13%) patients had a true scaphoid fracture (Table 1). A fracture was found in another carpal bone in 21 cases and in the distal radius in 24 cases. There were 16 soft tissue injuries.

There was a total of 52 physical appointments required for this group of 123 patients during a six-month follow-up period. The mean number of appointments per patient was patient was 0.42 (range 0 to 3, median 0, SD 0.65). There were 80 patients

**Table 1.** Total number of MRI abnormalities detected (n = 67).

MRI Finding	Abnormalities (n, %)
Scaphoid fracture	16 (13.0%)
Scaphoid bone bruising	2 (1.6%)
Other bone bruising	13 (10.6%)
Soft tissue injury	16 (13.0%)
Other carpal fracture	21 (17.0%)
Distal radius fracture	24 (19.5%)
Metacarpal fracture	9 (7.3%)

Some wrists had multiple abnormalities, therefore the column total exceeds 67. MRI = magnetic resonance imaging

**Table 2.** Diagnostic performance of clinical tests compared to MRI “gold standard” at diagnosis a true scaphoid fracture (in patients presenting three days or fewer after injury)

	TP	FN	FP	TN	Sens	Spec	PPV	NPV	Acc
<b>ASB pain</b>	13	0	76	5	100.0%	6.2%	14.6%	100.0%	94.7%
<b>Pain on thumb-index pinch</b>	5	8	41	40	38.5%	49.4%	10.9%	83.3%	48.9%
<b>ST tenderness</b>	8	5	49	32	61.5%	39.5%	14.0%	86.5%	60.9%
<b>Pain on axial compression</b>	8	5	50	31	61.5%	38.3%	13.8%	86.1%	61.7%
<b>ASB pain on ulnar deviation</b>	7	6	50	31	53.8%	38.3%	12.3%	83.8%	60.6%
<b>ASB pain on radial deviation</b>	7	6	42	39	53.8%	48.1%	14.3%	86.7%	52.1%
<b>Decreased active ROM</b>	6	7	35	46	46.2%	56.8%	14.6%	86.8%	43.6%

Acc = accuracy, ASB = anatomical snuff box, FN = false negative, FP = false positive, MRI = magnetic resonance imaging, NPV = negative predictive value, PPV = positive predictive value, ROM = range of motion, Sens = sensitivity, Spec = specificity, ST = scaphoid tubercle, TN = true negative, TP = true positive

who did not need a physical appointment in fracture clinic. They were phoned and discharged by telephone.

When the endpoint of true scaphoid fracture was examined in patients presenting 3 days or fewer after injury, pain in the ASB on palpation had a low specificity (6.2%), sensitivity (53.8%) and positive predictive value (12.3%). In this series, reliance on this finding would have resulted in six missed fractures. It would have also have identified 50 false positive cases. The other tests, applied individually, resulted in between 5 and 8 false positive findings (Table 2).

## DISCUSSION

This prevalence of true fracture in this population was 13%. This is similar to comparable studies and supports the generalisability of these findings. There was a lower rate clinic attendance than would occur in a traditional pathway. In a traditional pathway a patient would normally be expected to return to fracture clinic at two weeks for repeat examination, with definitive immobilisation being instituted for some at that clinic, further imaging arranged for others, and the majority discharged. A sub-group may have been brought back for a further review after another short period. Our protocol allowed a definitive diagnosis to be reached and treatment to be confidently commenced. Where there was no significant injury, this also allowed the patient to be “virtually” discharged with confidence. As such, only 0.42 physical appointments were required per patient.

In a standard pathway, this would be expected to be greater than 1 per patients, as every patient returns at least once for a clinical examination at two weeks. Patients were virtually discharged if they had abnormality found on MRI. They were also virtually discharged in many cases of minor soft tissue injury and undisplaced fractures of the distal radius and other carpal bones. This was in keeping with our unit’s protocols. Patients with suspected scaphoid fractures are generally managed in splints, and therefore these can be removed by the patient when symptoms reduce, and promote self-care.

This study also demonstrated that none of the previously suggested clinical examination techniques were sufficiently sensitive or specific to avoid significant false negative diagnoses [2, 10]. As such, we do not consider that any clinical rule, other than the presence of tenderness in the ASB, is useful or safe at reducing the number requiring further review or cross-sectional imaging. In particular, we were not able to reproduce the recently reported finding that lack of pain in their ASB on ulnar deviation of the wrist, within 72 hours of injury, predicted no underlying fracture [5]. In our study, there were six patients, without ASB pain on ulnar deviation, who had a fracture. We believe a significant limitation of this paper was the inclusion of true scaphoid fractures that were obvious on radiographs at the time of presentation. The examination, diagnosis and management of these patients is not contentious, and it is possible that findings related to the overall group of all scaphoid fractures are not translatable to the subgroup of those with a clinically suspected fracture.

The true scaphoid fracture rate in our study was also similar to that reported in a study of a clinical prediction score [6]. This test allocated 3 points to a ASB pain on palpation in ulnar deviation, tenderness of the scaphoid tubercle was given 2 points and pain on longitudinal compression was given 1 point. The authors test the hypothesis that a total score greater than or equal to 4 would be useful in diagnosis true fractures. They reported that the test had a NPV of 96%. Of the 13 true fractures, the test correctly identified 10, but missed 3 patients. It also identified 62 patients as having fracture, who did not (out of 72 positive findings). These authors state that it is not practically, ethically or financially possible to scan every injured wrist with MRI to prevent overtreatment. This conclusion is not in keeping with recent cost-effectiveness studies [8, 9].

Clinicians have been historically been wary about recommending widespread scanning due to the fact that little is actually known about the long term outcome of missed occult fractures and the potential for overdiagnosis of entities with unclear significance, such as bone bruising. A small study suggested that early MRI management was equivalent financially to the traditional management [11]. The protocol had the potential to reduce unnecessary immobilisation, overall treatment time, and healthcare usage. Due to the small number of patients it was unable to demonstrate reduced time off work or school. An American study of overall cost effectiveness showed that advanced imaging was dominant over empiric cast immobilisation, with lower health costs and better outcomes [9]. This study considered anticipated healthcare and societal savings. It reported MRI to be slightly more cost-effective based on the mean published diagnostic performance. It reported that imaging would have to cost more than \$2000 (USD) to become less cost-effective than traditional management. This finding is likely to be accurate in the US health market, but may be less generalisable to other health systems where advanced imaging is more difficult to access, and with more of a treatment delay. A separate cost effectiveness study examined seven different strategies for diagnosis and management and that immediate CT or MRI were the most cost-effective strategy for diagnosing suspected scaphoid fractures [8].

A strength of this study is the large number of

patients studies, with the use of MRI as a gold standard for diagnosis. It was also pragmatic in nature, as it recorded the clinical examination findings of a group of ED clinicians and emergency nurse practitioners (ENPs). This is likely to be representative of the wider diagnostic performance of this clinical group. Previous studies have tended to clinical examination performed by a single, highly trained, observer.

## CONCLUSION

This study demonstrated that a virtual pathway, in conjunction with MRI scanning, can reduce the need for physical review of suspected scaphoid fractures. It demonstrated that clinical signs, other than ASB tenderness on direct palpation, were associated with unacceptable false negative diagnosis rates, and could not be consistently used to reduce the need for MRI scanning.

## ARTICLE SUMMARY

### *Article focus*

- The aim of this audit was to investigate the effectiveness of a virtual pathway, incorporating early MRI scan, for suspected scaphoid fractures.
- The secondary aim was to investigate whether the accuracy of other clinical signs, such as ASB pain on wrist ulnar deviation, was sufficient to reduce the number of patients requiring a MRI scan.

### *Key message*

- This pathway was safe and effective at reducing the need for face-to-face review
- This pathway reduced the need for unnecessary immobilisation
- Clinical examination is not sufficiently sensitive to reduce the need for cross-sectional imaging

### *Strengths and limitations of this study*

- This study is unique in examining the impact of a virtual fracture clinic pathway on this common injury
- This study is pragmatic in that it has studied a typical UK ED and minor injuries unit rather than clinical examination limited to experienced

orthopaedic surgeons.

- This study is limited by failure to enroll all eligible patients to the audit

#### *Contribution of authors*

PJ conceived the study, designed the methodology, analysed the data and wrote the manuscript. SB led the study data collection in the Emergency Department and contributed to the manuscript. PM led the study data collection in the Minor Injuries Unit. KB collated and analysed the data and wrote the manuscript. DS assisted with data analysis. LAR conceived the study and wrote the manuscript.

#### *Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

#### *Funding Statement*

This audit was supported by a grant from the Scottish Government Whole System Patient Flow programme.

## REFERENCES

- [1] Duckworth AD, Jenkins PJ, Aitken SA, Clement ND, Court-Brown CM, McQueen MM. Scaphoid fracture epidemiology. *J Trauma Acute Care Surg* 2012;72:E41-5.
- [2] Unay K, Gokcen B, Ozkan K, Poyanli O, Eceviz E. Examination tests predictive of bone injury in patients with clinically suspected occult scaphoid fracture. *Injury* 2009;40:1265-8.
- [3] Harrison W, Newton AW, Cheung G. The litigation cost of negligent scaphoid fracture management. *Eur J Emerg Med* 2015;22:142-3.
- [4] Ring J, Talbot C, Price J, Dunkow P. Wrist and scaphoid fractures: a 17-year review of NHSLA litigation data. *Injury* 2015;46:682-6.
- [5] Duckworth AD, Buijze GA, Moran M, Gray A, Court-Brown CM, Ring D, et al. Predictors of fracture following suspected injury to the scaphoid. *J Bone Joint Surg Br* 2012;94:961-8.
- [6] Bergh TH, Lindau T, Soldal LA, Bernardshaw SV, Behzadi M, Steen K, et al. Clinical scaphoid score (CSS) to identify scaphoid fracture with MRI in patients with normal x-ray after a wrist trauma. *Emerg Med J* 2014;31:659-64.
- [7] Rhemrev SJ, Beeres FJP, van Leerdam RH, Hogervorst M, Ring D. Clinical prediction rule for suspected scaphoid fractures: a prospective cohort study. *Injury* 2010;41:1026-30.
- [8] Yin Z-G, Zhang J-B, Gong K-T. Cost-effectiveness of diagnostic strategies for suspected scaphoid fractures. *J Orthop Trauma* 2015;29:e245-52.
- [9] Karl JW, Swart E, Strauch RJ. Diagnosis of occult scaphoid fractures: a cost-effectiveness analysis. *J Bone Joint Surg Am* 2015;97:1860-8.
- [10] Duckworth AD, Ring D, McQueen MM. Assessment of the suspected fracture of the scaphoid. *J Bone Joint Surg Br* 2011;93:713-9.
- [11] Kelson T, Davidson R, Baker T. Early MRI versus conventional management in the detection of occult scaphoid fractures: what does it really cost? A rural pilot study. *J Med Radiat Sci* 2016;63:9-16.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# The relationship between atrial natriuretic peptide and microvascular complications of diabetes

Pınar Karakaya<sup>1</sup>, Bahar Özdemir<sup>2</sup>, Meral Mert<sup>1</sup>, Hakan Koçoğlu<sup>2</sup>, Abdulbaki Kumbasar<sup>2</sup>

<sup>1</sup>Department of Endocrinology and Metabolic Diseases, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey

<sup>2</sup>Department of Internal Medicine, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey

DOI: 10.18621/eurj.410990

## ABSTRACT

**Objectives:** In this study, we aimed to determine the relationship between the atrial natriuretic peptide and microvascular complications of diabetes.

**Methods:** Sixty patients with type 2 diabetes mellitus were enrolled into the study. Patients with a chronic disease other than diabetes mellitus were excluded from the study. The body-mass index, waist circumference, and hip circumference were measured and blood samples for routine biochemical tests were taken after at least 12 hours fasting. The microvascular complications of the patients were evaluated.

**Results:** Thirty-two of the patients had microvascular complications whereas 28 of them did not. Age, body mass index, waist and hip circumference, and atrial natriuretic peptide levels were significantly higher in the group with microvascular complications than those without complications. There was no significant difference in parameters like; waist-hip ratio, blood glucose, HbA1c, fasting insulin, fasting HOMA, sodium, potassium, magnesium, calcium and lipid levels between the two groups. When the relationship between atrial natriuretic peptide and obesity, retinopathy, neuropathy, nephropathy, duration of diabetes, HbA1c, and sex are evaluated separately, the only significant parameters related to atrial natriuretic peptide were the body-mass index, waist circumference, hip circumference measurements, and neuropathy.

**Conclusions:** Positive correlations between serum atrial natriuretic peptide levels and body-mass index, waist circumference, and hip circumference measurements were determined. Also, serum atrial natriuretic peptide levels were significantly higher in patients with obesity or neuropathy than those without obesity or neuropathy.

**Keywords:** Atrial natriuretic peptide, diabetes mellitus, microvascular complications

*Received: March 29, 2018; Accepted: June 17, 2018; Published Online: June 21, 2018*

Type 2 Diabetes Mellitus (DM) is the most widely seen metabolic disease. In developed countries 5-10% of the population is diabetic. In the worldwide, 90-95% of cases are type 2 diabetes, whereas 5-10% are type 1 and 2-3% are the other diabetes forms.

Hyperglycemia and insulin resistance play important role in the pathogenesis of diabetes. In the early phase of diabetes, intracellular hyperglycemia

causes abnormalities in blood flow. Chronic hyperglycemia leads to microvascular and macrovascular complications.

Atrial natriuretic peptide (ANP) inhibits the transport of sodium (Na) in the medullary collecting tubules of the kidney and increases renal blood flow and glomerular filtration rate (GFR). Besides its renal effects, ANP also induces some cardiovascular,



**Address for correspondence:** Hakan Koçoğlu, MD., Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Internal Medicine, İstanbul, Turkey  
E-mail: dr.hakankocoglu@gmail.com, Tel: +90 506 3809215

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

endocrinological and neural responses for decreasing the vascular volume and tonus [1].

There is Na retention and increased blood volume in diabetic patients. Most of these patients have high ANP or N-terminal proANP (1-98) levels in the circulation. These patients are probably in the early hyperfiltration phase of the disease or with the long-term complications. This data shows that ANP level may be important for diabetic patients with early hyperfiltration phase of the disease.

In this study, we aimed to study the relationship between ANP and microvascular complications.

## METHODS

A total of 60 patients (38 females/22 males) with type 2 diabetes are enrolled in this study. The patients' age range was 30 to 70 years old. Patients with known thyroid dysfunction, hepatic failure, heart failure, renal failure, malignancy, systemic chronic disease, collagen tissue disease, and with electrolyte imbalance, pregnancy, those having antihypertensive drug or insulin treatment were excluded from the study. Also, there was no patient taking any kind of SGLT 2 inhibitors or thiazolidinediones in our study. The study was performed according to Declaration of Helsinki and our Institutional Review Board approved the study. Informed consent was obtained from all patients.

Physical examination of all patients was undertaken. Body mass index (BMI) of patients were determined by "Tanita Body Composition Analyser". According to the World Health Organization (WHO), a BMI of greater than or equal to 30 is classified as obese. The HOMA values were calculated by using the formula:  $(\text{HOMA-IR} = \text{insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mmol/L)} / 22.5)$ . Waist circumference was measured from the midpoint of the distance between superior iliac crests and lowest chest ribs. Hip circumference was measured from the outermost surface of the gluteal area. Waist/hip ratios were calculated. Blood pressure of all patients was measured two times in 3 minutes by a sphygmomanometer from the left arm in sitting position after at least 5 minutes of resting. The mean value of the two measurements is recorded. Electrocardiograms of the patients are recorded and

evaluated. Pulse rates are also measured. Those patients with hypertension and rhythm disturbance are excluded from the study.

From all patients, after 12 hours of fasting, blood samples were taken at 8-9 am for measurement of fasting blood glucose, urea, creatinine, uric acid, total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglyceride, fasting insulin, HbA1c, sodium (Na), potassium (K), calcium (Ca), magnesium (Mg) levels. Blood samples for ANP level are taken into blood tubes containing EDTA and after rotated slowly 6-7 times the samples are put into tubes which contain 600-750 KIU aprotinin for every millimeter of blood. Then the tubes are rotated slowly with passive movements 6-7 times again. These blood samples are centrifuged at 4 C degree and 1600 cycles for 15 minutes. The isolated serum samples are preserved at - 80 C degree until the study time of the kit.

The first-morning urine samples were used to measure the microalbumin/creatinine ratios and total protein levels are measured in 24-hour urine samples. ANP levels were measured by their specific radioimmunoassays and serum samples other than ANP has been studied at the same day by routine biochemical analysis Roche Diagnostics brand Cobas at 8000 model biochemistry autoanalyzer (modul Cobas c 701) and hormone tests again the same brand (modul Cobas e 602) immunoassay analyzer with original kits (Beckman Coulter Inc, U.S.A.). Full Urine etude, at spot urine has been done with full automatic chemical and microscopic analyse system (Arkray, Japanese - Iris IQ200, USA).

All the patients are evaluated for diabetic retinopathy, diabetic peripheral neuropathy and diabetic nephropathy by related specialists. Indirect optical funduscopy was performed by the same ophthalmologist after mydriasis and angiofluorescence when necessary. Retinopathy was classified according to the Diabetic Retinopathy Research Group. The patients were divided according to whether they had the incipient form of retinopathy (background) or the severe form (pre-proliferative or proliferative). The grade of diabetic nephropathy was evaluated (exercise, drugs and urinary infection excluded) by urinary albumin excretion rate and classified as normal (value < 20  $\mu\text{g}/\text{min}$ ), microalbuminuria in the range 20-200  $\mu\text{g}/\text{min}$

**Table 1.** Descriptive data of type 2 diabetic patients with and without microvascular complications

	At least 1 microvascular complication		<i>p</i> value
	Present (n = 32)	Absent (n = 28)	
Age (year)	54 ± 9.5	47 ± 7.6	< 0.05
BMI (kg/m <sup>2</sup> )	32 ± 6.2	26 ± 5.6	< 0.05
Waist (cm)	103 ± 19	87 ± 17	< 0.05
Hip (cm)	114 ± 19	96 ± 18	< 0.05
WHR	0.89 ± 0.06	0.9 ± 0.04	0.851
FBG (mg/dl)	175 ± 71	157 ± 56	0.612
PPG (mg/dl)	260 ± 107	221 ± 64	0.576
HbA1c	9 ± 1.9	8 ± 1.9	0.912
Fasting Insulin (IU/ml)	15 ± 7	12 ± 7	0.752
Fasting HOMA	6.6 ± 4.2	4.7 ± 3.3	0.244
Na (mmol/L)	140 ± 3.3	139 ± 2.5	0.656
K (mmol/dL)	4.5 ± 0.4	4.4 ± 0.3	0.811
Mg (mmol/dL)	0.8 ± 0.05	0.8 ± 0.06	0.912
Ca (mg/dl)	10 ± 0.5	10 ± 0.6	0.904
Total-cholesterol (mg/dl)	205 ± 48	189 ± 40	0.349
LDL-C (mg/dl)	123 ± 32	114 ± 37	0.185
HDL-C (mg/dl)	47 ± 12	45 ± 9	0.205
Triglyceride (mg/dl)	167 ± 72	154 ± 43	0.417
ANP (ng/ml)	4.99 ± 2.89	3.45 ± 2.89	< 0.05

Data are shown as mean ± standard deviation. ANP = Atrial natriuretic peptide, BMI = Body mass index, FBG = Fasting blood glucose, HbA1c = Hemoglobin A1c, HDL-C = High-density lipoprotein cholesterol, HOMA = Homeostatic model assessment, LDL-C = Low-density lipoprotein cholesterol, NS = Not significant, PPG = Postprandial glucose, WHR = Waist-hip-ratio

(incipient nephropathy) or macroalbuminuria if > 200 µg/min (overt/clinical nephropathy). Peripheral neuropathy was diagnosed by Diabetic Neuropathy Index (DNI) and defined as a positive score of > 2 points on the DNI and evaluated by the same neurologist. Diabetic Neuropathy Score (DNS) was not evaluated and thus severity of neuropathy was not determined.

### Statistical Analysis

The data were analyzed in SPSS 11.5 (SPSS Inc., Chicago, IL, USA) software. Descriptive statistics for continuous variants were given as mean ± standard deviation and for categorical variants were given as the percentage (%). Between independent groups, the significance of the difference in mean values was evaluated by Student's t-test and Mann Whitney U test. The correlation analysis of all data was evaluated by Pearson correlation test. A *p* value of < 0.05 is defined as significant statistically.

### RESULTS

Thirty-two of the sixty diabetic patients had microvascular complications and the remaining 28 patients had no microvascular complications (Table 1). Among patients with microvascular complications 6 patients had retinopathy (all patients had background retinopathy), 16 patients had nephropathy (2 of them had macroalbuminuria whereas 14 had microalbuminuria), 18 patients had neuropathy. Two of the patients had both retinopathy and nephropathy, one patient had both retinopathy and neuropathy, and 2 patients had both nephropathy and neuropathy. Only 3 patients had all retinopathy, neuropathy, and nephropathy. Age, BMI, waist circumference, hip circumference and ANP levels were significantly higher in patients with microvascular complications than those without complications. But there was no significant difference in waist-hip ratio, blood glucose levels, HbA1c, fasting insulin, postprandial insulin,



**Table 2.** Variants in correlation with ANP

	<b>BMI (kg/m<sup>2</sup>)</b>	<b>Waist circumference (cm)</b>	<b>Hip circumference (cm)</b>
ANP (ng/dl)	r=0.415 <b>p = 0.001</b>	r=0.496 <b>p &lt; 0.001</b>	r=0.520 <b>p &lt; 0.001</b>

ANP = Atrial natriuretic peptide, BMI = Body mass index

fasting HOMA, postprandial HOMA, Na, K, Mg, Ca, and lipid levels between two groups.

The correlation analysis of patients are given in Table 2. Statistically significant positive correlations were determined between ANP level and BMI ( $r = 0.415, p = 0.001$ ), waist circumference ( $r = 0.496, p < 0.001$ ), and hip circumference ( $r = 0.520, p < 0.001$ ) measurements.

When the relationships between ANP level and obesity, retinopathy, neuropathy, nephropathy, duration of diabetes, HbA1c, and sex were evaluated separately and there was a significant relationship between ANP level and obesity, and neuropathy. The relationship between ANP levels and other parameters was not significant (Table 3).

**Table 3.** Factors related to ANP

		<b>n</b>	<b>ANP (ng/dl)</b>	<b>p value</b>
<b>Obesity</b>	Present	30	5.4 ± 2.8	<b>&lt; 0.001</b>
	Absent	30	2.8 ± 2.5	
<b>Sex</b>	Female	38	4.7 ± 2.8	0.163
	Male	22	3.2 ± 2.9	
<b>Retinopathy</b>	Present	6	3.4 ± 2.7	0.438
	Absent	54	4.2 ± 3	
<b>Nephropathy</b>	Present	16	4.8 ± 3.1	0.324
	Absent	44	3.9 ± 2.9	
<b>Neuropathy</b>	Present	18	5.4 ± 3.1	<b>&lt; 0.05</b>
	Absent	42	3.6 ± 2.7	
<b>Duration of diabetes</b>	≤ 10 years	37	3.9 ± 2.9	0.611
	> 10 years	23	4.4 ± 3.1	
<b>HbA1c</b>	< 7	16	3.9 ± 3.1	0.303
	≥ 7	44	4.2 ± 2.9	

Data are shown as mean±standard deviation. ANP = Atrial natriuretic peptide, NS = Not significant

## DISCUSSION

The best-known function of ANP is inhibiting the renin-angiotensin-aldosterone system by stimulating the wasting of salt and water via kidneys [2, 3]. The increase in plasma ANP level in response to acute hyperglycemia is important in diabetic patients. Because it was shown that Na sparing effect of insulin causes an increase in total Na pool and leads to an increase in extracellular volume which results in chronic stimulus for ANP [4]. This effect is also seen

in type 1 diabetic patients [5].

Neuropathy, retinopathy, and nephropathy are known as microvascular complications of diabetes. Some studies have evaluated the relationship between these complications and ANP level. Moro and Berlan [6] have investigated the peripheral and central effects of natriuretic peptides and they have reported that these peptides have important functions in hypertrophy and regulation of cardiomyocyte. They have shown in that study that plasma ANP level was increased in patients with unstable angina, acute

myocardial infarction, congestive heart failure, diabetic microangiopathy and isolated diastolic dysfunction [6]. Also, a previous study has shown a relation between microvascular complications of diabetes and serum vitamin D levels [7].

In our study, we found that plasma ANP levels in diabetic patients with neuropathy or nephropathy were higher than those without neuropathy or nephropathy; but ANP levels were significantly higher only in patients with neuropathy. There was no relation between ANP levels and retinopathy. This result could be caused by the limited number of patients included in this study. Because of this restricted number of patients, we were unable to compare ANP levels in the subgroups of patients consisted of microvascular complications with different severity. In addition to that, there were significant correlations between ANP level and BMI, waist circumference, and hip circumference measurements.

Jacobs *et al.* [8] claimed that the excess increase in urinary protein excretion - during 1-hour ANP infusion to type 1 diabetic patients with microalbuminuria - was not only related with glomerular pressure changes but also with the decrease of tubular protein reabsorption. In another study, McKenna *et al.* [9] investigated the physiopathological markers of the albuminuric effects of increased ANP concentrations in type 1 diabetic patients. They found a close relationship between plasma ANP level and acute or chronic hyperglycemia. In that study, they showed that ANP concentrations in type 1 diabetic patients (especially with chronic poor glycemic control) were high in subgroups with systemic hypertension and microalbuminuria [9]. In another study evaluating the relationship between ANP levels and nephropathy, natriuretic peptide levels of type 2 diabetic rats were significantly higher than nondiabetic rats [10]. In that study, the filtration rate in type 2 diabetic rats was decreased 48-79% when compared to nondiabetic ones and the investigators speculated that the increase in natriuretic peptide level was caused by the ineffective metabolize of the natriuretic peptides in kidneys [10].

In a study evaluating the relationship between ANP level and retinopathy, the investigators looked for ANP levels in vitreous fluids and epiretinal membranes of diabetic patients [11]. They found that the ANP levels in vitreous fluids of diabetic patients

with retinopathy were significantly higher than in patients without retinopathy. In addition to that, the ANP levels of patients without retinopathy were also higher than the control group [11]. In our study, there was no difference in serum ANP levels between the patients with and without retinopathy.

Salas-Ramirez *et al.* [12] studied the effect of increased plasma volume on ANP in diabetic patients with autonomous neuropathy and showed that there was no relationship between ANP levels and autonomic test changes. They concluded that salty water infusion would not lead to increase in ANP levels independent of autonomous neuropathy [12]. In our study, the plasma ANP levels of diabetic patients with neuropathy were significantly higher than in diabetic patients without neuropathy.

In our study, we detected that plasma ANP levels in diabetic patients with microvascular complications were higher than in patients without microvascular complications. This was independent of glycemic regulation. Also, there were significant correlations between ANP level and BMI, waist circumference and hip circumference measurements. When we evaluated the microvascular complications separately ANP level was only significantly high in patients with nephropathy. According to the literature, ANP plays an important role in diabetes physiopathogenesis. We need studies with greater patient size investigating the role of ANP in early diagnosis and treatment.

### Limitations

We had a limited number of study group and thus we were unable to compare ANP levels in the subgroups of patients consisted of microvascular complications with different severity. We could not exclude the silent hearth failure as we did not perform an echocardiographic evaluation to the patients. None of our patients were taking alcohol but physical activity and smoking habit were not assessed in statistical analysis.

### CONCLUSION

In this study, we found positive correlations between serum atrial natriuretic peptide levels and body-mass index, waist circumference, and hip circumference measurements in patients with type 2

diabetes mellitus. Also, serum atrial natriuretic peptide levels were significantly higher in patients with obesity or neuropathy than those without obesity or neuropathy.

#### *Authorship declaration*

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

#### *Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

#### *Financing*

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

- [1] de Bold AJ. Atrial natriuretic factor: a hormone produced by the heart. *Science*. 1985;230:767-70.
- [2] Nosadini R, Semplicini A, Fioretto P, Lusiani L, Trevisan R, Donadon V, et al. Sodium-lithium countertransport and cardiorenal abnormalities in essential hypertension. *Hypertension* 1991;18:191-8.
- [3] Fine LG, Badie-Dezfooly B, Lowe AG, Hamzeh A, Wells J, Salehmoghaddam S. Stimulation of Na<sup>+</sup>/H<sup>+</sup> antiport is an early event in hypertrophy of renal proximal tubular cells. *Proc Natl Acad Sci U S A* 1985;82:1736-40.
- [4] Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation* 2004;109:594-600.
- [5] Nannipieri M, Seghieri G, Catalano C, Prontera T, Baldi S, Ferrannini E. Defective regulation and action of atrial natriuretic peptide in type 2 diabetes. *Horm Metab Res* 2002;34:265-70.
- [6] Moro C, Berlan M. Cardiovascular and metabolic effects of natriuretic peptides. *Fundam Clin Pharmacol* 2006;20:41-9.
- [7] Boyuk B, Atalay H, Degirmencioglu S, Altay M, Guzel S, Celebi A, et al. Is there a relation between serum vitamin D level and microvascular complications in type 2 diabetes? *Eurasian J Med Oncol* 2017;1:190-6.
- [8] Jacobs EM, Vervoort G, Branten AJ, Klasen I, Smits P, Wetzels JF. Atrial natriuretic peptide increases albuminuria in type I diabetic patients: evidence for blockade of tubular protein reabsorption. *Eur J Clin Invest* 1999;29:109-15.
- [9] McKenna K, Smith D, Sherlock M, Moore K, O'Brien E, Tormey W, et al. Elevated plasma concentrations of atrial and brain natriuretic peptide in type 1 diabetic subjects. *Ir J Med Sci* 2005;174:53-7.
- [10] Vesely DL, Gower WR, Jr., Dietz JR, Overton RM, Clark LC, Antwi EK, et al. Elevated atrial natriuretic peptides and early renal failure in type 2 diabetic Goto-Kakizaki rats. *Metabolism* 1999;48:771-8.
- [11] Rollin R, Mediero A, Martinez-Montero JC, Roldan-Pallares M, Suarez-Leoz M, Vidal-Fernandez P, et al. Atrial natriuretic peptide in the vitreous humor and epiretinal membranes of patients with proliferative diabetic retinopathy. *Mol Vis* 2004;10:450-7.
- [12] Salas-Ramirez M, Ariza Andraca R, Frati Munari A, Munoz H, Altamirano P. Effect of plasma volume expansion on auricular natriuretic peptide in non-dependent insulin diabetic patients with autonomic neuropathy. *Arch Med Res* 1995;26:35-40.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# The relationship between psychopathology, psychosocial adjustment, social support and quality of life in multiple sclerosis

Vahap Ozan Kotan<sup>1</sup>, Zeynep Kotan<sup>2</sup>, Birgül Aydın<sup>3</sup>, Özlem Taşkapılıoğlu<sup>4</sup>, Berna Alkan<sup>5</sup>, Güven Özkaya<sup>6</sup>, Aslı Sarandöl<sup>7</sup>, Ömer Faruk Turan<sup>4</sup>, Selçuk Kırılı<sup>7</sup>

<sup>1</sup>Department of Psychiatry, Başkent University School of Medicine, Ankara, Turkey

<sup>2</sup>Department of Psychiatry, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey

<sup>3</sup>Specialist Psychologist, Dört Mevsim Psychological Counseling Center, Bursa, Turkey

<sup>4</sup>Department of Neurology, Uludağ University School of Medicine, Bursa, Turkey

<sup>5</sup>Department of Neurology, Başkent University School of Medicine, Ankara, Turkey

<sup>6</sup>Department of Biostatistics, Uludağ University School of Medicine, Bursa, Turkey

<sup>7</sup>Department of Psychiatry, Uludağ University School of Medicine, Bursa, Turkey

DOI: 10.18621/eurj.382894

## ABSTRACT

**Objectives:** Multiple Sclerosis (MS) is a chronic disease which affects physical, psychological and social functioning of patients. In this study we aim to indicate psychiatric comorbidity, some psychosocial factors and their associations with quality of life in patients with MS.

**Methods:** A total of 227 patients underwent psychiatric examination and the following scales were applied: Socio-demographic data form, Hospital Anxiety and Depression Scale (HADS), Multiple Sclerosis Quality of Life-54 (MSQOL-54), Psychosocial Adjustment to Illness Scale-Self report (PAIS-SR) and Multidimensional Scale of Perceived Social Support (MSPSS).

**Results:** Among 227 patients with MS, 67.8% (n = 154) had psychiatric diagnosis; 24.2% (n = 55) had depression, 19.8% (n = 45) had adjustment disorder, 14.9% (n = 34) had anxiety disorder, 7.1% (n=16) had dysthymic disorder and 1.8% (n = 4) had bipolar disorder. Patients with a psychiatric diagnosis had lower scores in role limitations due to emotional problems, emotional well-being, health perceptions, social function, cognitive function, health distress and mental health composite of MSQOL-54. PAIS-SR and MSPSS scores were significantly lower in MS patients with a psychiatric diagnosis. PAIS-SR scores were negatively correlated with role limitations-emotional, emotional well-being, social function, sexual function, satisfaction with sexual function, physical health composite and mental health composite scores of MSQOL-54. MSPSS total score was positively correlated with emotional well-being score of MSQOL-54.

**Conclusions:** In MS patients, there is a high prevalence of psychopathology and it is associated with quality of life, perceived social support and psychosocial adjustment of the patients. Quality of life is reduced especially in emotional and mental aspects in patients with a psychiatric diagnosis. Diagnosis and treatment of psychopathology in MS patients seems crucial to decrease disease burden.

**Keywords:** Multiple sclerosis, psychopathology, psychosocial adjustment, social support, quality of life

*Received: January 23, 2018; Accepted: March 7, 2018; Published Online: April 13, 2018*



**Address for correspondence:** Vahap Ozan Kotan, MD., Assistant Professor, Başkent University School of Medicine, Department of Psychiatry, Maresal Fevzi Çakmak Cad., No: 38/9, Bahçelievler, Ankara, Turkey  
E-mail: ozankotan79@yahoo.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

**M**ultiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system which causes motor and sensory impairment by progressive demyelination. It is the most common cause of neurologic disability in young and middle-aged adults. MS is twice as common in females as in males [1].

The relationship of psychological and psychiatric disorders with MS is complex. They might be related to psychosocial factors or they might be symptoms resulting from the neuropathological process. They aggravate physical symptoms like fatigue leading to disability, suffering and disruption of family, work and social life adding to the burden of the chronic inflammatory disease [2]. The rate of depression and other psychiatric disorders is greater in MS than in other chronic medical or neurological diseases [3, 4]. Treating depression actually results in improvements on a number of aspects of social support and there is evidence that depression itself may actually cause reduced social support [5, 6]. The lifetime prevalence of any anxiety disorder observed in MS was about 35.7%. Female gender, comorbidity of depression, and restricted social support were considered as risk factors, but the diagnosis of anxiety disorders had been overlooked and not been treated in most subjects [7].

The literature about bipolar disorder in patients with MS is scarce. Like depression, mania may occur as part of the physical disorder or secondary to drug treatments. There is a doubled rate of bipolar disorder in MS compared with the general population [8].

Psychosocial adjustment to MS can be understood as the ability to foster a positive outlook on life, continuing to grow and develop in spite of MS [9]. Among the key elements of successful adjustment to a chronic illness are the successful performance of adaptive tasks (eg, adjustment to disability, maintained emotional balance, healthy relationships), the absence of psychological disorders, the presence of low negative affect and high positive affect, adequate functional (eg, work) status, and the satisfaction and wellbeing in various life domains [10].

Social support is defined as the degree to which an individual's needs for socialization, assistance, cognitive guidance, social reinforcement, and emotional sustenance are met through interaction with the social network [11]. Recent research showed that social support acts as primary protective factor for

mortality, morbidity and disability in chronic patients by facilitating healthy behaviors and compliance to treatments [12]. In general, the research suggests that social support is related to better psychosocial adaptation to MS [13].

Chronic illnesses have a major impact on all aspects of an individual's life, affecting physical, psychological and social functioning [14]. Chronic symptoms, long-lasting treatment, incomplete recovery after relapses, the accumulation of new deficits, and the progressive nature of the condition interfere with daily activities of individuals and have negative impact on their wellbeing. Studies show that QoL measurements are constantly lower in patients with MS. Estimation of health related QoL (HRQoL) is necessary when analyzing the effectiveness of treatment modalities and in follow up of patients with chronic diseases such as MS. Main factors related with HRQoL are physical factors (sensitive/motor deficits, fatigue, pain, and sexual/bladder dysfunction), psychological factors (depression, anxiety, cognitive disturbances, and coping strategies) and social factors (family/social relationships and work activity) [15].

In the current study, we aim to investigate the features of psychosocial adjustment to disease, perceived social support, and their relations with health related quality of life in patients with MS. We also aim the relation of these variables with comorbid psychopathology.

## **METHODS**

This study was conducted at Psychiatry and Neurology Departments of Uludag University Medical Faculty Hospital in Turkey. Two hundred and fifty five patients who applied to Neurology department and were diagnosed as MS were recruited. The exclusion criteria for the patients were as follows: psychotic, demented or mentally retarded patients, alcohol or substance abusers, patients who were on psychiatric treatment during last 3 months, patients who had an active MS episode, patients who were on steroid treatment, patients who had an invasive procedure during last 3 months, patients with another chronic disease other than MS and illiterate patients. After applying the exclusion criteria, 227 patients were included in the study. Physical and neurological

examinations were done by a neurologist and routine blood tests were applied to all subjects. Patients underwent a psychiatric examination comprised of a semi-structured clinical interview of the DSM-IV-TR [16]. The Ethical Committee of the institution approved the study. All subjects gave written informed consent to participate in this study. The assessments were performed using the scales below: Socio-demographic data form, Hospital Anxiety and Depression Scale (HAD), Multiple Sclerosis Quality of Life-54 (MSQOL-54), Psychosocial Adjustment of Illness Scale – Self Report (PAIS-SR) and Multidimensional Scale of Perceived Social Support (MSPSS).

## Measures

### *Socio-demographic data form:*

A form prepared by the researchers in order to obtain socio-demographic data and to assess clinical features related with MS.

### *Hospital Anxiety and Depression Scale (HADS):*

The Hospital Anxiety and Depression Scale (HADS) is a 14-item scale that provides a brief state measure of anxiety and depression. Turkish version of HADS is valid and reliable in medically ill patients [17].

### *Quality of Life Scale (QOL) Short Form 36 (SF-36):*

The form was developed by Ware and Sherbourne [18]. Turkish validity study was done by Koçyiğit et al. [19]. It is composed of 36 items that measure eight dimensions: physical functioning, social functioning, limitations of role functioning based on physical problems, limitations of role functioning based on emotional problems, mental health, energy/vitality, body pain and general health perceptions. Higher scores point to increased quality of life [19].

### *Psychosocial Adjustment to Illness Scale-Self Report (PAIS-SR):*

Developed by Derogatis and Lopez in 1983, this is a multidimensional scale to examine the psychosocial adjustment to the disorder [20,21]. Lower scores from the PAIS-SR scale indicate good psychosocial adjustment to the disorder. PAIS-SR scores below 35 are considered as “good psychosocial

adjustment”, scores from 35 to 51 as “fair psychosocial adjustment” and scores above 51 as “poor psychosocial adjustment”. Turkish adjustment of PAIS-SR and its validity and reliability studies in Turkey were performed by Adaylar [20].

### *Multiple Sclerosis Quality of Life-54 (MSQOL-54):*

Quality-of-Life was measured by the disease-specific instrument MSQOL-54 (Turkish version). This questionnaire includes one of the most widely used QOL measures, the SF-36, as a generic core and an additional 18 items that are specific to MS. Scoring was performed using the Likert method, and higher values indicated better functioning and well-being. The Turkish adaptation was developed by Tulek in 2006. The MSQOL-54 consists of two sections as physical health composite (MSQOL-54P) and mental health composite (MSQOL-54M). It also has two section scores, 13 category scores and two independent items [22].

## Statistical Analysis

All statistical analyses were performed with SPSS ver. 22.0. Shapiro Wilk test was used as normality test. Continuous variables were compared using Student's t-test for normally distributed data and Mann-Whitney U test when the data were not normally distributed. Categorical variables were compared using Pearson's chi-squared test, Fisher's exact test and Fisher-Freeman-Halton test. Correlations between variables were tested using Spearman correlation coefficients. A  $p$  value  $< 0.05$  was considered as significant.

## RESULTS

Demographic findings including age, gender, marital status, education level, smoking status and exercise status and data about presence of a psychiatric diagnosis are given in Table 1. Among 227 patients, 32.2% ( $n = 73$ ) had no psychiatric diagnosis, 24.2% ( $n = 55$ ) had depression, 19.8% ( $n = 45$ ) had adjustment disorder, 14.9% ( $n = 34$ ) had anxiety disorder, 7.1% ( $n = 16$ ) had dysthymic disorder and 1.8% ( $n = 4$ ) had bipolar disorder.

The clinical characteristics of the patients are given in Table 2. There were no statistically significant difference between patients with or without a

**Table 1.** Demographic features of multiple sclerosis (MS) patients

Demographic features	MS patients (n = 227)
Age (years)	37.0 ± 9.9
<b>Gender</b>	
Male	64 (28.2%)
Female	163 (71.8%)
<b>Marital Status</b>	
Married	41 (18.1%)
Single	149 (65.6%)
Divorced or widowed	37 (16.3%)
<b>Education Level</b>	
Primary school	113 (49.8%)
High school	73 (32.2%)
University	41 (18.1%)
<b>Smoking Status</b>	
Smoking	49 (21.6%)
Nonsmoking	178 (78.4%)
<b>Exercise Status</b>	
Exercising	68 (30%)
Not exercising	159 (70%)
<b>Psychiatric Diagnosis</b>	
Depressive disorder	55 (24.2%)
Adjustment disorder	45 (19.8%)
Anxiety disorder	34 (14.9%)
Dysthymic disorder	16 (7.1%)
Bipolar disorder	4 (1.8%)
<b>No psychiatric diagnosis</b>	73 (32.2%)

Data are mean ± standard deviation or number (%). MS = multiple sclerosis

**Table 2.** Clinical characteristics of multiple sclerosis (MS) patients

Clinical Characteristics	MS Patients (n = 227)
<b>Type of MS</b>	
Clinically Isolated Syndrome	33 (14.5%)
Relapsing-remitting MS	158 (69.6%)
Primary progressive MS	20 (8.8%)
Progressive-relapsing MS	9 (4.0%)
Secondary progressive MS	7 (3.1%)
<b>Duration of disease (years)</b>	6.8 ± 3.5
<b>Number of attacks</b>	3.5 ± 1.8
<b>Number of hospitalizations</b>	3.1 ± 1.6
<b>Medication</b>	
Interferon beta	151 (66.5%)
Glatiramer acetate	36 (15.9%)
Natalizumab	29 (12.8%)
Other (Fingolimod, Mitoxantrone, Cyclophosphamide)	11 (4.8%)

Data are mean ± standard deviation or number (%). MS = multiple sclerosis

psychiatric diagnosis in terms of demographic variables, MS type, duration of MS, number of attacks and hospitalizations and medication type.

Table 3 shows mean scores of PAIS-SR, HADS, MSPSS and MSQOL-54 in two groups of MS patients with and without a psychiatric diagnosis. Depression ( $p < 0.001$ ) and anxiety ( $p < 0.001$ ) scores of patients with a psychiatric diagnosis are significantly higher than those without a psychiatric diagnosis. PAIS-SR scores of patients without a psychiatric diagnosis were significantly lower than those with a psychiatric diagnosis ( $p < 0.001$ ). Regarding MSPSS; total score, family, friends and significant other score were significantly higher ( $p < 0.05$ ) in patients without a psychiatric diagnosis. Emotional role limitations ( $p < 0.001$ ), emotional well-being ( $p < 0.001$ ), health perceptions ( $p < 0.05$ ), social function ( $p < 0.001$ ), cognitive function ( $p < 0.05$ ), health distress ( $p < 0.05$ ) and mental health composite ( $p < 0.001$ ) domains of MSQOL-54 differed significantly between groups. Patients without a psychiatric diagnosis had higher scores in these domains.

Correlation of age, duration of disease, number of attacks and hospitalizations were evaluated with the scores of applied scales. There was a positive correlation between the number of attacks and HADS anxiety score ( $r = .138, p = 0.037$ ) as the only correlation, and there was not any other significant correlation.

When the scale scores were evaluated, there were significant positive and negative correlations among each other. PAIS-SR scores were positively correlated with HADS depression ( $r = .307, p < 0.001$ ) and anxiety ( $r = .161, p = 0.015$ ) scores. PAIS-SR scores were negatively correlated with role limitations-emotional ( $r = -.192, p = 0.004$ ), emotional well-being ( $r = -.156, p = 0.019$ ), social function ( $r = -.225, p = 0.001$ ), sexual function ( $r = -.163, p = 0.014$ ), satisfaction with sexual function ( $r = -.179, p = 0.007$ ), physical health composite ( $r = -.144, p = 0.030$ ) and mental health composite ( $r = -.193, p = 0.004$ ) scores of MSQOL-54.

Multidimensional Scale of Perceived Social Support (MSPSS) total score was negatively correlated with HADS depression ( $r = -.243, p < 0.001$ ) and anxiety ( $r = -.146, p = 0.028$ ) scores. MSPSS total score was also positively correlated with emotional well-being ( $r = .134, p = 0.044$ ) score of

**Table 3.** Scale scores and p values of patients with and without psychiatric diagnosis

Scales	Patients with psychiatric diagnosis (n = 154)	Patients without psychiatric diagnosis (n = 73)	p value
<b>PAIS-SR</b>	62.2 ± 15.4	52.7 ± 16.9	< <b>0.001</b>
<b>HADS</b>			
Depression score	9.6 ± 4.0	4.6 ± 2.5	< <b>0.001</b>
Anxiety score	10.2 ± 3.4	6.1 ± 2.6	< <b>0.001</b>
<b>MSPSS</b>			
Total	58.7 ± 15.5	65.1 ± 13.8	<b>0.002</b>
Family	20.6 ± 6.5	22.9 ± 5.8	<b>0.016</b>
Friend	18.8 ± 6.7	20.8 ± 5.9	<b>0.029</b>
Significant other	19.9 ± 7.0	21.4 ± 5.4	<b>0.022</b>
<b>MSQOL-54</b>			
Physical function	55.7 ± 21.1	59.5 ± 22.6	0.256
Role limitations-physical	41.0 ± 22.1	45.9 ± 19.9	0.106
Role limitations-emotional	46.1 ± 20.9	63.8 ± 20.1	< <b>0.001</b>
Bodily pain	64.3 ± 18.7	66.5 ± 24.5	0.376
Emotional well-being	55.4 ± 15.6	70.3 ± 18.4	< <b>0.001</b>
Energy	51.3 ± 19.1	52.8 ± 18.8	0.639
Health perceptions	47.6 ± 18.9	54.5 ± 17.2	<b>0.006</b>
Social function	58.6 ± 18.8	75.4 ± 20.8	< <b>0.001</b>
Cognitive function	70.6 ± 19.1	76.4 ± 20.7	<b>0.017</b>
Health distress	59.8 ± 17.6	65.8 ± 20.8	<b>0.026</b>
Sexual function	61.6 ± 19.3	65.9 ± 23.1	0.162
Change in Health	52.9 ± 20.5	55.2 ± 19.9	0.455
Satisfaction with sexual function	55.6 ± 18.7	60.9 ± 22.3	0.124
Overall quality of Life	54.8 ± 17.6	59.1 ± 16.7	<b>0.066</b>
Physical health composite	52.7 ± 16.2	56.1 ± 16.5	0.172
Mental health composite	50.8 ± 16.0	65.6 ± 15.7	< <b>0.001</b>

HADS = Hospital Anxiety and Depression Scale, MSQOL-54 = Multiple Sclerosis Quality of Life-54, MSPSS = Multidimensional Scale of Perceived Social Support, PAIS-SR = Psychosocial Adjustment to the Illness Scale-Self-Report

MSQOL-54.MSPSS family score was negatively correlated with HADS depression ( $r = -.197$ ,  $p = 0.003$ ) score.MSPSS friend score was negatively correlated with HADS depression ( $r = -.176$ ,  $p = 0.008$ ) and anxiety ( $r = -.149$ ,  $p = 0.025$ ) scores. MSPSS significant other score was negatively correlated with HADS depression ( $r = -.141$ ,  $p = 0.033$ ) and positively correlated with health perceptions ( $r = .157$ ,  $p = 0.018$ ) and cognitive function ( $r = .141$ ,  $p = 0.034$ ) scores of MSQOL-54.

## DISCUSSION

In the present study, we found that among 227 patients with MS, 32.2% (n = 73) had no psychiatric

diagnosis, 24.2% (n = 55) had depression, 19.8% (n = 45) had adjustment disorder, 14.9% (n = 34) had anxiety disorder, 7.1% (n = 16) had dysthymic disorder and 1.8% (n = 4) had bipolar disorder. Our study revealed a high prevalence of psychopathology in patients with MS in comparison to what is expected in the general population. A significant prevalence of psychological and psychiatric symptoms in patients with MS, compared to general population and individuals with similar degrees of disability, has been reported in the literature [23]. Among the psychiatric disorders, depression is the most frequently related [24] as our study also reveals. Depression is thought to be more common in MS than in other chronic illnesses and neurologic disorders. Limited data on anxiety disorders in MS patients reveal that anxiety is



common enough to necessitate consideration in the clinical area [25]. Although, prevalence of bipolar disorder (1.8%) is only slightly higher than general population (1%) in our study, there are studies suggesting a higher prevalence of about 13% in MS [26]. General conception is that bipolar disorder and MS coexistence is not common but well proven [27]. To our knowledge there is no study investigating the prevalence of dysthymia in MS.

There are some studies which found associations between depression and severity and duration of disease, age and gender; but those findings could not be replicated in most of the other studies [3, 6, 25, 28]. Clinically, depression and anxiety seem to be associated with disease activity but not with duration or severity. No definite evidence supports the association between interferon beta and depression. Instead, the control of psychiatric symptoms seems to improve the adherence to long-term disease-modifying drugs [23]. In our study, we found no significant difference between psychiatric situation of patients with demographic and clinical characteristics of MS, in line with literature data.

A diagnosis of MS which usually comes in people's most productive years, has great psychosocial impact [29]. MS adds new demands and challenges to both the individual and the family. People with MS experience loss of roles, relationship changes and financial difficulties. These aspects of the disease have a direct effect on psychosocial wellbeing [30]. The high prevalence (14.9%) of adjustment disorders found in our study reflects the psychosocial burden of the disease. In the present study, PAIS-SR scores were significantly higher in MS patients with psychopathology indicating poorer psychosocial adjustment. Poorer psychosocial adjustment is found to be correlated with higher depression and anxiety scores. Literature data supports negative impact of psychopathology on psychosocial adjustment in physical illness [31, 32]. Poorer psychosocial adjustment to chronic illness has also negative impact on quality of life parameters [33]. In a recent study, psychosocial adjustment was found to be a statistically significant predictor of QoL in patients and caregivers in Parkinson's Disease. Psychosocial adjustment process helps patients to fit their social activities and expectations with their new situation and therefore

facilitate the reconstruction of their self-identity and their sense of control in the new situation that seems to affect their QoL [34]. Similarly, in the present study, PAIS-SR scores were found to be negatively correlated with role limitations-emotional, emotional well-being, social function, sexual function, satisfaction with sexual function, physical and mental health composite domain scores of MSQOL-54.

Social support is defined as a type of positive interaction and helpful behavior provided to a person in need of support [35]. A review of the literature revealed that social support was related to positive outcomes on individual's health and well-being and increased individual's adaptive capacity to deal with stress and illness [36]. Social support was found to be an important factor that helped people with MS cope with their diagnosis and symptoms [37]. Numerous studies indicate that social support is an important determinant of HRQoL and depression and anxiety in different chronic diseases [38, 39]. Increased social support positively affects outcomes through a number of mechanisms, including decreased levels of depressive affect, increased quality of life, increased access to health care, increased patient compliance with therapies, and direct physiologic effects on the immune system. Low levels of social support could be viewed as a risk factor for depression and anxiety and a target for early intervention by clinicians [40]. In line with this literature data, perceived total, family, friends and significant other social support was significantly lower in patients with psychopathology compared with patients without psychopathology in our study. Furthermore, MSPSS total score was negatively correlated with HADS depression and anxiety scores. Whether lower perceived social support increases the risk of psychopathology or the presence of psychopathology affects the perception of social support is controversial. Having a psychopathology itself could prevent socialization.

Schwartz and Frohner [41] indicated that social support in MS patients had a significant contribution to quality of life. HRQoL correlates strongly with measures of social stigma and perception of social desirability to which close personal relationships are perhaps the biggest influence [42]. In the present study; MSPSS total score was positively correlated with emotional well-being score of MSQOL-54

indicating relation of social support with emotional well-being. MSPSS significant other score was positively correlated with health perceptions and cognitive function scores of MSQOL-54 indicating the importance of close relationships in mental domains of QoL.

Health-related quality of life (HRQoL) has been more intensively studied in multiple sclerosis (MS) than in any other neurological disorder. Many psychosocial factors such as coping, mood, self efficacy, and perceived support influence the quality of life of patients with MS more than biological variables such as weakness or extent of MRI lesions [43]. Depression is one of the strongest predictors of HRQoL in MS [44]. Depression impairs motivation retarding physical progress, can distort an individual's view of the world and his/her health and reciprocally low quality of life can lead to depression [44]. Anxiety is also a known risk factor for poor HRQoL in many disorders but has rarely been studied in patients with MS. health anxiety involving fears of disease progression is most troubling for many patients with a physical disease [45]. In MS, anxiety has been linked with low HRQoL in some, but not all studies [46, 47]. Patients with myasthenia gravis and a psychiatric diagnosis were also found to have lower scores in general health, vitality, social functioning, emotional role and mental health domains of SF-36 compared with those patients without a psychiatric diagnosis. Four of these five domains (vitality, social functioning, emotional role and mental health) belong to mental health indicating that having a psychiatric diagnosis is related with decrement mostly in mental aspects of HRQoL [32]. Supporting literature data; mostly emotional and mental aspects of QoL (emotional role limitations, emotional well-being, health perceptions, social function, cognitive function, health distress and mental health composite) were more negatively affected in patients with a psychopathology in the present study. In the presence of psychopathology, the effects of chronic illness and of treatment could be perceived more negatively resulting with more decrement in HRQoL.

### Limitations

There are some limitations of the present study. Cross-sectional design is a major limitation which

does not allow to infer causality but only to show associations. Secondly, our study does not have a control group consisting of healthy individuals or patients with another chronic disease. Thirdly, personality disorders which could have a significant impact on psychosocial features were not evaluated in our study.

### CONCLUSION

We have shown a high prevalence of psychopathology in MS patients. Psychopathology has a significant impact on quality of life, perceived social support and psychosocial adjustment. Quality of life is reduced especially in emotional and mental domains if the patient had a psychiatric diagnosis. Social support is an important predictor of at least some domains of QoL and effects psychosocial adjustment. We suppose that our results may have a practical implication. We believe that psychiatric disorders should be carefully evaluated and treated in patients with MS in order to reduce disease burden. Psychiatric consultation should be considered as a key element of approach to MS. Interventions to increase social support should be considered in psychosocial therapeutic protocols. Prospective studies investigating the effects of psychiatric interventions on MS outcomes are needed to verify those findings.

### Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### Author contributions

Concept - VOK, ZK, BA, ÖT; Design - VOK, ZK, BA; Supervision - ÖT, ÖFT, SK; Resources and materials - ZK, BA, AS, ÖFT; Data collection and processing - VOK, BA, ÖT, AS; Analysis interpretation and literature search - GÖ, VOK, ZK, ÖT, BA; Writing manuscript - VOK, ZK; Critical review - ÖFT, SK.

### Conflict of interest

The authors disclosed no conflict of interest during

the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

- [1] Ebers GC. Environmental factors and multiple sclerosis. *Lancet Neurol* 2008;7:268-77.
- [2] Ghaffar O, Feinstein A. The neuro-psychiatry of multiple sclerosis: a review of recent developments. *Curr Opin Psychiatry* 2007;20:278-85.
- [3] Patten SB, Beck CA, Williams JV, Barbui C, Metz LM. Major depression in multiple sclerosis: a population-based perspective. *Neurology* 2003;61:1524-7.
- [4] Cummings JL, Arciniegas DB, Brooks BR, Herndon RM, Lauterbach EC, Piroo EP, et al. Defining and diagnosing involuntary emotional expression disorder. *CNS Spectr* 2006;11:1-7.
- [5] Gold SM, Irwin MR. Depression and immunity: inflammation and depressive symptoms in multiple sclerosis. *Neurol Clin* 2006;24:507-19.
- [6] Mohr DC, Classen C, Barrera M, Jr. The relationship between social support, depression and treatment for depression in people with multiple sclerosis. *Psychol Med* 2004;34:533-41.
- [7] Korostil M, Feinstein A. Anxiety disorders and their clinical correlates in multiple sclerosis patients. *Mult Scler* 2007;13:67-72.
- [8] Sanfilippo MP, Benedict RH, Weinstock-Guttman B, Bakshi R. Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. *Neurology* 2006;66:685-92.
- [9] Marks SF. Nursing assessment of positive adjustment for individuals with multiple sclerosis. *Rehabil Nurs* 1990;15:147-51.
- [10] Stanton AL, Collins CA, Sworowski LA. Adjustment to chronic illness: theory and research. In: Baum A, Revenson TA, Singer JE, eds. *Handbook of health psychology*. Mahwah, NJ: Erlbaum, 2001., pp. 387-403.
- [11] Hirsch BJ. Natural support systems and coping with major life changes. *Am J Comm Psychol* 1980;8:159-72.
- [12] Reblin M, Uchino BN. Social and emotional support and its implication for health. *Curr Opin Psychiatry* 2008;21:201-5.
- [13] Sullivan CL, Wilken JA, Rabin BM, Demorest M, Bever C. Psychosocial adjustment to multiple sclerosis. *Int J MS Care* 2004;6:98-105.
- [14] Fekete EM, Antoni MH, Scheiderman N. Psychosocial and behavioral interventions for chronic medical conditions. *Curr Opin Psychiatry* 2007;20:152-7.
- [15] Kes VB, Cengic L, Cesarik M, Tomas AJ, Zavoreo I, Matovina LZ, et al. Quality of life in patients with multiple sclerosis. *Acta Clin Croat* 2013;52:107-11.
- [16] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR*. 4th ed., text rev. Washington DC: American Psychiatric Press, 2000.
- [17] Aydemir Ö. Validity and Reliability of Turkish Version of Hospital Anxiety and Depression Scale. *Turk J Psychiatry* 1997;8:280-7.
- [18] Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
- [19] Koçyiğit H, Aydemir Ö, Ölmez N. Reliability and Validity of SF-36 in Turkish. *Med Treat J* 1999;12:102-6.
- [20] Adaylar M. Kronik hastalığı olan bireylerin hastalığına tutum, adaptasyon, algı ve özbakım yönelimleri. Doktora Tezi, İstanbul: İstanbul Üniversitesi Sağlık Bilimleri Enstitüsü, Hemşirelik Anabilim Dalı, 1995.
- [21] Derogatis LR. The psychosocial adjustment to illness scale (PAIS). *J Psychosom Res* 1986;30:77-91.
- [22] Tulek Z. Determination of Quality of Life in Multiple Sclerosis Patients Who Have Been Followed Regularly. Doctoral Thesis. Istanbul University, Institute of Health Sciences, Department of Nursing, Istanbul, 2006.
- [23] Jose Sa M. Psychological aspects of multiple sclerosis. *Clin Neurol Neurosur* 2008;110:868-77.
- [24] Feinstein A. Neuropsychiatric syndromes associated with multiple sclerosis. *J Neurol* 2007;254:73-6.
- [25] Wilken JA, Sullivan C. Recognizing and treating common psychiatric disorders in multiple sclerosis. *Neurologist* 2007;13:343-54.
- [26] Schiffer RB, Wineman NM, Weitkamp LR. Association between bipolar affective disorder and multiple sclerosis. *Am J Psychiatry* 1986;143:94-5.
- [27] Sidhom Y, Djebara MB, Hizem Y, Abdelkefi I, Kacem I, Gargouri A, et al. Bipolar disorder and multiple sclerosis: a case series. *Behav Neurol* 2014;2014:536503.
- [28] Galeazzi GM, Ferrari S, Giaroli G, Mackinnon A, Merelli E, Motti L, et al. Psychiatric disorders and depression in multiple sclerosis outpatients: impact of disability and interferon beta therapy. *Neurol Sci* 2005;26:255-62.
- [29] Compston A, Coles A. Multiple sclerosis. *Lancet* 2008;372:1502-17.
- [30] Mullins LL, Cote MP, Fuemmeler BF, Jean VM, Beatty WW, Paul RH. Illness intrusiveness, uncertainty and distress in individuals with multiple sclerosis. *Rehabil Psychol* 2001;46:139-53.
- [31] Kocaman N, Kutlu Y, Ozkan M, Ozkan S. Predictors of psychosocial adjustment in people with physical disease. *J Clin Nurs* 2007;16(3A):6-16.
- [32] Kotan VO, Kotan Z, Aydin B, Taskapilioglu O, Yalvac HD, Ozkaya G, et al. Psychopathology, psychosocial factors and quality of life in patients with myasthenia gravis. *J Neurol Sci-Turk* 2016;33:482-93.
- [33] de Ridder D, Geenen R, Kuijjer R, van Middendorp H. Psychological adjustment to chronic disease. *Lancet* 2008;372:246-55.
- [34] Navarta-Sánchez MV, Senosiain-García JM, Riverol M, Ursúa Sesma ME, de Cerio Ayesa SD, Bravo SA, et al. Factors influencing psychosocial adjustment and quality of life in Parkinson patients and informal caregivers. *Qual Life Res* 2016;25:1959-68.
- [35] Hupcey JE. Clarifying the social support theory research linkage. *J Adv Nurs* 1998;27:1231-41.
- [36] Foote AW, Piazza D, Holcombe J, Paul P, Daffin P. Hope, self-esteem, and social support in persons with multiple sclerosis. *J Neurosci Nurs* 1990;22:155-9.
- [37] Miller CM. The lived experience of relapsing multiple sclerosis: A phenomenological study. *J Neurosci Nurs* 1997;29:291-304.
- [38] Yilmaz Ozpolat AG, Ayaz T, Konag O, Ozkan A. Attachment style and perceived social support as predictors of biopsychosocial adjustment to cancer. *Turk J Med Sci* 2014;44:24-30.
- [39] Staniute M, Brozaitiene J, Burkauskas J, Kazukauskienė N, Mickuviene N, Bunevicius R. Type D personality, mental distress, social support and health-related quality of life in coronary artery disease patients with heart failure: a longitudinal observational study. *Health Qual Life Outcomes* 2015;13:1.
- [40] Cohen SD, Sharma T, Acquaviva K, Peterson RA, Patel SS, Kimmel PL. Social support and chronic kidney disease: an update. *Adv Chronic Kidney Dis* 2007;14:335-44.
- [41] Schwartz C, Frohner R. Contribution of demographic, medical, and social support variables in predicting the mental health dimension of quality of life among people with multiple sclerosis. *Health Soc Work* 2005;30:203-12.
- [42] Gulick EE. Social support among persons with multiple sclerosis.

Res Nurs Health 1994;17:195-206.

- [43] Mitchell AJ, Benito-León J, González JM, Rivera-Navarro J. Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing. *Lancet Neurol* 2005;4:556-66.
- [44] Lobentanz IS, Asenbaum S, Vass K, Sauter C, Klösch G, Kollegger H, et al. Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. *Acta Neurol Scand* 2004;110:6-13.
- [45] Herschbach P, Keller M, Knight L, Brandl T, Huber B, Henrich G, et al. Psychological problems of cancer patients: a cancer distress screening with a cancer-specific questionnaire. *Br J Cancer* 2004;91:504-11.
- [46] Stenager E, Knudsen L, Jensen K. Multiple sclerosis: correlation of anxiety, physical impairment and cognitive dysfunction. *Ital J Neurol Sci* 1994;15:99-103.
- [47] Janssens ACJW, van Doorn PA, de Boer JB, Kalkers NF, van der Meché FGA, Passchier J, et al. Anxiety and depression influence the relation between disability status and quality of life in multiple sclerosis. *Mult Scler* 2003;9:397-403.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Beyond weight loss after sleeve gastrectomy: improvement in health-related quality of life

Evren Dilektaşlı<sup>1</sup>

Department of General Surgery, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

DOI: 10.18621/eurj.413959

## ABSTRACT

**Objectives:** Obesity and related diseases are increasing and with the bariatric procedures both the excess weight and the prevalence of these related diseases are decreasing. Both obesity and related diseases lead to impairment on health-related quality of life of the patients. We aimed to evaluate the short-term effects of sleeve gastrectomy operation on health related quality of life in patients that were operated for morbid obesity.

**Methods:** Prospectively 62 patients that had sleeve gastrectomy operation enrolled in the study. The percentage of excess weight loss (%EWL) and the percentage of excess BMI loss (%EBMIL) were calculated 6 months after the operation. Anthropometric data and obesity-related co-morbidities were recorded. SF-36 questionnaire was used in order to evaluate the general health quality of the patients.

**Results:** The mean age of the patients was 37 years and the majority of the patients were female (74.2%). At the postoperative 6<sup>th</sup> month, mean %EWL was calculated as 52.7% and mean %EBMIL was 60.1%. Six months after the operation, with the significant weight loss achieved, obesity-related co-morbidities were improved. Short Form-36 subscale scores at 6 months following the operation were observed, when compared with the preoperative scores (all  $p < 0.001$ ). The mean physical health score significantly improved from 46.1 to 83.6 and the median mental health improved from 52 to 84, just 6 months after the sleeve gastrectomy operation. In multiple regression analysis %EWL was found to be a significant determinant of  $\Delta$  Mental health (B coefficient 0.490,  $p = 0.025$ ) and  $\Delta$  Physical health (B coefficient 0.388,  $p = 0.047$ ) after adjusting for gender, age, smoking, obstructive sleep apnea syndrome, hypertension, diabetes mellitus and coronary disease.

**Conclusions:** With the successive weight loss after sleeve gastrectomy, at the postoperative 6<sup>th</sup> month, the physical and mental health-related quality of life was significantly improved. Early and expedited regain of this quality of life after the operation is important for the patients and their social surroundings. Moreover it is important for the countries to decrease the medical expenses and increase labour productivity.

**Keywords:** Sleeve gastrectomy, quality of life, SF-36

*Received: April 9, 2018; Accepted: April 15, 2018; Published Online: April 19, 2018*

Obesity and the co-morbidities related to obesity are increasing. In the United States, 69% of the general population who are 20 years of age or older are overweight or obese according to the Centers for Disease Control and Prevention [1]. The prevalence of obesity has significantly increased among adult

Turkish population to 36% in 2010 (44% among women and 27% among men) [2]. While the number of obese people is continuously increasing, this increase is accompanied by an increase in obesity-related diseases, including type 2 diabetes, hypertension, cardiovascular diseases,



**Address for correspondence:** Evren Dilektaşlı, MD., FACS., Associate Professor, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Mimar Sinan Mah., Emniyet Cad., Polis Okulu Karşısı, Yıldırım, 16310 Bursa, Turkey  
E-mail: edilektasli@gmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

musculoskeletal diseases, lipid disorders, etc. World Health Organization report on 2016 that, in Turkey, the latest prevalence of iabetes mellitus (DM), hypertension (HT) and lipid disorder increased to 14%, 20% and 40% respectively [3].

Obesity and related co-morbid conditions make negative impact on overall quality of life of the patients. In many studies it was shown that morbid obese patients had lower health-related quality of life (QOL) levels when compared to the normal population. Both Physical and Mental QOL scores were found to be low on studies. These findings are important as the prevalence of obesity is rapidly increasing and because of the Obesity and related co-morbid conditions, the economical burden of the countries is increasing regarding the social services and medical expenses [4-6].

There are different tools for calculating the general quality of life. One of the most simple and easily accessible scales is the Short Form-36 (SF-36). SF-36 questionnaire has been a reliable test to evaluate the general health quality of the patients. The questionnaire consists of 36 questions and 8 scales that assess the impact of the disease, on the health status. SF-36 was translated into Turkish and validation studies of Turkish version of SF-36 were performed in different patient groups for Turkish population [7-9].

Previously, mid and long-term studies were performed for QOL after bariatric surgery. With the weight loss achieved, the results had shown that, there is a significant improvement on both physical and mental health domains of QOL [10,11]. Keeping in mind that the maximum weight loss trend is on the first 6 months (mid-term), with this present study we aimed to evaluate the mid-term (6 month) health related QOL improvement of sleeve gastrectomy, which was performed in the morbidly obese patients.

## METHODS

The study was conducted between January 2014-January 2015, and data were collected prospectively between the study dates. The institutional ethical committee of the Bursa Yüksek İhtisas Training and Research Hospital approved the study protocol. Patient consent forms were prepared and obtained

from all the patients that accepted to participate in the study. Patients with morbid obesity were consecutively enrolled in the study. Qualifying criteria's for bariatric surgery were;

- BMI > 40 kg/m<sup>2</sup> or
- BMI > 35 kg/m<sup>2</sup>, when diagnosed with obesity related diseases, including type 2 DM, HT, lipid disorders, and obstructive sleep apnea syndrome (OSAS) and
- Age 18-65 years.

Patients who declined to participate in the study or who were lost during the follow-up were excluded. The following variables were obtained either from the patients' electronic medical records and patient paper charts: age, gender, co-morbid diseases (HT, Type 2 DM, OSAS, history of coronary arterial disease, musculoskeletal complaints etc.), smoke abuse, preoperative weight and height. Additionally, 6<sup>th</sup> month postoperative weight and height data were obtained from the patient follow-up forms.

The percentage of excess weight loss (%EWL) and the percentage of excess BMI loss (%EBMIL) were calculated as follows:

$$\%EWL = [(Operative\ weight - Follow\ up\ weight) / Operative\ excess\ weight] \times 100\%$$

The ideal weight was determined using Metropolitan Life Foundation Height - Weight Charts [12].

$$\%EBMIL = (pre\text{-}operative\ BMI - current\ BMI) / (pre\text{-}operative\ BMI - ideal\ BMI) \times 100\%$$

For this formula a BMI of 25 kg/m<sup>2</sup> (upper limit of normal BMI) was taken as the ideal BMI.

SF-36 questionnaire was used in order to evaluate the general health quality of the patients. The questionnaire consists of 36 questions and 8 scales that assess the impact of disease on the health status. The eight scales of the questionnaire include: general health, physical functioning, bodily pain, role limitations due to physical problems, emotional wellbeing, social functioning, vitality, and role limitations due to emotional problems. The first four domains summarize the overall individual physical function. The remaining four domains summarize the overall individual mental function. Each scale is scored between 0-100 according to the results. Higher scores are associated with better and lower scores are associated with worse quality of life level [13].

**Table 1.** Preoperative and postoperative changes in weight, BMI, % excess BMI and % excess weight loss (n = 62)

	Preoperative	Postoperative 6 <sup>th</sup> month	p value <sup>†</sup>
Weight	131 ± 18.7	93 ± 12	< 0.001
BMI	48 ± 5.2	34 ± 3.5	< 0.001
%EBMI loss		60.1 ± 12.8	
% EWL (excessive weight loss)		52.7 ± 12.7	
Age (years)		37 ± 9.1	
Gender (Female %)		46 (74.2%)	
Smoking		9 (14.5%)	
History of coronary arterial disease		2 (3.2%)	

Data are shown as mean ± standard deviation or number (%). BMI = body mass index, EBMI = excess body mass index, EWL = excess weight loss, <sup>†</sup> Paired-samples t test

### Statistical Analysis

The data were analyzed for normal distribution of continuous variables using histograms and the Shapiro-Wilk test. The normally distributed continuous variables were reported as mean ± standard deviation (SD), while the non-normally distributed data were reported as medians (range). Categorical variables were reported as frequencies and percentages. To examine the differences between pre-operative and 6-month post-operative results, the continuous covariates were analyzed based on paired samples t test and Wilcoxon signed-rank tests. Categorical variables were analyzed with Chi-square test.

In multivariate analysis, in order to evaluate the effects of the change in the quality of life scores, with the weight loss after surgery and the other possible related conditions, a multiple linear regression model was constructed. By subtracting the pre-operative baseline scores of Mental and physical health, from the post-operative scores, the change of the scores were calculated. These changes that was referred as the Delta ( $\Delta$ ) Mental health and  $\Delta$  Physical health were further entered into the multiple linear regression analysis with the %EWL in that period and with the

other independent variables. Unless otherwise indicated, a 5% type-I error level was used to refer statistical significance. All statistical analysis was performed using SPSS for Mac version 20.0 (SPSS Inc., Chicago, IL, USA).

### RESULTS

During the study period sleeve gastrectomy operation was performed in 71 patients with the diagnosis of morbid obesity. While 4 patients were lost in the follow-up, 5 patients declined to participate to the study. Totally 62 patients were included in the data analysis. The mean age of the patients was 37 and the vast majority of the patients were female (74.2%). On the postoperative 6<sup>th</sup> month, the mean weight had decreased from 131 kg to 93 kg, and the mean BMI decreased from 48 to 34 kg/m<sup>2</sup>. Mean % EWL was calculated as 52.7 % and mean %EBMI loss was 60.1 % (Table 1).

Preoperative data showed that the major comorbidities were HT in 22.6%, Type 2 DM in 16.1% and OSAS in 8.1% of the patients. More than half of the patients (59.7%) had major musculoskeletal

**Table 2.** Univariate comparison of the comorbidities in the 6<sup>th</sup> month weight loss after sleeve gastrectomy

	Preoperative	Postoperative 6 <sup>th</sup> month	p value <sup>†</sup>
Hypertension	14 (22.6)	5 (8.1)	< 0.001
Type 2 Diabetes Mellitus	10 (16.1)	4 (6.5)	< 0.001
OSAS	5 (8.1)	1 (1.6)	0.08
Musculoskeletal complaints	37 (59.7)	14 (22.6)	< 0.001

Data are shown as number (%). OSAS = obstructive sleep apnea syndrome, <sup>†</sup> Chi-square test

complaints (MSC) preoperatively. Six months after the operation, with the significant weight loss achieved, the results revealed that these comorbid conditions were improved statistically (HT, DM, MSC;  $p < 0.001$  but except OSAS;  $p = 0.08$ ) (Table 2).

A significant improvement in all of the SF-36 subscale scores at 6 months following the operation was observed, when compared with the preoperative scores (all  $p < 0.001$ ). The mean physical health score significantly improved from 46.1 to 83.6. On the other

hand median mental health improved from 52 to 84, just 6 months after the sleeve gastrectomy operation. SF-36 questionnaire results and the subgroup comparisons are detailed in Table 3.

In multiple regression analysis %EWL was found to be a significant determinant of  $\Delta$  Mental health (B coefficient 0.490,  $p = 0.025$ ) and  $\Delta$  Physical health (B coefficient 0.388,  $p = 0.047$ ) after adjusting for gender, age, smoking, OSAS, HT, DM and coronary disease (Table 4 and 5).

**Table 3.** Univariate comparison of SF-36 questionnaire scales preoperatively and 6<sup>th</sup> month postoperatively

	Baseline preoperative	Postoperative 6 <sup>th</sup> month	<i>p</i> value <sup>a</sup>
Physical Functioning	43 [20-60]	80 [75-95]	< <b>0.001</b>
Role limitations due to a physical problem	25 [19-50]	100 [75-100]	< <b>0.001</b>
Pain	69 [39-84]	90 [80-100]	< <b>0.001</b>
General Health*	45.9± 16.8	78.7 ± 10.6	< <b>0.001</b> <sup>b</sup>
Role limitations due to an emotional problem	33 [33-67]	100 [67-100]	< <b>0.001</b>
Energy/Fatigue/Vitality	55 [40-61]	80 [70-90]	< <b>0.001</b>
Social Functioning	63 [25-75]	100 [75-100]	< <b>0.001</b>
Emotional wellbeing	64 [52-72]	74 [68-85]	< <b>0.001</b>
Physical health*	46.1 ± 17.5	83.6 ± 8.3	< <b>0.001</b> <sup>b</sup>
Mental health	52 [46-62]	84 [76-89]	< <b>0.001</b>

Data are shown as median [IQR25- IQR75] or mean ± standard deviation, <sup>a</sup> Wilcoxon signed-rank test, <sup>b</sup> Paired-samples t test

**Table 4.** Multiple linear regression for the change in SF-36 General Mental health domain

Dependent Variable	Independent Variables	B coefficient	Std. Error	Std (B)	t	P value	95% Confidence Interval	
							Lower bound	Upper bound
<b><math>\Delta</math>Mental health</b>	Smoking	0.865	3.767	0.032	0.230	0.816	-6.695	8.424
	OSAS	16.666	11.123	0.229	1.498	0.140	-5.653	38.985
	HT	4.062	6.778	0.086	0.599	0.552	-9.538	17.663
	DM	0.892	8.527	0.017	0.105	0.917	-16.219	18.002
	Coronary disease	2.341	23.638	0.015	0.099	0.921	-45.092	49.775
	%EWL	0.490	0.213	0.313	2.300	<b>0.025</b>	0.063	0.917
	Age	-0.208	0.325	-0.094	-0.639	0.526	-0.859	0.444
	Musculoskeletal complaints	0.833	5.726	0.021	0.146	0.885	-10.657	12.323
Gender	-10.114	7.249	-0.224	-1.395	0.169	-24.659	4.431	

DM = diabetes mellitus, EWL = excess weight loss, HT = hypertension, OSAS = obstructive sleep apnea syndrome



**Table 5.** Multiple linear regression for the change in SF-36 General Physical health domain

Dependent Variable	Independents	B	Std. Error	Std (B)	t	p value	95% Confidence Interval	
							Lower bound	Upper bound
<b>Δ Physical health</b>	<b>Smoking</b>	-1.755	3.366	-0.074	-0.521	0.604	-8.509	4.999
	<b>OSAS</b>	10.346	9.938	0.162	1.041	0.303	-9.596	30.289
	<b>HT</b>	0.778	6.056	0.019	0.129	0.898	-11.374	12.931
	<b>DM</b>	2.070	7.619	0.044	0.272	0.787	-13.218	17.359
	<b>Coronary disease</b>	1.183	21.121	0.009	0.056	0.956	-41.200	43.566
	<b>%EWL</b>	0.388	0.190	0.282	2.037	<b>0.047</b>	0.006	0.770
	<b>Age</b>	0.109	0.290	0.057	0.376	0.708	-0.473	0.691
	<b>Musculoskeletal complaints</b>	0.744	5.116	0.021	0.145	0.885	-9.522	11.011
<b>Gender</b>	0.910	6.477	0.023	0.140	0.889	-12.087	13.906	

DM = diabetes mellitus, EWL = excess weight loss, HT = hypertension, OSAS = obstructive sleep apnea syndrome

## DISCUSSION

Sleeve gastrectomy is rapidly increasing, as it is a promising procedure with early and late prosperous results of the %EWL, with minimal anatomical change and with its acceptable complication rates [14].

In current literature, with various surgical operations or with non-surgical endoscopic approaches, the %EWL at 6-months post-procedure was found to be 33.6% - 52.6%. In a study by Nocca *et al.* [15], %EWL was found to be 48.9% in the 6th postoperative month follow-up, specifically after sleeve gastrectomy. In accordance with previous reports, in our study group we found %EWL and %EBMIL to be 52.7% and 60.1%, respectively, 6 months after sleeve gastrectomy (Table 1). In a recent study, Nikolic *et al.* [16] found that 6 months after sleeve gastrectomy, 60% of the patients achieved success in weight loss (success is  $EWL \geq \% 50$ ). In our study population, 61.3 % of the patients achieved successful weight loss by the 6th month of sleeve gastrectomy.

There are many comorbid conditions that were found to be related with obesity, mainly cardiovascular diseases, Type 2 Diabetes Mellitus, pulmonary diseases like OSAS, asthma and musculoskeletal problems [17]. After weight loss operations it was shown that, these critical conditions and diseases are

improved and even totally cured [18, 19]. The main pathophysiology of this improvement still is not clear and it is not yet understood that if only the weight loss is responsible in this improvement or if there are any other possible reasons like complicated molecular mechanisms [20]. In the early period of bariatric procedures, it was shown that in a significant number of the patients these comorbid conditions were improved. Bobowicz *et al.* [19] reported that the improvement of HT, DM, OSAS and Osteoarthritis, 1 year after sleeve gastrectomy was 28.6%, 27.8%, 100% and 11.1% respectively [19]. In our study improvement for HT was 64%, for DM it was 60%, for OSAS it was 80% and for musculoskeletal complaints it was 62% in the 6th month of sleeve gastrectomy surgery. In the same study the 6<sup>th</sup> month EWL% was found to be 36.8%, which was far more less than our results (52.7%). We believe that this could be the possible reason of the superiorcomorbidity improvement that was found in our study population. When preoperative and postoperative comorbidity improvement was assessed, it was found that all documented comorbid conditions improved statistically ( $p < 0.001$  for all, except for OSAS in which  $p = 0.08$ ). This shows that in the early period of the procedure, the surgery success with better weight loss is important for the improvement of these comorbidities. As one can expect, this is

associated with the improvement on the health related quality of life in this patient population. Furthermore it was also previously shown that smoking has a negative impact on Health quality of life [21]. In this present study population we found that 14.5% of the patients are current smokers.

The previous studies focused on the improved scores of different QOL questionnaire's with different types of Bariatric surgical procedures. Major *et al.* [11] compared 2 bariatric procedure, Roux-en Y gastric bypass and SG regarding the obesity related disease and quality of life improvement and found no difference between these two procedures. But they found that the quality of life was enhanced significantly for both procedures [11]. Similar results were found after the Gastric band operations and sleeve gastrectomy when performed as primary procedures [6, 22]. Charalampakis *et al.* [22] showed that the steep increase in the QOL of the patients with SG has peaked at 12<sup>th</sup> months.

Our study showed an improvement on the scores for physical functioning and limitations due to physical problem, pain and general health. Generally physical health is found to be improved 6 months after surgery. The weight loss, leads to ease in the motions of the patients, moreover the pain decreases and this decline might be the reason for this movement capacity that even gets better. The improvement on the physical health is also improving the general health scores. Patients are much more active in daily life and this increase in movement lead to additive effect on weight loss as well.

The mental health domains are also improving after the operation. Although all changes in the mental health scores (vitality, social functioning, emotional wellbeing and limitations due to emotional problem) in the postoperative period were statistically significant (Table 3), the weakest improvement in the scores of SF-36 seems to be in the Emotional wellbeing scores. There are studies that even found that mental health scores are not improving after the surgery [23]. Nevertheless most of the studies show the statistical improvement in mental health domain as well. Social functioning is also improving in SF-36 domains and this finding supports that with the weight loss achieved early after SG operation patients express that they are feeling more confident in social associations and they feel less discriminations from others in the population

[10].

### Limitations

There are couples of limitations of our study. First of all the number of the patients that enrolled in our study is low and the lack of long-term follow-up is another downside. Secondly there is no control group with the other treatments for weight loss like medications, diet etc. Nevertheless this study is one of the first studies that show early benefit of surgical weight loss on QOL for the patients that are Morbidly obese.

### CONCLUSION

With the successive weight loss after sleeve gastrectomy operation, just 6 months after the operation, the physical and mental health related quality of life has improved. Results showing the pretentious improvement on quality of life after bariatric surgery might also explain the increased number of operations, despite the difficulty and potential complications of surgery. Early and expedited regain of this QOL after the operation, which was deteriorated during the obesity years, may lead to reduction in the economical burden of countries both in the social services and medical expenses.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

### Acknowledgements

We would like to thank Aslı Görek Dilektaşlı, MD for her contribution during data collection of the study.

### REFERENCES

- [1] Statistics NCfH. Health, United States, 2014: with special feature on adults aged 55-64. 2015.
- [2] Erem C. Prevalence of overweight and obesity in Turkey. IJC Metab Endocr 2015;8:38-41.

- [3] Organization WH. World health statistics 2016: monitoring health for the SDGs sustainable development goals: World Health Organization; 2016.
- [4] Simonson DC, Halperin F, Foster K, Vernon A, Goldfine AB. Clinical and Patient-Centered Outcomes in Obese Patients With Type 2 Diabetes 3 Years After Randomization to Roux-en-Y Gastric Bypass Surgery Versus Intensive Lifestyle Management: The SLIMM-T2D Study. *Diabetes Care*. 2018;41:670-9.
- [5] Monteiro F, Ponce DA, Silva H, Pitta F, Carrilho AJ. Physical function, quality of life, and energy expenditure during activities of daily living in obese, post-bariatric surgery, and healthy subjects. *Obes Surg* 2017;27:2138-44.
- [6] Busetto L, Mozzi E, Schettino AM, Furbetta F, Giardiello C, Micheletto G, et al. Three years durability of the improvements in health-related quality of life observed after gastric banding. *Surg Obes Relat Dis* 2015;11:110-7.
- [7] Pinar R. Reliability and construct validity of the SF-36 in Turkish cancer patients. *Qual Life Res* 2005;14:259-64.
- [8] Demiral Y, Ergor G, Unal B, Semin S, Akvardar Y, Kivırcık B, et al. Normative data and discriminative properties of short form 36 (SF-36) in Turkish urban population. *BMC Public Health* 2006;6:247.
- [9] Kasapoğlu Aksoy M, Altan L, Güner A. The effectiveness of soft and semi-rigid cervical collars on acute cervical radiculopathy. *Eur Res J* 2018;4:16-25.
- [10] Fezzi M, Kolotkin RL, Nedelcu M, Jaussent A, Schaub R, Chauvet MA, et al. Improvement in quality of life after laparoscopic sleeve gastrectomy. *Obes Surg* 2011;21:1161-7.
- [11] Major P, Matłok M, Pędzwiatr M, Migaczewski M, Budzyński P, Stanek M, et al. Quality of life after bariatric surgery. *Obes Surg* 2015;25:1703-10.
- [12] Height M, Tables W. Metropolitan life foundation. *Stat Bull* 1983;64:2-9.
- [13] Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
- [14] Gagner M, Hutchinson C, Rosenthal R. Fifth International Consensus Conference: current status of sleeve gastrectomy. *Surg Obes Relat Dis* 2016;12:750-6.
- [15] Nocca D, Krawczykowsky D, Bomans B, Noël P, Picot M, Blanc P, et al. A prospective multicenter study of 163 sleeve gastrectomies: results at 1 and 2 years. *Obes Surg* 2008;18:560-5.
- [16] Nikolić M, Kruljac I, Kirigin L, Mirošević G, Ljubičić N, Nikolić BP, et al. Initial weight loss after restrictive bariatric procedures may predict mid-term weight maintenance: results from a 12-month pilot trial. *Bariatric Surg Pract Patient Care* 2015;10:68-73.
- [17] Zeller MH, Inge TH, Modi AC, Jenkins TM, Michalsky MP, Helmuth M, et al. Severe obesity and comorbid condition impact on the weight-related quality of life of the adolescent patient. *J Pediatr* 2015;166:651-9.e4.
- [18] Dillon C, Peddle J, Twells L, Lester K, Midodzi W, Manning K, et al. Rapid reduction in use of antidiabetic medication after laparoscopic sleeve gastrectomy: The Newfoundland and Labrador Bariatric Surgery Cohort (BaSCo) Study. *Can J Hosp Pharm* 2015;68:113.
- [19] Bobowicz M, Lehmann A, Orłowski M, Lech P, Michalik M. Preliminary outcomes 1 year after laparoscopic sleeve gastrectomy based on Bariatric Analysis and Reporting Outcome System (BAROS). *Obes Surg* 2011;21:1843-8.
- [20] Ryan KK, Tremaroli V, Clemmensen C, Kovatcheva-Datchary P, Myronovych A, Karns R, et al. FXR is a molecular target for the effects of vertical sleeve gastrectomy. *Nature* 2014;509:183-8.
- [21] Jia H, Zack MM, Thompson WW, Dube SR. Quality-adjusted life expectancy (QALE) loss due to smoking in the United States. *Qual Life Res* 2013;22:27-35.
- [22] Charalampakis V, Bertsias G, Lamprou V, de Bree E, Romanos J, Melissas J. Quality of life before and after laparoscopic sleeve gastrectomy. A prospective cohort study. *Surg Obes Relat Dis* 2015;11:70-6.
- [23] Raaijmakers L, Pouwels S, Thomassen S, Nienhuijs S. Quality of life and bariatric surgery: a systematic review of short-and long-term results and comparison with community norms. *Eur J Clin Nutr* 2017;71:441-9.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Improvement of the cardiorespiratory endurance, perception of the effort and walking performance of the old people of the hospice Saint Marc of Kingasani by the practice of the adapted physical activities

Teddy Bofosa<sup>1</sup>, Eric Kam<sup>2</sup>, Betty Miangindula<sup>1</sup>, François Njimbu<sup>3</sup>, Constant Nkiama<sup>1</sup>

<sup>1</sup>Department of Physical Medicine and Rehabilitation, University Clinics of Kinshasa, University of Kinshasa, Kinshasa, Democratic Republic of Congo

<sup>2</sup>Department of Physical Medicine and Rehabilitation, Adult Neuro-Rehabilitation Unit, University Clinics of Kinshasa, Kinshasa, Democratic Republic of Congo

<sup>3</sup>Department of Physical Medicine and Rehabilitation, University Clinics / University of Kinshasa, Kinshasa, Democratic Republic of Congo

DOI: 10.18621/eurj.434150

## ABSTRACT

**Objective:** To verify the effects of functional rehabilitation associated with a program of physical activities adapted to the biomechanical parameters and perception of the effort of the elderly.

**Methods:** A longitudinal experimental study of 30 elderly people living in the old people's home was conducted during a 6-month period from July 2017 to January 2018. It consisted in evaluating the biomechanical parameters and perception of the effort of older people a functional rehabilitation program associated with the practice of adapted physical activities. The parametric t test of student was used to compare the averages of different parameters of study before and after the intervention program. The statistical test results used were interpreted at the  $p < 0.05$  significance level for statistical decision making.

**Results:** After 6 months of intervention, the elderly significantly improved their biomechanical parameters: balance ( $p = 0.002$ ), rate ( $p < 0.01$ ), walking speed ( $p = 0.03$ ), strength and muscular strength of the limbs lower ( $p = 0.041$ ), perception with effort ( $p = 0.03$ ). This program also allowed them to reduce their risk of falling ( $p = 0.057$ ) and to increase their motor autonomy ( $p = 0.003$ ).

**Conclusion:** This study shows that a biomechanical evaluation associated with functional rehabilitation improves the balance and motor autonomy of the elderly, which leads to an improvement in their quality of life.

**Keywords:** Endurance, perception of the effort, walking performance

*Received: Received: June 15, 2018; Accepted: August 19, 2018; Published Online: November 1, 2018*

It is mentioned that aging can be a public health problem and this may be the cause of balance and falling problems. It sometimes causes falls which constitute a major public health problem in terms of hospitalization, morbidity and cost [1, 2]. Falls are common among older people, one third of people over 65



e-ISSN: 2149-3189

**Address for correspondence:** Teddy Bofosa, MD., University of Kinshasa, University Clinics of Kinshasa, Department of Physical Medicine and Rehabilitation, Kinesiology Service, Medical Fitness Laboratory and Functional Exercises, Democratic Republic of Congo  
E-mail: bofosa.linkoko@unikin.ac.cd, Tel: +243 85 014 32 32

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

and 50% of those over 80 fall at least once a year [3, 4]. It has been stated that rehabilitation will increase the quality of life in elderly people. The importance of healthy aging has been emphasized. The maintenance of balance involves several structures such as sensory receptors, the central nervous system and effectors [5, 6].

The goal of aging should not only be to gain years of life, but above all, to improve quality of life. The challenge represented by a successful aging, would thus reside in the increase of life expectancy without disability. In this perspective, the practice of a regular physical activity holds a preponderant place: whether in the framework of primary prevention (by delaying the appearance) or secondary (by slowing down) of the "bad" aging, by improving the quality of life and by reducing the entry into an institution.

Regular physical activity has many beneficial effects on the various components of physiological aging [7-9].

In the Democratic Republic of Congo, we have found that care for the elderly living in hospices in Kinshasa is starting to increasingly associate functional rehabilitation with the practice of adapted activities.

However, no studies have been conducted to verify the effects of this management on the cardiorespiratory endurance, perception of the effort and walking performance parameters of older people which is why we conducted this study to fill this gap.

## METHODS

### Nature and Period of Study

In this study, we opted for the experimental method and conducted a longitudinal study which consisted in evaluating the biomechanical parameters and perception of the effort of the elderly subjected to a program of functional reeducation associated to the practice of the adapted physical activities during the period from July 2017 to January 2018.

### Framework of the Study

Our study took place at the old men's hospice Saint Marc of Kingasani in the commune of Kingasani, city of Kinshasa province / Democratic Republic of Congo.

### Study Population

The population of this study consisted of 50 elderly people in the hospice of old St. Mark of Kingasani.

### Sampling and Sample

In this population of 50 subjects, we randomly drew a sample of 30 seniors whose average age ranges from 76 to 85 years.

#### - Inclusion criteria

1. To have accepted to participate in this study;
2. Be present on the first and last day of the evaluation;
3. Have a medical report authorizing the practice of physical activities;
4. Being regular: having attended at least 95% of the functional rehabilitation sessions according to the attendance list;

#### - Exclusion criteria

All persons who did not meet the inclusion criteria above were excluded.

### Choice and Justification

#### ➤ Choice

Our choice was focused on the hospice of old men's hospice Saint Marc of Kingasani because of the large number of elderly people who live there.

#### ➤ Justification

The choice of this group is justified by the fact that we were authorized by the hospice to take care of the elderly.

### Data Collection Technique

Cardiorespiratory endurance, perception of the effort and walking performance parameters were assessed before and after the program. The walking speed was measured with a stopwatch, the elderly are timed while walking a distance of 6 m at their preferred speed or spontaneous speed, the normal walking speed in the elderly varies between 1.1 and 1.5 m / sec; the rate was measured as the number of steps per minute, the baseline was based on the size of the elderly person and ranged from about 90 steps / minute for tall subjects (1.83m) to about 125 steps / minute for small subjects (1.5m); Timed get up and go Test was evaluated thanks to the time taken by the

**Table 1.** Comparison of average cardiorespiratory endurance, perception of the effort and walking performance of men before and after the intervention program

Parameters	Men (n = 17)		p value
	Before	After	
Rate (pas/min)	35.2 ± 9.36	45.2 ± 3.42	<b>0.005</b>
Walking speed (m/sec)	0.37 ± 0.09	0.2 ± 0.44	<b>0.042</b>
Risk of falling	17.4 ± 1.51	27,4 ± 1.34	<b>&lt; 0.01</b>
LL muscle strength	2 ± 0.70	4.2 ± 0.44	<b>&lt; 0.01</b>
Motorskills (sec)	29.8 ± 0.44	18.8 ± 1.30	<b>&lt; 0.01</b>
Perception of effort	7.2 ± 0.83	4.4 ± 1.14	<b>0.002</b>

The values were presented as mean ± SD (standard deviation), LL = lower limb, *p* < 0.05 statistically significant

subject to get up from a chair, walk 3 meters, turn around, go back to the seat and sit down; Strength and muscle power of the lower limbs was measured using the number of sit-stand achieved by the subject in 30 seconds, An impossibility or low score below five sit-stand passages sign a level of dependence high and perceived effort was measured using the borg scale, rated from 0 (no effort) to 10 (very very difficult effort).

### Description of the Program

The intervention program consisted of static and dynamic balance exercises; exercise of walking on without obstacle then with obstacle; aerobic exercise, muscle strengthening exercises of the upper limbs, lower limbs then abdominals and relaxation exercises.

### Ethical Consideration

All subjects had consented in writing to participate in the study according to the Helsinki Declarations. The information collected from the elderly was kept confidential. And all Authors declare originality and ethical approval of research. Responsibilities of research: responsibilities against local ethics commission are under the Authors responsibilities.

The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

### Statistical Analysis

After being validated, the data was entered using Microsoft World and Excel 2013 software. Quantitative data were represented as mean ± standard deviation with their extremes in the tables. Statistical analyzes were performed using SPSS 20.0 software (Statistical Package Social Science). In univariate statistical analysis, the matched student t test allowed us to compare the averages of the study parameters before and after the intervention program. The statistical test results used were interpreted at the *p* < 0.05 significance level for statistical decision making.

## RESULTS

Comparison of means before and after the intervention program

### Sex effect

In men, the data in Table 1 shows a statistically significant difference for cadence parameters, fall risk,

**Table 2.** Comparison of average cardiorespiratory endurance, perception of the effort and walking performance parameters of women before and after the intervention program

Parameters	Women (n = 13)		p value
	Before	After	
<b>Rate (pas/min)</b>	35.2 ± 9.36	38,92 ± 11,43	0.005
<b>Walking speed (m/sec)</b>	0.372 ± 0.09	0.1 ± 0.12	0.05
<b>Risk of falling</b>	17.4 ± 1.51	20.04 ± 1.17	0.006
<b>LL muscle strength</b>	3 ± 0.70	1 ± 0.73	< 0.01
<b>Motorskills (sec)</b>	29.8 ± 0.44	30.6 ± 0.95	0.001
<b>Perception of effort</b>	7.2 ± 0.83	4.12 ± 0.88	< 0.01

The values were presented as mean ± SD (standard deviation), LL = lower limb, *p* < 0.05 statistically significant

**Table 3.** Comparison of means of cardiorespiratory endurance, perception of the effort and walking performance parameters at the first and third test

Parameters	1 <sup>st</sup> Passation	3 <sup>th</sup> Passation	p value
Rate (pas/min)	38.3 ± 11.05	47.63 ± 8.152	< 0.01
Walking speed (m/sec)	0.4 ± 0.12	0.37 ± 0.09	0.03
Risk of falling	17.1 ± 1.21	27.23 ± 1.194	0.007
LL muscle strength	1.97 ± 0.71	4.47 ± 0.571	0.041
Motorskills (sec)	30.47 ± 0.93	19.23 ± 1.478	0.003
Perception of effort	7.13 ± 0.86	4.33 ± 0.802	0.03

The values were presented as mean ± SD (standard deviation), LL = lower limb,  $p < 0.05$  statistically significant

perceived effort, lower limb strength and muscle power, motor skills, and speed of movement. walk after the program (Table 1).

We observed in the table above that elderly women living in the elderly home have statistically improved their cardiorespiratory endurance, perception of the effort and walking performance parameters after our intervention program (Table 2).

In Table 3 comparing the averages at the first and third tests, all the cardiorespiratory endurance, perception of the effort and walking performance parameters were significantly modified.

## DISCUSSION

We conducted a longitudinal experimental study that consisted in evaluating the cardiorespiratory endurance, perception of the effort and walking performance of 30 old people living in the home of old man subjected to a program of functional rehabilitation associated with the practice of the adapted physical activities during a period of 6 months from July 2017 to January 2018.

This study reveals that the cardiorespiratory endurance, perception of the effort and walking performance of older men were significantly modified after the intervention program.

These results are consistent with those observed in the Salma *et al.* [10] who indicated that the program of resistance exercises, stretching, games activities, games, circuits, dance and relaxation offered to the elderly, were effective in reducing their risk of falling and thus improved their cardiorespiratory endurance, perception of the effort walking performance.

Falls can be prevented by exercise programs aimed at normalizing or restoring muscle strength, restoring

balance and reducing the use of drugs [11].

In the literature, it has been demonstrated that muscle strengthening and stamina enhancement help to maintain functional abilities and complementary effects in balancing work on falls prevention [12-14]. With respect to the 13 older women after the intervention program, this study has shown that the latter have significantly improved their cardiorespiratory endurance, perception of the effort and walking performance. These results corroborate those found in the Soares and Sacchelli study [15], which showed that regular exercise by a group of elderly working women and another group of sedentary older women revealed that this activity has an influence positive on the maintenance of balance, which means that the chances of suffering a falls are lower in active older women.

It has been proven that the cognitive abilities, quality of life, prevention of age-related bone loss, etc. [16-18].

Our results differ from those found by Manckoundia [19] which emphasize that a management exclusively by progressive muscular reinforcement, brings an improvement in muscular strength, and certain functional activities (standing seated transfer) the speed of walking and a reduction of pain in patients. This is justified by the fact that Manckoundia *et al.* based their program exclusively on muscle strengthening exercises against us, we used several varieties of exercises.

Regarding the handover effect, we noticed that at the third handover compared to the first, the elderly significantly improved their rate ,walking speed , muscle strength and power of the lower limbs , motor skills , the risk of falling and the perception of effort. These results are similar to those of the literature which emphasize that the maintenance abilities of

balance functions and muscle strength are preserved in the elderly [19, 20]. The epidemiological studies have shown the benefit of regular exercise in reducing the risk of falling, regardless of the role of exercise on the prevention of osteoporosis. A meta-analysis of studies using the management of fallers showed that all management including exercises and balance work reduced the risk of falling. It has been clearly shown that some practices such as tai chi, lead to offer exercises conducive to better control of balance [21-23].

According to Buranello *et al.* [25], in their study, the risks of falls are closely linked to the maintenance of balance and that the practice of physical exercises is effective in reducing the risk of falls and improvement of cardiorespiratory endurance and walking performance.

Our results corroborate with those of the literature which emphasize that the balance training is the key to any fall prevention exercise program [25, 26].

The results of this study are different with those found by Mariama BAH in 2016, which does not seem to have given positive results on the improvement of the balance in the elderly following a management based exclusively on muscle strengthening exercises [27]. This difference is justified by the fact that the intervention program applied by the latter did not take into account the variety of exercises.

### Limitations

The small number of patients was relatively themain limitation of this study. So, a study with more patients wouldprovide a more comprehensive picture.

### CONCLUSION

This study shows that the regular practice of adapted physical activities associated with functional rehabilitation allows the elderly to improve not only their cardiorespiratory endurance, and walking performanceparameters but also their perception of the effort whatever the sex. Given the importance of the physical activities thus demonstrated, the hospices of old people must have a specialist in adapted physical activities in their multidisciplinary team. A study carried out on a large number of older people must be undertaken.

### Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

### Acknowledgment

Our thanks go to the authorities of the hospice of old men Saint Marc of Kingasani for allowing us to conduct our research within this institution and the elderly to have agreed to work with us.

### REFERENCES

- [1] Vaillant J. Kinesitherapy and improvement of the control of the balance of the elderly subjects effects of cognitive treatments, manual and instrumental, Thesis, To obtain the degree of Doctor of the University Grenoble 1 - Joseph Fourier, December 6, 2004.
- [2] Butler JP, Fujii M, Sasaki H. Balanced aging, or successful aging? *Geriatr Gerontol Int* 2011;11:1-2.
- [3] Dargent G. Prevention of falls in the elderly. *Leuven Med* 1998.
- [4] King AC. Interventions to promote physical activity by older adults. *J Gerontol A Biol Sci Med Sci* 2001;56 Spec No 2:36-46.
- [5] Keegan TH, Kelsey JL, Sidney S, Quesenberry CP Jr. Foot problems as risk factors of fractures. *Am J Epidemiol* 2002;155:926-31.
- [6] Pfitzenmeyer P. Assessment of the risk of falling. *Physiotherapy*, Masson, Paris, 2002.
- [7] Lord SR, Menz HB, Sherrington C. Home environment risk factors for falls in older people and the effectiveness of home modifications. *Age Aging* 2006;35 Suppl 2:ii55-9.
- [8] High Authority of Health, Recommendation for clinical practice. Prevention of accidental falls in the elderly. *Argument*, November 2005.
- [9] Mathias S, Nayak US, Isaacs B. Balance in elderly patients: the "get-up and go" test. *Arch Phys Med Rehabil* 1986;67:387-9.
- [10] Salma SS, Coelho FGM, Gobbi S, Stella F. [Effects of physical activity on cognitive functions, balance and risk of falls in elderly patients with Alzheimer's dementia]. *Rev Bras Fisioter* 2010;14:68-74. [Article in Portuguese]
- [11] Rydwik E, Frandin K, Akne G. Effects of physical training



- on physical performance in institutionalised elderly patients (70+) with multiple diagnoses. *Age and Ageing* 2004;33:13-23.
- [12] Trost SG, Owen N, Bauman AE, Sallis JF, Brown W. Correlates of adults' participation in physical activity: review and update. *Med Sci Sports Exerc* 2002;34:1996-2001.
- [13] Giaccardi Y, Laassel M. Evaluation of the risk of falling in EHPAD by GAITRite walking track, 3rd Annual Meeting of FFAMCO, 19 and 20 May 2015.
- [14] Tinetti ME, McAvay G, Claus E. Does multiple risk factor reduction explain the reduction in fall rate in the Yale FICSIT Trial? Frailty and Injuries Cooperative Studies of Intervention Techniques. *Am J Epidemiol* 1996;144:389-99.
- [15] Soares MA, Sacchelli T. [Effects of physical therapy on balance of elderly people]. *Rev Neurocienc* 2008;16:97-100. [Article in Portuguese]
- [16] Robertson MC, Campbell AJ, Gardner MM, Devlin N. Preventing injuries in older people by a meta-analysis of individual-level data. *J Am Geriatr Soc* 2002;50:905-11.
- [17] Kirby M, Denihan A, Bruce I, Coakley D, Lawlor BA. The clock drawing test in primary care: Sensitivity in dementia detection and specificity against normal and depressed elderly. *Int J Geriatr Psychiatry* 2001;16:935-40.
- [18] Taylor A, Cable N, Faulkner G, Hillsdon M, Narici M, van der Bij A. Physical activity and older adults: a review of health benefits and the effectiveness of interventions. *J Sports Sci* 2004;22:703-25.
- [19] Manckoundia P. *Physiotherapy in Geriatrics*, 3rd ed, Masson Paris, 2012.
- [20] Straube A, Botzel K, Hawken M, Paulus W, Brandt T. Postural control in the elderly: differential effect of visual, vestibular and somatosensory inputs. In: Amblard B, Berthoz A, Clarac F eds. *Posture and gait: development, adaptation and modulation*. Amsterdam: Elsevier, 1988: 105,114.
- [21] Kemoun G. *Physiology of walking: Particularities in the elderly*. *Physical Medicine and Rehabilitation - The Letter*. 2001.
- [22] Saint-Jean O, Yvain F. Economic consequences of falls in elderly patients. In: *The fall of the elderly*. Jacquot JM, Strubel D, Pelissier J (Eds). Masson; Paris, 2011.
- [23] Rivier E. *Falls evaluation in geriatrics pocket guide*, Rehabilitation Center of the Canton of Vaud Label CTR, Vaud, First edition - Vevey. 2007.
- [24] Direction générale de la santé publique. *La prévention des chutes dans un continuum de services pour les aînés vivant à domicile*. Santé et Services sociaux du Québec, 2004.
- [25] Buranello MC, Campos SA, Quemelo PR, Silva AV. Equilíbrio corporal e risco de quedas em idosos que praticam atividades físicas e sedentárias. *Rev Bras Cienc Enve Hum* 2011;8:313-23.
- [26] Guerra Jimenez G, Perez Fernández N. Reduction in posterior semicircular gain by age in video head impulse testing. *Observational study*. *Acta Otorrinolaringol Esp* 2016;67:15-22.
- [27] Horak FB, Wrisley DM, Frank J. The Balance Evaluation Systems Test (BESTest) to differentiate balance deficits. *Phys Ther* 2009;89:484-98.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Preoperative hemogram-related parameters to distinguish renal cell carcinoma from benign kidney masses: HERR score

Ali Rıza Türkoğlu<sup>1</sup>, Yasemin Üstündağ<sup>2</sup>

<sup>1</sup>Department of Urology, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

<sup>2</sup>Department of Clinical Biochemistry, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

DOI: 10.18621/eurj.408088

## ABSTRACT

**Objectives:** Renal cell carcinoma (RCC) accounts for approximately 90% of all kidney malignancies, and it is difficult to preoperatively distinguish between tumors and benign masses without a kidney biopsy in small renal masses. We investigated whether any preoperatively defined hemogram-related parameters had a predictive value that would distinguish RCC from benign kidney masses using a novel scoring method.

**Methods:** Between January 2011 and November 2017, 330 patients diagnosed with kidney masses and who received an operation were included. Fifty-six masses were benign. The neutrophil-to-lymphocyte count (NLR), platelet-to-lymphocyte count, lymphocyte-to-monocyte count, mean platelet volume, platelet count ratio, and hemoglobin to red cell distribution width ratios were calculated. The hemogram-related parameters were combined with the tumor size to establish the hemogram-related risk (HERR) score. The area under the receiver operating characteristics curve, sensitivity, specificity, and likelihood ratios were evaluated to preoperatively diagnose RCC.

**Results:** Histological findings confirmed RCC in 274 patients. The NLR [median (interquartile range)] was higher in patients with RCC, 3.7 (4.7), compared to a benign kidney mass, 2.4 (2.2) ( $p < 0.001$ ). A HERR score cut-off of  $\geq 3$  showed a good sensitivity at 78% with an LR+ of 10.8 [95% confidence interval (CI): 7.0-16.4] and an LR- of 1.2 (95% CI: 1.0-1.5).

**Conclusion:** Our study, despite being a preliminary validation, is the first to evaluate hemogram-related parameters for preoperatively discriminating between RCC and benign renal masses, and the HERR score serves as a potential diagnostic biomarker for this

**Keywords:** Renal cell carcinoma, kidney mass, hemogram-related risk score

*Received: March 20, 2018; Accepted: March 28, 2018; Published Online: April 7, 2018*

Renal cell carcinoma (RCC) is the most common solid kidney lesion, and it accounts for approximately 90% of all kidney malignancies [1]. Old age, hypertension, and lifestyle factors, such as smoking and obesity, are among the etiologic factors of RCC [1, 2].

Kidney masses are mostly asymptomatic until the late stages of the disease. However, with the development and widespread use of imaging modalities, such as ultrasound and computed tomography, the incidental diagnoses of RCC are increasing [3]. Because of the earlier diagnosis, these



Address for correspondence: Ali Rıza Türkoğlu, MD., University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Urology, Bursa, Turkey  
E-mail: a.turkoglu@hotmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

tumors are usually smaller in size and low-grade [4]. Studies indicate that it's difficult to distinguish between benign and malign kidney tumors radiologically without a kidney biopsy in small renal masses [5]. In fact, multiple studies demonstrated that the incidence of surgically treated benign renal tumors can be up to 20% [4, 6].

Host inflammatory response plays critical role in the initiation and progression of various malignancies, including RCC [7]. Cancer patients frequently present with systemic inflammatory responses as alterations in peripheral blood cell counts. Recently, a number of studies about circulating blood-cell-based biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which reflect the systemic inflammation, were shown to be effective predictors of the prognosis across various cancers, including RCC [8, 9].

A low lymphocyte-to-monocyte count ratio (LMR) was shown to be indicative of the aggressiveness of RCC [9]. Meanwhile, the hemoglobin (Hb) to red cell distribution width (RDW) ratio has been shown to be a new prognostic parameter in cancer patients [10]. A low preoperative MPV and high platelet count were demonstrated to be independent predictors of tumor-specific mortality in RCC patients [11]. The identification of noninvasive markers that can be used to screen RCC patients in the early stages is one of the challenges of urologists [12]. Currently, there is no diagnostic biomarker available for an accurate diagnosis of RCC other than incidental radiological discovery.

In this study, we aimed to investigate whether any of the preoperatively defined hemogram-related parameters, namely NLR, PLR, Hb to RDW, MPV to platelet count, and lymphocyte-to-monocyte count, had a predictive value for distinguishing RCC from benign kidney masses and to design a scoring system for this purpose.

## METHODS

This study was performed in accordance with Declaration of Helsinki in 1965 (as revised in 2013). Ethical clearance was granted by the Regional Ethics Committee. We performed a search of the database of our hospitals' Laboratory Information System, which

integrates information from several databases and includes the patient demographics, clinical diagnosis, order entry database, and laboratory results database. Between January 2011 and November 2017, patients diagnosed with a kidney mass and who had a radical nephrectomy or partial nephrectomy treated by either open or laparoscopic methods in our institute were included in the study. The exclusion criteria included patients with other known malignancies, hematologic diseases, autoimmune diseases, active infections, preoperative blood transfusions, those under anticoagulant treatment or prior steroid or anticancer therapy, or patients where perioperative routine laboratory tests were unavailable.

A total of 354 patients with a complete blood panel performed within 30 days prior to the surgery and available medical records were discovered. Finally, 330 out of 354 patients were included in the study, and 56 of them had benign tumors. The longest diameter of the tumor size (TS), histological cancer type, T-stage, Fuhrman grade, status of lymph node metastasis, and necrosis, defined as the presence of microscopic coagulative necrosis, were taken from the pathology reports.

The NLR was calculated by dividing the absolute number of neutrophils by the lymphocyte count. The PLR was calculated by dividing the absolute platelet count by the lymphocyte count. MPV to platelet count ratio, Hb to RDW ratio, and lymphocyte-to-monocyte count ratios were also calculated.

## Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 21; SPSS Inc., Chicago, IL, USA). The normality of the continuous variables was analyzed with the Kolmogorov Smirnov test. Results are expressed as mean  $\pm$  standard deviation (SD) or median (interquartile range). Normally distributed continuous variables were compared using the independent-samples t-test, and the Mann-Whitney U test was used if the distribution was skewed. Categorical data were compared using the chi-square test. The Kruskal-Wallis test was used for computing differences across groups. A *p*-value of 0.05 was considered to be statistically significant.

The ROC curve, a parameter that reflects the sensitivity and specificity of continuous variables, was

used to determine the cut-off values of the parameters. Youden’s index was applied to determine the optimal cut-off value.

Next, we stratified the hemogram-associated markers and analyzed them as categorical variables. We combined the hemogram-related parameters with tumor size to establish the hemogram-related risk (HERR) score as follows: patients with increased NLR ( $\geq 2.47$  and  $< 4.0$ , 1 point;  $> 4.0$ , 2 points), and MPV to PLT ( $\geq 0.028$ , 1 point), tumor size ( $\geq 4$  cm, 1 point), decreased LMR ( $\leq 4.20$ , 1 point), and Hb to RDW ratio ( $\leq 0.86$ , 1 point). The HERR score was calculated by totaling these individual scores. Using the postoperative pathological report as the gold standard, the sensitivity (SE), specificity (SP), positive and negative predictive values (PPV, NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were calculated.

## RESULTS

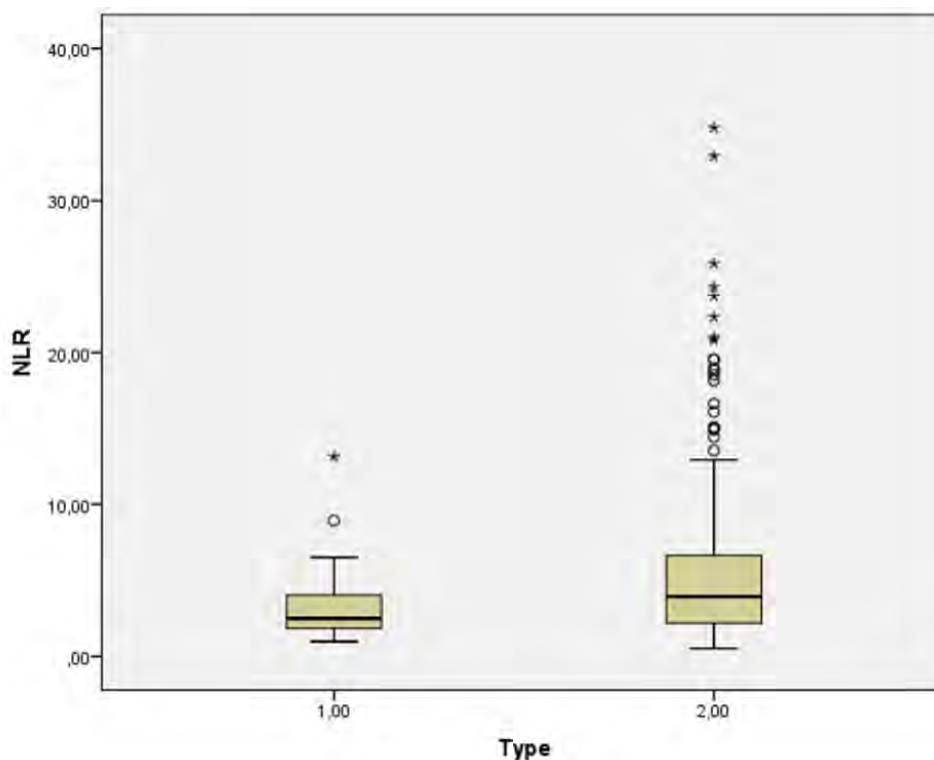
The histological findings confirmed RCC in 274

**Table 1. The diagnosis of patients**

Diagnosis	Number of patients
<b>Benign masses</b>	<b>56</b>
Renal cyst	26
Renal cortical adenoma	2
Oncocytoma	15
Anjomyolipom	13
<b>Renal cell cancers</b>	<b>274</b>
Clear renal cell carcinoma	225
Papillary renal cell carcinoma	26
Chromophobe renal cell carcinoma	11
Unclassified renal cell carcinoma	12

patients (Table 1). Of these, 168 (61%) were men, and 106 (39%) were women. The mean age of the patients with benign masses was  $58.5 \pm 12.7$  (22 to 82 years) and  $59.5 \pm 11.9$  (18 to 89 years) for malignant cases (Table 2). Out of these total RCC patients, 225 (82%) had renal clear-cell carcinoma, 26 (9.4%) had a papillary RCC, 11 (4%) had a chromophobe RCC, and 12 (4%) were unclassified.

In the benign group, 17 of the patients had a tumor



**Figure 1.** Neutrophil to lymphocyte ratio. The bar graphs show blood neutrophile to lymphocyte (NLR) levels in benign (type 1) and renal cell carcinoma (type 2) patients.

size ≤ 4 cm, 64 of the RCC patients had a tumor size ≤ 4 cm. Three of the benign patients had a tumor size > 10 cm, and 53 of the RCC patients had a tumor size > 10 cm. When the patients were stratified according to pathological stage, 51% were at stage pT1, 24% at stage pT2, 21% at stage pT3, and 2% at stage pT4 (Table 2). When renal clear-cell patients were stratified according to the Fuhrman grade, 47 patients were classified as grade I, 120 as grade II, 45 as grade III, and 14 as grade IV. Of the RCC patients, 154 underwent an open radical nephrectomy, 76 had a laparoscopic radical nephrectomy, 38 had an open

partial nephrectomy, and 6 had a laparoscopic partial nephrectomy. In the benign patient group, 22 underwent an open radical nephrectomy, 16 had a laparoscopic radical nephrectomy, 14 had an open partial nephrectomy, and 4 had a laparoscopic partial nephrectomy.

The NLR levels [median (interquartile range)] were higher in the patients in the malignant kidney mass group with a value of 3.7 (4.7) compared to a value of 2.4 (3.2) for the benign kidney mass group ( $p < 0.001$ ; Figure 1). The RDW, PLT, LMR, PLR, Hb to RDW, and MPV to PLT levels were similar between

**Table 2.** Characteristics of the entire study population (n = 330)

	Benign (n = 56)	RCC (n = 274)	p value
<b>Gender (M/F)</b>	31/25	170/104	0.018
<b>Age (years)</b>	58.5 ± 12.7	59.5 ± 11.9	0.995
<b>TNM Stage</b>			
pT1a		60	
pT1b		81	
pT2a		34	
pT2b		34	
pT3a		49	
pT3b		7	
pT3c		3	
pT4		6	
<b>WBC (10<sup>9</sup>/L)</b>	7.9 (3.7)	9.2 (5.0)	<b>0.001*</b>
<b>Neutrophile (10<sup>9</sup>/L)</b>	5.0 (2.5)	6.3(4.7)	<b>&lt; 0.001*</b>
<b>Lymphocyte (10<sup>9</sup>/L)</b>	1.8(1.0)	1.7 (1.1)	0.113
<b>RDW</b>	14.2 (2.1)	14.5 (2.3)	0.843
<b>PLT (10<sup>9</sup>/L)</b>	266 (112)	249 (102)	0.050
<b>MPV, fl</b>	8.5(1.5)	8.4	0.651
<b>PCT</b>	0.23 (0.07)	0.21 (0.09)	0.056
<b>PDW</b>	16.6 (0.4)	16.5 (1.6)	0.604
<b>Hb (g/dl)</b>	13.8 (2.7)	12.7 (2.8)	<b>0.008*</b>
<b>Hct (%)</b>	41.1 (7.4)	37.9 (7.8)	<b>0.014*</b>
<b>Hb to RDW</b>	0.92 ± 0.18	0.87 ± 0.19	0.092
<b>LMR</b>	3.1 (2.58)	3.1 (2.48)	0.680
<b>PLR</b>	142 (106)	147 (109)	0.533
<b>MPV to PLT</b>	0.031 (0.015)	0.033 (0.017)	0.127
<b>NLR</b>	2.4 (2.2)	3.7 (4.7)	<b>&lt; 0.001*</b>
<b>HERR score</b>	3.0 (1.0)	4.0 (2.0)	<b>&lt; 0.001*</b>

Data are shown as median (interquartile range). or number or mean ± standard deviation. F = female, Hb = hemoglobin, HbRDW = hemoglobin to red cell distribution width, Hct = hematocrit, HERR = hemogram-related risk, LMR = lymphocyte to monocyte ratio, M = male, MPV = mean platelet volume, NLR = neutrophile to lymphocyte ratio, RCC = renal cell carcinoma, PLR = platelet to lymphocyte ratio, PLT = platelet count, RDW = red blood cell distribution width, ROC = receiver operating characteristic, SE = standard error, WBC = white blood cell, \* $p < 0.05$

**Table 3.** ROC curve analysis, and cut-off values for prediction of RCC from hemogram

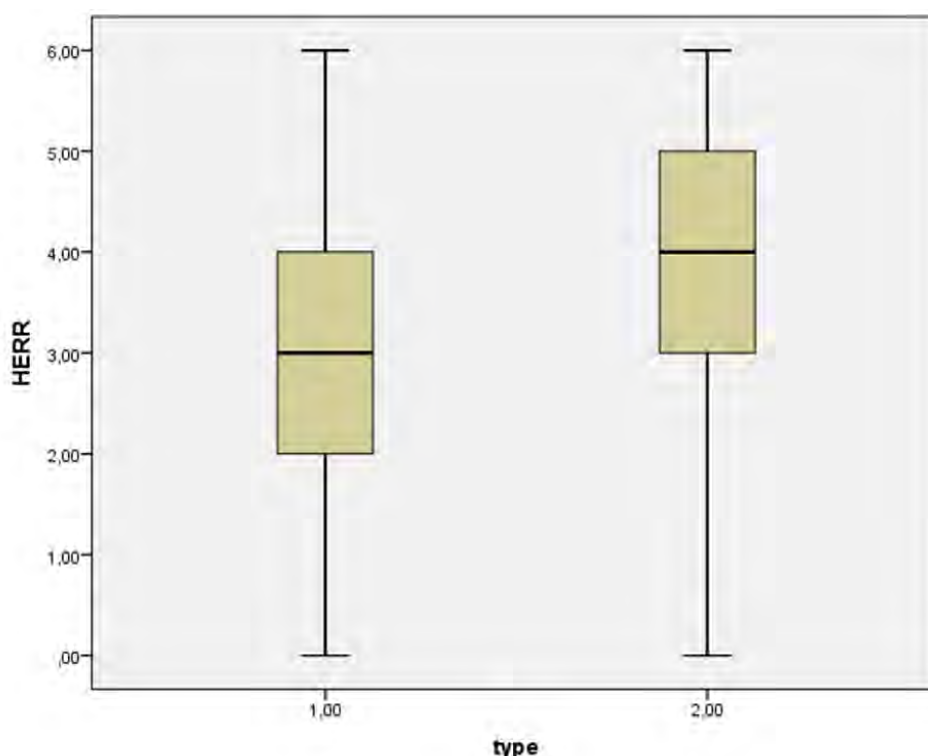
Parameter	AUC	SE	p value	95% confidence interval	Cut-off value
<b>MPV to PLT</b>	0.564	0.042	0.129	0.481-0.647	0.029
<b>Hb to RDW</b>	0.582	0.041	0.053	0.501-0.663	0.86
<b>PLR</b>	0.526	0.041	0.533	0.447-0.606	120
<b>LMR</b>	0.508	0.041	0.842	0.429-0.588	4.2
<b>NLR</b>	0.657	0.035	0.000*	0.588-0.727	2.47

AUC = Area under curve, Hb = hemoglobin, LMR = lymphocyte to monocyte ratio, MPV = mean platelet volume, NLR = neutrophile to lymphocyte ratio, RCC = renal cell carcinoma, PLR = platelet to lymphocyte ratio, PLT = platelet count, RDW = red blood cell distribution width, ROC = receiver operating characteristic, SE = standard error

the RCC and benign-mass patients (Table 2). The ROC analysis (Table 3) showed the ideal cut-off value for the NLR was 2.47 (area under curve [AOC]: 0.657), and 4.2 was the ideal cut-off value for the LMR (AUC: 0.508). The ROC analysis also showed that the discriminatory power for NLR was greater than any other individual parameter.

As mentioned above, the continuously coded parameters were analyzed as categorical variables that were subsequently used to calculate the HERR score. Using the Hb to RDW ratio alone ( $\leq 0.86$ ) for

diagnosing RCC, we obtained a specificity of 67, meaning that it correctly identified 67% of those who did not have RCC. Patients with benign masses showed a median HERR score of 3 (IQR: 2.7) while the RCC median HERR score was 4 (2.0) ( $p < 0.001$ ; Figure 2). We found the cut off value of the HERR Score as 3. The best value of the sensitivity and specificity of the parameters related to the hemogram is the cut off value. We calculated the cut off value as 3, in this sampling. Patients with a high HERR score ( $\geq 3$ ) were more likely to have RCC. Using the  $\geq 3$



**Figure 2.** Hemogram related risk score. The bar graphs show blood HERR scores in benign (type 1) and RCC (type 2) patients.

**Table 4.** Diagnostic power of hemogram-related indices

Parameter	SE (%) (95% CI)	SP (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR+* (95% CI)	LR-* (95% CI)
<b>Tumor size (<math>\geq 4</math> cm)</b>	37 (31-43)	75 (61-85)	88 (80-93)	20 (15-26)	7.3 (4.4-12.0)	4.0 (3.6-4.5)
<b>MPV to PLT (<math>\geq</math> cut-off)</b>	82 (77-87)	26 (16-40)	84 (79-88)	24 (14-37)	5.5 (4.1-7.3)	3.1 (2.4-3.9)
<b>Hb to RDW (<math>&lt;</math> cut-off)</b>	47 (41-53)	67 (53-79)	88 (81-92)	12 (15-27)	7.2 (4.7-11.2)	3.7 (3.3-4.2)
<b>PLR (<math>\geq</math> cut-off)</b>	69 (63-74)	44 (31-58)	86 (80-90)	22 (15-31)	6.0 (4.3-8.4)	3.4 (2.9-4.0)
<b>LMR (<math>&lt;</math> cut-off)</b>	70 (65-75)	29 (24-34)	83 (77-87)	17 (12-22)	4.8 (3.5-6.4)	5.1 (4.2-6.2)
<b>NLR (<math>\geq</math> cut-off)</b>	68 (62-73)	51 (38-65)	87 (82-91)	25 (17-34)	6.9 (4.8-9.8)	3.0 (2.5-3.5)
<b>HERR score (<math>\geq 3</math>)</b>	78 (73-83)	69 (56-80)	91 (87-94)	44 (34-54)	10.8 (7.0-16.4)	1.2 (1.0-1.5)

Hb = hemoglobin, HERR = hemogram-related risk, LMR = lymphocyte to monocyte ratio, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, MPV = mean platelet volume, MPV to PLT = mean platelet volume to platelet ratio, PPV = positive predictive value, NLR = neutrophil to lymphocyte ratio, NPV = negative predictive value, PLR = platelet to lymphocyte ratio, PLT = platelet count, RDW = red blood cell distribution width, SE = sensitivity, SP = specificity, \*weighted by prevalence

HERR score cut-off, we obtained a specificity of 69% (95% confidence interval [CI]: 56-80), meaning that it correctly identified 69% of those who did not have a malign tumor. We obtained a high LR+ ratio (10.8) for the HERR scores that are in the best indicator range for ruling the diagnosis as RCC, and a PPV of 91 (87-94) within this category of HERR score (Table 4).

## DISCUSSION

We hypothesized that there might be different degrees of circulating blood cell indices in RCC as compared to benign masses, and we explored the possibility that these indices could distinguish RCC from other benign renal masses. To provide comprehensive information for diagnosing RCC patients, we evaluated the NLR, PLR, LMR, and Hb to RDW ratios, and integrated them into a reliable scoring system that could be performed from a routine blood count to detect samples that could indicate RCC. While calculating the HERR score, platelet, monocyte, lymphocyte, neutrophil, and erythrocyte levels were evaluated simultaneously. Thus, a high HERR score

might reflect alterations that favor cancer initiation and progression.

Our findings demonstrated that combining hemogram parameters into an integrated HERR score to discriminate among the kidney masses preoperatively offered a low rate of false positives and an adequate LR+ level as compared to using these values separately. In the current study, we found that none of the evaluated hematological indices mentioned in the literature were significantly correlated with a diagnosis of RCC and that the HERR score was significantly better than any of these parameters.

Additionally, the preoperative NLR score had powerful diagnostic abilities compared to the other hematologic indices, and it showed the highest diagnostic specificity and sensitivity. The NLR combined the measurements of the increased protumor activity of neutrophils with those of the reduced antitumor immune response by lymphocytes into a single value [7, 8]. We found that the NLR levels were higher in the RCC group, which can reflect the status of the tumor microenvironment. Similarly to our study, a number of researchers have demonstrated that the preoperative NLR value was significantly higher in malignant renal masses compared to benign ones [8,

13, 14].

Platelets have been shown to facilitate tumor progression by contributing to the metastatic cascade, regulating tumor cell invasion, and playing a role in angiogenesis [15]. A meta-analysis reported by Wang *et al.* [9] reported that an elevated PLR and reduced LMR were associated with poorer overall survival in RCC patients. Monocytes can be recruited in tumor tissues and exert pre-tumoral actions, meaning that a decreased LMR could be associated with the less favorable prognosis that was observed in RCC [9].

Previously, the MPV/PLT ratio as a predictor of cancer gave inconsistent results [16, 17]. In our study, this ratio for RCC patients and the benign group was comparable. We did not find any previous reports assessing the MPV/PLT ratio for patients with RCC.

The Hb to RDW levels were non-significantly reduced in RCC compared to benign cases. Recently, a low Hb/RDW ratio was reported to be significantly associated with poor clinical outcomes and a greater risk of death in esophageal squamous cell carcinoma patients [10]. Because both HB and RDW are influenced by various non-cancer-related conditions, the Hb/RDW could therefore theoretically reflect generalized health information, such as the nutrition status, inflammatory status, and immune function.

All of the blood parameters measured are available in routine blood tests, are easy to perform by the vast majority of automated analyzers, and do not increase the cost of diagnosis. The HERR score in combination with a summary of clinical symptoms might alert physicians to the early detection of RCC. The goal of a reliable screening test is to get as close as possible to zero false negative results with a minimal percentage of false positive results. Although hematologic indices are easy to measure, their utility might be affected by several factors that could lead to different cut-off points from those already mentioned in every hospital [18].

### Limitations

The limitations of the present study include its retrospective nature and relatively small number of patients located at only one center. Due to biological differences between distinct patient cohorts, further studies in different cohorts with external validation are needed.

## CONCLUSION

In conclusion, our study, despite being a preliminary validation, is the first to evaluate hemogram-related parameters for preoperatively discriminating between RCC and benign renal masses. The HERR score developed herein is a potential diagnostic biomarker that aids in this discrimination.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

- [1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA. Cancer J Clin* 66 2016;66:7-30.
- [2] Tahbaz R, Schmid M, Merseburger AS. Prevention of kidney cancer incidence and recurrence: lifestyle, medication and nutrition. *Curr Opin Urol* 2018;28:62-79.
- [3] Acar C, Sözen S, Üre I, Batur AF, Gürocak S, Küpeli B. Nephron-sparing treatments in small renal tumors: surgical and ablative procedures. *Turk J Urol* 2009;35:87-95.
- [4] Özen H, Colowick A, Freiha FS. Incidentally discovered solid renal masses: what are they? *Br J Urol* 1993;72:274-6.
- [5] Kay FU, Pedrosa I. Imaging of solid renal masses. *Radiol Clin North Am* 2017;55:243-58.
- [6] Lane BR, Babineau D, Kattan MW, Novick AC, Gill IS, Zhou M, et al. A preoperative prognostic nomogram for solid enhancing renal tumors 7 cm or less amenable to partial nephrectomy. *J Urol* 2007;178:429-34.
- [7] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010;140:883-99.
- [8] Hu K, Lou L, Ye J, Zhang S. Prognostic role of the neutrophil-lymphocytaratio in renal cell carcinoma: a meta-analysis. *BMJ Open* 2015;5:e006404.
- [9] Wang X, Su S, Guo Y. The clinical use of the platelet to lymphocyte ratio and lymphocyte to monocyte ratio as prognostic factors in renal cell carcinoma: a systematic review and meta-analysis. *Oncotarget* 2017;8:84506-14.
- [10] Sun P, Zhang F, Chen C, Bi X, Yang H, An X, et al. The ratio of hemoglobin to red cell distribution width as a novel prognostic parameter in esophageal squamous cell carcinoma: a retrospective study from southern China. *Oncotarget* 2016;5:42650-60.
- [11] Prokopowicz G, Życzkowski M, Nowakowski K, Bogacki R, Bryniarski P, Paradysz A. Basic parameters of blood count as prognostic factors for renal cell carcinoma. *Biomed Res Int* 2016;2016:8687575.
- [12] Golovastova MO, Korolev DO, Tsoy LV, Varshavsky VA, Xu WH, Vinarov AZ, et al. Biomarkers of renal tumors: the current state and clinical perspectives. *Curr Urol Rep* 2017;18:3.
- [13] Gorgel SN, Ozer K, Kose O, Dindar AS. Can preoperative



neutrophil lymphocyte ratio predict malignancy in patients undergoing partial nephrectomy because of renal mass? *Int Braz J Urol* 2017;43. doi: 10.1590/S1677-5538.IBJU.2017.0225.

[14] Viers BR, Thompson RH, Lohse CM, Cheville JC, Leibovich BC, Boorjian SA, et al. Pre-treatment neutrophil-to-lymphocyte ratio predicts tumor pathology in newly diagnosed renal tumors. *World J Urol* 2016;34:1693-9.

[15] Stegner D, Dutting S, Nieswandt B. Mechanistic explanation for platelet contribution to cancer metastasis. *Thromb Res* 2014;2:149-57.

[16] Cho SY, Yang JJ, You E, Kim BH, Shim J, Lee HJ, et al. Mean

platelet volume/platelet count ratio in hepatocellular carcinoma. *Platelets* 2013;24:375-7.

[17] Inagaki N, Kibata K, Tamaki T, Shimizu T, Nomura S. Prognostic impact of the mean platelet volume/platelet count ratio in terms of survival in advanced non-small cell lung cancer. *Lung Cancer* 2014;83:97-101.

[18] Budak YU, Polat M, Huysal K. The use of platelet indices, plateletcrit, mean platelet volume and platelet distribution width in emergency non-traumatic abdominal surgery: a systematic review. *Biochem Med (Zagreb)* 2016;26:178-93.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Local resection for placenta accreta spectrum: a conservative uterus sparing technique for anterior placenta accreta

Gülsüm Uysal<sup>ORCID</sup>, Nefise Tanrıdan Okçu<sup>ORCID</sup>, Eda Eskimez<sup>ORCID</sup>, Esra Saygılı Yılmaz<sup>ORCID</sup>

Department of Obstetrics and Gynecology, University of Health Sciences, Adana Numune Training and Research Hospital, Adana, Turkey

DOI: 10.18621/eurj.382390

## ABSTRACT

**Objectives:** To evaluate and describe a surgical approach for uterine preservation and management of postpartum hemorrhage in placenta accreta spectrum (PAS).

**Methods:** We analyzed the data of patients who were diagnosed with placenta previa accompanied with PAS prenatally and subsequently performed cesarean section with local resection technique to manage postpartum hemorrhage and uterine preservation at our tertiary care center between January 2016 and August 2017. The technique includes the local resection of placental invasion site and suturing the new uterine edges without internal iliac artery ligation.

**Results:** The diagnosis of placenta accreta spectrum anterior in all 11 cases was confirmed intraoperatively. Only 1 case underwent hysterectomy in a second operation. Two of cases had bladder injury. The mean operative time was  $99 \pm 30$  minutes. The mean received packed red blood cells was  $2.3 \pm 1.0$  units. The mean length of postoperative hospital stay was  $4.5 \pm 1.4$  days. There was no late complications regarding coagulopathy and infection. No maternal mortality was observed.

**Conclusion:** Local resection is an effective, safe and fertility preserving approach in selected patients with PAS.

**Keywords:** Placenta accreta spectrum, maternal morbidity, fetal outcome, fertility preservation, uterus preserving surgery, local resection

*Received: January 22, 2018; Accepted: February 23, 2018; Published Online: April 11, 2018*

Placenta accreta spectrum (PAS) disorders, comprise the spectrum of adhesive placental invasions formerly called placenta accreta, increta, percreta [1-3]. PAS refers to an abnormal implantation of anchoring placental villi to myometrium, uterine serosa or adjacent organs instead of staying limited to decidua [2, 3]. Major risk factors include placenta previa and previous cesarean deliveries. Other risk factors are prior uterine scars (myomectomy, infertility treatments, cornual resection of ectopic pregnancy, hysteroscopic septum resections or removal of uterine

adhesions), recurrent abortions, dilatation and curettage (D/C), smoking, advanced maternal age and parity [2-4]. PAS became an important life-threatening obstetric problem since frequency of it has been rising constantly in recent decades due to increasing rates of cesarean deliveries. Moreover, adherent placenta has been replacing with uterine atony as major cause of cesarean hysterectomy [4, 5].

Antenatal diagnosis, and planned preterm cesarean hysterectomy (between 34-35 weeks gestation) with the placenta left in situ is the recommended treatment



Address for correspondence: Nefise Tanrıdan Okçu, MD., University of Health Sciences, Adana Numune Training and Research Hospital, Obstetrics and Gynecology, 01170 Adana, Turkey  
E-mail: nefise-tanridan@hotmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

in case of placenta accreta [6, 7]. It was also stated that surgical management should be individualized. Although planned preterm cesarean hysterectomy seems to be the safest and most common treatment for placenta accreta diagnosed before delivery, it is a skillful, serious, and maybe a fertility losing method [6]. Hence, gynecologists are looking for solutions for increasing cesarean delivery rates and medico-legal problems. Therefore, new methods of conservative management for fertility preservation and safe self-esteem of women with placenta percreta are appealing in recent years [8, 9]. Conservative management includes; leaving the placenta in situ, hysteroscopic resection of retained adherent placenta, partial en bloc resection with embolization, the Triple P procedure which involves perioperative placental localization, pelvic devascularization, myometrial excision with non-separated placenta and reconstruction of the uterine wall [10-15]. On the other hand uterine conservation and leaving the placenta in situ may be considered to mitigate the risk of hemorrhage or injury to other adjacent organs [2]. Uterine artery embolization, balloon occlusion, intravascular balloon catheter and embolization are the other techniques developed for PAS in literature [9]. However, there is no clear algorithm for adherent placenta management.

In this study, we evaluated the efficacy of local resection to preserve the uterus and aimed to share our clinical "local resection technique" results including maternal-fetal outcomes in patients with PAS.

## METHODS

In present retrospective, descriptive study, data were collected from the medical records of patients who had been diagnosed with placenta previa concomitant PAS (accreta, increta, percreta) between January 2016 and August 2017 in Department of Obstetrics and Gynecology at our hospital. The study was approved by local ethics committee of University of Health Sciences, Adana Numune Training and Research Hospital with the number of 7/113. Informed consent for review of records was deemed unnecessary in view of the retrospective nature of the study.

Placenta previa and PAS were diagnosed by color

flow Doppler (trans-abdominally and trans-vaginally with Toshiba Xario machine (Shimoishigami, Otawara-shi, Tochigi 324-8550, Japan) equipped with a 2.8-7 megahertz (MHz) transducer in all patients. Loss of normal hypoechoic retro-placental zone, thinner retro-placental myometrial thickness of 1 mm, presence of multiple vascular lacunas (Swiss-cheese appearance) or turbulent blood flow through lacune, increased sub-placental vascularity and presence of vessels bridging from placenta to uterine margin were used for diagnosis [4]. Moreover extension of villi into myometrium, serosa, or bladder and abnormalities of uterine serosa and bladder interface (such as interruption, thickening, irregularity of line and increased vascularity) were also confirmed by Doppler ultrasound for the accurate diagnosis.

All demographic and obstetric information regarding age, smoking, parity, gestational week at delivery, past history of cesarean section and presence of placenta previa were retrieved from the patients' data files. Length of hospital stay before and after operation, perioperative complications, comorbidities, preoperative and postoperative hemoglobin values were collected. Localization of placenta, maternal blood group, number of erythrocyte and/or fresh frozen plasma transfusions were all recorded from the patients' files. All transfusions were considered by expert team (surgeons and anesthesiologists) upon maternal hemodynamic status in line with the recommendations. Fetal weight and sex, Apgar scores, admission to intensive care unit as well as perinatal outcomes were also noted.

Our inclusion criteria were patients diagnosed with placenta previa concomitant PAS between the ages of 18-45 years with complete pre- and post-natal data. Exclusion criteria included patients with coagulopathy, multiple gestation and pregnancies complicated with fetal chromosomal or congenital malformations.

Prior to 2016, routine surgical management for patients with strongly suspected placenta percreta was planned preterm cesarean hysterectomy. Since then, our management option has been modified to the local resection of the uterine site invaded by the placenta with the preservation of the uterus for selected patients. The surgical techniques used for the present study are presented in Table 1.

General anesthesia was applied to all patients. The

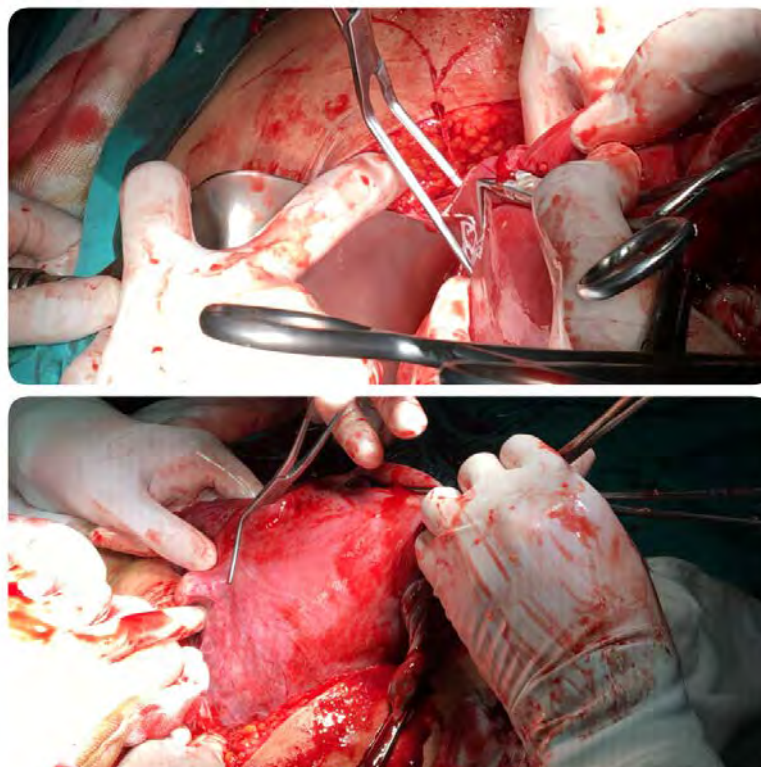
**Table 1.** Summary of local surgical resection technique of our clinic approach

1. Vertical midline incision, uterus exteriorized and followed by vertical fundal incision
2. Fetal delivery
3. Placenta was clamped inside the uterus, leaving in place avoiding any attempt
4. Clamping (one for cervical and uterine arteries and one for ovarian ligaments) ligaments with specialized vascular clamps (Figure 1)
5. Sharp and blunt dissection of the bladder, ligation of the perforating vessels between placenta and bladder serosa (Figure 2)
6. Tracing the placental zone and mapping the expected resection area (Figure 2)
7. Local (partial) resection of the uterine segment involving morbidly adherent placenta with the help of stretching remained placenta from the fundal incision (Figure 2)
8. Suturing the new uterine edges horizontally (Figure 2)
9. Applying a Latex Foley catheter 18 Fr/Ch (6.0 mm) inversely and filled with 80ml saline through the cervico-vaginal canal for tamponading sutured new uterine zone
10. Closing the fundal incision vertically and removing the all clamps

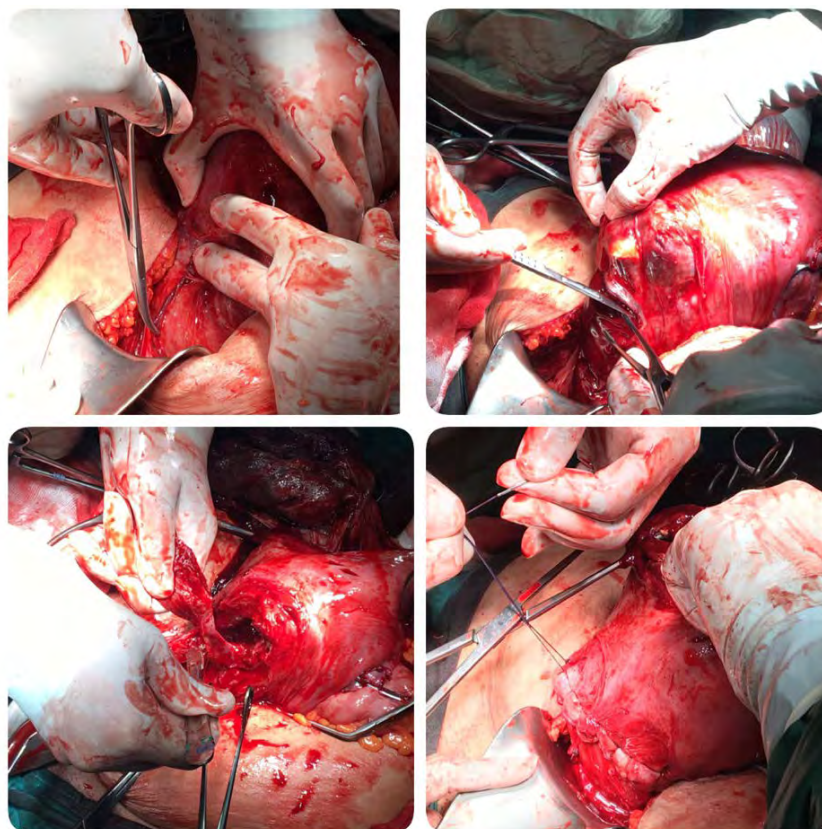
appropriate crystalloid infusion, blood or products according to the clinical circumstances were administered during the resection of the uterine portion. A routinely oxytocin 30 UI intravenous (i.v.) infusion and methylergobasine 0.2 mg i.v. in single dose in selected patients if indicated were also applied. Internal iliac artery ligation was not performed in any cases presented in this study. An abdominal suction drain was placed to all patients.

### Surgical technique

After the vertical midline incision, the uterus exteriorized and a vertical uterine fundal incision was performed. After fetal delivery, the placenta was clamped inside the uterus. Cervical and uterine arteries and ovarian ligaments were clamped with specialized vascular clamps (marked in Figure 1). After bladder dissection, perforating vessels between placenta and bladder serosa were ligated (marked in Figure 2).



**Figure1.** Clamping of cervical and uterine arteries and ovarian ligaments (Marked with arrows in the figures)



**Figure 2.** Perforating vessels between placenta and bladder serosa were ligated. After tracing the placental zone and mapping the expected resection area, local (partial) resection of the uterine segment involving morbidly adherent placenta were performed. New uterine edges were horizontally sutured. (Marked with arrows).

Placental zone and the expected resection area were mapped and traced. The uterine segment involving morbidly adherent placenta with the help of stretching remained placenta from the fundal incision was locally resected (marked in Figure 2). New uterine edges horizontally sutured. A latex Foley catheter 18 Fr/Ch (6.0 mm) filled with 80 ml saline was applied inversely through the cervicovaginal canal for tamponading sutured new uterine zone. All clamps were removed and the fundal incision was closed vertically (Table 1).

### Statistical Analysis

The clinical features of both groups were compared with the Statistical Package for Social Sciences (SPSS) for Windows, version 18.0 (SPSS Inc. IL, USA). Descriptive statistics were performed, including the description of quantitative variables, as the mean  $\pm$  SD and range, and description of qualitative variables as numbers and percentages. Normality of data distribution was tested with Kolmogorov-Smirnov test.

### RESULTS

In this study, 11 cases of placenta previa concomitant PAS were identified from medical records. Local resection technique as uterus sparing method was performed in 10 patients. Bilateral tubal ligation was performed in 5 patients according to their preferences. Maternal demographic and surgical characteristics were summarized in Table 2. Two patients were admitted to our clinic with active vaginal bleeding and the surgery of others were performed in a planned preterm cesarean delivery (35-37 weeks). Regarding risk factors, all except one patient (Case no 9) had at least one previous cesarean section. There was no smoking history in mothers and one case had gestational diabetes and one had hypertension. Vertical skin incision under general anesthesia were performed to all cases. The mean operative time was  $99 \pm 30$  minutes. All of the cases had predominantly anterior placenta previa and were diagnosed with PAS by using preoperative color doppler ultrasound. The diagnosis was confirmed intraoperatively and send to

**Table 2.** Demographic characteristics, maternal outcome and pathology of patients

Case No.	1	2	3	4	5	6	7	8	9	10	11
Age (years)	27	42	30	44	33	28	30	25	21	34	28
G/P/A	3.2.2000	5.4.2000	3.1.2001	3.2.2000	3.2.2000	2.1.2000	5.4.2000	3.2.2000	4.2.2001	3.2.2000	2.1.2000
Risk factors	PL Previa CSx2	PL. Previa CSx1	PL. Previa CSx1	PL. Previa CSx2 GDM	PL. Previa CSx2 HT	PL. Previa CSx1	PL. Previa CSx3	PL. Previa CSx2	PL. Previa CSx0	PL. Previa CSx2	PL. Previa CSx1
Gestational age at delivery (weeks)	34	29	35	35	35	32	37	35	36	36	35
Tubal ligation (bilateral)	0	1	0	1	1	0	1	0	0	1	0
Complications	none	none	none	ICU Bladder injury	none	none	ICU Bladder injury	none	none	none	C/SHys
Preop Hb (g/dl)	9.4	13.1	10.9	10.4	12.8	12	10.5	11.2	10.5	10.8	11
Postop Hb (g/dl)	6.7	7.3	9.5	9.6	12.5	11.1	10.8	9.4	9.5	9.3	8.5
Operative duration (min)	115	68	120	95	150	60	150	82	80	80	90
Blood transfusion rbc/ffp/h	2.2.2001	1/0/2	2.2.2000	4.2.2000	4.2.2000	1/0/0	3.1.2000	1.1.2000	1.1.2000	2/0/0	3.1.2000
Early-op stay	0	0	2	4	3	0	2	11	0	0	0
Post-op stay	3	3	6	4	4	3	3	7	3	4	5

G = gravida, P = parity, A = abortion, Hb = hemoglobin, ICU = intensive care unit, C/SHys = cesarean hysterectomy, rbc = packed red blood cells, ffp = fresh frozen plasma, h = Haemocompletan (Fibrinogen)

pathological evaluation for gross and the histopathologic examination of the resected part. Regarding histopathological reports the largest resected area was 10×6 cm and the minimum was 3×3 cm. The mean age of the patients was 31 ± 6.8 years, ranged from 21 to 44 years. The mean gestational week at delivery was 34 ± 2.2, ranged from 29 to 37 weeks. Regarding intraoperative complications, two patients had intraoperative bladder injury and urinary catheter was applied with a period of 10 days for these patients. Postoperative hemorrhage occurred in one

case and a cesarean hysterectomy performed in a second operation. Two patients were transferred to intensive care unit (ICU) postoperatively and stayed 2 days until hemodynamically stabilized. Before surgery, 4 units of packed red blood cells and fresh frozen plasma were prepared in case of emergency use for all patients. The mean preoperative and postoperative hemoglobin (Hb) level was 11 ± 1.1 g/dL, 9.2 ± 1.7 g/dL, respectively. All patients received at least one unit of red blood cells intraoperatively (min: 1-max: 4). The mean received packed red blood

**Table 3.** Fetal - Neonatal characteristics and outcomes of patients

Case No.	1	2	3	4	5	6	7	8	9	10	11
Gender	Male	Male	Female	Male	Female	Female	Female	Male	Female	Male	Female
Presentation	Breech	Vertex	Breech	Breech	Transvers	Breech	Breech	Vertex	Vertex	Vertex	Vertex
Birth weight (g)	2150	1310	2600	2750	2458	1700	3100	2700	2900	2850	2760
Head circumference (cm)	32	29	32	33	32	30	34	34	35	33	32
Height (cm)	45	40	43	47	47	42	49	49	48	48	47
Apgar 1st minute	9	7	6	7	7	7	7	9	7	7	6
Apgar 5th minute	10	9	8	8	9	9	9	10	9	9	8

cells was  $2.3 \pm 1.0$  units. A routinely abdominal drain were placed to all patients and mean removal day was one day. The mean length of postoperative hospital stay was  $4.5 \pm 1.4$  days. There was no late complications regarding coagulopathy and infection. No maternal mortality was observed.

Regarding follow-up controls (4 of patients lost follow-up) had no complaint about abnormal uterine bleeding or abnormal menstruation. Up to the time this research was conducted no patients had a new pregnancy after this operation.

Fetal and neonatal outcomes were summarized in Table 3. There was only 2 cases with  $< 7$  Apgar scores in the first minutes. All Apgar scores in 5th minutes were above 7. There were 6 non-vertex presentation. Since prematurity, 2 of babies were transferred to neonatal ICU. No neonatal death was observed.

## DISCUSSION

The present study has shown that local resection technique is a safe and effective method in treatment of anterior PAS disorders. The surgical results of 11 cases with PAS were presented in the present study, including maternal and fetal outcomes. Although it is not often possible to perform this technique to all patients, local resection should be reserved for the women with strong fertility desire or uterine sparing. PAS is a life-threatening condition causing maternal mortality and morbidity, and is no longer a rare obstetric situation. The incidence of PAS has increased from approximately one case per 1000 deliveries in the 1980s to three per 1000 deliveries in the past decade [1, 16]. As the number of caesarean section increases, the more number of morbidity invasive placenta will be encountered. Therefore, new uterine sparing methods are being suggested in the literature but conclusions about the superiority of any method still could not be drawn.

The main risk factor for placenta accreta is placenta previa [1, 10]. Repeated caesarean sections and multiple uterine D/C are also important risks factors, due to myometrial damage. In the present study there was only one patient without any cesarean history, but had a D/C history. Clinicians should be careful regarding placental invasion abnormalities even in patients with placenta previa without any

cesarean history.

Lower uterine segment, a highly vascularized structure, is perfused by the cervical artery, the inferior vesical artery and by the upper, middle and lower vaginal arteries [17]. Regarding this anastomotic compensation internal iliac artery ligation or occlusion is insufficient for PAS. Also, bilateral internal iliac artery ligation is skillful and an unsuitable procedure with difficulties in observation. Unlike other situations (myoma uteri), due to fragile tissues of adhesive placenta, tourniquet of cervix may not be suitable. In this local resection technique we used specialized vascular clamps, one for cervical and uterine arteries and one for ovarian ligaments. Therefore, we blocked the anastomotic compensation and uterine blood flow. We preferred this procedure instead of internal iliac artery ligation or balloon catheter occlusion.

Palacios *et al.* [10] first described en bloc resection of myometrium in patients with placenta percreta in 2004. They ligated bilateral uterine arteries and local bleeding was controlled with additive sutures selectively including the anterior and posterior cervical and vaginal arteries. After resection they covered primarily sutured area with absorbable mesh and fibrin glue. Uterine conservation was managed in 50 (74%) of the 68 women.

Chandaran *et al.* [11] described triple P technique in 2006 in a case series of 4 women with anterior placenta percreta. According to this procedure firstly horizontal incision was made 2 finger breadths above the placental edge. Secondly, preoperatively placed intraarterial balloon catheters were inflated after delivery. Thirdly en bloc myometrial excision was made and new zone was repaired [11]. The potential benefit of this procedure was to minimize the surgical dissection while removing the adhesive placenta in appropriately selected patients. In our study we performed vertical fundal incision for fetal delivery to prevent high blood loss.

Shabana *et al.* [12] reported modified surgical approach in the form of stepwise cesarean section in 71 patients with placenta percreta. They also made horizontal uterine incision for fetal birth and after bilateral internal iliac artery ligation, en bloc resection of adhesive myometrial region was performed. They emphasized conservative rather than radical surgical aspects.

Karaman *et al.* [15] also reported that local

resection of percreta site is an effective, safe, and fertility preserving approach. They presented 12 cases with placenta percreta and 4 of these underwent hysterectomy. One of our cases was underwent second laparotomy because of excessive bleeding through abdominal suction drain. The greatest difference between two techniques (local resection) was internal iliac artery ligation. In our study, we performed pelvic devascularization with a more simple way of ligation by vascular clamps in a short period of time. Similar to our study, the presence of placenta previa was predominating anteriorly in most of their cases. In patients with placenta previa regarding laterally and posterior predominating localization, both diagnosis and treatment are difficult. The preservation of uterus remains challenging with adhesive parts to the neighboring organs. In those patients we recommend cesarean hysterectomy instead of local resection.

Since biopsy is obtained in an area without invasion or with a degree of minor penetration, the histopathological study of invasive placenta does not always constitute a diagnostic “gold standard” [10]. For this reason, a mismatch between histology and the surgical finding may occur in some cases. Therefore, we preferred to define placenta accreta according to its clinical-surgical characteristics in this study.

In recent studies, fetal outcomes of placenta previa were conflicting [18, 19]. Rosenberg *et al.* [18] revealed an association between placenta previa and intrauterine growth retardation. Yenieli *et al.* [19] explored only neonatal outcomes and did not find an association between either fetal growth restriction or fetal demise with placenta previa. In our study, there were only two cases with < 7 Apgar scores in the first minutes. All Apgar scores in 5th minutes were above 7. General anesthesia may affect may affect Apgar scores in the first minutes. There were no intrauterine growth retardation in our study.

The major strength of our local resection technique is its easy procedure with daily used equipment leading safe and effective results. Moreover, this is probably the first study that fully investigates the resection procedure on fetal outcomes in patients with PAS.

### Limitations

The main limitation of the present study was its retrospective design. Another potential limitation was

that we could not have ascertained all cases because of absent data.

### CONCLUSION

Local resection technique is easy to perform and does not require special equipment or skills. This rapid procedure could be the management approach of choice not only for patients who want to retain their uterus and fertility, but also for patients with invasive placenta who are at increased risk of surgical morbidity. Nevertheless, the present results should be confirmed with further randomized prospective trials.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

### REFERENCES

- [1] Wu S, Kocherginsky M, Hibbard JU. Abnormal placentation: twenty-year analysis. *Am J Obstet Gynecol* 2005;192:1458-61.
- [2] Fox KA, Shamshirsaz AA, Carusi D, Secord AA, Lee P, Turan OM, et al. Conservative management of morbidly adherent placenta: expert review. *Am J Obstet Gynecol* 2015;213:755-60.
- [3] Kutuk MS, Ak M, Ozgun MT. Leaving the placenta in situ versus conservative and radical surgery in the treatment of placenta accreta spectrum disorders. *Int J Gynaecol Obstet* 2018;140:338-44.
- [4] Silver RM, Fox KA, Barton JR, Abuhamad AZ, Simhan H, Huls CK, et al. Center of excellence for placenta accreta. *Am J Obstet Gynecol* 2015;212:561-8.
- [5] Imudia AN, Awonuga AO, Dbouk T, Kumar S, Cordoba MI, Diamond MP, et al. Incidence, trends, risk factors, indications for, and complications associated with cesarean hysterectomy: a 17-year experience from a single institution. *Arch Gynecol Obstet* 2009;280:619-23.
- [6] Fitzpatrick KE, Sellers S, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. The management and outcomes of placenta accreta, increta, and percreta in the UK: a population-based descriptive study. *BJOG* 2014;121:62-70.
- [7] Committee on Obstetric Practice. Committee opinion no. 529: placenta accreta. *Obstet Gynecol* 2012;120:207-11.
- [8] Jeremiah M. Fecundity, Barrenness and the importance of motherhood in two Nigerian plays. *Int J Humanit Soc Sci* 2014;4:213-21.
- [9] Clausen C, Lonn L, Langhoff-Roos J. Management of placenta percreta: a review of published cases. *Acta Obstet Gynecol Scand* 2014;93:138-43.
- [10] Palacios Jaraquemada JM, Pesaresi M, Nassif JC, Hermosid S.



Anterior placenta percreta: surgical approach, hemostasis and uterine repair. *Acta Obstet Gynecol Scand* 2004;83:738-44.

[11] Chandraharan E, Rao S, Belli AM, Arulkumaran S. The Triple-P procedure as a conservative surgical alternative to peripartum hysterectomy for placenta percreta. *Int J Gynaecol Obstet* 2012;117:191-4.

[12] Shabana A, Fawzy M, Refaie W. Conservative management of placenta percreta: a stepwise approach. *Arch Gynecol Obstet* 2015;291:993-8.

[13] Lin K, Qin J, Xu K, Hu W, Lin J. Methotrexate management for placenta accreta: a prospective study. *Arch Gynecol Obstet* 2015;291:1259-64.

[14] Hequet D, Morel O, Soyer P, Gayat E, Malartic C, Barranger E. Delayed hysteroscopic resection of retained tissues and uterine conservation after conservative treatment for placenta accreta. *Aust N Z J Obstet Gynaecol* 2013;53:580-3.

[15] Karaman E, Kulusarı A, Çetin O, Çim N, Alkış İ, Yıldızhan R, et

al. Local resection may be a strong alternative to cesarean hysterectomy in conservative surgical management of placenta percreta: experiences from a tertiary hospital. *J Matern Fetal Neonatal Med* 2017;30:947-52.

[16] Publications Committee, Society for Maternal-Fetal Medicine, Belfort MA. Placenta accreta. *Am J Obstet Gynecol* 2010;203:430-9.

[17] Palacios Jaraquemada JM, Garcia Monaco R, Barbosa NE, Ferle L, Iriarte H, Conesa HA. Lower uterine blood supply: extrauterine anastomotic system and its application in the surgical devascularization techniques. *Acta Obstet Gynecol Scand* 2007;86:228-34.

[18] Rosenberg T, Pariente G, Sergienko R, Wiznitzer A, Sheiner E. Critical analysis of risk factors and outcome of placenta previa. *Arch Gynecol Obstet* 2011;284:47-51.

[19] Yeniel AO, Ergenoglu AM, Itil IM, Askar N, Meseri R. Effect of placenta previa on fetal growth restriction and stillbirth. *Arch Gynecol Obstet* 2012;286:295-8.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Assessment of cyber abuse in sexually abused children and adolescents

Merve Çıkılı Uytun<sup>1</sup>, Sevgi Özmen<sup>2</sup>, Esra Demirci<sup>2</sup>

<sup>1</sup>Department of Child and Adolescent Psychiatry, Kayseri Training and Research Hospital, Kayseri, Turkey

<sup>2</sup>Department of Child and Adolescent Psychiatry, Erciyes University School of Medicine, Kayseri, Turkey

DOI: 10.18621/eurj.392361

## ABSTRACT

**Objectives:** Child sexual abuse is associated with adverse outcomes, including increased vulnerability, that may explain the risk of revictimization via cyber media and cyber abuse may be a risk factor for sexual abuse. The aims of the study were to explore cyber abuse prevalence in sexual abuse cases, the direct and indirect links between child sexual abuse and cyber abuse and to study the differences in internet use between children and adolescents who were sexually abused and the control group.

**Methods:** We assessed 75 children and adolescents aged 7-18 who had experienced sexual abuse and were referred to us between 01.01.2014-01.01.2015. Additionally, 45 typical developing subjects who did not have any abuse history were recruited from pediatrics clinic of or hospital as the control group. We used our semi-structured questionnaire to assess cyber abuse.

**Results:** The rates of internet use were high in the control group (97.8%) compared to those of sexually abused teens (82.7%). However, the rates of cyber abuse were similar between the groups. The most used web site/application was different between the groups. Facebook was the most used web site/application in the sexually abused group (69.4%). This ratio was only 20.5% in the control group.

**Conclusions:** We assessed cyber abuse in a population exposed to sexual abuse. As several authors have previously emphasized, the implementation of preventative steps is essential. There is a great need to develop and evaluate interventions with those children and young people, particularly in sexually abused children and adolescents who are thought to be more vulnerable to cyber abuse.

**Keywords:** child, abuse, sexual, cyber

*Received: February 8, 2018; Accepted: June 5, 2018; Published Online: June 12, 2018*

Computer and internet use has become a necessary requirement in our daily lives with introduction of the new technologies. Facilitating communication and research was the original aim of the Internet [1]. Besides adults, child and adolescents are increasingly using texting and online social networking sites to connect with other children and adolescents, with 63%

reporting exchanging text messages daily, 29% reporting daily communication through social networking sites and 95% of youth ages 12-17 are online [2]. However, the dramatic increase in the use of internet in the recent years has led to abusive behaviors between peers or cyberbullying in children and adolescents [3, 4].



**Address for correspondence:** Merve Çıkılı Uytun, MD., Kayseri Training and Research Hospital, Department of Child and Adolescent Psychiatry, Kayseri, Turkey  
E-mail: merveuytun@gmail.com, Tel: +90 535 473 0013, Fax: +90 352 3512244

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

Cyber abuse is a broad term that includes online abusive behaviors including online bullying, stalking, sexual solicitation, and problematic exposure to pornography. Cyber abuse occurs perniciously via web-based and other forms of modern technology such as phone messages. Cyberbullying includes the use of e-mail, cell phones, and internet sites to threaten, harass, embarrass, exclude, or damage reputations and friendships [3, 5, 6]. Cyberstalking as an extension of physical stalking, involves use of the Internet to target victims and ranges from continuous unwanted contact to threats of violence and can escalate into attempts to control an individual's behavior [7]. Sexual solicitation involves requests to engage in sexual activities/talk or to provide personal sexual information, where the requests are uninvited and/or constitute an illegal relationship. Pornography can be identified as the production and circulation of sexual content through technology such as the Internet and cell phones. Problematic exposure to pornography includes either exposure to pictures of people who are naked or having sex, without having expected or looked for the pictures [8], or compulsively seeking pornography [9].

The term of child sexual abuse is defined as 'the use of a child or adolescent who has not yet completed sexual development by threatening or deceiving, using force to meet sexual desires and needs by an adult [10]. In a recent meta-analysis study, it was reported that the incidence of sexual abuse in girls was 8-31% and in males it was 3-17% [11]. Recent large scale cross-sectional studies on the prevalence of cyber abuse demonstrate that this is a growing problem, in which commonly recognized forms of child maltreatment (sexual and emotional abuse) are being pursued via the Internet [12-16]. Recent research has shown that cyber dating abuse and other forms of adolescent relationship abuse frequently overlap. Using a school based sample of adolescents, Zweig *et al.* [17] found that 26% of adolescents in dating relationships experienced cyber dating abuse and it was highly correlated with experiencing physical dating violence, psychological dating abuse, and sexual coercion. It is showed that cyber abuse and other types of abuse especially sexual abuse is related to each other, however very few reports have explored possible links between sexual abuse and cyber abuse

yet [18].

Understanding that cyber abuse may be a risk factor for sexual abuse and correlates of cyber abuse in this sample may guide prevention to reduce such abuse and possible sexual abuse and help improve children and adolescents health.

## METHODS

Our research team included three members – the authors. We assessed 75 children and adolescents aged 7-18 who had experienced sexual abuse and were referred to us between 01.01.2014-01.01.2015. Additionally, 45 typical developing subjects who did not have any abuse history were recruited from pediatrics clinic of or hospital as the control group. Inclusion criteria for both groups were: i) clinically no mental retardation; ii) children living in their own family house iii) no history of psychiatric diagnosis; vi) no neurological or other serious medical diseases. Written consent was obtained from parents and verbal assent was requested from children and adolescents to participate. After the study, the patients were followed up in our polyclinic.

We used our semi-structured questionnaire to assess cyber abuse. In our country, there is no questionnaire to assess all types of cyber abuse. Therefore, we constructed our questionnaire to assess cyber abuse in children and adolescents.

Our questionnaire includes three sections. The first section includes information about sociodemographic characteristics. The second section includes information about sexual abuse for only children and adolescents who were sexually abused. The third section includes information about cyber abuse. Table 1 shows the questionnaire on cyber abuse. The types of cyber abuse were explained by our research team. This study was approved by the Ethics Committee of Erciyes University. Written consent was obtained from parents and verbal assent was requested from children and adolescents to participate.

## Statistical Analysis

We used the Shapiro-Wilk test to analyze homogeneity of variables. Among-group differences on demographic variables were analyzed using the

**Table 1.** Third section of our questionnaire about cyber abuse

Do you use the internet?	0. No 1. Yes
Which tool do you use most frequently for accessing the internet?	1. Own mobile phone 2. Computer 3. Tablet 4. Other’s phone 5. Cafe etc.
Have you ever been abused via cyber media?	0. No 1. Yes
Which type of cyber abuse were you exposed to?	1. Cyberbullying 2. Cyberstalking 3. Cyber sexual solicitation 4. Pornography
Who were you abused by?	1. Real friend 2. Someone you know before 3. Stranger
How many times were you abused?	1. 1 2. 2-4 3. More than 5
Have you ever abused any person via cyber media?	0. No 1. Yes
Which type of cyber abuse do you perform?	1. Cyberbullying 2. Cyberstalking 3. Cyber sexual solicitation 4. Pornography
How were you affected after you were cyber abused? (After this event, is there any change in your thoughts, feelings or your daily life?)	1. No effect 2. Short-term effect (<1 month) 3. Long- term effect (>1 month) 4. Result in sexual abuse

Mann-Whitney U test and the Independent Sample-t test. Associations between categorical variables were examined using Chi-Square Fisher-Exact analysis. Data analysis was performed using SPSS 21.0 and *p* values < 0.05 were considered statistically significant.

**RESULTS**

The sexual abuse and control groups were matched in terms of gender ratio. As shown in Table 2, there were no significant differences in mean of age, substance use, mean age of fathers, tobacco use of fathers, alcohol/substance use of mothers and fathers, father’s psychiatric disorder and family situation. There were significant differences in tobacco use, mean age of mothers, the age of the mother when the child was born, any psychiatric disorder in the mother, mean year of mother’s education and tobacco use of mother.

**Demographics of sexually abused group**

The demographic characteristics of the sexually abused group can be found in Table 3.

**Variables and differences associated with abuse**

Table 4 shows the differences of variables associated with abuse that are statistically significant (*p* < 0.05). The variables include physical abuse, perpetrator of physical abuse, perpetrator of emotional abuse, use of internet, the most used web site/application, gender ratio of cyber abuse and perpetrator of cyber abuse and were found to be statistically significant between groups.

**DISCUSSION**

There is a growing body of research on cyber abuse of children and adolescents [3, 19, 20]. However, to the best of our knowledge, there is only

**Table 2.** Demographic characteristics of both groups

Sociodemographic variables		Sexually abused group (n = 75)	Control group (n = 45)	Statistical significance
<b>Age (years)</b>		13.16 ± 2.64	13.22±3.52	F = 1,85 p = 0.372
<b>Gender</b>	Female	65 (86.7%)	39 (86.7%)	X <sup>2</sup> = 0 p = 1
	Male	10 (13.3%)	6 (13.3%)	
<b>Tobacco use</b>	Yes	17 (22.7%)	1 (2.2%)	X <sup>2</sup> = 9.22 p = 0.002*
	No	58 (77.3%)	44 (97.8%)	
<b>Substance use</b>	Yes	5 (6.7%)	-	X <sup>2</sup> = 3.13 p = 0.156
	No	70 (93.3%)	45 (100%)	
<b>Mean age of mother (years)</b>		37.9 ± 6.12	40.11 ± 5.75	F = 2.06 p = 0.020*
<b>The age of mother when child born (years)</b>		24.75 ± 5.97	26.8 ± 5.38	F = 2.03 p = 0.028*
<b>Any psychiatric disorder in mother</b>	No	51 (69.9%)	40 (88.9)	X <sup>2</sup> = 5.72 p = 0.05*
	Maybe	5 (6.8%)	1 (2.2)	
	Yes	17 (23.3%)	4 (8.8)	
<b>Mean duration of mother's education (in years)</b>	0-1	8 (10.7%)	4 (8.9)	X <sup>2</sup> = 12.23 p = 0.016*
	2-5	48 (64.0%)	19 (42.2)	
	6-8	6 (8%)	11 (24.4)	
	9-11	10 (13.3%)	4 (8.9)	
	more than 11	3 (4%)	7 (15.6)	
<b>Tobacco use of mother</b>	Yes	32 (42.7%)	11 (24.4%)	X <sup>2</sup> = 4.52 p = 0.048*
	No	42 (56%)	34 (75.6%)	
<b>Alcohol/substance use of mother</b>	Yes	2 (2.7%)	-	X <sup>2</sup> = 1.25 p = 0.52
	No	73(97.3%)	45 (100%)	
<b>Mean age of father</b>		43.04 ± 9.57	43.97 ± 6.15	F = 1.93 p = 0.139
<b>Mean duration of father's education (in years)</b>	0-1	3 (4.1%)	-	X <sup>2</sup> = 2.06 p = 0.72
	2-5	26 (39.2%)	15 (33.3%)	
	6-8	16 (21.6%)	9 (20%)	
	8-11	21 (28.4%)	12 (26.7%)	
	more than 11	8 (10.9%)	9 (20%)	
<b>Any psychiatric disorder of father</b>	Yes	63 (85.1%)	42 (93.3%)	X <sup>2</sup> = 3.01 p = 0.22
	No	8 (10.8%)	1 (2.2%)	
	Maybe	3 (4.1%)	2 (4.4%)	
<b>Tobacco use of father</b>	Yes	52 (69.3%)	29 (64.4%)	X <sup>2</sup> = 0.374 p = 0.55
	No	23 (30.6%)	16 (35.6%)	
<b>Alcohol/substance use of father</b>	Yes	6 (8%)	2 (4.4%)	X <sup>2</sup> = 0.62 p = 0.70
	No	69 (92%)	43 (95.6%)	
<b>Family situation</b>	Both parents	56 (74.6%)	39 (86.7%)	X <sup>2</sup> = 10.3 p = 0.32
	Divorced- living with mother	9 (12%)	2 (4.4%)	
	Divorced-livinig with father	5 (6.6%)	-	
	Mother dead- living with father	1 (1.3%)	-	
	Father dead- living with mother	2 (2.7%)	4 (8.9%)	
	Adopted	1 (1.3%)	-	
	Living with grandparents	1 (1.3%)	-	

Data are shown as mean±standard deviation or number (%).

**Table 3.** Demographic characteristics of sexual abused group

Sociodemographic variables		Data (n = 75)
<b>Mean age of abused (years)</b>		12.42 ± 2.78
<b>Gender</b>	Female	86.7%
	Male	13.3%
<b>Abuser</b>	Boy friend	26 (34.6%)
	Someone you know before	16 (21.3%)
	A friend	11 (14.7%)
	Stranger	9 (12%)
	Father	5 (6.7%)
	Relative	5 (6.7%)
	Teacher/School manager	3 (4%)
<b>Mean age of abuser (years)</b>		27.5 ± 12.7
<b>Type of abuse</b>	Nonpenetran	40 (%53.3)
	Anal penetration	13 (%17.3)
	Vaginal penetration	19 (%25.3)
	Oral penetration	3 (%4)
<b>Repeated abuse</b>	No	44 (58.7%)
	1-3	13 (17.3%)
	4-6	10 (13.3%)
	7 and more	8 (10.7%)
<b>More than one abuser</b>	No	71 (94.7%)
	Yes	4 (5.3%)
<b>Marital status of abuser</b>	Single	34 (45.3%)
	Married	18 (24%)
	Divorced	5 (6.7%)
	Unknown	18 (24%)
<b>Way of meet with abuser person</b>	No	9 (12%)
	Relative	12 (16%)
	School	10 (13.3%)
	Family friend	4 (5.3%)
	Neighborhood	23 (30.7%)
	Via Friends	11 (14.7%)
	Via internet	6 (8%)

Data are shown as mean ± standard deviation or number (%).

one study investigating the relationship between sexual abuse and cyber abuse in the literature [18]. The aim of the present study was to detect cyber abuse prevalence in sexual abuse cases, to identify whether internet use is a risk factor for sexual abuse in children by retrospectively reviewing internet use and cyber abuse in victims of sexual abuse and to determine the differences in internet use between healthy populations and children exposed to sexual abuse.

When sociodemographic differences were assessed between the sexual abuse group and controls, smoking rate was found to be significantly higher in

the sexual abuse group than in controls. In previous studies, it was shown that smoking rate was increased by childhood physical and sexual abuse [21]. In our study, no definitive conclusion could be made on smoking status since we did not ask whether smoking behavior began before or after sexual abuse.

Another important difference in sociodemographic findings was younger maternal age and lower age when child born in the sexual abuse group. In a longitudinal study by Brown *et al.* [22], a positive association was found between maternal youth and occurrence of sexual abuse. In another

**Table 4.** Variables and differences associated with abuse

Variables associated with abuse		Sexually abused group	Control group	Statistical significance
<b>Physical abuse</b>	Yes	19 (25.3%)	5 (11.1%)	$X^2 = 3.687$ $p < 0.05^*$
	No	56 (74.7%)	40 (88.9%)	
<b>Perpetrator of physical abuse</b>	Mother	6 (31.6%)	1 (20%)	$X^2 = 8.40$ $p = 0.03^*$
	Father	12 (63.2%)	2 (40%)	
	Mother and Father	1 (5.3%)	-	
	Brothers	-	2 (40%)	
<b>Victim of physical abuse</b>	Only child	12 (63.2%)	3 (60%)	$X^2 = 0.35$ $p = 0.83$
	Only mother	1 (5.3%)	-	
	Child and mother	6 (31.6%)	2 (40%)	
<b>Neglect</b>	Yes	3 (4.1%)	-	$X^2 = 1.87$ $p = 0.17$
	No	72 (95.9%)	45 (100%)	
<b>Emotional abuse</b>	No	62 (82.4%)	41 (91.1%)	$X^2 = 1.72$ $p = 0.19$
	Yes	13 (17.6%)	4 (8.9%)	
<b>Perpetrator of emotional abuse</b>	Father	4 (30.8%)	2 (50%)	$X^2 = 5.88$ $p < 0.05^*$
	Mother	8 (61.5%)	-	
	Brother/sister	1 (7.7%)	2 (50%)	
<b>Use of internet</b>	Yes	62 (82.7%)	44 (97.8%)	$X^2 = 6.23$ $p = 0.01^*$
	No	13 (17.3%)	1 (2.2%)	
<b>The most used tool for internet</b>	Own mobile phone	29 (46.8%)	21 (47.7%)	$X^2 = 6.53$ $p = 0.16$
	Computer	21 (33.9%)	10 (22.7%)	
	Tablet	1 (1.6%)	3 (6.8%)	
	Other's phone	8 (12.9%)	10 (22.7%)	
	Cafe etc.	3 (4.8%)	-	
<b>The most used web site/application</b>	Facebook	43 (69.4%)	9 (20.5%)	$X^2 = 39.65$ $p < 0.001^*$
	Instagram	1 (1.6%)	7 (15.9%)	
	Twitter	-	1 (2.3%)	
	Whatsapp/tango	-	9 (20.5%)	
	You tube	7 (11.3%)	4 (9.1%)	
	Game web sites	10 (16.1%)	8 (18.2%)	
	Surfing on the internet	1 (1.6%)	6 (13.6%)	
<b>Cyber abuse</b>	Yes	26 (35.1%)	14 (31.1%)	$X^2 = 0.16$ $p = 0.68$
	No	49 (64.9%)	31 (68.9%)	
<b>Gender ratio of cyber abuse (female/male)</b>	Yes	24/2	14/-	$X^2 = 3.60$ $p < 0.05^*$
	No	41/8	25/6	
<b>Type of cyber abuse</b>	Cyberbullying	6 (23.1%)	5 (35.7%)	$X^2 = 0.62$ $p = 0.1$
	Cyberstalking	11 (42.3%)	9 (64.3%)	
	Cyber sexual solicitation	5 (19.2%)	-	
	Pornography	4 (15.4%)	-	
	More than one type	-	-	
<b>Perpetrator of cyber abuse</b>	Real friend	2 (8%)	5 (35.7%)	$X^2 = 6.25$ $p = 0.044^*$
	Someone you know	4 (16%)	-	
	Stranger	20 (76%)	9 (64.3%)	
<b>The number of cyber abuse</b>	1	4 (15.4%)	1 (7.1%)	$X^2 = 2.70$ $p = 0.25$
	2-4	14 (53.8%)	4 (28.5%)	
	More than 5	8 (30.8%)	9 (74.4%)	
<b>The effect of cyber abuse</b>	No effect	13 (50%)	9 (64.3%)	$X^2 = 3.80$ $p = 0.14$
	Short-term effect	7 (26.9%)	5 (35.7%)	
	Long-term effect	-	-	
	Result in sexual abuse	6 (23.1%)	-	

Data are shown as number (%).

study, Mian *et al.* [23] found that the mothers of victims were younger than the mothers of nonvictims. In the literature, maternal age is defined as a risk factor for sexual abuse and our findings are in agreement with the literature.

In our study, we also found that maternal educational level was lower and maternal smoking rate was higher in the sexual abuse group when compared to controls. In many studies, it was found that maternal education was negatively correlated with the occurrence of child sexual abuse [24-26]. It is showed that in a study, the children of women who smoked during pregnancy were exposed to higher levels of social disadvantage, parental deviance, and family dysfunction throughout childhood compared with the children of women who did not smoke during pregnancy. Mothers who smoked during pregnancy were younger, less well educated, and of a lower socioeconomic status compared with nonsmoking mothers [27]. These factors related to mother's smoking is known that associated with child abuse and thus, it was thought that smoking of the mother could indirectly affect the sexual abuse of the child through these factors.

The prevalence of psychiatric disorders of mothers were found higher in the sexually abused group than control group. It is shown that maternal mental health problems increased the risk for child sexual abuse in some studies [28, 29]. Our result was consistent with these studies.

In our study, no significant difference was found in terms of emotional abuse between groups; however, it is striking that offenders in terms of emotional abuse were more commonly the mother in the sexual abuse group, reaching statistical significance when compared to the controls. In many of the studies that examined a hypothesized relationship between sexual abuse status and maternal sensitivity, or closeness with the mother, most had significant findings. In the majority of these studies, it was found that mothers who have closer, more positive relationships with their children are less likely to have children who are sexually abused [28, 30-32]. Studies conducted in adolescents victims of sexual abuse showed that support from the nonoffending parent (the mother in the majority of cases is strong), has been identified as playing a crucial role in influencing outcomes in survivors as well as their capacity to cope with later

adverse life events or potentially abusive situations [33]. It seems that maternal support is a protective factor that serves as a barrier for negative outcomes and decreases the risk for repeated victimization of these vulnerable youth.

When internet use was compared between groups, it were higher in the control group (97.8%) compared to those of the sexually abused group teens (82.7%). However, no significant difference were found in the rate of exposure to cyber abuse. The lack of significant difference in cyber abuse while the rate of internet use was lower indicates that rates of exposure to cyber abuse/internet use were higher in the sexual abuse group. In the recent study of Hebert *et al.* [18], they found that twice as many sexually abused girls experienced cyberbullying (33.47%) compared to nonsexually abused girls (17.75%) and a similar ratio was observed for boys (29.62 vs. 13.29%). The results of that study and our study show that cyber abuse is a major concern that affects a significant proportion of teenagers, in particular those who are more vulnerable, namely victims of child sexual abuse. These results can be explained by the fact that sexually abused adolescents are more likely to experience subsequent sexual, psychological, and physical victimization, whether it be in the context of romantic relationships or other types of interpersonal relationships [34, 35]. Previous studies have shown that the period following sexual abuse may translate into a sense of betrayal, shame, stigmatization, associated with a significant impact on interpersonal functioning which in turn may lead to increased vulnerability to revictimization [36, 37].

When the frequency of exposure to cyber abuse was assessed, 2-4 times was most common in both groups. In the national youth internet safety study of Ybarra *et al.* [38], the authors found that thirty-two percent of internet using young people aged 10-17 reported chronic harassment (such as  $\geq 3$  times during the prior year). The higher rates found in our study were interpreted as showing that the rate has increased in recent years [38].

One of the most striking findings was the difference in web pages/applications used by groups. Facebook was the most commonly used web page/application in 70% of subjects in the sexual abuse group while there was balanced distribution in the use of web pages/applications in the control group.



Facebook is a social network that has increased its number of users in recent years. This social network provides attractive communication and interaction opportunities to the user. Millions of people including teenagers and elders intentionally use Facebook to find friends, a romantic relationship or work and for communication. However, Facebook encourages but does not force its users to share personal information such as birthday, mobile phone number or place of residence. Sharing personal information on Facebook paves the way for cyber abuse by violation of private life via stealing personal data, documents, pictures and videos [39]. Likewise, using the Internet for social media, instant messaging, blogging, and chat room use increases the odds of being a target of Internet harassment versus those who do not engage in these online activities [38, 40]. In particular, excessive personal information available on social networks such as Facebook and Twitter can lead the more cyber abuse [40].

In our study, it was seen that the offenders were mostly an unfamiliar person in the sexual abuse group. It is known that adolescents were found to easily develop both friendships and romantic relationships online, relationships that were highly valued and considered as important as in real life relationships [41]. Also in adolescents, the use of emails and messages was reported by 50.7% in a romantic relationship [42]. It is thought that more common use of Facebook where personal information can be accessed by friends as well as unfamiliar persons led to cyber abuse by unfamiliar offenders [39]. In summary, electronic communication technology could create new opportunities for abuse and new victims and/or perpetrators of sexual abuse through cyber abuse [43].

It was seen in both groups that children and adolescents do not feel high levels of distress due to cyber abuse. In the national youth internet safety study of Ybarra *et al* they found that 38% of the harassed youth reported distress as a result of the incident [38]. In our study, this rate was 35.7% in the control group and 26.9% in the sexual abuse group. Ybarra *et al*. [38], also examined the factors related to emotional distress and they showed that children and adolescents who were targeted by adults, asked to send a picture of themselves, received an aggressive offline contact

(eg, the harasser telephoned or came to the young person's home), and were preadolescents were each significantly more likely to report distress because of the experience. Conversely, those who visited chat rooms were significantly less likely to be distressed by harassment [38].

It was found that cyber abuse resulted in sexual abuse in 6 subjects (23.1%) in the sexual abuse group. To the best of our knowledge, there is no study reporting such a rate in the literature but as a similar in community sample, Zweig *et al*. [17] found that, 11% of adolescents between 12-18 years, reported experience of sexual cyber dating violence. However, it is thought that the prevention of cyber abuse will be effective in preventing sexual abuse.

Our study has some limitations including its small sample size due to its being a single center study, lack of a validated and reliable scale.

## CONCLUSION

In conclusion, we assessed cyber abuse in a population exposed to sexual abuse. As several authors have previously emphasized, the implementation of preventative steps is essential. There is a great need to develop and evaluate interventions with those children and young people, particularly in sexually abused children and adolescents who are thought to be more vulnerable to cyber abuse. Additionally, the importance of educating parents, caregivers and teachers about the potential risks associated with online activities must be emphasized. Parents need to become more knowledgeable about the risks presented by the Internet. Parents and other significant adults in children's lives also require effective strategies to engage with their children regarding online activity. Although little clinical knowledge appears to exist in this area, the growing nature of this phenomenon demands greater attention. Further research is also necessary to explore the impact of cyber abuse on sexual abuse and prevention strategies.

### Authors contribution

MCU, SO and ED assessed the patients. MCU wrote the article, SO and ED review the article. All authors read and approved the final manuscript.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

### Acknowledgement

We would like to Gökmen Sakar for providing help with language.

This research was presented at the 25<sup>th</sup> National Congress on Child and Adolescent Psychiatry, April 1-4, 2015, Istanbul, Turkey

## REFERENCES

- [1] Kuss DJ, Griffiths MD. Internet and gaming addiction: a systematic literature review of neuroimaging studies. *Brain Sci* 2012;2:347-74.
- [2] Lenhart A, Madden M, Smith A, Purcell K, Zickurh K, Rainie L. Teens, kindness and cruelty on social network sites. Washington, DC: Pew Research Center's Internet and American Life Project 2011.
- [3] Patchin JW, Hinduja S. Bullies move beyond the schoolyard a preliminary look at cyberbullying. *Youth Violence Juv Justice* 2006;4:148-69.
- [4] Juvonen J, Gross EF. Extending the school grounds?--Bullying experiences in cyberspace. *J Sch Health* 2008;78:496-505.
- [5] Hinduja S, Patchin J. Cyberbullying: an exploratory analysis of factors related to off ending and victimization. *Deviant Behav* 2008;29:129-56.
- [6] Williams KR, Guerra NG. Prevalence and predictors of Internet bullying. *J Adolesc Health* 2007;41:14-21.
- [7] Philips F, Morrissey G. Cyberstalking and cyberpredators: a threat to safe sexuality on the Internet. *Convergence* 2004;10: 66-79.
- [8] Mitchell KJ, Wolak J, Finkelhor D. Trends in youth reports of sexual solicitations, harassment and unwanted exposure to pornography on the Internet. *J Adolesc Health* 2007;40:116-26.
- [9] Quayle E, Taylor M. Young people who sexually abuse: The role of the new technologies. In: Erooga M, Masson H, eds. Children and young people who sexually abuse others: Current developments and practice responses, 2nd ed. New York: Routledge, 2006.
- [10] Işeri E. Cinsel istismar. In: Çetin FC, Pehlivanlı B, Uhal F, eds. Çocuk ve Ergen Psikiyatrisi Temel Kitabı, 1.Baskı. Ankara: Hekimler Yayın Birliği. 2008;470-477.
- [11] Barth J, Bermetz L, Heim E, Trelle S, Tonia T. The current prevalence of child sexual abuse worldwide: a systematic review and meta-analysis. *Int J Public Health* 2013;58:469-83.
- [12] Berson IR, Berson MJ, Ferron JM. Emerging risks of violence in the digital age: lessons for educators from an online study of adolescent girls in the United States. *Meridian* 2002;5:1-32.
- [13] Mitchell KJ, Finkelhor D, Wolak J. Risk factors for and impact of online sexual solicitation of youth. *JAMA* 2001;285:3011-4.
- [14] Mitchell KJ, Finkelhor D, Wolak J. The exposure of youth to unwanted sexual material on the Internet: a national survey of risk, impact, and prevention. *Youth Soc* 2003;34:330-358.
- [15] Ybarra ML, Mitchell KJ. Youth engaging in online harassment: associations with caregiver-child relationships, internet use, and personal characteristics. *J Adolesc* 2004;27:319-36.
- [16] Ybarra ML, Mitchell KJ. Online aggressor/targets, aggressors, and targets: a comparison of associated youth characteristics. *J Child Psychol Psychiatry* 2004;45:1308-16.
- [17] Zweig JM, Dank M, Yahner J, Lachman P. The rate of cyber dating abuse among teens and how it relates to other forms of teen dating violence. *J Youth Adolesc* 2013;42:1063-77.
- [18] Hébert M, Cénat JM, Blais M, Lavoie F, Guerrier M. Child sexual abuse, bullying, cyberbullying, and mental health problems among high schools students: a moderated mediated model. *Depress Anxiety* 2016;33:623-9.
- [19] Beran T, Li Q. Cyber-harassment: a study of a new method for an old behavior. *J Educ Comput Res* 2005;32:265-77.
- [20] Shariff S. Cyber-dilemmas in the new millennium: balancing free expression and student safety in cyberspace. *McGill J Educ* 2005;40:467-87.
- [21] Kristman-Valente AN, Brown EC, Herrenkohl TI. Child physical and sexual abuse and cigarette smoking in adolescence and adulthood. *J Adolesc Health* 2013;53:533-8.
- [22] Brown J, Cohen P, Johnson JG, Salzinger S. A longitudinal analysis of risk factors for child maltreatment: findings of a 17-year prospective study of officially recorded and self-reported child abuse and neglect. *Child Abuse Negl* 1998;22:1065-78.
- [23] Mian M, Marton P, LeBaron D, Birtwistle D. Familial risk factors associated with intrafamilial and extrafamilial sexual abuse of three to five year old girls. *Can J Psychiatry* 1994;39:348-53.
- [24] Fergusson DM, Lynskey MT, Horwood LJ. Childhood sexual abuse and psychiatric disorder in young adulthood: I. Prevalence of sexual abuse and factors associated with sexual abuse. *J Am Acad Child Adolesc Psychiatry* 1996;35:1355-64.
- [25] Lewin L, Bergin C. Attachment behaviors, depression, and anxiety in nonoffending mothers of child sexual abuse victims. *Child Maltreat* 2001;6:365-75.
- [26] Leifer M, Kilbane T, Jacobsen T, Grossman G. A three generational study of transmission of risk for sexual abuse. *J Clin Child Adolesc Psychiatry* 2004;33:662-72.
- [27] Fergusson DM, Woodward LJ, Horwood LJ. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. *Arch Gen Psychiatry* 1998;55:721-7.
- [28] Mullen PE, Martin JL, Anderson JC, Romans SE, Herbison GP. Childhood sexual abuse and mental health in adult life. *Br J Psychiatry* 1996;163:721-32.
- [29] Fleming J, Mullen P, Bammer G. A study of potential risk factors for sexual abuse in childhood. *Child Abuse Negl* 1997;21:49-58.
- [30] Nelson EC, Heath AC, Madden PA, Cooper ML, Dinwiddie SH, Bucholz KK et al. Association between self-reported childhood sexual abuse and adverse psychosocial outcomes: results from a twin study. *Arch Gen Psychiatry* 2002;59:139-45.
- [31] Mullen PE, Martin JL, Anderson JC, Romans SE, Herbison GP. The long-term impact of the physical, emotional, and sexual abuse of children: a community study. *Child Abuse Negl* 1996;20:7-21.
- [32] Sypeck MF. Attachment style and child sexual abuse: A longitudinal examination. Unpublished doctoral dissertation, The American University, Washington, DC., 2004.
- [33] Zajac K, Ralston ME, Smith DW. Maternal support following childhood sexual abuse: associations with children's adjustment post-disclosure and at 9-month follow-up. *Child Abuse Negl* 2015;44:66-75.
- [34] Messman-Moore TL, Long PJ. The role of childhood sexual abuse sequelae in the sexual revictimization of women: an empirical review and theoretical reformulation. *Clin Psychol Rev* 2003;23:537-71.
- [35] Classen CC, Palesh OG, Aggarwal R. Sexual revictimization a review of the empirical literature. *Trauma Violence Abuse* 2005;6:103-29.
- [36] Davis JL, Petretic-Jackson PA. The impact of child sexual abuse on

adult interpersonal functioning: a review and synthesis of the empirical literature. *Aggress Violent Behav* 2000;5:291-328.

[37] Walsh K, Galea S, Koenen K. Mechanisms underlying sexual violence exposure and psychosocial sequelae: a theoretical and empirical review. *Clin Psychol (New York)* 2012;19:260-75.

[38] Ybarra ML, Mitchell KJ, Wolak J, Finkelhor D. Examining characteristics and associated distress related to Internet harassment: findings from the Second Youth Internet Safety Survey. *Pediatrics* 2006;118:1169-77.

[39] Durmuş B, Kılıç B, Yurtkoru ES, Ulusu Y. Facebooktayız: Sosyal Paylaşım Ağlarının Bireylere ve İşletmelere Yönelik İncelenmesi: Facebook Üzerine Bir Çalışma. Beta Press. İstanbul, Turkey, 2010.

[40] Gotfried K. Citizens in 24 Countries Assess Bullying via

Information Technology For a Total Global Perspective. [www.ipsos.com](http://www.ipsos.com). 2011. Accessed 25.12.2016.

[41] Mishna F, Saini M, Solomon S. Ongoing and online: children and youth's perceptions of cyber bullying. *Child Youth Serv Rev* 2009;31:1222-8.

[42] Carlson W, Rose AJ. Brief report: activities in heterosexual romantic relationships: Grade differences and associations with relationship satisfaction. *J Adolesc* 2012;35:219-24.

[43] Stonard KE, Bowen E, Lawrence TR, Price SA. The relevance of technology to the nature, prevalence and impact of Adolescent Dating Violence and Abuse: A research synthesis. *Aggress Violent Behavior* 2014;19:390-417.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Effectiveness of kinesiotaping on diaphragm thickness, diaphragmatic thickening fraction, and intercostal muscle thickness in patients undergoing mechanical ventilation: a pilot study

Burcu Metin Ökmen<sup>1</sup>, Korgün Ökmen<sup>2</sup>

<sup>1</sup>Department of Physical Medicine and Rehabilitation, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

<sup>2</sup>Department of Anesthesiology and Reanimation, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

DOI: 10.18621/eurj.373465

## ABSTRACT

**Objective:** We aimed to evaluate the effects of kinesiotaping applied on the chest wall on the diaphragmatic muscle and intercostal muscles in patients receiving mechanical ventilation.

**Methods:** In this prospective, randomized, controlled, double-blind study, 24 patients who underwent mechanical ventilation in the intensive care unit were included the study. Randomization was used to identify the side of patients that the kinesiotaping was applied to. Group 1: side that kinesiotaping was applied (n = 24) and Group 2 (control group): side that kinesiotaping was not applied (n = 24). Kinesiotaping was changed in every 3 day. Thicknesses of diaphragmatic muscle, seventh intercostal muscle and ninth intercostal muscle were evaluated by using ultrasound in pretreatment, third day, sixth day and ninth day.

**Results:** In both groups; a statistically significant decrease was found in all the evaluation parameters at all the measurement times when compared to the pretreatment values ( $p < 0.05$ ). On the third day and sixth day; a statistically significant difference was found in favor of group 1 in all the evaluation parameters except thickness of seventh intercostal muscle ( $p < 0.05$ ). On the ninth day; there was no statistically significant difference between the two groups ( $p > 0.05$ ).

**Conclusion:** In conclusion, our study results showed that kinesiotaping decelerated the decrease in the diaphragmatic muscle and the intercostal muscles thickness until sixth day.

**Keywords:** Kinesiotaping, diaphragmatic muscle thickness, intercostal muscles thickness, pulmonary rehabilitation, mechanical ventilation

*Received: January 1, 2018; Accepted: February 15, 2018; Published Online: April 5, 2018*

About 40% of patients in the intensive care unit (ICU) require mechanical ventilatory support [1]. Ventilator-induced diaphragmatic dysfunction (VIDD) is defined as the loss of diaphragmatic force-

generating capacity associated with the use of mechanical ventilation [1-3]. Immobility of the diaphragm for protection during controlled mechanical ventilation is thought to play a role in the



**Address for correspondence:** Burcu Metin Ökmen, MD., University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Mimar Sinan Mah., Emniyet Street, Yıldırım, Bursa, Turkey  
E-mail: burcumetinokmen@gmail.com, Tel: +90 224 295 50 00, Fax: +90 224 295 54 97

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

development of VIDD [4]. In addition, imbalance in protein production and degradation as well as reactive oxygen species (ROS) as a result of mitochondrial dysfunction have been also shown to be involved in the pathogenesis of diaphragmatic dysfunction [5].

Approximately 20 to 25% of patients on mechanical ventilation experience difficulty in weaning from mechanical ventilation and VIDD is one of the most common reasons [1-3]. It has been accepted as the most specific “side effect” of prolonged mechanical ventilation [4]. Although the condition has been termed as VIDD, intercostal muscles along with major respiratory muscles (diaphragm) are thought to be involved to a certain extent [4-7]. Esophageal and gastric balloons, phrenic nerve stimulation, diaphragmatic biopsy, and ultrasonography are commonly used in the diagnosis of diaphragmatic atrophy [1, 8-10]. Ultrasound-guided detection of diaphragmatic atrophy allows measurement of diaphragmatic thickening and evaluation of the diaphragmatic function [11]. Intercostal muscle exercises, various mechanical ventilator settings, phrenic nerve stimulation, and drugs are used to prevent development of VIDD [12].

Kinesiotaping, which was first developed by Kenso Kase, is used in the treatment of musculoskeletal system disorders, sports injuries, and neurological and pediatric diseases. The kinesiotape is a thin, latex-free, elastic adhesive and it stretches up to the 40-60% of its original length; its structure resembles elastic features of the human skin [13, 14]. Skin is elevated with kinesiotaping and this increases subcutaneous interstitial area and therefore increases circulation and mobility. Increased circulation and mobility in turn decreases inflammation in the treated area. This treatment therefore aims at reducing pain, increasing performance, re-educating neuromuscular system, preventing injury, and accelerating circulation and tissue healing [13-17]. The treatment by applying a constant pulling force improves blood and lymph circulation by producing proprioceptive stimulation in the nerve endings [13, 14, 18]. In addition, there are also studies suggesting that the method sends signals to the central nervous system by stimulating mechanoreceptors and increases proprioception through a positional stimulation in the applied area [19-21]. There are also some side effects of the kinesiotaping. Skin that is applied depending on the

use of kinesiology band reactions can be seen. These are allergic reactions or may be in the form of local irritation [14].

Kinesiotaping has been employed for the purpose of increasing the respiratory capacity [22]. Additionally there are several studies which suggested muscle strengthening by kinesiotaping [23, 24]. However, we could not find any report evaluated the effect of kinesiotaping on the respiratory muscle thickness in the literature. In the present study, we aimed to evaluate the effects of kinesiotaping applied on the chest wall on the diaphragmatic muscle and intercostal muscles in patients receiving mechanical ventilation.

## METHODS

In this prospective, randomized, controlled, double-blind study, a total of 40 patients who were requiring mechanical ventilation were evaluated for eligibility after local ethics committee approval (The decision number is 2011-KAEK-25 2016/20-01). The study was conducted in accordance with the principles of Declaration of Helsinki.

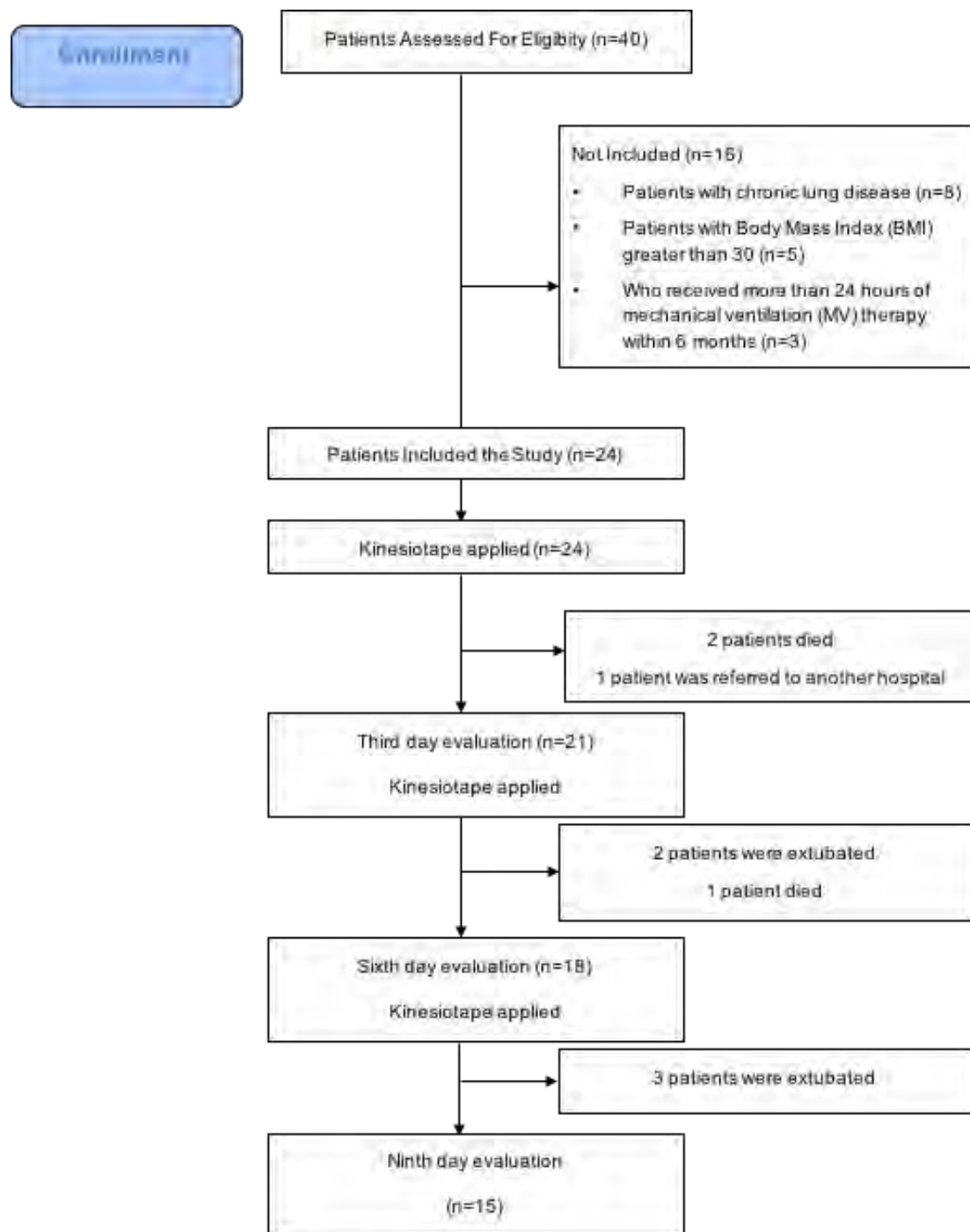
### Patient selection

Patients who were given mechanical ventilation in the intensive care unit between the ages of 20-70 and were approved by their relatives were included in the study. Patients with chronic lung disease, a body mass index (BMI) greater than 30, neuromuscular disease, and who received more than 24 hours of mechanical ventilation therapy within 6 months were excluded from the study. Patients who connected mechanical ventilation for less than 72 hours during testing were dropped out from the study.

Sixteen patients were excluded from the study and the reasons were given in the Figure 1. Twenty four patients who were eligible for the study were included to the study. Forms detailing the patients' demographic characteristics and pre-treatment (D0) measurements were completed.

### Randomization

A computer-generated random number table was used to randomize which side of patients the kinesiotaping was to be applied to. Group 1:



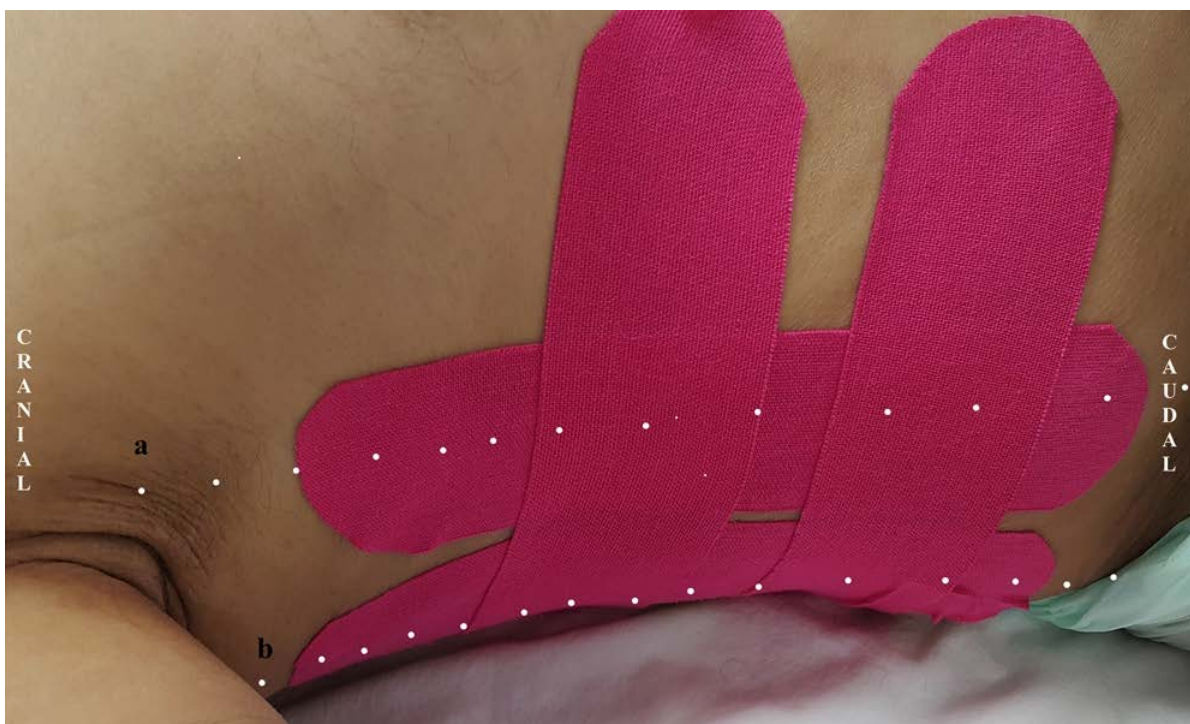
**Figure 1.** Flow chart of the study.

kinesiotaping applied side (n=24) and Group 2 (control group): kinesiotaping not applied side (n=24) (Figure 1).

### Interventions

Kinesio Tex Gold (Kinesio Tex Gold, Kinesio®; Albuquerque, New Mexico) was used for

kinesiotaping application. Kinesiotaping was applied unilaterally. The other side of the chest wall was used as the control group. Kinesiotaping was changed in every 3 day by a certificated physiatrist who has previously attended the kinesiotaping training course. It was applied by the same physiatrist. When the patients were at the end of the expiration, it was



**Figure 2.** Kinesiotape application; anterior axillary line (a), posterior axillary line (b).

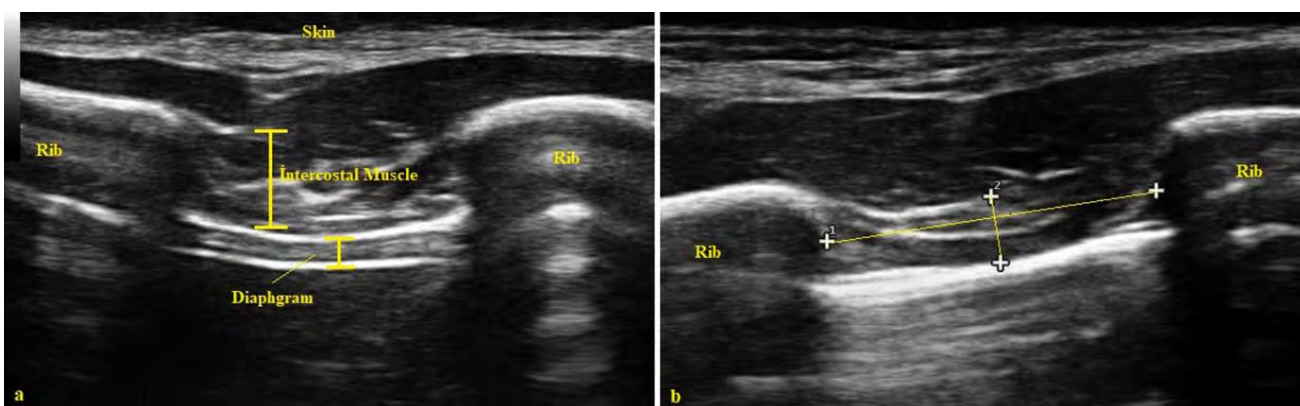
applied on the 5<sup>th</sup>-6<sup>th</sup> and 9<sup>th</sup> -10<sup>th</sup> intercostals muscles transversally and on the anterior and posterior axillary line longitudinally with %50 tension (Figure 2). The fascilitation technique was used.

**Ultrasound measurements**

Diaphragmatic muscle and intercostal muscles were evaluated using 7-12 MHz linear ultrasonography (GE LOGIQ P6 Pro Wauwatosa, U.S.A.) transducer in B-mode. While the patients were

lying at a 20<sup>o</sup> head-up position, US probe was placed on the anterior axillary line in the 7-8 or 9-10 intercostal space in sagittal position to visualize intercostal muscles and the diaphragm [11, 25, 26]. The measurements were obtained from the midline of the pleural line to the midline of the peritoneum to obtain the most accurate measurements of diaphragmatic muscle thickness (DMT) [11, 25, 26] (Figure 3).

The percent change in diaphragm thickness (Tdi)



**Figure 3.** Ultrasonic images of diaphragm and intercostal muscles. The diaphragm muscle measurements were obtained from the midline of the pleural line to the midline of the peritoneum (a), the midpoint of the intercostal muscles between the two ribs was labeled and intercostal muscles thickness were measured at this point (b).

between end\_expiration and end\_inspiration ( $\Delta Tdi\%$ ) was calculated as  $(Tdi_{end\_inspiration} - Tdi_{end\_expiration} / Tdi_{end\_expiration}) \times 100$ . The  $\Delta Tdi\%$  for each patient represented the mean of three breaths [27]. Before the measurement, kinesiotope was removed and the physician that performed measurements was kept blind to the treatment. The same researcher, who was blind to the side of kinesiotope application, completed third day (D3), sixth day (D6) and ninth day (D9) evaluations and recorded the data.

### Statistical Analysis

Analysis of the collected data was performed using IBM SPSS 22.0 statistical package program. The Pearson chi square ( $\chi^2$ ) or Yates  $\chi^2$  tests were used in the comparison of the categorical variables. Normal distribution of the data was tested using Shapiro-Wilk test. When it was distributed normally, independent samples t test was used for between-groups comparisons and paired sample t test for intra-group comparisons. Values with a probability of ( $p$ )  $\alpha < 0.05$  was accepted as significant.

**Table 1.** Demographic data of patients (n = 21)

Characteristics	Data
Age (year)	42.95±6.63
Gender	
Male	17 (81%)
Female	4 (19%)
BMI (kg/m <sup>2</sup> )	24.11± 2.21

Data are shown as mean ± standard deviation or number (%). BMI = Body Mass Index

### RESULTS

A total of three patients were excluded from the study because two patients died and one patient was referred to an another hospital in the first three days. A total of 21 patients were evaluated at the end of the third day (D3). Eighteen patients were evaluated at the end of the sixth day (D6) because two patients were extubated and one patient died between D3-D6. Fifteen patients were evaluated at the end of the ninth day (D9) because three patients were extubated between the D6-D9. No patient was left out of the study due to any side effect of the treatment (Figure

**Table 2.** Comparison of the D0, D3, D6 and D9 values within the groups and between the groups

	D0 (n = 21)	D3 (n = 21)	(D3-D0) <i>p</i>	D6 (n = 18)	(D6-D0) <i>p</i>	D9 (n = 15)	(D9-D0) <i>p</i>
<b>Diaphragm</b>							
Group 1	26.52 ± 3.83	24.81 ± 3.67	< <b>0.001</b>	23.11 ± 3.63	< <b>0.001</b>	19.93 ± 3.51	< <b>0.001</b>
Group 2	25.71 ± 4.39	22.14 ± 4.13	< <b>0.001</b>	20.33 ± 4.10	< <b>0.001</b>	17.53 ± 3.56	< <b>0.001</b>
<i>p</i>	0.528	<b>0.033</b>		<b>0.039</b>		0.074	
<b>Tdi</b>							
Group 1	43.52 ± 3.46	41.95 ± 3.38	< <b>0.001</b>	39.88 ± 3.55	< <b>0.001</b>	38.2 ± 3.03	< <b>0.001</b>
Group 2	43.62 ± 3.04	39.62 ± 3.11	< <b>0.001</b>	37.61 ± 2.89	< <b>0.001</b>	37.33 ± 2.85	< <b>0.001</b>
<i>p</i>	0.925	<b>0.025</b>		<b>0.042</b>		0.426	
<b>IMT9</b>							
Group 1	43.38 ± 4.51	42.14 ± 4.48	< <b>0.001</b>	40.55 ± 4.90	< <b>0.001</b>	37.07 ± 3.75	< <b>0.001</b>
Group 2	43.71 ± 4.86	39.14 ± 4.42	< <b>0.001</b>	37.11 ± 4.91	< <b>0.001</b>	35.60 ± 4.48	< <b>0.001</b>
<i>p</i>	0.819	<b>0.035</b>		<b>0.043</b>		0.340	
<b>IMT7</b>							
Group 1	40.71 ± 2.94	39.52 ± 2.58	< <b>0.001</b>	37.67 ± 2.72	< <b>0.001</b>	36.20 ± 4.07	<b>0.006</b>
Group 2	40.57 ± 2.93	38.43 ± 2.87	< <b>0.001</b>	35.83 ± 2.87	<b>0.001</b>	34.00 ± 2.59	< <b>0.001</b>
<i>p</i>	0.876	0.201		0.058		0.089	

Data are shown as mean ± standard deviation. Independent sample test was used inter-group comparisons paired and sample test was used in intra-group comparisons. Tdi = The percent change in diaphragm thickness, IMT = Intercostal muscle thickness, D0 = Day 0 (pre-treatment), D3 = Day 3, D6 = Day 6, D9 = Day 9, Group 1 = kinesiotope applied side, Group 2 (control group) = kinesiotope not applied side.



**Table 3.** Comparison of the difference scores between the groups.

	<b>D3-D0</b> <b>(n = 21)</b>	<b>D6-D0</b> <b>(n = 18)</b>	<b>D9-D0</b> <b>(n = 15)</b>
<b>Diaphragm</b>			
Group 1	-1.71 ± 0.78	-4.28 ± 1.23	-6.00 ± 1.25
Group 2	-3.57 ± 0.75	-5.72 ± 1.44	-7.33 ± 1.50
<i>p</i>	<b>&lt; 0.001</b>	<b>0.001</b>	<b>0.013</b>
<b>Tdi</b>			
Group 1	-1.57 ± 0.51	-3.56 ± 1.25	-5.73 ± 2.34
Group 2	-4.00 ± 1.61	-6.22 ± 1.44	-6.20 ± 1.74
<i>p</i>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	0.541
<b>IMT9</b>			
Group 1	-1.24 ± 0.54	-2.83 ± 0.92	-5.47 ± 1.46
Group 2	-4.57 ± 3.17	-6.67 ± 3.41	-7.40 ± 1.64
<i>p</i>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	<b>0.002</b>
<b>IMT7</b>			
Group 1	-1.19 ± 0.93	-2.72 ± 2.87	-4.53 ± 5.38
Group 2	-2.14 ± 1.88	-4.39 ± 2.87	-6.53 ± 3.27
<i>p</i>	<b>0.044</b>	0.090	0.229

Data are shown as mean ± standard deviation. Independent sample test was used inter-group comparisons. Tdi = The percent change in diaphragm thickness, IMT = Intercostal muscle thickness, D0 = Day 0 (pre-treatment), D3 = Day 3, D6 = Day 6, D9 = Day 9, Group 1 = kinesiotape applied side, Group 2 (control group) = kinesio tape not applied side.

1).

Distribution of the age, gender, and body mass index (BMI) of the patients are presented in Table 1. The pre-treatment evaluation values of the parameters in the both groups are presented in Table 2. There was no statistically significant difference between the two groups for the pretreatment evaluation parameters ( $p > 0.05$ ).

In both groups; a statistically significant decrease was found in all the evaluation parameters at all the measurement times when compared to the pre-treatment (D0) values ( $p < 0.05$ ) (Table 2).

On the D3 and D6; a statistically significant difference was found in favor of group 1 (side treated with kinesiotaping) in all the evaluation parameters except seventh intercostal muscle thickness ( $p < 0.05$ ). The seventh intercostal muscle thickness measurements showed no statistically significant difference between the two groups ( $p > 0.05$ ) (Table 2).

On the ninth (D9) day; there was no statistically significant difference between the two groups in all evaluation parameters ( $p > 0.05$ ) (Table 2).

In comparison of the difference scores of the two

groups; a statistically significant difference was found in all the evaluation parameters for D3-D0 and in all the evaluation parameters except for the seventh intercostal muscle thickness in D6-D0, in favor of Group 1 ( $p < 0.05$ ). In D9-D0, there was no statistically significant difference between the two groups in the Tdi and seventh intercostal muscle thickness ( $p > 0.05$ ), while in the other evaluation parameters a statistically significant difference was found in favor of Group 1 ( $p < 0.05$ ) (Table 3)

## DISCUSSION

The present study found significantly lower diaphragmatic muscle thickness, diaphragmatic thickening fraction, and ninth intercostal muscle thickness measured on the third and sixth days in the side on which kinesiotaping were not applied. There was no significant difference in all measured parameters between the two groups on the ninth day.

Previous studies have shown mechanical ventilation-induced diaphragmatic atrophy in both humans and animals. Studies made in humans

reported that more than 50% decrease in the cross-sectional areas of type I (slow-twitch) and type II (fast-twitch) diaphragmatic fibers after mechanical ventilation for 18-69 hours [5, 27-29]. It is considered that mechanical ventilation decreases the mobility of diaphragm and immobility in turn results in diaphragmatic atrophy [5, 30, 31]. It has been reported accelerated proteolysis as a result of the suppression of diaphragmatic contractility and increase in net protein loss upon depression of protein synthesis; as a result, atrophy occurs in the diaphragmatic muscle fibers [5]. Another theory suggests that rapid increase in mitochondrial reactive oxygen species (ROS) emission caused by mechanical ventilation might play a role in the development of VIDD and that the resulting accelerated protein turnover causes rapid activation of key proteolytic systems. Increased production of ROS was found to cause an increase in protease activation and diaphragmatic atrophy [5, 30, 31].

In the current practice, ultrasonography is commonly used to diagnose diaphragmatic atrophy [1, 31, 32]. Ultrasonographic imaging of the respiratory system was used by Cohn *et al.* [11] and the results of the measurements were compared with autopsy measurements. The authors reported a variability of 0.2 mm and suggested the use of ultrasound measurements as a reproducible, cost-effective, and non-invasive tool.

In the literature, there are many studies using US in the diagnosis and follow-up of VIDD [3, 32-34]. Schepens *et al.* [33] evaluated 54 patients who underwent mechanical ventilation and attempted to detect diaphragmatic dysfunction and associated risk factors using US measurements. The authors reported a 9% decline in the diaphragmatic thickness at 24 hours, 20% decline at 48 hours, and 26% decline at 72 hours compared to baseline values. Inconsistent with the literature data, Cartwright *et al.* [35] reported that US measurement was not useful to demonstrate diaphragmatic weakness.

On the other hand, difficulty in weaning from mechanical ventilator is a more significant problem which seems to be the basic problem associated with VIDD [12]. Various studies have attempted to establish potential treatment strategies in order to prevent weaning problems which occurs approximately in 20 to 25% of the patients [12, 36-

38]. As pharmacological therapies to decrease ROS and diaphragmatic activity are thought to be protective against VIDD [38], various studies have used treatment strategies that focused on maintaining diaphragmatic activity [36, 37]. Diaphragm exercises have been structured and performed as inspiratory muscle training in the preoperative period [36, 37].

There are also studies which attempted to prevent VIDD and maintain contractile strength of the diaphragmatic muscle in the intensive care unit patients [12, 39]. Martin *et al.* [12] studied on inspiratory muscle training and evaluated patients who received mechanical ventilatory support for a mean duration of 6.5 weeks and who failed to wean from the ventilator more than once. The authors found an about 35% increase in maximum inspiratory pressure that was measured in the tracheal tube of patients in the inspiratory muscle strain training (IMST) group and they were able to wean 7% of the patients in the IMST group from mechanical ventilator. Goligher *et al.* [34] suggested the use of muscle preserving mechanical ventilation. The authors reported that inspiratory effort could prevent changes in the configuration of the diaphragm by titrating aeration during mechanical ventilation.

Kinesiotaping is particularly used in the treatment of musculoskeletal disorders and also in the treatment of cerebral palsy, stroke rehabilitation and postoperative pain management (thoracotomy, and video-assisted thoracoscopic surgery) [23, 24, 40, 41]. In a prospective study, Thelen *et al.* [23] evaluated the efficacy of kinesiotaping in patients with shoulder impingement syndrome and rotator cuff tendinitis and found a significant improvement in shoulder abduction in the kinesiotaping group. Therefore, the authors suggested that improvement in shoulder abduction could be associated with strengthening of motor unit in supraspinatus muscle due to increased proprioceptive stimulation which might, therefore, increase mobility. Jaraczewska *et al.* [24] evaluated the effects of kinesiotaping in hemiplegic patients in improving postural disorders of the upper extremity, balancing muscle tone and increasing muscle strength. The authors reported a decrease in muscle weakness and postural disorders and a significant improvement in upper extremity functions. Another study investigated the effects of kinesiotaping on motor functions of the upper extremity in pediatric patients

with intracranial pathologies such as head trauma, encephalitis, brain tumor, and stroke [40]. The authors detected that occupational therapy combined with kinesiotaping provided significant improvement in motor control and functions of the upper extremity. In a study, kinesiotaping applied on the chest wall was used in the management of postoperative pain. They reported that kinesiotaping could be used as an auxiliary method in postoperative pain management [41]. However, we could not find any report evaluated the effect of kinesiotaping on the respiratory muscle thickness in the literature.

Increasing body awareness by increasing proprioception on the chest wall and aiding respiration efforts is thought to be one of the action mechanisms of kinesiotaping on the diaphragmatic muscle. Furthermore, elimination of ROS by increasing blood flow to the affected area or deceleration of muscle wasting in secondary respiratory muscles (intercostal muscles) could be possible secondary mechanisms by which diaphragmatic functions are improved. This mechanism explains lesser muscle wasting in the intercostal muscles in kinesiotaping side of the thorax in the present study. The measurements which are comparable on ninth day of the follow-up period are considered to be associated with the attempts of weaning and supporting or allowing spontaneous respiration.

### Limitations

The limitations of the present study include small sample size, the use of unrecorded degree of sedation, and the use of uncontrolled positive end-expiratory pressure between 5-10 cm H<sub>2</sub>O.

### CONCLUSION

In conclusion, our study results showed that kinesiotaping decelerated the decrease in diaphragmatic muscle and intercostal muscle thickness until sixth day during follow-up, whereas this effect was unable to be sustained after sixth day. Based on these results, although kinesiotaping alone is not sufficient in preventing VIDD, we consider that it can be used as an adjunct to other treatment methods in pulmoner rehabilitation.

### Informed consent

Informed consent was obtained from all individual participants' relatives included in the study.

### Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

- [1] Grosu HB, Lee YI, Lee J, Eden E, Eikermann M, Rose KM. Diaphragm muscle thinning in patients who are mechanically ventilated. *Chest* 2012;142:1455-60.
- [2] Vassilakopoulos T, Petrof BJ. Ventilator-induced diaphragmatic dysfunction. *Am J Respir Crit Care Med* 2004;169:336-41.
- [3] Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* 2008;358:1327-35.
- [4] Berger D, Bloechlinger S, von Haehling S, Doehner W, Takala J, Z'Graggen WJ, et al. Dysfunction of respiratory muscles in critically ill patients on the intensive care unit. *J Cachexia Sarcopenia Muscle* 2016;7:403-12.
- [5] Futier E, Constantin JM, Combaret L, Mosoni L, Roszyk L, Sapin V, et al. Pressure support ventilation attenuates ventilator induced protein modifications in the diaphragm. *Crit Care* 2008;12:R116.
- [6] Gayan-Ramirez G, Testelmans D, Maes K, Rácz GZ, Cadot P, Zádor E, et al. Intermittent spontaneous breathing protects the rat diaphragm from mechanical ventilation effects. *Crit Care Med* 2005; 33: 2804-9.
- [7] Powers SK, Wiggs MP, Sollanek KJ, Smuder AJ. Ventilator induced diaphragm dysfunction: cause and effect. *Am J Physiol Regul Integr Comp Physiol* 2013;305:R464-77.
- [8] Mariani LF, Bedel J, Gros A, Lerolle N, Milojevic K, Laurent V, et al. Ultrasonography for screening and follow-up of diaphragmatic dysfunction in the ICU: a pilot study. *J Intensive Care Med* 2016;31:338-43.
- [9] Matamis D, Soilemezi E, Tsagourias M, Akoumianaki E, Dimassi S, Boroli F, et al. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. *Intensive Care Med* 2013;39:801-10.
- [10] Doorduyn J, van Hees HW, van der Hoeven JG, Heunks LM. Monitoring of the respiratory muscles in the critically ill. *Am J Respir Crit Care Med* 2013;187:20-7.
- [11] Cohn D, Benditt JO, Eveloff S, McCool FD. Diaphragm thickening during inspiration. *J Appl Physiol* 1997;83:291-6.

- [12] Daniel Martin A, Smith BK, Gabrielli A. Mechanical ventilation, diaphragm weakness and weaning: a rehabilitation perspective. *Respir Physiol Neurobiol* 2013;189:77-83.
- [13] Orhan C, Kaya Kara O, Kaya S, Akbayrak T, Kerem Gunel M, Baltaci G. The effects of connective tissue manipulation and kinesiotaping on chronic constipation in children with cerebral palsy: a randomized controlled trial. *Disabil Rehabil* 2016;28:1-11.
- [14] Kase K, Wallis J, Kase T. *Clinical therapeutic applications of the kinesiotaping method*. 2nd ed. Tokyo: Ken Ikai Co Ltd; 2003.
- [15] Cools AM, Witvrouw EE, Danneels LA, Cambier DC. Does taping influence electromyographic muscle activity in the scapular rotators in healthy shoulders? *Man Ther* 2002;7:154-62.
- [16] Morris D, Jones D, Ryan H, Ryan CG. The clinical effects of Kinesio®Tex taping: a systematic review. *Physiother Theory Pract* 2013;29:259-70.
- [17] Lim EC, Tay MG. Kinesiotaping in musculoskeletal pain and disability that lasts for more than 4 weeks: is it time to peel off the tape and throw it out with the sweat? A systematic review with meta-analysis focused on pain and also methods of tape application. *Br J Sports Med* 2015;49:1558-66.
- [18] Iosa M. The application of Kinesiotaping in children with cerebral palsy. *Dev Med Child Neurol* 2015;57:11-2.
- [19] Slupik A, Dwornik M, Bialoszewski D, Zych E. Effect of Kinesiotaping on bioelectrical activity of vastus medialis muscle. Preliminary report. *Ortop Traumatol Rehabil* 2007;9:644-51.
- [20] Chen CY, Lou MY. Effects of the application of Kinesio-tape and traditional tape on motor perception. *Br J Sports Med* 2008;42:513-4.
- [21] Halseth T, McChesney J, DeBeliso M, Vaughn R, Lien J. The effect of Kinesiotaping on proprioception at the ankle. *J Sports Sci Med* 2004;3:1-7.
- [22] Çeliker R, Güven Z, Aydoğ T, Bağış S, Atalay A, Çağlar Yağcı H, et al. [The kinesiological taping technique and its applications]. *Turk J Phys Med Rehabil* 2011;57:225-35. [Article in Turkish]
- [23] Thelen MD, Dauber JA, Stoneman PD. The clinical efficacy of kinesiotape for shoulder pain: a randomized, double-blinded, clinical trial. *J Orthop Sports Phys Ther* 2008;38:389-95.
- [24] Jaraczewska E, Long C. Kinesiotaping in stroke: improving functional use of the upper extremity in hemiplegia. *Top Stroke Rehabil* 2006;13:31-42.
- [25] Sarwal A, Walker FO, Cartwright MS. Neuromuscular ultrasound for evaluation of the diaphragm. *Muscle Nerve* 2013;47:319-29.
- [26] Ferrari G, De Filippi G, Elia F, Panero F, Volpicelli G, Aprà F. Diaphragm ultrasound as a new index of discontinuation from mechanical ventilation. *Crit Ultrasound J* 2014;6:8.
- [27] Andrade FH, Reid MB, Westerblad H. Contractile response of skeletal muscle to low peroxide concentrations: myofibrillar calcium sensitivity as a likely target for redox-modulation. *FASEB J* 2001;15:309-11.
- [28] Anzueto A, Peters JI, Tobin MJ, de los Santos R, Seidenfeld JJ, Moore G, et al. Effects of prolonged controlled mechanical ventilation on diaphragmatic function in healthy adult baboons. *Crit Care Med* 1997;25:1187-90.
- [29] Bernard N, Matecki S, Py G, Lopez S, Mercier J, Capdevila X. Effects of prolonged mechanical ventilation on respiratory muscle ultrastructure and mitochondrial respiration in rabbits. *Intensive Care Med* 2003;29:111-8.
- [30] Burd NA, Andrews RJ, West DW, Little JP, Cochran AJ, Hector AJ, et al. Muscle time under tension during resistance exercise stimulates differential muscle protein sub-fractional synthetic responses in men. *J Physiol* 2012;590:351-62.
- [31] Kumar V, Atherton PJ, Selby A, Rankin D, Williams J, Smith K, et al. Muscle protein synthetic responses to exercise: effects of age, volume, and intensity. *J Gerontol A Biol Sci Med Sci* 2012;67:1170-7.
- [32] Zambon M, Greco M, Bocchino S, Cabrini L, Beccaria PF, Zangrillo A. Assessment of diaphragmatic dysfunction in the critically ill patient with ultrasound: a systematic review. *Intensive Care Med* 2017;43:29-38.
- [33] Schepens T, Verbrugghe W, Dams K, Corthouts B, Parizel PM, Jorens PG. The course of diaphragm atrophy in ventilated patients assessed with ultrasound: a longitudinal cohort study. *Crit Care* 2015;19:422.
- [34] Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, et al. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. *Intensive Care Med* 2015;41:642-9.
- [35] Cartwright MS, Kwayisi G, Griffin LP, Sarwal A, Walker FO, Harris JM, et al. Quantitative neuromuscular ultrasound in the intensive care unit. *Muscle Nerve* 2013;47:255-9.
- [36] Hulzebos EH, Helders PJ, Favié NJ, De Bie RA, Brutel de la Riviere A, Van Meeteren NL. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. *JAMA* 2006;296:1851-7.
- [37] Nomori H, Kobayashi R, Fuyuno G, Morinaga S, Yashima H. Preoperative respiratory muscle training. Assessment in thoracic surgery patients with special reference to postoperative pulmonary complications. *Chest* 1994;105:1782-8.
- [38] Weiner P, Zeidan F, Zamir D, Pelled B, Waizman J, Beckerman M, et al. Prophylactic inspiratory muscle training in patients undergoing coronary artery bypass graft. *World J Surg* 1998;22:427-31.
- [39] Francis CA, Hoffer JA, Reynolds S. Ultrasonographic evaluation of diaphragm thickness during mechanical ventilation in intensive care patients. *Am J Crit Care* 2016;25: e1-8.
- [40] Yasukawa A, Patel P, Sisung C. Pilot study: investigating the effects of kinesiotaping in an acute pediatric rehabilitation setting. *Am J Occup Ther* 2006;60:104-10.
- [41] Imperatori A, Grande A, Castiglioni M, Gasperini L, Faini A, Spampatti S, et al. Chest pain control with kinesiology taping after lobectomy for lung cancer: initial results of a randomized placebo-controlled study. *Interact Cardiovasc Thorac Surg* 2016;23:223-30.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# The incidence of polyneuropathy and its relation with disease parameters in chronic obstructive pulmonary disease

Nalan Ogan<sup>1</sup>, Refah Sayın<sup>2</sup>, Ayşe Baha<sup>1</sup>, Evrim Eylem Akpınar<sup>1</sup>, Meral Gülhan<sup>3</sup>

<sup>1</sup>Department of Chest Diseases, Ufuk University School of Medicine, Ankara, Turkey

<sup>2</sup>Department of Neurology, Ufuk University School of Medicine, Ankara, Turkey

<sup>3</sup>Department of Chest Diseases, Hitit University School of Medicine, Çorum, Turkey

DOI: 10.18621/eurj.367066

## ABSTRACT

**Objective:** Chronic Obstructive Pulmonary Disease (COPD) is accompanied by several concomitant conditions due to its systemic effects. Hypoxia and oxidative stress associated with COPD are also believed to contribute to the disease course through the effects of several inflammatory mediators. Major causative agents causing of peripheral neuropathy are age, hypoxia, duration and severity of COPD, hypercapnia and smoking. The present study aimed to investigate the incidence of polyneuropathy and its relation with disease parameters in COPD patients.

**Methods:** Of a total number of 45 patients who had been followed up between January 1, 2015 and December 31, 2016 with a diagnosis of COPD at Ufuk University School of Medicine were enrolled retrospectively. All patients underwent electroneuromyography, arterial blood gas measurements and pulmonary function tests. Patients were divided as those with or without neuropathy, and factors contributing to the development of neuropathy were investigated based on clinical and laboratory findings.

**Results:** Eleven (24.4%) patients were women and 34 (74.6%) were men, and the mean age was 73.2 years. Mean PaO<sub>2</sub> was 58.2 mmHg, pCO<sub>2</sub> was 41.2 mmHg, and FEV1 was 45.3%. Neuropathy was diagnosed in twenty (44.4%) patients. Significant differences were found in pO<sub>2</sub>, pCO<sub>2</sub>, SO<sub>2</sub>, mMRC, smoking status and number of exacerbations per year ( $p < 0.05$ ).

**Conclusions:** Patients who experience frequent exacerbations and those with hypoxemia or hypercapnia as demonstrated should be taken into more careful clinical assessments with respect to polyneuropathy.

**Keywords:** chronic obstructive pulmonary disease, neuropathy, hypoxemia, hypercapnia, modified Medical Research Council

*Received: December 16, 2017; Accepted: January 21, 2018; Published Online: April 2, 2018*

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [1].

COPD has several systemic effects and the concurrent systemic inflammation was shown to be associated with different concomitant diseases. Polyneuropathy is a clinical manifestation resulting from concomitant and common impairment of peripheral nerves due to the same causes and physiopathological processes.



**Address for correspondence:** Nalan Ogan, MD., Assistant Professor, Ufuk University School of Medicine, Department of Chest Diseases, Ankara, Turkey  
E-mail: nalanogan@gmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

Causes of peripheral neuropathy include but not limited to diabetes mellitus, malignancy, Sjögren's syndrome, dysproteinemia, AIDS, Vitamin B12 deficiency, polyneuropathies due pyridoxine intoxication and hereditary or idiopathic sensorial polyneuropathies [2]. COPD is one of these causes (3). However, in patients who are diagnosed with peripheral neuropathy, COPD is usually ignored while the other potential causes are prioritized. This process that follows a chronic and deteriorating course eventually results in tissue hypoxemia and affects not only the lungs but the whole body. Previous studies investigated how the peripheral nerves and muscles are affected from this process. The objectives of the present study were to evaluate the neurophysiological changes in peripheral and central nervous systems in hypoxemic and/or hypercapnic COPD cases and to investigate the correlations of these changes with disease stage and the severity of dyspnea.

## METHODS

Of a total number of 45 patients who had been followed up between January 1, 2015 and December 31, 2016 with a diagnosis of COPD at Ufuk University Faculty of Medicine were enrolled retrospectively. Complete blood count, biochemistry, Vitamin B<sub>12</sub>, folic acid and thyroid function test (TFT) results of all patients were evaluated. Patients with a history of cancer that might have caused peripheral neuropathy and those with a diagnosis of diabetes mellitus, vitamin B<sub>12</sub> deficiency, renal failure or hypothyroidism were excluded from the study. The study was conducted after approval was obtained from the ethics committee of our hospital.

### Pulmonary Function Tests

Pulmonary function tests (PFTs) were performed by 'VMAX'; 'Encore system (Germany)' device. During PFTs, post-bronchodilator force vital capacity in one second (FEV<sub>1</sub>), force vital capacity (FVC) and FEV<sub>1</sub>/FVC values were recorded based on GOLD criteria. For COPD staging, patients with FEV<sub>1</sub> values > 80% were considered to have mild, FEV<sub>1</sub>: 80-50% were considered to have moderate, FEV<sub>1</sub>: 50-30% were considered to have severe and FEV<sub>1</sub> <30% were considered to have very severe COPD.

### Arterial Blood Gas Analyses

Analyses were performed by 2001 version of the "Instrumentation Laboratory-Synthesis 25" device. pH, partial arterial oxygen pressure (PaO<sub>2</sub>), partial arterial carbon dioxide pressure (PaCO<sub>2</sub>) and arterial oxygen saturation (SaO<sub>2</sub>) values were recorded.

### Electrophysiological Examination

The examinations were performed using Medelec Synergy EMG device. In accordance with clinical definition of peripheral neuropathy (nerve conduction studies of at least 2 extremities); median nerve sensorial and motor conduction, ulnar nerve sensorial and motor conduction of the upper extremities and peroneal nerve motor conduction, tibial nerve motor conduction and sural nerve sensorial conduction of the lower extremities, as well as all motor and sensorial nerve conduction studies were performed. A diagnosis of carpal tunnel syndrome (CTS) was made in the presence of a deceleration in median sensorial conduction velocity, prolongation of median motor nerve distal latency, a decrease in motor action potentials and the presence of at least 0.3 ms latency difference or latencies longer than 0.5 msec when the ulnar-median nerve peak latency difference was compared to the other extremity. CTS was classified as mild, moderate and severe. Moreover; during each nerve conduction study, F wave (in at least one nerve for both an upper and a lower extremity) as one of the late latencies was investigated irrespective to the presence of findings supporting polyneuropathy criteria. Most frequently, the right upper and lower extremities of the patients were studied. In patients who were found to have carpal tunnel syndrome, upper extremity nerve conduction studies were also evaluated.

### Statistical Analysis

Statistical analysis was performed by SPSS 12 (Statistical Program for Social Sciences) software. Data were evaluated by using descriptive statistics (mean, standard deviation). Independent sample test was used to compare the two groups and chi-square test was used to compare qualitative data. Data that were not normally distributed were compared between the two groups by Mann-Whitney U test. A *p* value < 0.05 were considered significant in all statistical analyses of study data.

## RESULTS

Eleven (24.4%) patients were women and 34 (75.6%) were men and their mean age was 73.22 ± 9.42 years. (Table 1) Never-smokers constituted 17.8% (n = 8) of the study population, while 71.1% (n = 32) were ex-smokers and 11.1% (n = 5) were active smokers. Mean smoking history was 43.13 ± 28.3 pack-years. Body mass index (BMI) in neuropathy present group was 25.67 ± 6.69 kg/m<sup>2</sup>. Mean values of arterial blood gases (ABG) were as follows: pH: 7.41, PaO<sub>2</sub>: 58.28 mmHg, PaCO<sub>2</sub>: 41.27 mmHg, SO<sub>2</sub>: 89.68%. Mean PFT results were as follows: FEV<sub>1</sub>:46.71% (1.19 lt), FVC:63.82% (2.18 lt), FEV<sub>1</sub>/FVC:55.93. Of all patients, 4 (8.9%) had electrophysiological changes while no change was noted in remaining 41 (91.1%) patients (see Table 1). Patients were divided into two groups as those with or without neuropathy. Of the patients with neuropathy, one had motor neuropathy, 8 had sensorimotor neuropathy and 11 patients had sensorial neuropathy based on electrophysiological findings. In total, 7 patients had findings of carpal tunnel syndrome. Neuropathy was diagnosed in 44.4% (n = 20) of the patients, while the remaining 55.6% (n = 25) did not have neuropathy (Table 1).

In total, 7 (63.64%) women and 13 (38.24%) men had neuropathy and their mean age was 75.30±9.07 years. Of 25 patients without neuropathy, 21 (61.76%) were men and 4 (36.36%) were women and their mean age was 71.56 ± 9.55 years. Mean age and gender distribution were not significantly different between the two groups ( $p = 0.204$  and  $p = 0.145$ , respectively). In terms of ABG findings, mean pH of patients with neuropathy was 7.39 ± 0.05 (Table 2). There were significantly different between the two groups in term of pO<sub>2</sub> ( $p = 0.012$ ), pCO<sub>2</sub> ( $p = 0.003$ ), SO<sub>2</sub> ( $p = 0.001$ ) and number of exacerbations per year ( $p < 0.001$ ). Moreover, the percentage of smoking (pack-year) and mean modified Medical Research Council (mMRC) scores were also significantly different ( $p = 0.040$  and  $p = 0.001$ , respectively). Mean age, smoking history, pH, FEV<sub>1</sub> (%), FEV<sub>1</sub> liters (lt), FVC (%), FVC lt, FEV<sub>1</sub>/FVC (%), BMI and time since diagnosis of COPD (years) and co-morbidities (Coronary heart disease, Congestive heart disease, Alzheimer disease)

**Table 1.** Overall demographical characteristics

Parameter	Data
<b>Gender</b>	
Women	11 (24.4%)
Men	34 (75.6%)
<b>Age (mean)</b>	73.22 ± 9.42
<b>Smoking</b>	
Never-smoker	8 (17.8%)
Ex-smoker	32 (71.1%)
Active-smoker	5 (11.1%)
<b>Smoking (packet-year)</b>	43.13 ± 28.30
<b>Concomitant diseases</b>	
Present	32 (71.1%)
Absent	13 (28.9%)
<b>pH</b>	7.41 ± 0.044
<b>pO<sub>2</sub>, mmHg</b>	58.28 ± 9.95
<b>pCO<sub>2</sub>, mmHg</b>	41.27 ± 9.70
<b>SO<sub>2</sub>, %</b>	89.68 ± 5.79
<b>FEV<sub>1</sub>, %</b>	46.71 ± 16.15
<b>FEV<sub>1</sub>, lt</b>	1.19 ± 0.51
<b>FVC, %</b>	63.82 ± 14.65
<b>FVC, lt</b>	2.18 ± 0.70
<b>FEV<sub>1</sub>/FVC, %</b>	55.932 ± 11.37
<b>Electrophysiological Changes</b>	
Present	4 (8.9%)
Absent	41 (91.1%)
<b>Neuropathy</b>	
Present	20 (44.4%)
Absent	25 (55.6%)

Data are shown as mean ± standart deviation or number (%). FVC = force vital capacity, FEV<sub>1</sub> = force vital capacity in one second, pO<sub>2</sub> = partial oxygen pressure, pCO<sub>2</sub> = partial carbon dioxide pressure, SO<sub>2</sub> = oxygen saturation

were not significantly different between the two groups ( $p > 0.05$ ) (Table 2). According to GOLD 2017 guideline, twenty-six (57.8%) patients were GOLD-Stage C, 19 (42.2%) were GOLD-Stage D. There were 5 (19.2%) patients in GOLD-Stage C and 11 (57.9%) patients in GOLD-Stage D, and this difference was statistically significant ( $p = 0.001$ ).

Nerve conduction studies demonstrated significant differences in both median nerve distal latencies, right sural conduction velocity, right tibial nerve distal latency, both median nerve sensorial conduction velocity, right peroneal and tibial nerve motor conduction velocities between the two groups are shown in Table 3 ( $p < 0.05$ ).

**Table 2.** Comparison of the parameters between study groups

	Neuropathy present (n = 20)	Neuropathy absent (n = 25)	p value
Age (years)	75.30 ± 9.07	71.56 ± 9.55	0.204
Smoking	39.05 ± 31.92	46.40 ± 25.22	0.605
pH	7.39 ± 0.05	7.41 ± 0.03	0.224
pO <sub>2</sub> , mmHg	54.81 ± 10.18	61.75 ± 7.76	<b>0.012</b>
pCO <sub>2</sub> , mmHg	46.67 ± 11.16	36.95 ± 5.48	<b>0.003</b>
SO <sub>2</sub> , %	86.67 ± 5.86	92.09 ± 4.56	<b>0.001</b>
FEV <sub>1</sub> (%)	44.60 ± 14.17	48.40 ± 17.68	0.444
FEV <sub>1</sub> (lt)	1.15 ± 0.46	1.23 ± 0.56	0.775
FVC (%)	62.35 ± 14.20	64.70 ± 14.60	0.631
FVC (lt)	2.00 ± 0.62	2.33 ± 0.74	0.132
BMI, kg/m <sup>2</sup>	25.67 ± 6.69	25.39 ± 5.75	0.486
Time since COPD diagnosis (years)	9.40 ± 7.57	7.32 ± 6.27	0.313
Number of exacerbations per year	2.00 ± 0.85	1.04 ± 1.31	<b>&lt; 0.001</b>
mMRC			<b>0.001</b>
1	0 (0%)	10 (40%)	
2	10 (50%)	13 (52%)	
3	9 (45%)	2 (8%)	
4	1 (5%)	0 (0%)	
Smoking, (packet-year)			<b>0.040</b>
Non-smoker	6 (30%)	2 (8%)	
Ex-smoker	13 (65%)	19 (76%)	
Active-smoker	1 (5%)	4 (16%)	

Data are shown as mean ± standart deviation or number (%). BMI = body mass index, COPD = Chronic Obstructive Pulmonary Disease, FEV<sub>1</sub> = force vital capacity in one second, FVC = force vital capacity, mMRC = modified medical research council, pO<sub>2</sub> = partial oxygen pressure, pCO<sub>2</sub> = partial carbon dioxide pressure, SO<sub>2</sub> = oxygen saturation

**Table 3.** Comparison of neurophysiological changes in electroneuromyography between groups

	Neuropathy present	Neuropathy absent	p value
RMNSL	2.14 ± 1.87	2.89 ± 0.94	0.679
LMNSL	2.78 ± 1.30	2.92 ± 0.71	0.671
RUNSL	2.31 ± 1.44	2.71 ± 0.33	0.739
RSNV	19.36 ± 18.13	36.33 ± 8.18	<b>&lt; 0.001</b>
RMNML	3.84 ± 0.69	3.34 ± 0.50	<b>0.012</b>
LMNML:	3.49 ± 0.59	3.12 ± 0.43	<b>0.032</b>
RUNML	2.54 ± 0.53	2.47 ± 0.57	0.449
RCPNL	4.15 ± 2.40	4.49 ± 1.19	0.575
PTNL	4.79 ± 0.99	4.23 ± 0.55	<b>0.047</b>
RMNSV	21.60 ± 18.80	38.28 ± 11.85	<b>&lt; 0.001</b>
LMNSV	31.42 ± 14.43	39.38 ± 8.59	<b>0.001</b>
RUNMV	27.66 ± 16.68	40.84 ± 4.12	<b>&lt; 0.001</b>
RCPNV	36.34 ± 19.39	46.17 ± 11.51	<b>0.037</b>
RPTNV	42.29 ± 5.03	45.93 ± 5.48	<b>0.022</b>

Data are shown as mean ± standart deviation. RMNSL = Right median nerve sensory latency, LMNSL = Left median nerve sensory latency, RUNSL = Right ulnar nerve sensory latency, RSNV = Right sural nerve velocity, RMNML = Right median nerve motor latency, LMNML = Left median nerve motor latency, RUNML = Right ulnar nerve motor latency; RCPNL: Right common peroneal nerve latency, RPTNL = Right posterior tibial nerve latency, RMNSV = Right median nerve sensory velocity, LMNSV = Left median nerve sensory velocity, RUNMV = Right ulnar nerve motor velocity, RCPNV = Right common peroneal nerve velocity, RPTNV: Right posterior tibial nerve velocity



## DISCUSSION

The neuropathic patients are more hypoxic and hypercarbic than neuropathic and electrophysiologically normal COPD patients in our study.  $pO_2$ ,  $pCO_2$ ,  $SO_2$  and number of exacerbations per year were significantly different between the two groups. Moreover, mean modified Medical Research Council (mMRC) scores were also significantly different. The relation between chronic hypoxemia and peripheral neuropathy (PN) in COPD has been known for a long time [4, 5]. Hypoxia blocks energy metabolism of peripheral nerve tissue [6]. The severity of hypoxia may increase due to endothelial cell hyperplasia which results in luminal occlusion in capillary veins [4]. In rats with induced chronic hypoxemia, a reduction in nerve conduction velocity was observed as a result of axonal degeneration [7]. Stoebner *et al.* [8] observed microangiopathy caused by hypoxemia in peripheral nerves. While several studies reported a relation of hypoxemia and its severity with PNP, Jann *et al.* [9] found such a relation with the severity of COPD and hypercapnia.

Systemic inflammation is the key for linking COPD and most of its dependent comorbidities. In addition to inflammation, imbalance of proteinases and antiproteinases and the oxidative stress are important in the pathogenesis of COPD. In advanced COPD, the lung capacity reduces for gas exchange, producing hypoxemia and, later on, hypercapnia [10]. In the present study, significant associations were noted both with hypoxemia and hypercapnia. Also, frequent hospitalizations and therapies like systemic corticosteroids might contribute this situation [11].

Hypoxia and/or hypercapnia may occur or will get worse in COPD patients, especially during exacerbation. The inflammation also increases. Accordingly, we found a significant relationship between annual attack rate and frequency of neuropathy in our study. In addition mMRC dyspnea and frequency of neuropathy was directly correlated. The reason for this may be the probability of increased damage of neurons innervating diaphragm and other respiratory muscles by neuropathy.

The most important external source of oxidants is tobacco smoke and its constituents. Tobacco smoke damages the lungs, both by triggering inflammation and by direct effects of the inhaled particles and gases

[12, 13]. Tobacco smoke causes protease-antiprotease imbalance by suppressing antiprotease activity. Resultant tissue damage may lead to local and systemic inflammation. In a previous study, Faden and Agrawal reported a correlation between smoking habits and sensorial nerve functions [14, 15]. Kayacan *et al.* [16] highlighted the concomitant relation between the brainstem auditory evoked potentials (BAER). According to that study, smoking affects the ponto-medullary brain region potentially by altering  $PaCO_2$ ,  $HCO_3$  and pH levels. On the contrary, Ulubay *et al.* [17] did not demonstrate such a relation in their study. The significant relation noted between smoking habits and neuropathy incidence in the present study can be explained by the high proportion of smokers in the study group.

In the present study peripheral neuropathy has occurred at an incidence of 44.4% in patients with COPD. The prevalence of PN among COPD patients showed wide variety in previous studies (5% to 100%) [4, 5, 16, 18, 20-26]. In line with the previous studies, the distribution and types of neuropathic parameters mostly indicated involvement of lower extremities and manifestation as sensorial NP [4, 20, 23, 24]. Neuropathy incidence varies depending on the clinical and electrophysiological criteria used to define the abnormalities.

## CONCLUSION

In conclusion, chronic obstructive pulmonary disease is a systemic disorder that does not only involve the lungs, but also affects non-pulmonary organs through inflammation. This is important in terms of quality of life. Electroneurophysiological changes are rather common among patients who experience frequent hospitalizations, who are severely hypoxemic and/or hypercapnic. Nowadays, better identification of the comorbidities accompanying COPD may be beneficial for the patients in terms of early initiation of specific medical or supportive therapies.

### *Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

## Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

- [1] Global Initiative for Chronic Obstructive Lung Disease. Pocket guide to COPD diagnosis, management, and prevention. A Guide for Health Care Professionals 2017 edition. 2017.
- [2] Kazi K, Mehta A, Mulla M. Electrophysiological evaluation of peripheral nerves in patients with chronic obstructive pulmonary disease. *Int J Basic Appl Physiol* 2012;1:83-7.
- [3] Sönmezler A, Yoldaş TK, Ünsal İ, Çalık M, Karakaş E. [Who gets the diagnosis of polyneuropathy?] *Journal of Harran University Medical Faculty* 2012;9:65-7. [Article in Turkish]
- [4] Pfeiffer G, Kunze K, Bruch M, Kutzner M, Ladurner G, Malin JP, et al. Polyneuropathy associated with chronic hypoxaemia: prevalence in patients with chronic obstructive pulmonary disease. *J Neurol* 1990;237:230-3.
- [5] Paramelle B, Vila A, Pollak P, Muller P, Gavelle D, Reymond F, et al. Incidence of polyneuropathies in chronic obstructive bronchopneumopathies. *Presse Med* 1986;15:563-7.
- [6] Tuck RR, Schmelzer JD, Low PA. Endoneurial blood flow and oxygen tension in the sciatic nerves of rats with experimental diabetic neuropathy. *Brain* 1984;107:935-50.
- [7] Low PA, Schmelzer JD, Ward KK, Yao JK. Experimental chronic hypoxic neuropathy: relevance to diabetic neuropathy. *Am J Physiol* 1986;250:94-9.
- [8] Stoebner P, Mezin P, Vila A, Grosse R, Kopp N, Paramelle B. Microangiopathy of endoneurial vessels in hypoxemic chronic obstructive pulmonary disease (COPD). A quantitative ultrastructural study. *Acta Neuropathol (Berl)* 1989;78:388-95.
- [9] Jann S, Gatti A, Crespi S, Rolo J, Beretta S. Peripheral neuropathy in chronic respiratory insufficiency. *J Peripher Nerv Syst* 1998;3:69-74.
- [10] Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009;33:1165-85.
- [11] Mantilla CB, Sieck GC. Neuromotor control in chronic obstructive pulmonary disease. *J Appl Physiol* 2013;114:1246-52.
- [12] Wright JL, Lawson LM, Pare PD, Wiggs BJ, Kennedy S, Hogg JC. Morphology of peripheral airways in current smokers and ex-smokers. *Am Rev Respir Dis* 1983;127:474-7.
- [13] Hunninghake GW, Crystal RG. Cigarette smoking and lung destruction. Accumulation of neutrophils in the lungs of cigarette smokers. *Am Rev Respir Dis* 1983;128:833-8.
- [14] Faden A, Mendoza E, Flynn F. Subclinic neuropathy associated with chronic obstructive pulmonary disease. Possible pathologic role of smoking. *Arch Neurol* 1981;38:639-42.
- [15] Agrawal D, Vohra R, Gupta PP, Sood S. Subclinical peripheral neuropathy in stable middle-aged patients with chronic obstructive pulmonary disease. *Singapore Med J* 2007;48:887-94.
- [16] Kayacan O, Beder S, Deda G, Karnak D. Neurophysiological changes in COPD patients with chronic respiratory insufficiency. *Acta Neurol Belg* 2001;101:160-5.
- [17] Ulubay G, Ulasli SS, Bozbas SS, Ozdemirel T, Karatas M. Effects of peripheral neuropathy on exercise capacity and quality of life in patients with chronic obstructive pulmonary diseases. *Arch Med Sci* 2012;8:296-302.
- [18] Gupta PP, Agarwal D. Chronic obstructive pulmonary disease and peripheral neuropathy. *Lung India* 2006;23:25-33.
- [19] Gasnault J, Moore N, Arnaud F, Rondot P. Peripheral neuropathies during hypoxaemic chronic obstructive airways disease. *Bull Eur Physiopathol Respir* 1987;11:199-202.
- [20] Moore N, Lerebours G, Senant J, Ozenne G, David P, Nouvet G. Peripheral neuropathy in chronic obstructive lung disease. *Lancet* 1985;11:1311.
- [21] Shah S, Salvi, Kowale A. Peripheral nerves in chronic obstructive pulmonary disease: a review. *Int J Adv Physiol Allied Sci* 2016;3:78-87.
- [22] Ozge A, Atis S, Sevim S. Subclinical peripheral neuropathy associated with chronic obstructive pulmonary disease. *Electromyogr Clin Neurophysiol* 2001;41:185-91.
- [23] Demir R, Özel L, Özdemir G, Kocatürk İ, Ulvi H. Neurophysiological changes in patients with chronic obstructive pulmonary diseases. *Eur J Gen Med* 2014;11:153-6.
- [24] Jarratt JA, Morgan CN, Twomey JA, Abraham R, Sheaff PC, Pilling JB, et al. Neuropathy in chronic obstructive pulmonary disease: a multicentre electrophysiological and clinical study. *Eur Respir J* 1992; 5:517-24.
- [25] Çağlar T, Aka MT, Tabakoğlu E, Utku U, Agun K. [Peripheral neuropathy in chronic obstructive pulmonary disease]. *Balkan Med J* 1994;11:185-91. [Article in Turkish]
- [26] Oncel C, Baser S, Cam M, Akdağ B, Taspınar B, Evyapan F. Peripheral neuropathy in chronic obstructive pulmonary disease. *COPD* 2010;7:11-6.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# The association of carotid intima-media thickness with body mass index and cortisol level in fibromyalgia syndrome

Tuba Tülay Koca<sup>1</sup>, Ayla Çimen<sup>2</sup>

<sup>1</sup>Department of Physical Medicine and Rehabilitation, Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey

<sup>2</sup>Department of Radiology, Malatya Training and Research Hospital, Malatya, Turkey

DOI: 10.18621/eurj.376343

## ABSTRACT

**Objective:** Patients with fibromyalgia syndrome (FMS) may have the risk for atherosclerotic disease because of chronic stress, disrupted neuroendocrine axis, high BMI and inflammation. This is study aimed to research the stress and the stress-related diseases in patients with FMS by measuring obesity, morning serum cortisol level, and carotid intima-media thickness (CIMT), which is the early indicator of the atherosclerosis.

**Methods:** This is a case-control study. It is included 57 patients who were diagnosed with FMS according to 2010 American College of Rheumatology (ACR) Criteria and visited the outpatient clinic in February 2016. As a control group, 36 healthy females who visited the outpatient clinic in the same month were included. Carotid intima-media thickness and cortisol levels were analysed.

**Results:** The present study included 93 females (between 15 and 79 years old) in total. The mean age of the 57 females with FMS and 37 healthy females was  $44.5 \pm 10.6$  years and  $47.9 \pm 18.5$  years, respectively ( $p = 0.260$ ). The mean CIMT value of the FMS and control groups was  $0.64 \pm 0.17$  mm and  $0.59 \pm 0.16$  mm, respectively ( $p = 0.170$ ). The morning blood cortisol level in the FMS and control groups was  $7.8 \pm 3.3$  ng/dL and  $8.7 \pm 2.8$  ng/dL, respectively ( $p = 0.460$ ). The CIMT and morning blood cortisol level were not correlated in the FMS group.

**Conclusion:** According to the present study, CIMT value and morning blood cortisol level were not found significantly different in FMS group, and also were not found correlated with each other.

**Keywords:** Atherosclerosis, carotid intima-media thickness, fibromyalgia syndrome

*Received: January 8, 2018; Accepted: March 11, 2018; Published Online: April 11, 2018*

Intima-media thickness (IMT) is also called as intimal medial thickness. It is the measure of the thickness of the innermost two layers of the arterial wall called tunica intima and tunica media. This measurement is usually done by external ultrasonography (US) and rarely by the internal invasive US catheters [1].

The role of the IMT is not clear, and it is rarely used in clinic. Carotid IMT (CIMT) is measured in

various epidemiologic and clinical studies. A significant correlation was found between CIMT and several diseases such as type 2 diabetes mellitus, disrupted glucose tolerance, familial hypercholesterolemia, rheumatoid arthritis, and nonalcoholic fatty liver disease, as well as air pollution. An IMT value higher than 0.9-1 mm is an indicator of atherosclerosis and other cardiovascular diseases [2, 3].



Address for correspondence: Tuba Tülay Koca, MD., Assistant Professor, Sütçü İmam University School of Medicine, Department of Physical Medicine and Rehabilitation, Kahramanmaraş, Turkey  
E-mail: tuba\_baglan@yahoo.com, Phone: +90 506 3819295

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

Fibromyalgia syndrome (FMS) is characterized by chronic skeletal and muscular pain, and its pathogenesis still is not known. In clinical studies, endocrinologic responses differ in patients with FMS, but clinical findings are conclusive, too. The dysfunction of hypothalamus-pituitary-adrenal axis is commonly seen [4]. Commonly, abnormal cortisol levels and corticotropin releasing hormone response are reported in FMS patients [5, 6].

Obesity and overweight, often present in FMS patients, are related to the severity of FMS worsening the quality of life in terms of higher pain, fatigue, worsened sleep quality and higher incidence of mood disorders. Weight control is thus an effective tool to improve the symptoms [7]. To best of our knowledge, there are no other publications in the literature that analysis atherosclerosis and CIMT in FMS patients. This study explored the association of CIMT with body mass index (BMI) and cortisol level in fibromyalgia syndrome.

## METHODS

This study included 57 patients who were diagnosed with FMS according to 2010 American College of Rheumatology Criteria (ACR) and visited the Physical Medicine and Rehabilitation outpatient clinic on February 2016 [8]. Only patients attended at between 7:00 am and 9:00 am, included the study. Any patient who has any disease related hypothalamus-pituitary-adrenal axis dysfunction, serious atherosclerosis cardiac disease, using hormone supplement was excluded from the study.

As a control group, 36 healthy females who visited the outpatient clinic in the same month were included. The cortisol level of the patients was determined from their brachial venous blood samples. The basal cortisol level was taken as 6.2-19.4 ng/dL (7:00-9:00 am). Data on patient age, height, weight, BMI, and medical history (hypertension and diabetes) were recorded.

The thickness of the bilateral common carotid artery was measured by the same radiologist (CIMT assessor was blinded) using both ultrasound (US) and a high-resolution, real-time scanner with 7.5 MHz transducer. The measurements were taken when the patients were in the supine position, and maximum IMT values were recorded. The patients whose IMT

value was higher than 1 mm formed the risk group.

## Statistical Analysis

SPSS 17 (SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc, USA) was used for statistical analysis. The normal distribution of the data was evaluated using Kolmogorov–Smirnov test. Some descriptive tests were used for the descriptive data. For each parameter, a comparison was done between the two groups. The t test was used for the groups that showed normal distribution. The Mann-Whitney U test was used for the groups that did not show normal distribution. A  $p$  value  $< 0.05$  was considered statistically significant. The study has been done in accordance with the principles of Helsinki declaration.

## RESULTS

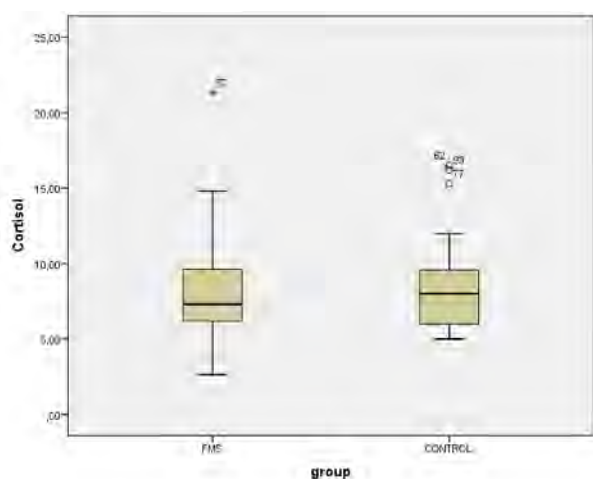
This study included 93 females (between 15 and 79 years old) in total. The mean age of the 57 females with FMS and 37 healthy females was  $44.5 \pm 10.6$  years and  $47.9 \pm 18.5$  years, respectively ( $p = 0.260$ ). The mean BMI value of the FMS and control groups was  $28.6 \pm 4.7$  kg/m<sup>2</sup> and  $28.1 \pm 5.4$  kg/m<sup>2</sup>, ( $p = 0.490$ ) respectively. The descriptive characteristics for the groups are shown in Table 1. Diabetes mellitus was detected in five (5.3%) patients (two FMS/three control), and hypertension was detected in six (6.4%) patients (four FMS/two control).

The mean morning blood cortisol level in the FMS and control groups was  $7.8 \pm 3.3$  ng/dL and  $8.7 \pm 2.8$  ng/dL, respectively. No statistical difference was found in the morning blood cortisol level of these two groups ( $p = 0.460$ ) (Figure 1). The mean CIMT value of the FMS and control groups was  $0.64 \pm 0.17$  mm

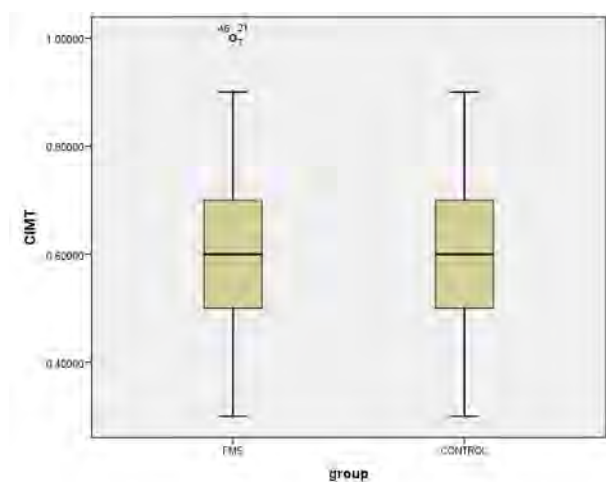
**Table 1.** The descriptive data of the patients according to the groups

	Control (n = 36)	FMS (n = 57)	p value
Age	$47.9 \pm 18.5$	$44.5 \pm 10.6$	0.260
BMI	$28.15 \pm 5.4$	$28.69 \pm 4.78$	0.490
Cortisol	$8.71 \pm 2.81$	$7.85 \pm 3.34$	0.460
CIMT	$0.59 \pm 0.16$	$0.64 \pm 0.17$	0.170

Data are shown as mean  $\pm$  standard deviation. BMI = body mass index, CIMT = carotid intima-media thickness, FMS = fibromyalgia syndrome



**Figure 1.** The distribution of serum cortisol in fibromyalgia syndrome and control group.



**Figure 2.** The distribution of carotid intima media thickness (CIMT) in fibromyalgia syndrome and control group.

and  $0.59 \pm 0.16$  mm, respectively, with no statistically significant difference ( $p = 0.170$ ) (Figure 2). The CIMT and morning blood cortisol level were not correlated in FMS group ( $p = 0.500$ ). The CIMT values were positively correlated with age ( $p < 0.01$ ) and BMI in all group ( $p < 0.01$ ). In the FMS group, 3 (5.5%) subjects; in the control group 0 subjects had CIMT  $> 1.00$  mm ( $p = 0.083$ ).

## DISCUSSION

According to the study, we did not find any significant difference between the results of morning cortisol, CIMT and BMI in the FMS group with

control. CIMT was positively correlated with age and BMI.

IMT is usually used for detecting atherosclerotic diseases. It was first described by Pignoli [9] in 1984. IMT became a useful tool to monitor the noninvasive changes on the artery wall [9]. IMT is a complex process and depends on several factors such as local hemodynamics, blood pressure, and stress [1-4]. The symptoms of chronic stress-related diseases, such as obesity, hyperactivity in CRH neurons, disrupted cortisol secretion on a daily basis, common anxiety disorder, obsessive-compulsive personality and A-type personality disorder, sleep disorder, and chronic pain, are significant in the patients with FMS [10-12]. Chronic pain and stress-related deviations in hormonal secretion occur in patients with FMS. Hypothalamic-corticotrophin-releasing hormone (CRH) neurons are activated in the central nervous system depending on chronic stress [10-12].

Since the sleep pattern is disrupted in women with FMS, it may lead to some changes in the circadian rhythm and disrupt the serum cortisol secretion. The circadian oscillation of the cortisol is abnormal in women with FMS [10-12]. A study by Fatima *et al.* [11] found the cortisol level in women with FMS to be significantly higher at night. In both genders, testosterone and DHEAS were found negatively correlated with cortisol [11]. To be able to detect hormonal changes in patients with FMS, Riedel *et al.* [10] injected CRH into their patients and observed high cortisol, low insulin like growth factor (IGF)-1 and triiodothyronine (T3), increase in the follicle stimulating hormone (FSH) level, and decrease in the basal estrogen level. Yeung *et al.* [12] also observed a more linear cortisol profile in adult patients with FMS who were exposed to childhood neglect. Riva *et al.* [4] measured the saliva cortisol level in patients with FMS who had pain, stress, and sleep disorders with depression. Despite these severe complaints, they found their saliva cortisol levels low, especially in the morning and the rest of the day [4]. In the present study, no significant difference was found in the morning cortisol level (measured at 7:00-9:00 am) between the two groups. Also we didnt find any relation with CIMT and BMI.

Since most of the women with FMS are overweight, BMI-related hormonal changes may be seen in these patients [13]. We observed no significant

difference in the BMI values of the two groups in the present study. This may be because of being overweight, which is common in Turkish female population. Additionally, a positive correlation was noted between BMI and CIMT values. In the study by Rus *et al.* [13] cardiovascular disease-related biomarkers such as C-reactive protein and apolipoprotein B levels were found to be higher in women with FMS compared with the control group. Since the CIMT level is usually higher in obese individuals, CIMT can play an important role in detecting future pre-atherosclerotic changes [14]. Detecting atherosclerotic symptoms can take years, but it is important to identify them early especially in individuals who carry a high atherosclerotic risk [15]. FMS is used to be classified in non-inflammatory soft tissue diseases, but stress and stress-related diseases may induce an chronic inflammation causative for atherosclerosis. We found no significant difference in CIMT and cortisol levels in FMS group. But CIMT was positively correlated with age and BMI. In a similar study, Eller *et al.* [16] measured CIMT levels of 95 participants and detected a significantly negative correlation between CIMT and both age and high HDL in males and also a correlation between CIMT and morning cortisol level. We observed that the association between psychosocial stress and CIMT value was investigated in a few researches. Few number of studies reporting a correlation between morning cortisol level and IMT are available. Eller *et al.* [15] found a correlation between IMT and cortisol level in the saliva of women and indicated that a high morning cortisol might be correlated with a low CIMT.

Atherosclerosis is an important risk factor for stroke development. Approximately 25% to 40% of patients with stroke, largely younger patients, are not associated with any conventional stroke risk factors. Neuropsychiatric diseases like FMS might enhance stroke development, possibly through inflammation and atherosclerosis. In the study by Tseng *et al.* [17] the outcomes imply that FMS is a significant risk factor for stroke and that patients with FMS, particularly younger patients, require close attention and rigorous measures for preventing stroke. Obesity causes various complications associated with high inflammation [18]. FMS affects the quality of life of these young and productive women negatively as a

reason of mainly obesity, hormonal dysfunction, sleep and mood disorders etc.[19].

### Limitations

The limitations of this study include the small sample size, single-site location of the investigation. All these factors may limit the generalizability of the results. Additionally, if the parameters of inflammation were taken into consideration, better results about atherosclerosis in FMS could be obtained.

### CONCLUSION

Patients with FMS may harbor the risk for atherosclerotic disease cause of chronic stress, neuroendocrine disruption, high BMI and inflammation. As an easily accessible and noninvasive method, CIMT and the morning cortisol secretion due to stress and changes in hormonal levels might be useful in the early diagnosis of atherosclerosis.

According to the present study, CIMT value and morning blood cortisol level were not found significantly different in FMS group, and also were not found correlated with each other.

With contradictory results about cortisol levels in FMS patients in the literature, to the best of our knowledge the present study was the first to research the association between CIMT with cortisol and BMI in FMS patients.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

### REFERENCES

- [1] de Groot E, van Leuven SI, Duivenvoorden R, Meuwese MC, Akdim F, Bots ML, et al. Measurement of carotid intima-media thickness to assess progression and regression of atherosclerosis. *Nat Clin Pract Cardiovasc Med* 2008;5:280-8.
- [2] Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P, Brevetti G, et al. Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. *J Am Coll Cardiol* 2010;56:2006-20.

- [3] Sharma K, Blaha MJ, Blumenthal RS, Musunuru K. Clinical and research applications of carotid intima-media thickness. *Am J Cardiol* 2009;103:1316-20.
- [4] Riva R, Mork PJ, Westgaard RH, Rø M, Lundberg U. Fibromyalgia syndrome is associated with hypocortisolism. *Int J Behav Med* 2010;17:223-33.
- [5] Semiz EA, Hizmetli S, Semiz M, Karadağ A, Adalı M, Tuncay MS, et al. Serum cortisol and dehydroepiandrosterone-sulfate levels after balneotherapy and physical therapy in patients with fibromyalgia. *Saudi Med J* 2016;37:544-50.
- [6] Rossi A, Di Lollo AC, Guzzo MP, Giacomelli C, Atzeni F, Bazzichi L, et al. Fibromyalgia and nutrition: what news? *Clin Exp Rheumatol* 2015;33(1 Suppl 88):S117-25.
- [7] Koca TT, Tanrikut E, Acet G, Talu B. Evaluation of sleep disorder and its effect on sexual dysfunction in patients with fibromyalgia syndrome. *Turk J Obstet Gynecol* 2016;13:167-71.
- [8] Sarzi-Puttini P, Atzeni F, Masala IF, Salaffi F, Chapman J, Choy E. Are the ACR 2010 diagnostic criteria for fibromyalgia better than the 1990 criteria? *Autoimmun Rev* 2018;17:33-35.
- [9] Pignoli P. Ultrasound B-mode imaging for arterial wall thickness measurement. *Atherosclerosis Rev* 1984;12:177-84.
- [10] Riedel W, Layka H, Neeck G. Secretory pattern of GH, TSH, thyroid hormones, ACTH, cortisol, FSH, and LH in patients with fibromyalgia syndrome following systemic injection of the relevant hypothalamic-releasing hormones. *Z Rheumatol* 1998;57:81-7.
- [11] Fatima G, Das SK, Mahdi AA, Verma NS, Khan FH, Tiwari AM, et al. Circadian rhythm of serum cortisol in female patients with fibromyalgia syndrome. *Indian J Clin Biochem* 2013;28:181-4.
- [12] Yeung EW, Davis MC, Ciaramitaro MC. Cortisol profile mediates the relation between childhood neglect and pain and emotional symptoms among patients with fibromyalgia. *Ann Behav Med* 2016;50:87-97.
- [13] Rus A, Molina F, Gassó M, Camacho MV, Peinado MÁ, Moral ML. Nitric oxide, inflammation, lipid profile, and cortisol in normal- and overweight women with fibromyalgia. *Biol Res Nurs* 2016;18:138-46.
- [14] Önal ZE, Soydan L, Öztürk HE, Sağ Ç, Gürbüz T, Nuhoglu Ç, et al. Carotid intima media thickness in obese children: is there an association with hyperlipidemia? *J Pediatr Endocrinol Metab* 2016;29:157-62.
- [15] Eller NH, Netterstrøm B, Hansen AM. Cortisol in urine and saliva: relations to the intima media thickness, IMT. *Atherosclerosis* 2001;159:175-85.
- [16] Eller NH, Netterstrøm B, Allerup P. Progression in intima media thickness--the significance of hormonal biomarkers of chronic stress. *Psychoneuroendocrinology* 2005;30:715-23.
- [17] Tseng CH, Chen JH, Wang YC, Lin MC, Kao CH. Increased risk of stroke in patients with fibromyalgia: a population-based cohort study. *Medicine (Baltimore)* 2016;95:e2860.
- [18] Koca TT. Does obesity cause chronic inflammation? The association between complete blood parameters with body mass index and fasting glucose. *Pak J Med Sci* 2017;33:65-9.
- [19] Tulay KT, Emrullah T, Aydin A, Ciledag OF. The effect of fibromyalgia syndrome to gravidity, parity and duration of breastfeeding; A prospective study from Turkey. *Pak J Med Sci* 2016;32:545-9.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Do antiepileptics have any potential to induce insulin resistance? A comparison between levetiracetam and valproic acid

Gökhan Özer<sup>1b</sup>

Department of Neurology, Sanko University School of Medicine, Gaziantep, Turkey

DOI: 10.18621/eurj.382538

## ABSTRACT

**Objective:** To explore whether levetiracetam and valproic acid are associated with insulin resistance and to determine their effects on glucose and insulin levels among different age groups.

**Methods:** Demographic data were collected for epileptic patients from different age groups with a normal body mass index and no chronic endocrine disease who were on levetiracetam or valproic acid therapy. In addition to routine laboratory tests, fasting insulin level was checked and Homeostatic Model Assessment for insulin resistance calculated for all patients. Based on these measurements, the effects of levetiracetam and valproic acid on laboratory parameters were compared statistically.

**Results:** A total of 61 patients (30 males, 31 females) diagnosed with epilepsy were included in the study. Thirty-four (55.7%) the patients were less than 15 years of age and the others were older. Twenty-three (37.7%) patients were on valproic acid therapy and 38 (62.3%) patients were receiving levetiracetam. Thirty-two (52.5%) the patients tested positive for insulin resistance and others were insulin resistance-negative. Nine (28.1%) patients on valproic acid treatment and 71.9% (n = 23) of patients on levetiracetam treatment were insulin resistance-positive.

**Conclusions:** In the present study, contrary to the published literature, levetiracetam was found to be associated with further negative effects on insulin and blood glucose metabolism compared to valproic acid. We determined that levetiracetam had a distinct pharmacokinetic profile in pediatric patients as demonstrated by its effects on glucose and insulin metabolism.

**Keywords:** insulin resistance, levetiracetam, epilepsy, valproic acid

*Received: January 23, 2018; Accepted: February 25, 2018; Published Online: April 10, 2018*

Altered patterns of hormonal secretion due to direct action of epileptic discharges have been shown in humans and animals, but it is difficult to establish the underlying cause of untoward effects of antiepileptic medications which can be multifactorial in epileptic patients. Monotherapy should be preferred whenever possible to avoid occurrence of adverse

effects and complicated problems [1-5].

However, prolonged use of antiepileptic drugs is known to be associated with adverse effects such as metabolic and organ toxicity, endocrine disturbance, negative cognitive effects, and psychiatric problems, particularly with alterations in thyroid function in patients with epilepsy. Some antiepileptic drugs are



Address for correspondence: Gökhan Özer, MD., Assistant Professor, Sanko University School of Medicine, Department of Neurology, Gaziantep, Turkey  
E-mail: primernordr@gmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>



enzymes responsible for vitamin D metabolism to the inactive metabolites of 25 (OH) 2 D vitamin. 1.25 (OH) 2 D vitamin level Decreases the calcium absorption so the second hyperparathyroidism, increased bone resorption and bone loss it is developing [6-9].

Studies have clearly demonstrated the impact of antiepileptic drugs, on hormonal status including effects on fertility, sexual function, bone structure and thyroid hormone. While studies evaluating thyroid function status in epileptic patients suggest that thyroid hormone levels are not directly related to epilepsy, some changes in thyroid function tests could be associated with the prescribed antiepileptic drugs [10].

Levetiracetam is structurally unrelated to other antiepileptic drugs although its effect on CYP450 enzyme induction is not clear. Levetiracetam specifically binds to the synaptic vesicle protein (SV2A) which is commonly found in the central nervous system and endocrine tissues [11]. It was observed that levetiracetam induces secretion of testosterone and estrogen without stimulating release of gonadotropin from ovarian follicular cells. This observation suggests that endocrine functions are affected by levetiracetam particularly in women of childbearing age [12]. Previous studies have shown that thyroid functions are not significantly influenced by LEV in children and adults [13]. In case-control studies, valproic acid was shown to lower blood glucose concentration independent of weight gain and hyperinsulinemia [14]. There are no studies in literature on the impact of levetiracetam on serum insulin and/or glucose levels.

## METHODS

Non-diabetic patients with epilepsy for at least one year, using epilepsy medication for at least a year and a normal body mass index who admitted to Gaziantep Sanko University School of Medicine in 2017 and were on monotherapy were included in the study after being examined by a neurologist. Ethical approval was obtained from the ethics committee of the same hospital. Patients were stratified into two groups using 15 years of age as a cut-off (Group 1, less than 15 y and Group 2,  $\geq 15$  y). Patients receiving levetiracetam

were compared with those on valproic acid. Valproic acid was chosen for the study due to its potential to induce weight gain and hyperinsulinemia and known effects on endocrine metabolism. In addition to routine biochemistry panel, fasting insulin values were measured for all patients. Medical history, age, and gender data were recorded by specialist neurologist. Height and body weight were measured to obtain body mass index (kg/m<sup>2</sup>) and age- and sex-specific body mass index percentiles. Associations between average doses of study medications and blood glucose, insulin and HOMA-IR values were examined in relation to age and gender. Insulin resistance was calculated using the The homeostasis model assessment of insulin resistance (HOMA-IR) formula of fasting insulin (uU/mL)  $\times$  fasting glucose (mmol/L) / 405 using a cut-off value of 2.5 [15]. HOMA-IR is a noninvasive and effective alternative method to evaluate insulin sensitivity based on the glucose level and the level of serum insulin measured in fasting conditions. HOMA-IR is considered a standard method of measuring insulin resistance in epidemiological studies [16].

## Statistical Analysis

Normality assumption for numerical variables was checked using the Shapiro-Wilk normality test. Mann-Whitney U test was used to compare numerical variables between independent groups and chi-square test was applied to investigate the relationship between categorical variables. Statistical analyses were conducted in SPSS for Windows, version 24.0 and a p value less than 0.05 was considered statistically significant.

**Table 1.** Demographic characteristics of patients

Variables		n	%
<b>Age (years)</b>	<15	34	55.7
	$\geq 15$	27	44.3
<b>Gender</b>	Male	30	49.2
	Female	31	50.8
<b>Medication</b>	VPA	23	37.7
	LEV	38	62.3
<b>HOMA-IR status</b>	IR (+)	32	52.5
	IR (-)	29	47.5

HOMA-IR = Homeostatic model assessment for insulin resistance, IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, LEV = levetiracetam, n = the number of patients, VPA = valproic acid

## RESULTS

A total of 61 patients were included in the study, of whom 30 (49.2%) were males. Thirty-four patients were less than 15 years of age and the others were older. Twenty-three (37.7%) patients were on valproic acid therapy and the remaining patients were on levetiracetam therapy. Thirty-two (52.5%) patients were tested positive for insulin resistance and other patients were insulin resistance-negative (Table 1).

Mean glucose value was 92.2 mg/dL, mean insulin value was 26.2 µU/mL and mean HOMA-IR value was 5.94 among insulin resistance-positive patients receiving valproic acid (Table 2). Mean glucose value was 95.91 mg/dL, mean insulin value was 21.2 µU/mL and mean HOMA-IR value was 5.29 among insulin resistance-positive patients receiving levetiracetam (Table 3). Among patients less than 15 years of age, 46.9% insulin resistance-positive and in patients older than 15 years of age, 53.1% were insulin resistance-

**Table 2.** Relationship between valproic acid, glucose, insulin, HOMA-IR

VPA group	IR (+) (n = 9)	IR (-) (n = 14)	p value
Glucose (mg/dL)	92.22 ± 16.79	83.57 ± 9.43	0.305
Insulin (µU/mL)	26.26 ± 12.67	35.72 ± 116.39	<b>0.001</b>
HOMA-IR	5.94 ± 3.02	0.94 ± 0.65	<b>0.001</b>

HOMA-IR = Homeostatic model assessment for insulin resistance, IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, n = the number of patients, VPA = valproic acid

**Table 3.** Relationship between levetiracetam, glucose, insulin, HOMA-IR

LEV group	IR (+) (n = 23)	IR (-) (n = 15)	p value
Glucose (mg/dL)	95.91 ± 8.18	81.67 ± 24.42	<b>0.006</b>
Insulin (µU/mL)	21.8 ± 13.29	75.47 ± 173.69	<b>0.005</b>
HOMA-IR	5.29 ± 3.55	1.59 ± 1.61	<b>0.001</b>

HOMA-IR = Homeostatic model assessment for insulin resistance, IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, LEV = levetiracetam, n = the number of patients

**Table 4.** Relationship between age, gender, medication and insulin resistance.

Variables	IR (+)		IR (-)		p value*	
	n	%	n	%		
Age (years)	<15	15	46.9	19	65.5	0.143
	≥15	17	53.1	10	34.5	
Gender	Male	14	43.8	16	55.2	0.373
	Female	18	56.2	13	44.8	
Medication	VPA	9	28.1	14	48.3	0.105
	LEV	23	71.9	15	51.7	

IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, LEV = levetiracetam, n = the number of patients, VPA = valproic acid, \*Chi-square test

**Table 5.** Comparison of total dose between IR (+) and IR (-) groups.

Variable	Medication	n	IR (+)	n	IR (-)	p value
Total dose (mg/day)	VPA	9	1922.22 ± 3068.7	14	489.29 ± 203.98	<b>0.016*</b>
	LEV	23	860.87 ± 501.58	15	860 ± 636.73	0.768
	Overall	32	1686.35±507.52	29	681.03±507.52	<b>0.046*</b>

IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, LEV = levetiracetam, n = the number of patients, VPA = valproic acid, \*Mann-Whitney U test

**Table 6.** Relationship between medication use and IR for different age groups

Age (years)	Medication	IR (+)		IR (-)		p value*
		n	%	n	%	
< 15	VPA	5	33.3	12	63.2	0.084
	LEV	10	66.7	7	36.8	
≥ 15	VPA	4	23.5	2	20.0	0.831
	LEV	13	76.5	8	80.0	

IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, LEV = levetiracetam, n = the number of patients, VPA = valproic acid, \*Chi-square test

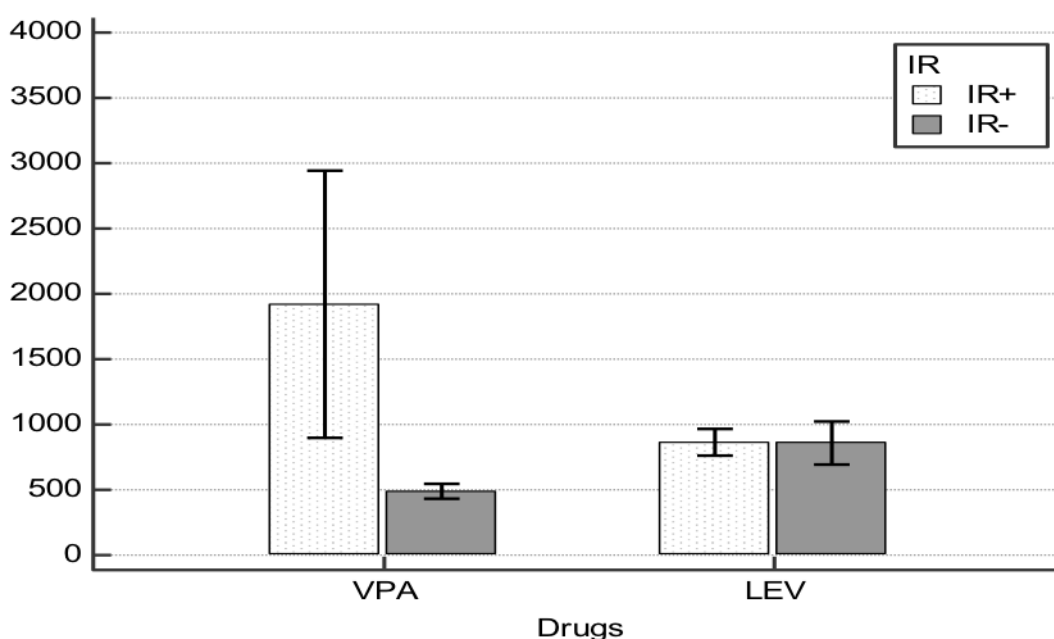
positive. Insulin resistance was detected in 56.2% of female patients. Twenty-three (71.9%) patients receiving levetiracetam treatment and 28.1% (n = 9) of patients receiving valproic acid treatment were insulin resistance-positive. No significant association was found between insulin resistance and pharmacological agents in question, age, and gender when analyzed by chi-square test (Table 4). Total dose was significantly higher in insulin resistance-positive patients for valproic acid ( $p = 0.016$ ) and overall comparison ( $p = 0.046$ ). However, no significant difference was detected for levetiracetam ( $p = 0.768$ ) (Table 5). There was no statistically significant association between valproic acid or levetiracetam use and insulin resistance in different age groups (Table 6). Insulin resistance was more likely to develop with

increased dose of medication, particularly among patients using valproic acid (Figure 1).

### DISCUSSION

Insulin resistance is a pathogenic factor for type 2 diabetes mellitus [17]. Increased insulin secretion and chronic hyperinsulinemia can develop, when pancreatic beta cells can no longer compensate and maintain glucose homeostasis, leading to the development of type 2 diabetes mellitus [18]. In adults, a cut-off value of 2.5 is generally used for HOMA-IR but at present, there is not a well-established cut-off for HOMA-IR in children.

One study in obese prepubertal and pubertal



**Figure 1.** IR positivity increases with increased total dose of VPA. IR (-) = insulin resistance-negative, IR (+) = insulin resistance-positive, LEV = levetiracetam, VPA = valproic acid.

children and adolescents (aged 5-18 years) determined that HOMA-IR cut-off values ranged from 2.67 to 5.22 for boys and 2.22 to 3.82 for girls (19). Another study in 691 apparently healthy Indian adolescents (aged 10-17 years) established a HOMA-IR cut-off of 2.5 [20].

Notably, in the current study HOMA-IR values were higher than those previously reported in pediatric patients, with an average of 2.6 in normal weight children and 4.1 to 4.3 in overweight and obese children. In a prevalence study, insulin resistance was positive in 28.9% of females and 25.1% of males [21]. A pediatric study involving 42 children with a mean age of 10.3 years and normal body weight reported an average blood glucose of 86 mg/dL, an insulin value of 11.9  $\mu$ U/mL and a HOMA-IR of 2.6 [22]. In our study, mean glucose values were 92.2 mg/dL and 95.9 mg/dL in insulin resistance-positive valproic acid and levetiracetam groups, respectively, which were greater than those found in patients with normal body weight.

In one study, on average, 25% of overweight individuals had insulin resistance; however, in the present study, 52.5% of the total study sample tested positive for insulin resistance although our patients had normal body weight [23]. As reported in literature, some children with normal body weight show a higher-than-average HOMA value and the underlying cause of this is not clear. It is possible that children in this age group (9-10 years) have higher HOMA-IR scores, perhaps due to the onset of puberty, where insulin levels have been reported to increase [24, 25]. However, as clearly shown by the current study, antiepileptic drugs have an impact on glucose and metabolism, at least to some extent.

### Limitations

A limitation of the present study is the lack of comparison of data before and after initiation of the antiepileptic medication. Additionally, we did not evaluate other parameters that could influence insulin resistance such as diet, genetic and hormonal factors. Future studies might focus on these and other parameters.

### CONCLUSION

Potential effects of antiepileptic drugs on glucose

and insulin metabolism should be investigated in larger patient series and a wider range of antiepileptics. Patients may be screened for insulin resistance before starting antiepileptic treatment and care should be exercised when choosing an antiepileptic drug to avoid potential future development of diabetes mellitus in a susceptible patient. Patients at risk for diabetes mellitus should be educated about measures that help prevent insulin resistance including diet modification and physical activity and antiepileptics associated with development of insulin resistance should be avoided.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

### REFERENCES

- [1] Edwards HE, Burnham WM, Ng MM, Asa S, MacLusky NJ. Limbic seizures alter reproductive function in the female rat. *Epilepsia* 1999;40:1370-7.
- [2] Edwards HE, Burnham WM, MacLusky NJ. Partial and generalized seizures affect reproductive physiology differentially in the male rat. *Epilepsia* 1999;40:1490-8.
- [3] Feeney DM, Gullotta FP, Gilmore W. Hyposexuality produced by temporal lobe epilepsy in the cat. *Epilepsia* 1998;39:140-9.
- [4] Herzog AG. A relationship between particular reproductive endocrine disorders and the laterality of epileptiform discharges in women with epilepsy. *Neurology* 1993;43:1907-10.
- [5] Banczerowski P, Csaba Z, Csernus V, Gerendai I. Lesion of the amygdala on the right and left side suppresses testosterone secretion but only left-sided intervention decreases serum luteinizing hormone level. *J Endocrinol Invest* 2003;26:429-34.
- [6] Gaitatzis A, Sander JW. The long-term safety of antiepileptic drugs. *CNS Drugs* 2013;27:435-55.
- [7] Jovanovic M, Jovic-Jakubi B, Stevanovic D. Adverse effects of antiepileptic drugs and quality of life in pediatric epilepsy. *Neurol India* 2015;63:353-9.
- [8] Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *Lancet Neurol* 2012;11:792-802.
- [9] Shen C, Chen F, Zhang Y, Guo Y, Ding M. Association between use of antiepileptic drugs and fracture risk: a systematic review and meta-analysis. *Bone* 2014;64:246-53.
- [10] Svalheim S, Sveberg L, Mochol M, Tauboll E. Interactions between antiepileptic drugs and hormones. *Seizure* 2015;28:12-7.
- [11] Pennell PB. Hormonal aspects of epilepsy. *Neurol Clin* 2009;27:941-65.
- [12] Harden CL, Nikolov BG, Kandula P, Labar DR, Pannullo S. Effect of levetiracetam on testosterone levels in male patients. *Epilepsia* 2010;51:2348-51.

- [13] Taubøll E, Gregoraszcuk EL, Tworzydło A, Wójtowicz AK, Ropstad E. Comparison of reproductive effects of levetiracetam and valproate studied in prepubertal porcine ovarian follicular cells. *Epilepsia* 2006;47:1580-3.
- [14] Aygün F, Ekici B, Aydinli N, Aydin BK, Baş F, Tatli B. Thyroid hormones in children on antiepileptic therapy. *Int J Neurosci* 2012;122:69-73.
- [15] Martin CK, Han H, Anton SD, Greenway FL, Smith SR. Effect of valproic acid on body weight, food intake, physical activity and hormones: results of a randomized controlled trial. *J Psychopharmacol* 2009; 23:814-25.
- [16] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412-9.
- [17] Wallace TM, Matthews DR. The assessment of insulin resistance in man. *Diabet Med* 2002;19:527-34.
- [18] Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Meigs JB, et al. Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. *Diabetes* 2004;53:1782-9.
- [19] Gungor N, Hannon T, Libman I, Bacha F, Arslanian S. Type 2 diabetes mellitus in youth: the complete picture to date. *Pediatr Clin North Am* 2005;52:1579-609.
- [20] Kurtoglu S, Hatipoglu N, Mazicioglu M, Kendirici M, Keskin M, Kondolot M. Insulin resistance in obese children and adolescents:HOMA-IR cut-off levels in the prepubertal and pubertal periods. *J Clin Res Pediatr Endocrinol* 2010;2:100-6.
- [21] Singh Y, Garg MK, Tandon N, Marwaha RK. A study of insulin resistance by HOMA-IR and its cut-off value to identify metabolic syndrome in urban Indian adolescents. *J Clin Res Pediatr Endocrinol* 2013;5:245-51.
- [22] Kaya A, Turan E, Uyar M, Bayram F, Turan Y. The prevalence of insulin resistance in the Turkish population: a study conducted with 3331 participants. *EJMO* 2017;1:202-6.
- [23] Beccarelli LM, Scherr RE, Newman JW, Borkowska AG, Gray IJ, Linnell JD, et al. Associations among fatty acids, desaturase and elongase, and insulin resistance in children. *J Am Coll Nutr* 2018;37:44-50.
- [24] Guzzaloni G, Grugni G, Mazzilli G, Moro D, Morabito F. Comparison between beta-cell function and insulin resistance indexes in prepubertal and pubertal obese children. *Metabolism* 2002;51:1011-6.
- [25] Tobisch B, Blatniczky L, Barkai L. Cardiometabolic risk factors and insulin resistance in obese children and adolescents: relation to puberty. *Pediatr Obes* 2015;10:37-44.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Neurological findings in autosomal dominant polycystic kidney disease

Demet Yıldız<sup>1</sup>, Abdülmecit Yıldız<sup>2</sup>

<sup>1</sup>Department of Neurology, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

<sup>2</sup>Department of Neurology, Uludağ University School of Medicine, Bursa, Turkey

DOI: 10.18621/eurj.379970

## ABSTRACT

**Objective:** Autosomal dominant polycystic kidney disease (ADPKD) mainly affects the kidneys, but other abnormalities like intracranial aneurysms (ICAs) are not uncommon. In this study, we aimed to investigate retrospectively frequency of ICA and other neurological abnormalities in ADPKD patients.

**Methods:** One hundred and forty patients with ADPKD who did not receive replacement therapy and followed-up at outpatient clinic were evaluated.

**Results:** The mean age of the patients was  $43.4 \pm 13$  years and mean glomerular filtration rate was  $87 \pm 15$  ml/min. ICA was detected in four (2.8%) patients. Three patients were from the same family. Thirteen (9.3%) patients had magnetic resonance angiography due to their family stories, but aneurysm was not seen in them.

**Conclusion:** Individuals with ADPKD who have a history of aneurysm or hemorrhage in their family should be screened for aneurysm due to mortality and risk of recurrent rupture.

**Keywords:** Autosomal dominant, polycystic kidney disease, intracranial aneurysms, arachnoid cysts

*Received: January 17, 2018; Accepted: February 12, 2018; Published Online: April 12, 2018*

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic systemic disease that characterized by cysts in kidneys and other organs like liver, pancreas, brain and vascular bed. The gene that mostly (in 85% of the cases) causes the disease is polycystic kidney disease 1 (PKD1) gene on the short arm of chromosome 16 (16p13.3). In 15% of the cases, polycystic kidney disease 2 (PKD2) gene on the long arm of chromosome 4 (4q21) results in ADPKD. Both genes are pleiotropic and influence many phenotypic characteristics. For instance, abdominal hernias, mitral valve prolapse, aorta dilatation and intracranial aneurysms (ICAs) can be observed clinically in the ADPKD cases. Frequency of ICA varies depending on the family history and was reported to change between

6% to 20% [1, 2]. Arachnoid cysts (8%) and meningeal cysts (2%) are other structural abnormalities of central nervous system (CNS) [3, 4]. The most feared clinical picture of ICA is rupture. Although localization, size and rupture story determine prognosis, there is no sufficient data about this issue in ADPKD [5]. It was reported that rupture risk of ICA increases fivefold in ADPKD patients compared to overall population. Family clustering of ADPKD patients with ICA story is apparent, but the presence of ICA among the family members who have the disease is heterogeneous. Besides, the frequency of ischemic stroke is expected to rise in ADPKD cases because of the increased cardiovascular risk. In this study, ADPKD patients were investigated with regard



Address for correspondence: Demet Yıldız, MD., University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Neurology, Bursa, Turkey  
E-mail: demetyildiz@gmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

to CNS abnormalities. Such abnormalities detected with imaging methods were analyzed as well.

## METHODS

One hundred and forty patients who were conclusively diagnosed with ADPKD based on the family story, clinical findings and imaging methods and consulted to outpatient clinic of Uludağ University School of Medicine Nephrology Department were evaluated retrospectively in the study. The patients who underwent renal replacement therapy were excluded from the study, since they would not be followed-up at outpatient clinic. Ultrasound criteria suggested by Pei *et. al.* [6]. were used as diagnosis criteria of ADPKD. Over the course of routine outpatient clinic controls, all of the patients were investigated with regard to possible extrarenal findings, comorbid diseases, smoking history, family history of sudden death, presence of ICA and history of cerebrovascular disease. All of the patients with ICA story in family have been screened with magnetic resonance angiography. The cases that contain aneurysm were consulted to Neurosurgery department.

### Statistical Analysis

As part of statistical analysis, descriptive analyses were performed with SPSS version 22. Variables were given as mean  $\pm$  standard deviation.

## RESULTS

The mean age of the patients was  $43.4 \pm 13$  years. There were 61 males and 79 females. Sixty-eight percent of the patients did not have smoking history. Hypertension was not detected in 33.6% ( $n = 47$ ) of the patients. Of the whole group, 44.3% ( $n = 62$ ) had controlled hypertension and 22.1% ( $n = 31$ ) had uncontrolled hypertension. Fifty-five (39.3%) patients were found to have liver cyst which was the most common extrarenal finding (Mean age:  $47 \pm 12$  years, 36 females, 19 males). Mean glomerular filtration rate was  $87 \pm 15$  ml/min. In terms of neurological findings, ICA was seen in four (2.8%) patients. The aneurysms detected were saccular with a mean diameter of 4.5 mm. In three patients, they were located on the right

and left middle cerebral artery. One patient had aneurysm on posterior inferior cerebellar artery (PICA). This patient who was determined to have 3.5 mm aneurysm on the left and 4.5 mm on the right admitted to the hospital due to bleeding stroke. He died within one month following the operation. Of other three patients, two underwent an operation in which elective clamp was placed, and one had clamped after hemorrhage. Follow-up of these three patients, who were operated electively or emergency have shown no sign of neurological deficiency. Thirteen (9.3%) patients had magnetic resonance angiography due to their family story of ICA, but no aneurysm was detected. With respect to other neurological findings in history, one patient had subdural hematoma, two patients had arachnoid cyst and two patients had epilepsy. Oligodendroglioma was reported (WHO grade 2) in a patient with epilepsy history in frontal region. The patient had postoperative radiotherapy and followed-up without any neurological deficiency. As part of the investigation about cerebrovascular disease, only one patient was detected to have a story of ischemic stroke. Two patients were examined because of headache. Pituitary macroadenoma was observed in one patient, but the lesion with spontaneous shrinking size was interpreted as pituitary cyst. Other patient was diagnosed with migraine.

## DISCUSSION

In our series, aneurysm frequency of ADPKD patients followed-up was lower than that of literature. However, compared to overall population, it was supposed to be higher. This finding may result from the exclusion of the patients who had renal replacement therapy [7]. The findings such as age of onset, hypertension and uremia which are not specific to the disease may improve cerebral hemorrhage risk. It is consistent with literature that the patients who were determined to have aneurysm rupture and asymptomatic aneurysm were in the same family. Intracranial vascular imaging is essential especially for these patients with story of ICA rupture. In literature, it is reported that ADPKD patients with ICA rupture had a mortality rate of 50% [5, 7, 8]. If ADPKD patients whose genetic penetrance are 100%

**Table 1.** Type and location of intracranial aneurysm

Cases	Initial presentation	Location	Diameter (mm)	Outcome
1	Subarachnoid hemorrhage	Left and right PICA	5.5/3.5	Death
2	Subarachnoid hemorrhage	Anterior	3	at follow-up no neurological deficit
3	Elective surgery	Anterior	35	at follow-up no neurological deficit
4	Elective surgery	Anterior	3	at follow-up no neurological deficit

PICA = posterior inferior cerebellar artery

had family stories of sudden death, they can be investigated with regard to presence of ICA. This slowly progressive disease and the emergence of renal failure after the fifth decade make us think that premature death cases seen in the families of patients may result from ICA rupture. In line with this observation, the aneurysm rupture in ADPKD is experienced at a younger age compared to overall population [9]. In general, ICAs seen in ADPKD cases are detected in anterior circle of Willis [3]. In our study, the aneurysms determined in all cases, except one were in the anterior circulation. In a recent meta analysis which evaluated ADPKD with 563 aneurysms, mean diameter of non-ruptured aneurysm was 4.4 mm and the middle cerebral artery was the main location among half of the patients [8]. In three of our patients, the involvement location was the right and left middle cerebral artery and the diameter of aneurysm was lower than literature (Table 1). There was only one posterior circulation aneurysm that located at PICA, was died. Different aneurysm location of that patient who was in the same family with other two patients make us think that rupture risk may differ despite the presence of aneurysm in the same family. In a case in which pituitary macroadenoma was detected and hormone profile is normal, diameter of adenoma shrank and the lesion was considered as a cyst later. Therefore, we speculated that most of the extrarenal findings in those patients may be associated with PKD1 gene or PKD2 gene.

## CONCLUSION

In conclusion, our results confirm that ICA

bleeding in ADPKD patients tends to cluster in families and family history is so important and can provide invaluable information about rupture risk.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

### Acknowledgments

We thank Prof. Hasan Kocaeli, M.D., Faculty Member in Neurosurgery Department, and his team who performed intracranial aneurysm operations.

## REFERENCES

- [1] Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet* 2007;369:1287-301.
- [2] Chebib FT, Torres VE. Autosomal dominant polycystic kidney disease: core curriculum 2016. *Am J Kidney Dis* 2016;67:792-810.
- [3] Luciano RL, Dahl NK. Extra-renal manifestations of autosomal dominant polycystic kidney disease (ADPKD): considerations for routine screening and management. *Nephrol Dial Transplant* 2014;29:247-54.
- [4] Leung GK, Fan YW. Chronic subdural haematoma and arachnoid cyst in autosomal dominant polycystic kidney disease (ADPKD). *J Clin Neurosci* 2005;12:817-9.
- [5] Belz MM, Fick-Brosnahan GM, Hughes RL, Rubinstein D, Chapman AB, Johnson AM, et al. Recurrence of intracranial aneurysms in autosomal-dominant polycystic kidney disease. *Kidney Int* 2003;63:1824-30.
- [6] Pei Y, Obaji J, Dupuis A, Paterson AD, Magistroni R, Dicks E, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol* 2009;20:205-12.
- [7] Xu HW, Yu SQ, Mei CL, Li MH. Screening for intracranial aneurysm in 355 patients with autosomal-dominant polycystic kidney disease. *Stroke* 2011;42:204-6.



[8] Cagnazzo F, Gambacciani C, Morganti R, Perrini P. Intracranial aneurysms in patients with autosomal dominant polycystic kidney disease: prevalence, risk of rupture, and management. A systematic review. *Acta Neurochir (Wien)* 2017;159:811-21.

[9] Schrier RW, Belz MM, Johnson AM, Kaehny WD, Hughes RL,

Rubinstein D, et al. Repeat imaging for intracranial aneurysms in patients with autosomal dominant polycystic kidney disease with initially negative studies: a prospective ten-year follow-up. *J Am Soc Nephrol* 2004;15:1023-8.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# The importance of red cell distribution width and neutrophil-lymphocyte ratio as a new biomarker in rheumatoid arthritis

Tuba Tülay Koca<sup>1</sup>, Aydın Arslan<sup>2</sup>, Filiz Çiledağ Özdemir<sup>3</sup>, Ejder Berk<sup>1</sup>

<sup>1</sup>Department of Physical Medicine and Rehabilitation, Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey

<sup>2</sup>Department of Orthopaedics and Traumatology, Gelişim University School of Medicine, Elit Medical Center, İstanbul, Turkey

<sup>3</sup>Department of Physiotherapy and Rehabilitation, İnönü University Faculty of Health Sciences, Malatya, Turkey

DOI: 10.18621/eurj.376346

## ABSTRACT

**Objective:** Rheumatoid arthritis (RA) is a long-lasting autoimmune disorder that primarily affects the joints. Various biomarkers have been used for the prognosis and clinical follow-up. There are few studies that have investigated whether or not neutrophil-lymphocyte ratio (NLR) and red cell distribution width (RDW) are good indicators of systemic inflammation. The present study aims to explore the prognostic value of RDW and NLR in rheumatoid arthritis (RA) as a new inflammatory marker.

**Methods:** RA patients (n = 124) who presented to the Rheumatology outpatient clinic in our hospital between March 2015 and May 2015 were included in this study retrospectively. As a first group, 47 clinically active RA patients who had high acute phase proteins were included. In the second group, 73 clinically in-remission RA patients who had normal acute phase proteins were included. Fifty-five healthy volunteers constituted the control group.

**Results:** The mean RDW was found to be  $15.2 \pm 2.9$  in the active group;  $14.6 \pm 2$  in the inactive group and  $13.4 \pm 1.4$  in the control group ( $p < 0.01$ ). The mean NLR was found to be  $3.7 \pm 2.2$  in the active group;  $3.7 \pm 1.6$  in the inactive group and  $3.2 \pm 0.9$  in the control group ( $p = 0.190$ ). There were statistically significant differences between the RDW values of the active-period RA patients with the control group ( $p < 0.01$ ). There was statistically significant difference between RDW values of active RA and inactive RA patients ( $p < 0.01$ ). The NLR results between the RA group and the control group ( $p = 0.700$ ); the active RA group, and the inactive RA group ( $p = 0.169$ ) were similar. There was not statistically difference between the NLR values of active RA patients with the control group ( $p = 0.360$ ). There was statistically difference between the NLR values of inactive RA patients with the control group ( $p = 0.047$ ).

**Conclusion:** RDW was found higher in all RA group than control, additionally was also higher in active RA group than remission group. NLR values of remission group was higher than control.

**Keywords:** rheumatoid arthritis, erythrocyte distribution width, biomarker, neutrophil-lymphocyte ratio

*Received: January 8, 2018; Accepted: March 20, 2018; Published Online: April 12, 2018*

Rheumatoid arthritis (RA) is a long-lasting autoimmune disorder that primarily affects the joints. It typically results in warm, inflated, and painful joints [1]. The course of disease in RA is variable.

Various biomarkers have been used for the prognosis and clinical follow-up [1, 2].

Red cell distribution width (RDW) is a measurement that shows heterogeneity of erythrocyte



Address for correspondence: Tuba Tülay Koca, MD., Assistant Professor, Sütçü İmam University School of Medicine, Department of Physical Medicine and Rehabilitation, Kahramanmaraş, Turkey  
E-mail: tuba\_baglan@yahoo.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

volume, a condition also known as anisocytosis. RDW has been shown in recent studies to be increased in inflammatory as well as in arteriosclerotic cardiac diseases [2].

The neutrophil to lymphocyte ratio (NLR) is usually calculated by dividing the number of neutrophils into the number of lymphocytes in peripheral blood samples; it can sometimes be obtained from infiltrated tissue cells such as tumor tissue [3, 4]. This ratio has been used as a subclinical inflammation marker for many diseases. RDW and NLR are one of the important total blood cell count parameters [1-4].

Sometimes, markers such acute phase proteins, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are insufficient to show disease activity. Acute phase proteins are insufficient to indicate a systemic inflammatory response, because they increase only as an indirect result of local inflammatory processes. In addition, ESR and CRP values can be affected by a recent infection and therefore are nonspecific for prediction of the inflammation [5-8].

However, there are few studies that have investigated whether or not NLR and RDW are good indicators of systemic inflammation. The present study aims to explore the prognostic value of RDW and NLR in RA as a new inflammatory marker.

## METHODS

RA patients ( $n = 124$ ) who attempt to the Rheumatology outpatient clinic of our hospital between March 2015 and May 2015 were included in this study. As a first group, 47 clinically active RA patients who had high acute phase proteins were included. In the second group, 73 clinically in remission RA patients who had normal acute phase proteins were included. Fifty-five healthy volunteers constituted the control group.

Diagnosis of RA was done according to the 2010 American College of Rheumatology (ACR)/ The European League Against Rheumatism (EULAR) classification criteria. Inclusion criteria were RA diagnosis without any infection, any other systemic inflammatory disease, trauma history, bleeding and malignancy. Biochemical, hematological, and

inflammatory parameters were measured. Clinical anamnesis and complete blood parameters and derivatives, RDW and NLR values, rheumatoid factor (RF, 0-20), CRP (0-4.9 mg/L), ESR (0-20 mm/h) were obtained from the hospital data in all groups. Laboratory parameters CRP > 15 mg/L, ESR > 28 mm/h values were accepted as high inflammation together with clinical signs.

The study approved by the local ethics committee and was adhered to the principles of Helsinki declaration.

## Statistical Analysis

The SPSS 16 version was used for data analysis. Descriptive data were presented as mean  $\pm$  standard deviation and median scores. The coherence of variables to normal distribution (normality) was analyzed using the Kolmogorov-Smirnov test. One-way Anova and student t tests were used to analyze normally distributed data and Kruskal Wallis test was used to compare abnormal distributed data among groups. A  $p$  value of < 0.05 was considered statistically significant.

## RESULTS

Descriptive characteristics of the groups were shown in Table 1. The mean age of RA patients in the active period was  $53.5 \pm 13.7$  years; the mean age of RA patients in the inactive period of the disease was  $48.7 \pm 13.61$  years; the mean age of the control group was  $48.3 \pm 13.81$  years ( $p = 0.027$ ).

The mean RDW was found to be  $15.2 \pm 2.9$  in the active group;  $14.6 \pm 2$  in the inactive group and  $13.4 \pm 1.4$  in the control group ( $p < 0.01$ ). The mean NLR was found to be  $3.7 \pm 2.2$  in the active group;  $3.7 \pm 1.6$  in the inactive group and  $3.2 \pm 0.9$  in the control group ( $p = 0.190$ ).

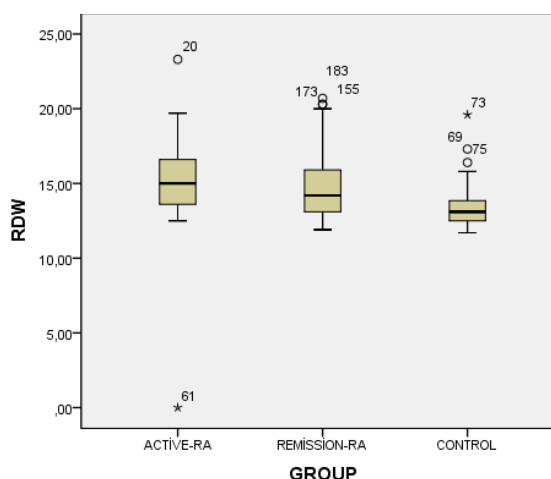
There were statistically significant differences between the RDW values of the active-period RA patients with the control group ( $p < 0.01$ ) (Figure 1) (Table 1). There was statistically significant difference between RDW values of active RA and inactive RA patients ( $p < 0.01$ ).

The NLR results between the RA group and the control group ( $p = 0.700$ ); the active RA group, and the inactive RA group ( $p = 0.169$ ) were similar. There

**Table 1.** Characteristics of demographic and laboratory data

	Active RA (n = 47)	Inactive RA (n = 73)	Control (n = 55)	p value
Age (year)	53.5 ± 13.7	48.7 ± 13.61	48.3 ± 13.81	<b>0.027</b>
Gender (M/F)	9/52	13/64	13/43	0.47
Sedimentation (mm/h)	49.51 ± 13.4	20.00 ± 9.30	17.38 ± 9.05	<b>&lt; 0.01</b>
CRP (mg/dL)	2.22 ± 2.9	0.52 ± 0.28	0.39 ± 0.22	<b>0.02</b>
Leukocyte (×10 <sup>3</sup> )	7.68 ± 1.7	7.75 ± 2.42	7.45 ± 1.93	0.370
Erythrocyte (×10 <sup>3</sup> )	4.73 ± 0.4	4.8 ± 0.40	4.92 ± 0.47	0.270
Thrombocyte (K/mm <sup>3</sup> )	297.0 ± 65.0	268.8 ± 49.4	263.49 ± 53.80	0.110
Hemoglobin (gr/dL)	13.06 ± 1.26	13.55 ± 1.12	14.06 ± 1.70	<b>&lt; 0.01</b>
Lymphocyte (×10 <sup>3</sup> )	2.16 ± 0.67	2.3 ± 0.89	2.34 ± 0.64	0.570
Monocyte (×10 <sup>3</sup> )	0.67 ± 0.23	0.62 ± 0.21	0.52 ± 0.19	0.870
Basophil (×10 <sup>3</sup> )	0.05 ± 0.02	0.05 ± 0.02	0.04 ± 0.02	0.080
Eosinophil (×10 <sup>3</sup> )	0.14 ± 0.09	0.18 ± 0.13	0.17 ± 0.11	0.370
RDW (%)	15.2 ± 2.9	14.6 ± 2	13.4 ± 1.4	<b>&lt; 0.01</b>
NLR (%)	3.7 ± 2.2	3.7 ± 1.6	3.2 ± 0.9	0.190

Data are shown as mean ± standard deviation. CRP = C- reactive protein (CRP), NLR = neutrophil-lymphocyte ratio, RA = rheumatoid arthritis, RDW = red cell distribution width



**Figure 1.** Boxplot of red cell distribution width (RDW) values among the groups.

was not statistically difference between the NLR values of active RA patients with the control group ( $p = 0.360$ ). There was statistically difference between the NLR values of inactive RA patients with the

control group ( $p = 0.047$ ).

When we divide our RA patients into two groups on the bases of RF-positive and RF-negative, statistically difference was found in RDW values between the groups ( $p = 0.041$ ) (Table 2) (Figure 2).

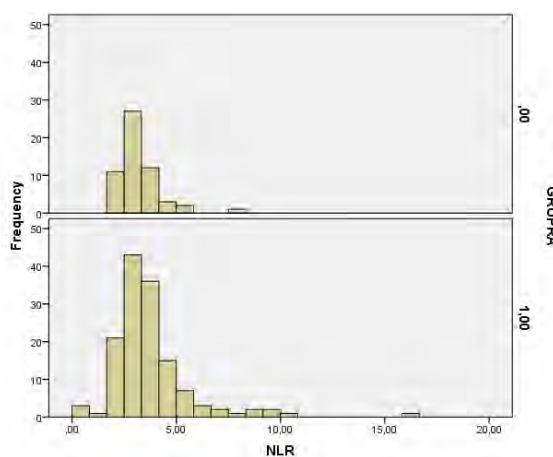
**Table 2.** Comparisons of RF presence with RDW/NLR

	RF negative RA (n = 60)	RF positive RA (n = 64)
RDW	$p = 0.041$	
NLR	$p = 0.260$	

NLR = neutrophil-lymphocyte ratio, RA = rheumatoid arthritis, RF = rheumatoid factor, RDW = red cell distribution width

## DISCUSSION

RA is a chronic autoimmune disease that is characterized by widespread synovitis results in joint damage and erosion in the articular cartilage and marginal bone [1]. RA pathophysiology shares the



**Figure 2.** Histogram of neutrophil-lymphocyte Ratio (NLR) values between rheumatoid arthritis (number 1) and control (number 0) groups.

common cascades with atherosclerosis, including endothelial dysfunction related to the underlying chronic inflammation [5].

At the onset of the disease, many patients are negative for the rheumatoid factor (RF), but 85% of the patients will show positivity in the course of disease. High RF levels indicate destructive joint disease. In recent years, many laboratory tests specific to disease monitoring have been developed in RA [9].

RDW is a quantitative measurement that shows the volume heterogeneity of red blood cells and RDW has been used in differential diagnosis of anemia. Many studies have shown that RDW, also called anisocytosis, increases during systemic inflammation or the cardiometabolic effect [6, 7]. In addition to differential diagnosis of anemia, recent evidence shows that anisocytosis is an important indication for cancer, cardiovascular disease, venous thromboembolism, diabetes, community-acquired pneumonia, chronic obstructive pulmonary disease, kidney and liver failure, and other acute and chronic illness [10, 11].

It is a well-known fact that red blood cell life is approximately 120 days, and rapid changes in RDW values are more powerful for predicting chronic inflammation in RA patients with acute infections as compared with ESR and CRP levels. Many studies have found RDW to be positively correlated with CRP and ESR [12-14].

In the study by Baynes *et al.* [15], which evaluated hematological parameters of 265 RA patients,

measurements of iron-related RDW of RA patients were studied. In all study groups, a slight decrease in hemoglobin and mean corpuscular volume (MCV) values were found to be related to an increase in RDW, ESR, and platelet levels. In another study by Hassan *et al.* [16], RDW level was found to be a useful parameter to show inflammation and high risk of progress. A high level of RDW also had a strong and independent correlation with ESR and CRP in systemic lupus erythematosus [17, 18], Sjögren syndrome [19], systemic sclerosis [20], and familial mediterranean fever [21] patients in recent studies. RDW has also been found to be related to cardiovascular disease in various diseases [22].

High numbers of neutrophils are mostly associated with poor prognosis and an increased mortality rate. In recent years, studies that addressed the relation between inflammation and neutrophils subtypes have shown an increasing trend. It has been reported that the NLR value increases in response to activity in various inflammatory diseases [22-26]. However, the clinical importance of these values for evaluating RA progression remains unclear. In the study by Mercan *et al.* [23], NLR was shown to be an inexpensive and easily measurable method for evaluating the disease activity in patients with RA and AS. According to the study by Fu *et al.* [24], the NLR is found positively correlated with ESR, CRP, and disease activity score (DAS 28) values in RA patients. Uslu *et al.* [25] have reported that NLR and the platelet-lymphocyte ratio (PLR) values showed a positive correlation in RA patients. Another study by Tekeoglu *et al.* [26] also

showed that mean platelet volume (MPV) and NLR values change according to activity level of the disease.

The NLR has also been used as a marker for various systemic autoimmune diseases such as ankylosing spondylitis [27], familial mediterranean fever [21, 28], Behçet syndrome [29], Sjögren syndrome [19], systemic lupus erythematosus [30], and psoriasis [31]. In recent years, complete blood parameters and derivatives are guiding us in showing the severity of diseases especially in inflammatory rheumatic diseases [32-34].

In this study, statistically significant differences of RDW values among the three groups have led us to think that the RDW might be positively related to inflammation and also to ESR and CRP values. ESR and CRP values were used to separate the two groups of RA patients. Those two parameters sometimes are not able to diagnose active disease, in half of active RA patients these parameters may be found normal. They are also affected by the infection. On the other hand, RDW values of both RA groups were found higher compared with those of the control group. This indicates that RDW can be used as an inflammation marker, both in diagnosis and clinical follow-up.

When RA patients were separated into two groups as RF positive and negative, it was observed that the RDW value was higher in positive group. According to that result, we can conclude that RDW might be used as a biomarker for determining the severity of the disease.

We compared the values of NLR among all three groups. We only found a statistically difference between the NLR values of remission period-RA patients with control group. In the light of this result, we may say that NLR may show chronic inflammation. We should also conclude that there could be other factors that affect NLR. In elderly patients who are in an active period of the disease may be seen as normal in laboratory and it may have affected the results of the study. Additionally, NLR was not found to be related with the RF. In young patients at an early stage of the disease, the positivity of RF is 15%, which is independent of disease progression; it becomes positive over time. These younger patients could have affected the results of the study.

## Limitations

One of the limitation of our study is having a small sample size due to low prevalence of the disease. Additionally as it is a retrospective study, we could not calculate DAS 28 score because most of the patients' visual analogous score (VAS), number of tender and swollen joints and duration of morning stiffness were not found in the hospital data. In most of RA patients chronic anemia is observed over time. But we didn't consider the hemoglobin, vitamin B12, and folic acid values that may affect the RDW values.

## CONCLUSION

According to our study; RDW was found higher in all RA group than control, additionally was also higher in active RA group than remission group. NLR values of remission-RA group was found higher than control. Biomarkers that measures the activity of RA disease is a rapidly growing field in recent years. RDW and NLR biomarkers might contribute as a potential marker to detect diagnosis and disease activity in RA patients.

## Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

## Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

- [1] Majithia V, Geraci SA. Rheumatoid arthritis: diagnosis and management. *Am J Med* 2007;120:936-9.
- [2] Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakawaza T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med* 2007;146:797-808.
- [3] Wang X. Neutrophil to lymphocyte ratio in relation to risk of all-cause mortality and cardiovascular events among patients undergoing angiography or cardiac revascularization: a meta-analysis of observational studies. *Atherosclerosis* 2014;234: 206-13.
- [4] Wang J. The clinical significance of tumor-infiltrating neutrophils and neutrophil-to-CD8+ lymphocyte ratio in patients with resectable esophageal squamous cell carcinoma. *J Transl Med* 2014;12:7.
- [5] Chimenti MS, Triggianese P, Conigliaro P, Candi E, Melino G,

- Perricone R. The interplay between inflammation and metabolism in rheumatoid arthritis. *Cell Death Dis* 2015;17:e1887.
- [6] Giles JT. Cardiovascular disease in rheumatoid arthritis: Current perspectives on assessing and mitigating risk in clinical practice. *Best Pract Res Clin Rheumatol* 2015;29:597-613.
- [7] Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red cell distribution width: a simple parameter with multiple clinical applications. *Crit Rev Clin Lab Sci* 2015;52:86-105.
- [8] Goodnow CC. Multistep pathogenesis of autoimmune disease. *Cell* 2007;130:25-35.
- [9] Holzinger D, Föll D. [Biomarkers for chronic inflammatory diseases]. *Z Rheumatol* 2015;74:887-97. [Article in German]
- [10] Sanmartí R, Gómez-Puerta JA. [Biomarkers in rheumatoid arthritis]. *Rheumatol Clin* 2011;6S3:S25-8. [Article in Spanish]
- [11] Sertoglu E, Kayadibi H, Uyanık M. Is single red cell distribution width without iron, folic acid and vitamin B12 enough to decide? *Hepatol Res* 2014;44:1371.
- [12] Peng YF, Zhang Q, Cao L, Liu Y, Chen D, Sun YK, et al. Red blood cell distribution width: a potential marker estimating disease activity of ankylosing spondylitis. *Int J Clin Exp Med* 2014;7:5289-95.
- [13] Peristein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. *Arch Intern Med* 2009;169:588-94.
- [14] Harrington AM, Ward PC, Kroft SH. Iron deficiency anemia, beta-thalassemia minor, and anemia of chronic disease: a morphologic reappraisal. *Am J Clin Pathol* 2008;29:466-71.
- [15] Baynes RD, Bothwell TH, Bezwoda WR, Gear AJ, Atkinson P. Hematologic and iron-related measurements in rheumatoid arthritis. *Am J Clin Pathol* 1987;87:196-200.
- [16] Hassan S, Antonelli M, Ballou S. Red cell distribution width: a measure of cardiovascular risk in rheumatoid arthritis patients. *Clin Rheumatol* 2015;34:1053-7.
- [17] Vaya A, Hernandez JL, Calvo J, Mico L, Romagros M, et al. RDW in patients with systemic lupus erythematosus influence of anemia and inflammatory markers. *Clin Hemorrhheol Microcirc* 2013;54:333-9.
- [18] Hu ZD, Chen Y, Zhang L, Sun Y, Huang YL, Wang QQ, et al. Red blood cell distribution width is a potential index to assess the disease activity of systemic lupus erythematosus. *Clin Chim Acta* 2013;425:202-05.
- [19] Hu ZD, Sun Y, Guo J, Huang YL, Qin BD, Gao Q, et al. Red blood cell distribution width and neutrophil/lymphocyte ratio are positively correlated with disease activity in primary Sjögren's syndrome. *Clin Biochem* 2014;47:287-90.
- [20] Farkos N, Szabo A, Larond V, Sarlos DP, Minier T, Prohaszka Z, et al. Clinical usefulness of measuring red blood cell distribution width in patients with systemic sclerosis. *Rheumatology (Oxford)* 2014;53:1439-45.
- [21] Özer S, Yılmaz R, Sönmezgöz E, Karaaslan E, Taşkın S, Bütün İ, et al. Simple markers for subclinical inflammation in patients with familial Mediterranean fever. *Med Sci Monit* 2005;21:298-303.
- [22] Rodriguez-Carrio J, Alperi-Lopez M, Lopez P, Alonso-Castro S, Ballina-Garcia FJ, Suarez A. Red cell distribution width is associated with cardiovascular risk and disease parameters in rheumatoid arthritis. *Rheumatology (Oxford)* 2015;54:641-6.
- [23] Mercan R, Bitik B, Tufan A, Bozbulut UB, Atas N, Ozturk MA, et al. The association between neutrophil/lymphocyte ratio and disease activity in rheumatoid arthritis and ankylosing spondylitis. *J Clin Lab Anal* 2016;30:597-601.
- [24] Fu H, Qin B, Hu Z, Ma N, Yang M, Wei T, et al. Neutrophil- and platelet-to-lymphocyte ratios are correlated with disease activity in rheumatoid arthritis. *Clin Lab* 2015;61:269-73.
- [25] Uslu AU, Küçük A, Şahin A, Ugan Y, Yılmaz R, Güngör T, et al. Two new inflammatory markers associated with disease activity score-28 in patients with rheumatoid arthritis: neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. *Int J Rheum Dis* 2015;18:731-5.
- [26] Tekeoğlu İ, Gürol G, Harman H, Karakeçe E, Çiftçi İH. Overlooked hematological markers of disease activity in rheumatoid arthritis. *Int J Rheum Dis* 2016;19:1078-82.
- [27] Gökmen F, Akbal A, Reşorlu H, Gökmen E, Güven M, Aras AB, et al. Neutrophil-lymphocyte ratio connected to treatment options and inflammation markers of ankylosing spondylitis. *J Clin Lab Anal* 2015;29:294-8.
- [28] Uslu AU, Deveci K, Korkmaz S, Aydın B, Senel S, Sancakdar E, et al. Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial Mediterranean fever? *Biomed Res Int* 2013;2013:185317.
- [29] Alan S, Tuna S, Türkoğlu EB. The relation of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume with the presence and severity of Behçet's syndrome. *Kaohsiung J Med Sci* 2015;31:626-31.
- [30] Qin B, Ma N, Tang Q, Wei T, Yang M, Fu H, et al. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. *Mod Rheumatol* 2016;26:372-6.
- [31] Kim DS, Shin D, Lee MS, Kim HJ, Kim DY, Kim SM, et al. Assessments of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in Korean patients with psoriasis vulgaris and psoriatic arthritis. *J Dermatol* 2016;43:305-10.
- [32] Koca TT. Does obesity cause chronic inflammation? The association between complete blood parameters with body mass index and fasting glucose. *Pak J Med Sci* 2017;33:65-69.
- [33] Yunchun L, Yue W, Jun FZ, Qizhu S, Liumei D. Clinical significance of red blood cell distribution width and inflammatory factors for the disease activity in rheumatoid arthritis. *Clin Lab* 2016;62:2327-31.
- [34] He Y, Liu C, Zeng Z, Ye W, Lin J, Ou Q. Red blood cell distribution width: a potential laboratory parameter for monitoring inflammation in rheumatoid arthritis. *Clin Rheumatol* 2018;37:161-7.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Association between serum uric acid and inflammation markers in ankylosing spondylitis patients treated with tumor necrosis factor- $\alpha$ or nonsteroidal anti-inflammatory drugs

Betül Sargin<sup>1</sup>, Gülcan Gürer<sup>1</sup>, Gülnur Taşçı Boztaş<sup>2</sup>, Hakan Öztürk<sup>3</sup>

<sup>1</sup>Department of Physical Medicine and Rehabilitation, Division of Rheumatology, Adnan Menderes University School of Medicine, Aydın, Turkey

<sup>2</sup>Department of Physical Medicine and Rehabilitation, Adnan Menderes University School of Medicine, Aydın, Turkey

<sup>3</sup>Department of Biostatistics, Adnan Menderes University School of Medicine, Aydın, Turkey

DOI: 10.18621/eurj.359504

## ABSTRACT

**Objectives:** Uric acid has an important role in the production of various inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Although serum uric acid levels in various rheumatic diseases have been performed the relationships between serum uric acid levels with inflammatory markers and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores in ankylosing spondylitis patients treated with anti-TNF- $\alpha$  and nonsteroid anti-inflammatory drugs (NSAIDs) have not been described yet. The aim of this study was to compare the relationships between serum uric acid levels, inflammatory markers and BASDAI scores in ankylosing spondylitis patients treated anti-TNF- $\alpha$  and NSAIDs.

**Methods:** A total of 132 ankylosing spondylitis patients fulfilling the 1984 Modified New York Criteria who had serum uric acid, erythrocyte sedimentation rate and C-reactive protein levels in medical records were included in this retrospective cross-sectional study. Patients were divided in two groups (anti-TNF- $\alpha$  and NSAIDs). Their files were examined in detail. Later demographic and laboratory features were recorded to the research form.

**Results:** Serum uric acid levels were significantly lower in the anti-TNF- $\alpha$  group (mean: 4.9 mg/dL, range: 4.10-5.45 mg/dL) than in the NSAIDs group (mean: 5.20 mg/dL, range 4.70-5.90 mg/dL) ( $p = 0.021$ ). Also, positive correlations were found between C-reactive protein ( $p = 0.003$ ) and BASDAI ( $p = 0.009$ ) with serum uric acid.

**Conclusions:** According to this study, we can consider that serum uric acid level could be used as an inflammatory laboratory marker, such as C-reactive protein in ankylosing spondylitis patients. However, we believe that more studies are needed about this research.

**Keywords:** Uric acid, inflammation, ankylosing spondylitis

*Received: November 29, 2017; Accepted: January 21, 2018; Published Online: April 1, 2018*

Ankylosing spondylitis (AS) is an inflammatory rheumatic disorder and a prototype of spondyloarthritis, characterized by axial skeleton and sacroiliac joint involvement. About 90% of patients develop the first symptoms before 40-45 years and the average age is 28.3 [1]. Uric acid is an end product of purine metabolism [2]. It has been found to induce monocyte



**Address for correspondence:** Betül Sargin, MD., Assistant Professor, Adnan Menderes University School of Medicine, Department of Physical Medicine and Rehabilitation, Division of Rheumatology, Aydın, Turkey  
E-mail [betul.cakir@yahoo.com](mailto:betul.cakir@yahoo.com), [betulcakir834@gmail.com](mailto:betulcakir834@gmail.com), Fax: +90-256-2136064

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>



chemoattractant protein-1 (MCP-1) from vascular smooth muscle cells through activation of nuclear factor- $\kappa$ B (NF- $\kappa$ B) and p38 mitogen-activated protein kinase (MAPK) [3]. Uric acid stimulates production of proinflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-1 $\beta$ , IL-6 and IL-8 from mononuclear cells [4]. NF- $\kappa$ B signalling pathway leads to the production of various inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$  [5].

Some studies about serum uric acid (SUA) levels in various rheumatic diseases such as rheumatoid arthritis (RA) [6], systemic lupus erythematosus (SLE) [7], psoriasis [8-11], and AS [15] has been performed. We also compared to the SUA levels in AS patients treated with anti-TNF- $\alpha$  and nonsteroid anti-inflammatory drugs (NSAIDs) in present study. Furthermore, we investigated the relationships between SUA levels with erythrocyte sedimentation rates (ESR) and C-reactive protein (CRP) values and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores. To the authors' knowledge, this is the first study in AS patients which evaluated the relationships between SUA levels with inflammatory markers and BASDAI scores. We aimed to determine that SUA level could be used as an inflammatory laboratory marker, such as CRP in AS patients.

## METHODS

Our study was carried out at Department of Physical Medicine and Rehabilitation, Division of Rheumatology, Aydın, Turkey from January 2017 to June 2017. The ethics committee of the Institution approved the study and all patients signed the Informed consent form. One hundred ninety-one patients who were diagnosed with AS according to the 1984 Modified New York criteria were included. We determined that 18 patients had no SUA levels in medical records. Kidney failure was existed in one patient, nonalcoholic fatty liver disease was existed in five patient, peripheral arterial disease was existed in five patient, hypertension was existed in five patient, cardiovascular diseases was existed in five patient, diabetes mellitus was existed in five patient. Four patient hypoglycemic agent, four patient lipid-lowering drug, four patient angiotensin-converting enzyme inhibitor, three patient corticosteroids were

using. Therefore, a total of 59 patients were excluded from the study.

Forty-nine (32 male, 17 female) patients were treated with anti-TNF $\alpha$  and 83 (47 male, 36 female) patients were treated with NSAIDs. We examined patients' files in detail and recorded ages, genders, use of drugs, BASDAI scores, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and SUA levels to the research form. SUA levels of the patients before anti-TNF $\alpha$  and NSAIDs uses were checked from medical records.

Demographic features of patients were presented in Table 1. We used BASDAI which is a tool for evaluation of disease activity in AS patients. SUA level is measured by spectrophotometric assay (Abbott Diagnostics) in our hospital.

The patients' SUA status are defined as the following: (1) Normal: SUA level normal ranges (2.6-6 mg/dL); (2) Hypouricemia: SUA level lower than 2.6 mg/dL; and (3) Hyperuricemia: SUA level over 6 mg/dL [16].

ESR (normal range: 0-20 mm/h) is analysed by Westergren method using Vacuplus (Roche). CRP (normal range: 0-5 mg/L) is analysed by turbidimetry test using Prestij (Abbott Diagnostics) in our hospital.

Exclusion criteria for our study were pregnancy, lactation, presence of additional co-morbidities (metabolic syndrome, diabetes mellitus, dyslipidemia, nonalcoholic fatty liver disease, cardiovascular diseases, peripheral arterial disease, hypertension, kidney failure, etc). In addition to these disorders, patients who had use of several kinds of drugs such as hypoglycemic agents (metformin), weight-reducing drugs (orlistat), lipid-lowering drugs (fenofibrate, simvastatin, ezetimibe, atorvastatin), calcium channel blockers (amlodipine), angiotensin-converting enzyme inhibitors (captopril, enalapril, ramipril), angiotensin II receptor antagonists (losartan), estrogens, corticosteroids, and the dietary food supplements vitamin C, vitamin A, iron, flavonoids, omega 3 fatty acids, zinc and  $\beta$ -carotene were excluded. Since these conditions can alter SUA levels we determined them as exclusion criterias.

## Statistical Analysis

T-test was applied to compare for normally distributed variables. Mann-Whitney U test was applied to compare for non-normally distributed

**Table 1.** Demographic and laboratory features of patients with ankylosing spondylitis

	Anti-TNF- $\alpha$ group (n = 49)	NSAIDs group (n = 83)	p value
Age (years)	41.4 $\pm$ 9.5	44.4 $\pm$ 11.1	0.148
Gender			0.424
Male	32 (24.2%)	47 (35.6%)	
Female	17 (12.9%)	36 (27.3%)	
Disease duration (years)	15.5 (7.5-18.6)	16.2 (7.7-19.8)	0.640
BMI (kg/m <sup>2</sup> )	26.6 $\pm$ 4.4	27.8 $\pm$ 4.6	0.117
AST (U/L)	18.0 (14.5-21.5)	20.0 (16.0-24.0)	0.085
ALT (U/L)	19.0 (15.0-23.5)	20.0 (15.0-30.0)	0.110
Urea (mg/dL)	27.0 (21.0-34.0)	26.0 (22.0-34.0)	0.861
Creatinine (mg/dL)	0.77 (0.70-0.84)	0.75 (0.70-0.82)	0.463
Uric acid (mg/dL)	4.90 (4.10-5.40)	5.40 (4.40-6.20)	<b>0.021</b>

Data are shown as mean  $\pm$  standard deviation or number (%) or median (25-75th percentiles). Anti-TNF- $\alpha$  = anti-tumor necrosis factor- $\alpha$ , NSAIDs = nonsteroid antiinflammatory drugs, BMI = body mass index, AST = aspartate transaminase, ALT = alanine aminotransaminase

variables. Correlations between ESR and CRP levels with SUA levels and SUA and BASDAI of the all patients were assessed using Spearman’s correlation test. Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS), ver 19.0 ( IBM Corp.; Armonk, NY, USA) and  $p < 0.05$  was considered to be statistically significant.

**RESULTS**

Significant difference was not found among groups in terms of age, sex and BMI ( $p > 0.05$ ). The mean age of AS patients in the anti-TNF- $\alpha$  group was 41.4  $\pm$  9.5 years and 44.4  $\pm$  11.1 years in the NSAIDs group (Table 1). The gender distribution was 17 women and 32 men among the patients with anti-TNF- $\alpha$  group and 36 women and 47 men among the NSAID group. Mean disease duration was 16.3  $\pm$  9.8 years for

anti-TNF- $\alpha$  group and 16.6  $\pm$  12.3 years for NSAID group. Mean BMI (kg/m<sup>2</sup>) was 26.6  $\pm$  4.4 for anti-TNF- $\alpha$  group and 27.8  $\pm$  4.6 for NSAID group. The mean AST level was 18.0 U/L for anti-TNF- $\alpha$  group and 20.0 U/L for NSAID group ( $p > 0.05$ ). Mean ALT level was 19.0 U/L for anti-TNF- $\alpha$  group and 20.0 U/L for NSAID group ( $p > 0.05$ ). Mean urea level was 27.0 mg/dL for anti-TNF- $\alpha$  group and 26.0 mg/dL for NSAID group ( $p > 0.05$ ). Mean creatinine level was 0.77 mg/dL for anti-TNF- $\alpha$  group and 0.75 mg/dL for NSAID group ( $p > 0.05$ ) (Table 1).

Serum uric acid levels were significantly lower in the anti-TNF- $\alpha$  group (mean: 4.9 mg/dL, range: 4.10-5.45 mg/dL) than in the NSAIDs group (mean: 5.20 mg/dL, range 4.70-5.90 mg/dL) ( $p = 0.021$ ) (see Table 1).

Positive correlations were found between SUA levels with CRP levels ( $r = 0.228$ ,  $p = 0.003$ ) and BASDAI ( $r = 0.148$ ,  $p = 0.009$ ) (Table 2).

**Table 2.** Correlations between serum uric acid levels with ESR, CRP levels and BASDAI of the ankylosing spondylitis patients

	ESR (mm/h)	CRP (mg/L)	BASDAI
Uric acid (mg/dL)			
r	-0.063	0.228	0.148
p	0.415	<b>0.003</b>	<b>0.009</b>

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rates

**DISCUSSION**

Serum uric acid levels were investigated in various rheumatic diseases [6-11, 15]. Choe *et al.* [6] studied SUA levels in RA patients and it's association between inflammatory markers such as ESR and CRP in 23 patients treated with methotrexate (MTX) and 27 patients treated with MTX and leflunomide. They reported that leflunomide was reduced SUA levels. However they announced that any correlation between

SUA levels with inflammatory markers was not found. Sheikh *et al.* [7] detected hyperuricemia in 16.1% of 204 SLE patients and found that hyperuricemia was associated with the occurrence of stroke, peripheral neuropathy, hypertension, hyperlipidemia, and history of arterial thrombosis. Also, SUA levels were studied in psoriasis patients [8-11]. Prasad *et al.* [8] studied SUA and rheumatoid factor levels in 472 psoriasis patients and in outcome, found that SUA levels were above normal in 18 out of the 40 (45%) psoriatic patients. Kwon *et al.* [9] investigated SUA levels and its correlation between Psoriasis Area and Severity Index (PASI) in 198 Korean patients with psoriasis. As a result of this study, SUA levels was not significantly different from healthy population ( $p > 0.05$ ). They found a positive correlation between SUA levels and PASI. They proposed that an increased epidermal cell turnover could be an important cause of raised SUA in psoriasis patients. Gisoni *et al.* [10] researched SUA levels in 119 psoriatic patients and 119 healthy controls. They found higher SUA levels in psoriatic patients (psoriatic patients, mean: SUA:  $5.61 \pm 1.6$  mg/dL, healthy controls, mean: SUA:  $4.87 \pm 1.4$  mg/dL). They suggested that hyperuricaemia in psoriasis could be simply a consequence of obesity, metabolic disorders, and psoriasis itself. Li *et al.* [11] explained a meta-analysis to identify the SUA levels in subjects with psoriasis and to determine whether there is an associated risk between psoriasis and hyperuricemia.

Kanellis *et al.* [12] announced that UA is a mediator of endothelial dysfunction, inflammation and vascular disease including hypertension and atherosclerosis. Its inflammatory and proliferative effects have been described on vascular smooth muscle cells (VSMCs). Its effects on the vasculature have been linked to increased chemokine and cytokine expression, induction of the renin-angiotensin system, and to increased vascular CRP expression. Correlation between SUA and CRP has been investigated in two studies. In Isha *et al.*'s study [13] 25 new psoriatic patients having active disease, 25 patients of various skin diseases other than psoriatic lesion and 25 normal subjects were included before and after 12 weeks of treatment. In conclusion, mean SUA concentration was found to be significantly higher in patients with psoriasis ( $p < 0.05$ ). After 12 weeks of treatment, mean

value for SUA was found to be significantly decreased ( $p < 0.05$ ). Mean value for CRP was found to be increased by more than 20 folds in patients with psoriasis, which was subsequently reduced to nearly 50% of the initial value after 12 weeks of treatment. These patients also showed hyperuricemia. They suggested that both CRP and UA levels should be monitored in patients with psoriasis. In the other study, Lyngdoh *et al.* [14] evaluated the association between SUA levels with CRP, TNF- $\alpha$ , interleukin-6 (IL-6) and interleukin-1 $\beta$  (IL-1 $\beta$ ) levels in 6085 healthy participants. As a result of their study SUA was associated positively with CRP ( $p < 0.001$ ), TNF- $\alpha$  ( $p < 0.001$ ) and IL-6 ( $p < 0.001$ ), and negatively with IL-1 $\beta$  ( $p = 0.027$ ). These results suggested that UA contributes to systemic inflammation and may have a role in inflammation and subsequent inflammatory related diseases.

In the scanning literature, there is only one study according to our scan results that investigated SUA levels in the AS patients [15]. In this study, it was reported that hyperuricemia was found in 5 of 23 AS patients. These patients had a higher frequency of uveitis, lesser degree of clinical activity of the disease ( $p < 0.001$ ), lower levels of ESR ( $p < 0.05$ ), a lesser degree of ankylosis of the spine and a better functional prognosis. Normouricemia was found in 8 of 23 AS patients. As a result of their study they report that serial analysis of UA can determine the prognosis.

As a result of our study we found positive correlations between SUA levels with CRP levels and BASDAI scores. However, we did not detect any correlation among SUA and ESR levels. CRP as a better acute phase reactant than ESR in AS patients was indicated in some studies [17-19]. SUA levels were significantly lower in the anti-TNF- $\alpha$  group than in the NSAIDs group. As a result, anti-TNF- $\alpha$  treatment suppresses inflammatory process more strongly, so we may have found lower levels of SUA in anti-TNF- $\alpha$  group. But more randomised controlled studies are needed to demonstrate these findings.

## CONCLUSION

According to this study, we can consider that SUA level could be used as an inflammatory laboratory

marker, such as CRP in AS patients. However, we believe that more studies are needed about this research.

### *Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### *Financing*

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

- [1] Reveille JD, Weisman MH. The epidemiology of back pain, axial spondyloarthritis and HLA-B27 in the United States. *Am J Med Sci* 2013;345:431-6.
- [2] Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. *Ann Intern Med* 2005;143: 499-516.
- [3] Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, et al. Uric acid stimulate monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension* 2003;41:1287-93.
- [4] Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003;41:1183-90.
- [5] Oeckinghaus A, Ghosh S. The NF-kappaB family of transcription factors and its regulation. *Cold Spring Harb Perspect Biol* 2009;1:a000034.
- [6] Choe JY, Kim SK. Association between serum uric acid and inflammation in rheumatoid arthritis: perspective on lowering serum uric acid of leflunomide. *Clin Chim Acta* 2015;438:29-34.
- [7] Sheikh M, Movassaghi S, Khaledi M, Moghaddasi M. Hyperuricemia in systemic lupus erythematosus: is it associated with the neuropsychiatric manifestations of the disease? *Rev Bras Reumatol Engl Ed* 2016;56:471-77.
- [8] Prasad PV, Bikku B, Kaviarasan PK, Senthilnathan A. A clinical study of psoriatic arthropathy. *Indian J Dermatol Venereol Leprol* 2007;73:166-70.
- [9] Kwon HH, Kwon IH, Choi JW, Youn JI. Cross-sectional study on the correlation of serum uric acid with disease severity in Korean patients with psoriasis. *Clin Exp Dermatol* 2011;36:473-8.
- [10] Gisondi P, Targher G, Cagalli A, Girolomoni G. Hyperuricemia in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2014;70:127-30.
- [11] Li X, Miao X, Wang H, Wang Y, Li F, Yang Q, et al. Association of serum uric acid levels in psoriasis: a systematic review and meta-analysis. *Medicine (Baltimore)* 2016;95:e3676.
- [12] Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin Nephrol* 2005;25:39-42.
- [13] Isha VK, Lal JH. C-reactive protein and uric Acid levels in patients with psoriasis. *Ind J Clin Biochem* 2011;26:309-11.
- [14] Lyngdoh T, Marques-Vidal P, Paccaud F, Preisig M, Waeber G, Bochud M, et al. Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based Colaus study. *PLoS One* 2011;6:e19901.
- [15] Jiménez Balderas FJ, Robles EJ, Juan L, Badui E, Arellano H, Espinosa Said L, et al. Purine metabolism in ankylosing spondylitis: clinical study. *Arch Invest Med (Mex)* 1989;20:163-70.
- [16] Van Leeuwen AM, Bladh ML. *Davis's Comprehensive Handbook of Laboratory and Diagnostic Tests with Nursing Implications*. 6th ed. Philadelphia, PA: PA. Davis Company, 2015., p.329.
- [17] Nashel DJ, Petrone DL, Ulmer CC, Sliwinski AJ. C-reactive protein: a marker for disease activity in ankylosing spondylitis and Reiter's syndrome. *J Rheumatol* 1986;13:364-7.
- [18] Benhamou M, Gossec L, Dougados M. Clinical relevance of C-reactive protein in ankylosing spondylitis and evaluation of the NSAIDs/coxibs' treatment effect on C-reactive protein. *Rheumatology (Oxford)* 2010;49:536-41.
- [19] Siebuhr AS, Bay-Jensen AC, Karsdal MA, Lories RJ, de Vlam K. CRP and a biomarker of type I collagen degradation, C1M, can differentiate anti inflammatory treatment response in ankylosing spondylitis. *Biomark Med* 2016;10:197-208.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Foam sclerotherapy combined with saphenofemoral ligation procedure: long-term results

Lütfi Soylu<sup>ORCID</sup>, Oğuz Uğur Aydın<sup>ORCID</sup>

Department of Surgery, Ankara Güven Hospital, Ankara, Turkey

DOI: 10.18621/eurj.390495

## ABSTRACT

**Objective:** To evaluate the clinical effect of the foam sclerotherapy combined with saphenofemoral ligation (FS-SFL) in a selected group of patients with varicose disease and present the long-term results of ten-year ultrasonographic follow-up.

**Methods:** Sixty-five patients with primary varicose veins due to the great saphenous vein incompetence who had been treated with FS-SFL were retrospectively reviewed over a period of ten years. The patients were assessed before and after the treatment by Doppler ultrasonography and clinical examination.

**Results:** The mean age of the patients was  $44.6 \pm 11$  years (range: 19 to 87 years), and 51 were females and 14 were males. Follow-up for all patients was ten years. The most common complication was skin pigmentation. There were no major complications. No recanalization of the great saphenous vein was seen in any patient.

**Conclusions:** FS-SFL is a safe and effective method of treating varicose veins. This treatment have a low rate of recanalization in their long-term follow-up.

**Keywords:** varicose veins, foam sclerotherapy, surgery, ultrasonography

*Received: February 5, 2018; Accepted: February 23, 2018; Published Online: April 5, 2018*

The superficial venous system and/or the deep venous system can both be affected by chronic venous insufficiency (CVI). Moreover, acquired or congenital or disorders may result in venous dysfunction [1, 2].

Age increases the prevalence of CVI. In Europe, in adults between 30 and 70 years of age, 5% to 15% were reported to have CVI, 1% of which also had varicose ulcers. In the USA, reports have shown that approximately 7 million people suffer from CVI, accounting for 70% to 90% of all lower extremity ulcers [3-5].

CVI, which is a progressive, relapsing and chronic disease, remains far from being fully understood or

properly treated, despite there being many methods and theories which can be implemented with relative immediate success [6].

Although presently no causal therapies for the treatment of chronic venous diseases have been found, many newly developed methods for the treatment of varicose veins are actively being promoted in the literature. Recently, minimally invasive techniques have increased in popularity, which has led to a shift away from traditional surgery. However, the long-term follow-up results of these treatment methods have only just begun to be published.

In this study, we aimed to combine foam sclerotherapy and saphenofemoral ligation (FS-SFL)



Address for correspondence: Lütfi Soylu, MD., Ankara Güven Hospital, Department of Surgery, Şimşek Sokak, Kavaklıdere, 06540 Ankara, Turkey  
E-mail [lutfisoylu@hotmail.com](mailto:lutfisoylu@hotmail.com), Tel: +90 312 457 24 73, Fax: +90 312 457 28 86

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

and present the long-term results using the 10-year ultrasonography follow-up of a select group of patients.

## METHODS

### Patients

From January 2006 through to March 2007, a total of 167 patients underwent treatment with FS-SFL. Patient selection is shown in Table 1. This study included 65 patients, comprising of 51 females and 14 males, aged between 19 and 87 years (mean 44.6 years ± 11 years), who were treated for varicose veins with the great saphenous vein reflux. The patients were analyzed retrospectively between January 2006 and April 2017, in our center.

Our patients endured symptoms from 1 to 30 years before seeking surgical treatment. Only 1 leg from each patient was included in this study. The patients were classified as ‘clinical, aetiological, anatomical, and pathologic’ (CEAP). There were 25 patients in C3 class (with varicose veins or swelling), 31 patients in C4 class (with pigmentation), 7 patients in C5 class (with active ulcer), and 2 patients in C6 class (with previous bleeding episodes) (Table 2).

The indications for treatment were based on

**Table 1.** Inclusion and exclusion criteria

#### Inclusion criteria

Patients with primary symptomatic varicosities involving the GSV system

No previous treatment for varicose veins

#### Exclusion criteria

Maximum diameter of the greater saphenous vein was greater than 8 mm

Patients with primary varicosities involving both the GSV and small saphenous vein

Patients with previous surgery for varicose veins

Patients previously treated with sclerotherapy for varicosities

Previous DVT

Peripheral vascular disease

Known allergy to local anesthetic or sclerosing agents

Patient was unable to undergo the procedure

Patients who can not follow

DVT = deep venous thrombosis, GSV = great saphenous vein

**Table 2.** Demographic characteristics of the study patients

Variables	Data
Age (years)	44.6 ± 11
<b>Limbs</b>	
Right	27 (41.5%)
Left	38 (58.5%)
<b>Sex</b>	
Female	51 (78.5%)
Male	14 (21.5%)
<b>CEAP</b>	
C3	25 (38.5%)
C4	31 (47.7%)
C5	7 (10.8%)
C6	2 (3.1%)
<b>Diameter of the GSV (mm)</b>	6.7 ± 1.2 (range;4.3-8.0)

Data are shown as mean ± standard deviation or number (%). CEAP = clinical, aetiological, anatomical, and pathologic classification, DVT = deep venous thrombosis, GSV = great saphenous vein

patient preference. The most common indication for FS-SFL was large bulging varicosities and accompanying symptoms, such as lower extremity swelling, eczema, pigmentation, stasis dermatitis, and ulceration. All of the patients underwent duplex scanning to document the patency of the deep veins.

### Technique

The patients received either spinal (55 patients) or general (10 patients) anesthesia. Varicosities were treated by phlebectomy using Müller’s hooks, through multiple small incision. This technique involved making a 2 cm incision near the inguinal ligament, and then exposing and ligating the great saphenous vein and its tributaries 0.5 cm distal to the saphenofemoral junction. Venous access was obtained by a 1 cm incision made at knee level, allowing direct cannulation of the great saphenous vein. After entering the vein, a catheter was inserted.

The foam was then prepared by mixing 2 mL of 3% polidocanol (Aethoxysklerol, Cem farma, Turkey) with 6 mL of air using Tessari’s technique; two 10-mL syringes and a 3-way tap. The resulting 8 mL of foam was injected into the collapsed vein via the angiography catheter, as this was withdrawn along the length of the vein about 8-10 seconds.

The limb was then elevated to 45° and the sclerosing foam was injected. All of the patients

received a prophylactic dose of low molecular weight heparin at the completion of the procedure. Use of prophylactic antibiotics was left to the discretion of the treating surgeon. The prophylactic dose of low molecular weight heparin was continued for 1 week after the operation.

### Postoperative Management and Follow-up

An elastic bandage was applied for 7 days after the procedure, followed by graduated compression stockings for 1 month to 3 months. Patients were advised to ambulate as early as possible. Further assessments were scheduled after 1 week, 1 month, 3 months, and then 6 months. Patients were rechecked after an average of 10 years.

Follow-up included any symptoms, or residual and recurrent varicose veins determined by physical examination. The color duplex examination stratified the great saphenous vein system as fully obliterated, partially obliterated or reflux, or not obliterated. In addition, the presence of deep vein thrombosis was sought. The common femoral vein, the femoral vein, the popliteal vein, the posterior tibial veins, the peroneal veins, the soleal veins, and the medial and lateral gastrocnemius veins were investigated by color duplex ultrasonography using a standardized technique.

## RESULTS

Technical success was observed in all of the patients (100%). At a mean of 9 years, 8 months

**Table 3.** Complications after FS-SFL

Complications	Limbs
Groin infection	1 (1.5%)
Skin pigmentation	3 (4.6%)
Superficial thrombophlebitis	1 (1.5%)
DVT	1 (1.5%)
PE	0 (0%)
Saphenous nerve injury	0 (0%)
Hematoma	0 (0%)
Allergy	0 (0%)
Recanalization	0 (0%)

Data are shown as number (%). DVT = deep venous thrombosis, FS-SFL = foam sclerotherapy combined with saphenofemoral ligation, PE = pulmonary embolism

**Table 4.** Pre-treatment and post-treatment clinical CEAP classification change

	C0	C1	C2	C3	C4	C5	C6
<b>Pre-treatment (n)</b>				25	31	7	2
<b>Post-treatment (n)</b>	24	26	11		4		

CEAP = clinical, aetiological, anatomical, and pathologic classification

(range: 8 years, 8 months-11 years, 3 months) after surgery follow-up, satisfactory results were obtained with improvement.

One patient (1/65; 1.5%) had symptomatic deep vein thrombosis and recovered with coumadin. One patient (1/65; 1.5%) had symptomatic superficial thrombophlebitis and there was mild hyperpigmentation in 3 patients (3/65; 4.6%) at the 6-month follow-up. One groin (1/65; 1.5%) infection occurred in a patient, which was treated successfully with antibiotics. The time until return to work or back to normal activity ranged from 1 to 5 days (median 2 days).

There were no other complications, such as pulmonary embolism, peripheral nerve injury, skin necrosis, groin hematoma, or allergic reaction to the sclerosing drug (Table 3).

Ten years after treatment, 24 patients were classified as CEAP C0, 26 patients were classified as C1, 11 patients were classified as C2, and 4 patients were classified as C4 (Table 4).

Doppler ultrasonography was performed for all of the patients 10 years after surgery. The results showed the great saphenous vein atresia without blood flow signals, the great saphenous vein was obliterated in all of the patients with thrombosis (65/65; 100%).

## DISCUSSION

For the management of varicose veins, many well-established minimal access techniques have been reported in the literature and several new endovenous treatment methods have been recently introduced. Treatment classically comprises the great saphenous vein stripping with high ligation at the saphenofemoral junction, either with or without phlebectomy. When compared to conventional surgery, minimal invasive

ablation techniques provide a significant reduction in morbidity and pain post-procedurally.

An association between a lower reflux recurrence rate and the saphenofemoral junction ligation in conjunction with the great saphenous vein stripping was reported by Rutgers and Kitslaar [7], and Jones *et al.* [8]. when they compared their results to that of the saphenofemoral junction ligation alone. The saphenofemoral junction ligation without the great saphenous vein stripping is insufficient as a long-term control of varices and can be associated with a high recurrence rate [9-11].

In as much as 10% of cases, incompetence of the anterior accessory saphenous vein results in a recurrence after the great saphenous vein stripping, and in 1% of cases, a missed true duplex the great saphenous vein was reported [12] as a result of inadequate dissection and the saphenofemoral junction tributary division.

In 1944. Orbach [13] first described foam sclerosants. In 2000, Tessari [14] described a new technique for creating foam via small bubbles, using 2 syringes and a 3-way tap, he was able to produce sclerosant foam. When compared to liquid for treating saphenous trunk incompetence and large varices, foam sclerotherapy has shown definite advantages [15], which have proven to be maximally effective. The early results reported between liquid and foam sclerotherapy were compared by Hamel-Desmos *et al.* [16]. In their study, using 88 randomized limbs at the 3-week follow-up, they reported the great saphenous vein obliteration at a rate of only 40% using liquid sclerotherapy and 84% using foam sclerotherapy. Following sclerotherapy, recanalization of the great saphenous vein is the most common cause of the high incidence of recurrence.

In a study by Hobbs [17] on truncal saphenous incompetence, a good outcome was reported 10 years after treatment for 71% of surgically-treated patients compared to only 6% of sclerotherapy-treated patients.

At first, as was considered with residual varicose veins, it was thought that most of the recurrences resulted from inadequate surgical techniques. Later, however, through ultrasonography, it was discovered that a significant number of recurrences will occur even in the event of proper surgical treatment. The process of neovascularization is responsible for recurrent varicose vein formation. Over time

postoperatively, patients form new blood vessels that eventually replace the function of the insufficient trunk vein that was removed, most often the great saphenous vein.

In this study, foam sclerotherapy and the saphenofemoral junction ligation were combined. Theoretically, this treatment would provide a recurrence rate which would be lower than with sclerotherapy on its own. At the saphenofemoral junction, flush ligation complemented by foam sclerotherapy decreases the recurrence rate postoperatively, providing an expectation of a much better result compared to those reported by liquid sclerosant. Moreover, back pressure from the blood column in the femoral vein at the saphenofemoral junction has no effect on the head of foam in the proximal vein, which can occur in closed procedures, because the great saphenous vein, during this procedure, is dissociated from the deep femoral vein. Moreover, at this point, there is no risk to the deep system of foam spillage, although there is still concern about seepage through perforators.

We reported a lower the great saphenous vein recanalization rate than that of Cavezzi *et al.* [18] , who in their study, used a technique which was similar, but did not include the saphenofemoral junction ligation. Admittedly, they used a technique which was different than ours. An additional advantage of the saphenofemoral junction ligation includes ligation of the tributaries during this procedure. These can remain in the patent after sclerotherapy and might cause a recurrence.

Surgical treatment can include complications such as hematomas and pain postoperatively, specifically, along the path of the saphenous vein that was removed by stripping [19]. In our study, no hematoma or nerve damage was reported in any of the patients.

Treatment complications potentially include venous thrombosis (coagulation system activation during sclerotherapy has been reported), tissue necrosis and allergic reactions. Accidental intra-arterial administration is among the complications which are most serious, which could cause limb necrosis, possibly resulting in the necessity for amputation of that limb. Migrating gas bubbles are a complication specific to the foam method, and mostly travel into pulmonary circulation. If a patent foramen ovale is present, however, systemic circulation



migration of the gas bubbles might occur. In cases such as this, central nervous system damage may result, temporarily causing headaches, visual disturbances, and even the rare possibility of a stroke. Another theory includes endothelin activity which increases post-procedurally causing neurological complications, affecting the cerebral vessels [20]. In our study, deep vein thrombosis developed in one patient.

## CONCLUSION

Foam sclerotherapy in combination with saphenofemoral ligation was found to be a safe, effective, and less expensive method for severe lower extremity varicosis, resulting in a treatment time which is shorter a much faster recovery and low recurrence rates.

### Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

- [1] Labropoulos N, Leon L, Kwon S, Tassiopoulos A, Gonzalez-Fajardo JA, et.al. Study of the venous reflux progression. *J Vasc Surg* 2005;41:291-5.
- [2] Fiebig A, Krusche P, Wolf A, Krawczak M, Timm B, Nikolaus S, et.al. Heritability of chronic venous disease. *Hum Genet* 2010;127:669-74.
- [3] Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: the Framingham Study. *Am J Prev Med* 1988;4:96-101.
- [4] Heit JA, Rooke TW, Silverstein MD, Mohr DN, Lohse CM, Petterson TM, et.al. Trends in the incidence of venous stasis syndrome and venous ulcer: a 25-year population-based study. *J Vasc Surg* 2001;33:1022-7.
- [5] Caggiati A, Rosi C, Heyn R, Franceschini M, Acconcia MC. Agerelates variations of varicose veins anatomy. *J Vasc Surg* 2006;44:1291-5.
- [6] Araújo AL, Ferreira RCA, Oliveira CAB. Semelhança morfológica entre lesões vasculares: varizes dos membros inferiores aterosclerose. *Rev Angiol Cir Vasc* 2007;6:29-33.
- [7] Rudgers PH, Kirslaar PJ. Randomised trial of stripping versus high ligation combined with sclerotherapy in the treatment of the incompetent greater saphenous vein. *Am J Surg* 1994;168:311-5.
- [8] Jones L, Braithwaite BD, Selwyn D, Cooke S, Earnshaw JJ. Neovascularisation is the principal cause of varicose vein recurrence: results of a randomised trial of stripping the long saphenous vein. *Eur J Vasc Endovasc Surg* 1996;12:442-5.
- [9] Sarin S, Scurr JH, Coleridge Smith PD. Stripping of the long saphenous vein in the treatment of primary varicose veins. *Br J Surg* 1994;81:1455-8.
- [10] Dwerryhouse S, Davies B, Harradine K, Earnshaw JJ. Stripping the long saphenous vein reduces the rate of reoperation for varicose veins: five-year results of a randomizer trial. *J Vasc Surg* 1999;29:589-92.
- [11] Tong Y, Royle J. Recurrent varicose veins following high ligation of long saphenous vein; a duplex ultrasound study. *Cardiovasc Surg* 1995;3:485-7.
- [12] Ricci S, Caggiati A. Does a double long saphenous vein exist? *Phlebology* 1999;14:59-64.
- [13] Orbach E. Sclerotherapy of varicose veins: utilisation of an intravenous air-block. *Am J Surgery* 1944;66:362-6.
- [14] Tessari L. Nouvelle technique d'obtention de la sclero-mousse [A new technique for producing sclerosing foam]. *Phlebologie* 2000;53:129-33. [Article in French]
- [15] Yamaki T, Nozaki M, Iwasaka S. Comparative study of duplex-guided foam sclerotherapy and duplex-guided liquid sclerotherapy for the treatment of superficial venous insufficiency. *Dermatol Surg* 2004;30:718-22.
- [16] Hamel-Desnos C, Desnos P, Wollmann JC, Ouvry P, Mako S, Allaert FA. Evaluation of the efficacy of pilodocanol in the form of foam compared with liquid form in sclerotherapy of the greater saphenous vein: initial results. *Dermatol Surg* 2003;29:1170-75.
- [17] Hobbs JT. Surgery or sclerotherapy for varicose veins: 10-year results of a random trial. In: Tesi M, Dormandy JA, eds. *Superficial and Deep Venous Diseases of the Lower Limbs*. Turin, Italy: Panminerva Medica, 1984, pp. 243-48.
- [18] Cavezzi A, Mosti G, Di Paolo S, Tessari L, Campana F, Urso SU. Re: 'catheter-directed foam sclerotherapy of great saphenous veins in combination with pre-treatment reduction of the diameter employing the principals of perivenous tumescent local anesthesia'. *Eur J Vasc Endovasc Surg* 2014;48:597.
- [19] Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O, et.al. Prospective randomized study of endovenous radiofrequency obliteration (closure procedure) vs ligation and stripping in a selected patient population (EVOLVES Study). *J Vasc Surg* 2003;38:207-14.
- [20] Sarvananthan T, Shepherd AC, Willenberg T, Davies AH. Neurological complications of sclerotherapy for varicose veins. *J Vasc Surg* 2012;55:243-51.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Evaluation of nursing students' diagnoses using the Omaha System

Elif Ateş<sup>ORCID</sup>, Bahire Ulus<sup>ORCID</sup>

Department of Nursing, Acibadem University, Faculty of Health Sciences, İstanbul, Turkey

DOI: 10.18621/eurj.372163

## ABSTRACT

**Objective:** Nursing process guides the students in the diagnosing, planning, intervention and evaluation of patients/families, and it also gives a systematic point of view. The Omaha System is used as a nursing classification system in public health nursing course practice areas. It was conducted in order to examine the nursing diagnoses identified by the students according to the Omaha System.

**Method:** It was a retrospective, analytical research. Practice files of 51 students who took the public health nursing course created the sample.

**Results:** According to the Omaha problem classification list (PCL), the students in the study identified a total of 412 problems. According to Omaha PCL, the students mostly used the area of health behavior, followed by the physiological, psychosocial and environmental areas respectively. It was determined that 73% of the students had sufficient skills to use the Omaha System and 26.8% of them were inadequate.

**Conclusion:** It was observed that the nursing diagnoses identified by the students in line with the determined learning targets were sufficient.

**Keywords:** Education, Omaha System, evaluation, public health nursing

*Received: December 28, 2017; Accepted: March 31, 2018; Published Online: May 14, 2018*

Nursing process guides the students in the diagnosis, planning, intervention and evaluation of patients, and it also gives a systematic point of view [1, 2]. In a study by Erdoğan and Esin [3], which measured the efficacy of the Omaha System, a total of 1,783 nursing interventions were presented and defined. Results of this study revealed a high reliability, and the Omaha System was reported to be useful in defining public health nursing practices [3].

In our country, most of the undergraduate nursing schools offer nursing courses and training according to the specific type of nursing practice required. For example, in clinical practice, the NANDA Nursing

Diagnoses Classification is usually used, while within the public health practice the Omaha System is used for planning home visits [3, 4]. Nevertheless, students can be expected to experience difficulties in the nursing process as they attempt to apply what they have learned during classroom lectures.

The Omaha System was developed by the Visiting Nurse Association of Omaha, Nebraska in 1975 in the United States and was approved by the American Nursing Association (ANA) in 1992 [5]. The Omaha System has been actively used in Turkey since 1999 in nursing degree programs and public health nursing education. Both educators and students have found



Address for correspondence: Elif Ateş, MSc., Acibadem University, Faculty of Health Sciences, Department of Nursing, İstanbul, Turkey  
E-mail [elifates83@gmail.com](mailto:elifates83@gmail.com), Telephone: +90 216 500 4166

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

this system very useful for developing students information management skills [2]. The Omaha System outlines the terms and codes which define health and which range from the general to the specific. The taxonomy of the system is arranged for use by nurses as well as professionals in other disciplines. The model is composed of the Problem Classification Scheme (PCS), the Problem Rating Scale (PRS), and the Nursing Intervention Scheme (NIS), all of which are compatible with each other [6, 7]. The PCS consists of four domains: environmental, psychosocial, physiological, and health behaviors. These contain 42 past, existing, or probable health problems and nursing diagnoses of family and community. An implemented intervention also has four domains: the problem, category, target, and definition of care. These encompass education, guidance and counseling, treatment procedures, case management and surveillance. The results and progressions obtained at the end of nursing interventions are evaluated with the PRS. With this scale, the acquired information, behavior, and status are evaluated with a minimum score of 1 and a maximum score of 5. The use of the PRS with the other two components of the Omaha System creates a comprehensive problem solving model for education, application and research [7, 8].

A review of the literature showed studies which used the Omaha System in occupational health nursing, school health nursing, nursing homes and some clinical fields [6, 9-14]. These studies focused specifically on the use of the Omaha System. As noted earlier, this classification system is used in the public health nursing courses in our country. Although it differs from the nursing process that students learn for three years and from the North American Nursing Diagnosis Association (NANDA) nursing diagnosing list, no studies have reported any difficulties in using the Omaha System in undergraduate education. This study was carried out with the aim of evaluating the nursing diagnoses made by third-year public health nursing students using the Omaha System.

## METHODS

This study was carried out as a retrospective, analytical study between 02 March-18 May 2016. It

was planned to include 51 students who took the public health nursing course. Data were collected same academics years. However, the study was continued with 41 students as 10 of them did not agree to participate in the study. The practice files of these students who applied at 4 Family Health Centers (ASM) located in Umraniye, Istanbul province were examined.

## Characteristics of Students

At Acibadem University, Faculty of Health Sciences, Nursing Department, 3rd year students took part in the research. Students who took the Public Health Nursing course during the spring semester had internal medicine, surgery, pediatrics, and gynecology nursing courses before taking the course. On top of this knowledge, the public health nursing course was given the students as 3 hours of theoretical lectures and 8 hours of practical lectures per week.

The nature of the public health nursing course is different from the nature of the clinical field courses. The learning objectives are therefore different and broad. Within the scope of the research, the practice objectives of the public health nursing course expected from the students are as follows:

- To know the basic philosophy, duties, powers and responsibilities of public health nursing,
- To provide health services to the individuals from all age groups as a public health nurse,
- Pregnancy follow-up and follow-up of the child between 0-1 years of age
- Use Omaha System and make appropriate nursing diagnose
- To be able to make at least 1 nursing diagnosis suitable for 4 separate areas of Omaha System

## Researchers' Characteristics

There were 1 assistant Professor and 1 lecturer in the field of Public Health Nursing at same institution in the study.

## Phases of Teaching Omaha System

To enable students to use the Omaha System professionally as a part of the research:

- In the public health nursing course, the Omaha System was explained for 2 hours theoretically.
- After the theoretical presentation, the instructors explained the care plan based on one

sample case, according to the Omaha System.

- The class of 51 people was divided into 10 groups. 10 separate case scenarios were given and students were asked to prepare a nursing care plan according to the Omaha System.

- The workshops were conducted by presenting the cases prepared by the groups in the class environment.

- Two separate families were assigned to the students when they went out for field practice. The students were requested to collect data from the families according to the Omaha System.

- The students visited each of the families they were assigned 3 times and prepared the practice file.

- The practice files prepared by the students were discussed with the instructors in the practice field.

- The instructors made home visits at least once with each student. During these home visits, the instructors identified problems for the family according to the Omaha System.

- One of these practice files prepared by the students is included in the research.

In accordance with the practice objectives of the course, the practice files were examined according to the following criteria (Table 1). According to the Table 1; at least one nursing diagnosis must be placed in each area. The qualifications of the students are determined according to the types and number of diagnoses that they put.

**Data Collection**

The data were collected with the "Characteristics of Family Form", the "File Assessment Form (Student)", and the "File Assessment Form (Educator)", which were created by the researchers in accordance with the literature.

*1. Characteristics of Family Form:* The surname of the family, family type, number of family members

and their ages were recorded on this form.

*2. File Evaluation Form (Student):* This form consists of problems in Omaha PCL. In this form, problem areas and nursing diagnoses identified by the students are marked.

*3. File Evaluation Form (Instructor):* This form consists of problems in Omaha PCL. In this form, the problem areas and nursing diagnoses identified by the instructors are marked.

**Research Questions:**

1- Can students choose the nursing diagnoses included in the Omaha system they were introduced to recently?

2- What are the levels of competence of students to identify nursing diagnoses in the Omaha system they were introduced to recently?

**Ethical Aspects of the Research**

This study was approved by the ethical review boards at the authors institution (Number: ATADEK: 2016-11).

**Statistical Analysis**

The data were evaluated using the number and percentage distributions of variables in the SPSS 15 statistical program.

**RESULTS**

When the practice files of 41 students who took the public health nursing course and followed 2 families in practice area were examined, the following findings were obtained.

**The Characteristics of Examined Families**

Of the families who examined in the research, 87.8% (n = 36) were living in a nuclear family and 9.8% (n = 4) were living in extended families. Thirty-

**Table 1.** Levels of competence according to nursing diagnoses determined by students

Qualification Level	Environmental Domain	Psychosocial Domain	Physiological Domain	Health Behavior Domain
Inadequate	<1	<1	<1	<1
Adequate	1	1	1	1
Good	1	2	3	4
Excellent	>1	>2	>3	>4

**Table 2.** Students' nursing diagnoses

Diagnosis Domain and Nursing Diagnosis	Symptoms and Findings	Number	%
<b>Physiological Domain</b>			
22. Teeth	03. Tooth decay	11	9.7
33. Antepartum/Postpartum	06. Difficulty in breastfeeding	12	10.6
<b>Health-Related Behaviors Domain</b>			
35. Nutrition	05. Imbalanced nutrition	18	10.9
37. Physical Activity	02. Inadequate / irregular exercise	17	10.3
38. Personal Hygiene	05. Insufficient oral care/ brushing of teeth and flossing	15	9.1
39. Substance Use	03. Smoking	17	10.3
40. Family Planning	01. Having incorrect/ inadequate knowledge about family planning methods	24	14.6

nine percent of the families had three members, 24.4% had four members and 36.6% had five members. The age range of mothers was between 21-30 years (53.6%), while the age range of fathers was between 26-30 (34.1%). Most of the families (43.9%) had one child, while 29.3% of the families had two children.

**Making Nursing Diagnoses Using the Problem Classification Scheme**

We observed that the students identified 412 problems using the Omaha PCS. The most commonly identified domain was health behavior (n =164), the second was physiological (n = 112), the third was psychosocial (n = 76), and the fourth was the environmental domain.

Using the Omaha PCS, educators identified and examined 1,142 problems. The most common problem was in the health behavior domain, followed by physiological (n = 273), psychosocial (n = 245), and environmental domains (n = 223).

The most common problems that the students selected in the PSC were having incorrect/ inadequate knowledge about family planning methods (n = 24), imbalanced nutrition (n = 18), smoking (n = 17), inadequate/irregular exercise (n = 17), insufficient oral care/brushing of teeth and flossing (n = 15), difficulty in breastfeeding (n = 12) and tooth decay (n = 11) (Table 2).

The most commonly selected problems by the educators in the PCS were insufficient oral care/brushing teeth and flossing (n = 35); inadequate/irregular exercise (n = 30); inadequacies in periodic dental and medical checkups (n =

30);imbalanced nutrition (n = 27); frequently waking up at night (n=26); having incorrect/inadequate knowledge about family planning methods (n = 26); using a method with a limited effect/using it irregularly (n = 25); sedentary life style (n = 25); tooth decay (n = 25); difficulty in coping with stress (n = 25); inappropriate exercise/resting/nutrition behaviors (n = 23); scarcity of external stimuli/leisure activities (n = 21), and low income (n = 21) (Table 3).

**Competence Levels of Students in Determining Nursing Diagnosis by Using Omaha System**

Of the 41 practice files examined, 24.3% of the students were found to be adequate, 26.8% of the students were good, and 21.9% of them were found at a very good level in determining the nursing diagnosis from the Omaha System. 26.8% of the students were found to be inadequate to determine the nursing diagnosis according to the Omaha System.

**The Distribution of Categories of Nursing Intervention in the Diagnosis Domain**

Students identified 397 categories of nursing intervention for 412 problem domains. When these categories were examined, it was seen that intervention categories intended for health education, guidance and counseling (n = 377), case management (n = 15) and treatment process (n = 5) were most often implemented. For 1,142 problem domains identified by the educators, 1,144 nursing intervention categories were identified. After careful consideration, the first nursing intervention category was identified as health education, guidance and counseling (n = 1,118); the

**Table 3.** Educators' nursing diagnoses

Diagnosis Domain and Nursing Diagnosis	Symptoms and Findings	Number	%
<b>Environmental Domain</b>			
01. Income	01. Low income	21	9.4
<b>Psychosocial Domain</b>			
07. Social Contact	03. Scarcity of external stimuli /leisure activities	21	8.6
12. Emotional Stability	09. Difficulty in coping with stress	25	6.1
<b>Physiological Domain</b>			
22. Teeth	03. Tooth decay	25	6.1
33. Antepartum/Postpartum	02. Inappropriate exercise/resting/ nutrition behaviors	23	8.4
<b>Health-Related Behaviors Domain</b>			
35. Nutrition	05. Imbalanced nutrition	27	6.6
36. Sleep and Rest Patterns	02. Frequently waking up at night	26	6.4
37. Physical Activity	01. Sedentary life style	25	6.1
	02. Inadequate/ irregular exercise	30	7.4
38. Personal Hygiene	05. Insufficient oral care/ brushing teeth and flossing	35	8.6
40. Family Planning	01. Having incorrect / inadequate knowledge about family planning methods	26	6.4
	02. Using a method with a limited effect/using it irregularly	25	6.1
41. Health Care Supervision	01. Inadequacies in periodic dental and medical examinations	30	7.4

second was the treatment process (n = 14); and the third was case management (n = 12).

## DISCUSSION

In this study, the practice files prepared by students during the practice of public health nursing were examined. Both students and educators identified the problems related to the health behavior domain during the home visits as ranking in first place. It can be said that the students are similar to the educators in the nursing skills of this area. The problems related to the physiological domain ranked second, and the psychosocial and environmental domains ranked third and fourth respectively. The study by Erdoğan and Esin [3] also identified and listed problems in the same order of health behavior, physiological, psychosocial and environmental domains. However, this order was psychosocial, environmental, physiological, and health behavior domains in the study by Slack and McEwen [15]. In the other studies using the Omaha System, physiological health problems were identified as the most important [1, 10, 11, 13-15].

It was determined that 73% of the students were adequate when considering the nursing diagnoses determined according to the Omaha System. However, 26.8% of the students were inadequate in establishing a nursing diagnosis using the Omaha System. This inadequacy of the students has been mainly in identifying the nursing diagnosis of the environmental and psychosocial areas. In the first 3 years of nursing education, students are more concentrated on the physiological problems of the individual by performing clinical field applications. In public health nursing class, it is thought that students use nursing diagnoses specific to the field of health behavior more because the educational role of public health nurses is emphasized.

In accordance with the PCS, students determined that the most commonly-coded diagnoses in the health behavior domain were having incorrect/inadequate knowledge about family planning methods, imbalanced nutrition, smoking, and inadequate/irregular exercise (Table 2). Diagnoses identified by the educators were in the areas of personal hygiene, inadequacy in periodic dental and medical examinations, inadequate/irregular exercise,

having incorrect/inadequate knowledge about family planning methods, and waking up frequently at night (Table 3). In the study by Kulakçı and Emiroğlu [13], the most frequently identified nursing diagnoses within the health domain were related to personal care, physical activity, sleep, resting and nutrition. The study by Martin *et al.* [8] reported that problems were discovered in the domains of pregnancy and nutrition, health care supervision in health management, and interpersonal relations and mental health. In the study by Brooten *et al.* [6], health care supervision and nutrition received the most frequently assigned diagnoses, especially for women with high-risk pregnancies. Inadequacy in periodic dental and medical checkups was found to be one of the most important health care supervision problems. In the study by Slack and McEwen [15], 67% of the community required education about diet, physical activity, and nutrition. Although the studies were conducted on different populations, some basic nursing diagnoses had common factors (e.g. physical activity, nutrition). The results of this current study showed similarities to the literature.

The most frequent nursing diagnoses in the physiological domain, which were coded by the students, targeted tooth decay and difficulty in breastfeeding, whereas the educators coded tooth decay, inappropriate exercise/resting/nutrition behaviors in this same domain. Differences and similarities were observed between the nursing diagnoses coded by the students and the educators. The differences in this domain could be attributed to students' focus on the breastfeeding training that they would give to women who had recently given birth, whereas the educators could interact with the women with a more holistic point of view. Although the study by Gür *et al.* [11] identified most of the problems to be in the physiological domain, the teeth were reported to be the fourth most important problem. Aylaz *et al.* [1] found that 36.4% of the individuals had inadequate oral and dental care. The results of this study were similar to those of the literature.

Within the parameters of the PCS, none of the nursing diagnoses in the psychosocial domain were cited as the most frequent diagnosis by students who indicated that they experienced difficulties in collecting data in the psychosocial domain. These

areas included sexuality, abuse, neglect, contact with community resources, and social relations. They also stated that they recognized the limits of the interventions to be implemented. The nursing diagnoses identified by the educators within the psychosocial domain were the scarcity of external stimuli/leisure activities and the difficulty in coping with stress. The Yoo *et al.*'s study [5] also reported problems in stress management in this domain.

While referring to the PSC, students were unable to identify a nursing diagnosis for the environmental domain. They expressed that they felt they were not experienced enough to do so. On the other hand, the educators identified the nursing diagnosis of low income from this domain. In the study of Aylaz *et al.* [1], the diagnosis of low income (30.9%) and difficulty to provide their needs (27.3%) in the families were determined mostly. Additional support for this nursing diagnosis comes from the Monsen *et al.*'s study [12] which determined that mothers and children with low income were at high risk for developing serious health problems. Another study by Brooten *et al.* [6] reported the income diagnosis in every domain.

Students and educators determined the nursing intervention categories after identifying the domains with problems. Both groups found a high number of nursing diagnoses belonging to the categories of health education and guidance and counseling. The same conclusions were reached in the study by Erdoğan and Esin [3]; and our own study reflected similar results. The study by Brooten *et al.* [6] determined that surveillance was the main nursing intervention category to be reported. Yet the results of our study differ from the Brooten *et al.*'s study [6].

## CONCLUSION

Students were found to be at a sufficient level to determine nursing diagnosis using Omaha System. They choose the nursing diagnoses included in the Omaha System. However, it is thought that the instructors should use a wider range of environmental and psychosocial areas that are 2 of the 4 areas of Omaha PCL, which are used in the field of public health nursing course.

We recommend that students be offered more case studies to be reviewed and assessed using the Omaha System in their public health nursing practice courses. We also suggest the following:

- Create more opportunities for case discussion and simulation methods to facilitate students' learning how to execute a comprehensive assessment approach to the family and its environment.
- Emphasize that each stage of the nursing process as featured in the Omaha System is connected to the others, and these should be evaluated together.
- Require students to prepare more case studies in the practice fields.

### Highlights

- In accordance with the Omaha Classification List, students found 412 problems, whereas the educators found 1,142 problems.
- We observed that the students identified 412 problems using the Omaha Problem Classification Scheme. The most commonly identified domain was health behavior (n = 164), the second was physiological (n = 112), the third was psychosocial (n=76), and the fourth was the environmental domain.
- Using the Omaha Problem Classification Scheme, educators identified and examined 1,142 problems. The most common problem was in the health behavior domain, followed by physiological (n = 273), psychosocial (n = 245), and environmental domains (n = 223), respectively.
- Although there were similarities between the nursing diagnoses identified by the students and the educators, the problems identified by the students were limited.

### Authorship Declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### Author contributions

All of the authors have contributed to the study on conception and design, drafting the article, revising it critically for important intellectual content, and final approval of the version to be published. All authors are in agreement with the content of the manuscript.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

### Acknowledgements

We thank all of the third year students who gave their time and made this study possible.

## REFERENCES

- [1] Aylaz R, Bilgin N, Omaç M, Ulukoca N. Impact of using the Omaha System of public health nursing students working at community health care centers on family health. *Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi* 2010;13:28-35.
- [2] Erdogan S, Secginli S, Cosansu G, Nahcivan NO, Esin MN, Aktas E, et al. Using the Omaha System to describe health problems, interventions, and outcomes in home care in Istanbul, Turkey: a student informatics research experience. *Comput Inform Nurs* 2013;31:290-8.
- [3] Erdoğan S, Esin N. [The Turkish version of the Omaha System: its use in the community nursing baccalaureate education]. *Florence Nightingale Hemşirelik Dergisi* 2004;13:11-22. [Article in Turkish]
- [4] Terzioğlu F, Apay SE, Akkuş Y, Irmak Z, Baybuğa M, Özer N, et al. [Nursing students' status of identifying nursing diagnosis and interventions on cases for trauma patient]. *Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi* [Article in Turkish]
- [5] Yoo IY, Cho WJ, Chae SM, Kim MJ. Community health service needs assessment in Korea using OMAHA Classification System. *Int J Nurs Stud* 2004;41:697-702.
- [6] Brooten D, Youngblut J, Deatrick J, Naylor M, York R. Patient problems, Advanced Practice Nurse (APN) interventions, time and contacts among five patient groups. *J Nurs Scholarsh* 2003;35:73-9.
- [7] Martin KS. *The Omaha System: A Key To Practice, Documentation and Information Management*: St. Louis, MO: Elsevier Saunders; 2005.
- [8] Martin KS, Monsen KA, Bowles KH. The Omaha system and meaningful use: applications for practice, education, and research. *Comput Inform Nurs* 2011;29:52-8.
- [9] Naylor MD, Bowles KH, Brooten D. Patient problems and advanced practice nurse interventions during transitional care. *Public Health Nurs* 2000;17:94-102.
- [10] İşçi F, Esin MN. [Evaluation of occupational health nursing interventions using Omaha scheme in a company]. *Dokuz Eylül Üniversitesi Hemşirelik Yüksekokulu Elektronik Dergisi* 2009;2:39-55. [Article in Turkish]
- [11] Gür K, Ergün A, Yıldız A, Kadioğlu H, Erol S, Kolaç N, et al. [Health problems of students according to Omaha problem classification scheme in a primary school]. *Hemşirelikte Araştırma Geliştirme Dergisi* 2008;10:1-14. [Article in Turkish]
- [12] Monsen KA, Fulkerson JA, Lytton AB, Taft LL, Schwichtenberg LD, Martin KS. Comparing maternal child health problems and outcomes across public health nursing agencies. *Matern Child Health J* 2010;14:412-21.
- [13] Kulakçı H, Emiroğlu ON. [Evaluation of the usability of the Omaha



System in the care of elderly people live in residential home]. Dokuz Eylül Üniversitesi Hemşirelik Yüksekokulu Elektronik Dergisi 2011;4:25-33. [Article in Turkish]  
[14] Coşansu G, Cangöl S, Erdogan S. [The use of Omaha System in the nursing care of children with acute care needs]. Florence Nightingale

Hemşirelik Dergisi. 2014;22:137-44. [Article in Turkish]  
[15] Slack MK, McEwen MM. The impact of interdisciplinary case management on client outcomes. Fam Community Health 1999;22:30-48.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Evaluation of the relationship between perception of tobacco packaging pictorial warnings and the nicotine addiction levels of smokers who admitted to smoking cessation clinic in Malatya, Turkey

Seda Beyhan Sağmen<sup>1</sup>, Mikail Özdemir<sup>2</sup>

<sup>1</sup>Department of Pulmonary Medicine, Malatya State Hospital, Malatya, Turkey

<sup>2</sup>Department of Public Health, Osmaniye Province Health Administration, Osmaniye, Turkey

DOI: 10.18621/eurj.381904

## ABSTRACT

**Objective:** In this study, we aimed to investigate relationship between perception of tobacco packaging pictorial warnings and the nicotine addiction levels of smokers who admitted to smoking cessation clinic in Malatya, Turkey.

**Methods:** Three hundred fifty-six patients were enrolled from the Malatya State Hospital Smoking Cessation Clinic. The characteristics of the patients, and number of cigarettes smoked were evaluated. The Fagerström test for nicotine dependence was used. Fourteen of the best-known and most effective pictorial health warnings on cigarette packages were shown and evaluated.

**Results:** The two best-known pictorial warnings in both male and female participants were pictorial 6, “Smoke contains benzene, nitrosamines, formaldehyde, and hydrogen cyanide” and pictorial 7, “Smoking causes fatal lung cancer”. The third best-known pictorial warning for female was pictorial 4, “Smokers die younger,” and for male it was pictorial 1, “Smoking may reduce blood flow and causes impotence”. Female were most affected by pictorial 11, “Protect children; don’t make them breathe your smoke”, and male were most affected by pictorial 1, “Smoking may reduce blood flow and causes impotence” ( $p < 0.043$  and  $p = 0.01$ , respectively). Fagerström scores compared with pictures mostly known and affected by participants, the highest and lowest scores belongs to same pictures; the highest Fagerström score was  $8.29 \pm 2.14$  for best known and  $8.25 \pm 2.19$  for most affected picture is number 2; the lowest Fagerström score was  $6.46 \pm 2.55$  for best known and  $6.56 \pm 2.68$  for most affected picture is number 3.

**Conclusion:** The effect of pictures about the decision to quit smoking may be investigated by a qualitative study especially for pictures 1, 2, 4, 6, 7, and 11.

**Keywords:** pictorial health warnings, smoking cessation, cigarette, tobacco

*Received: January 20, 2018; Accepted: June 17, 2018; Published Online: June 25, 2018*

Smoking is among the worst public health problems of Turkey. As is the case in the entire world, smoking is a widespread and considerable public health problem. Approximately one fifth of the world’s population smokes and about 6 million people die every year due to tobacco use. According to



Address for correspondence: Seda Beyhan Sağmen, MD., Malatya State Hospital, Department of Pulmonary Medicine, Malatya, Turkey  
E-mail: sedabeyhan05@yahoo.com

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

estimations, this figure is expected to reach 10 million in 2020 [1, 2].

Today, over 80% of smokers start smoking when they are aged younger than 18 years [3]. There are various methods for the purposes of educating society on the detriments caused by smoking. One of the most cost effective measures is printing warning messages on cigarette packages; because a person who smokes a pack of cigarettes every day must see the packaging more than 7000 times a year.

First, written warnings were printed on packs. Later, assuming that pictorial warnings could be much more effective, pictorials emphasizing the detriments were included. Warning messages were first written on cigarette packs in 1965, and pictorial health warnings were first used on cigarette packs in Canada in 2001 [4]. There are legal sanctions and measures against cigarette use in Turkey. The World Health Organization's MPOWER pack, which has a considerable place with regard to smoking control, includes essential applications such as preventing passive smoking, providing support to smokers to stop smoking, increasing taxes, banning advertising or promotion of tobacco products, training and warning society as to the detriments of tobacco products. It also aims to monitor and evaluate smoking control process.

There are various applications for the purposes of educating society on the detriments of smoking. One of the most significant and effective applications is inclusion of pictorial warning messages on cigarette

packs because they are much more effective than text alone. Printed and pictorial messages on cigarette packs were obligatory in Turkey as of 2011 [5, 6].

In this study, we evaluated relationship between perception of tobacco packaging pictorial warnings and the nicotine addiction levels of smokers who admitted to smoking cessation clinic in Malatya, Turkey.

## METHODS

The study was conducted on 356 patients who attended the Malatya State Hospital Smoking Cessation Clinic. Patients who presented to the clinic between March 2015 and July 2015 were shown the 14 pictorial warnings and questioned as to which was the best known, and which one led them to apply to the Smoking Cessation Clinic. The study included an initial screening using a structured self-administered questionnaire used to collect the following information: socio-demographic variables including age, gender, and education. The degree of nicotine dependence was assessed at baseline with the Fagerström test of nicotine dependence (FTND) consisting of six questions designed to measure tobacco dependence, which predicts smoking cessation and includes components of cigarette consumption and its typology. Typology has been

**Table 1.** Demographic variables of participants

		n	%
<b>Gender</b>	Women	111	31.2
	Men	245	68.8
<b>Age</b>	≤ 20	17	4.8
	21-30	104	29.2
	31-40	113	31.7
	41-50	76	21.3
	51-60	30	8.4
	> 60	16	4.5
<b>Education Status</b>	Did not finish any school	3	0.8
	Primary education	114	32
	Secondary education	89	25
	University	139	39
	Master Degree	11	3.1
<b>Total</b>		356	100.



Figure 1. The best known warnings among men and women.

constructed to describe smokers according to when and why they smoke and their capability to refrain from smoking. The FTND score can range from 0 to 10 point with a score of 0-2 indicate minimum nicotine dependence whereas a score of 8-10 indicate very high dependence.

### Statistical Analysis

Statistical analyzes were performed using the SPSS version 15.0 program. Normal distribution of variables was examined by histogram graphs and Kolmogorov-Smirnov test. Nominal variables were compared with Pearson Chi Square and Fisher's Exact Tests. Statistically significant results were obtained when the p value was below 0.05.

### RESULTS

One hundred ten female and 246 male applied to the Malatya State Hospital Smoking Cessation Clinic and were included in the study. The average age of the patients was 35 years (range, 14 to 75 years); the average smoking period was 16 years (range, 2 to 55 years). The sociodemographic characteristics of the participants are shown in Table 1.

Forty-two percent of the group were university graduates, and the remaining 58% were high school or primary school graduates. The two best-known pictorial warning were pictorial 6, “Cigarette smoke contains carcinogens such as benzene nitrosamine, formaldehyde, and hydrogen cyanide” (female/male: 21.9%/22.2%) and pictorial 7, “Smoking causes fatal lung cancer” (female/male: 20.4%; 20%). The third best known for female was “Smokers die younger” (12.6%), and for male it was pictorial 1, “Smoking reduces blood flow and causes impotence” (16.7%) (Figure 1). Pictorial 11, “Protect your children; don't make them breathe your smoke” mostly affected female, and pictorial 1, “Smoking reduces blood flow and causes impotence” mostly affected male ( $p < 0.043$  and  $p = 0.01$ , respectively) (Figure 2).

When Fagerström scores compared with pictures mostly known and affected by participants, the highest and lowest scores belongs to same pictures; the highest Fagerströmscore was  $8.29 \pm 2.14$  for best known and  $8.25 \pm 2.19$  for most affected picture is number 2; the lowest Fagerström score was  $6.46 \pm 2.55$  for best

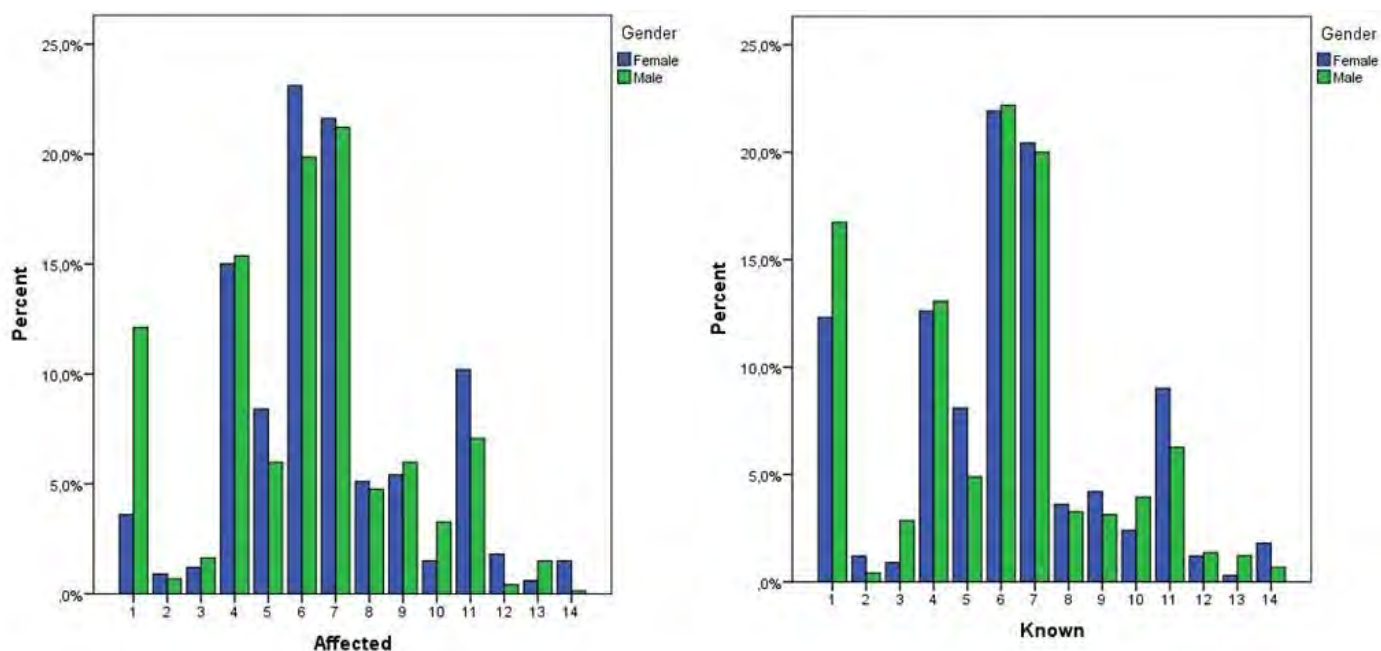


Figure 2. The most impactful pictorial warnings among men and women.

Table 2. Fagerström scores for mostly known pictures

Picture Number	Fagerström Scores (Mean ±SD)
1	7.19 ± 2.10
2	8.29 ± 2.14
3	6.46 ± 2.55
4	6.86 ± 2.39
5	6.89 ± 2.26
6	6.86 ± 2.29
7	7.05 ± 2.26
8	7.06 ± 2.43
9	6.65 ± 2.56
10	7.11 ± 2.27
11	6.83 ± 2.02
12	7.50 ± 2.50
13	7.00 ± 2.45
14	7.55 ± 1.57

Table 3. Fagerström scores for mostly affected pictures

Picture Number	Fagerström Scores (Mean ±SD)
1	7.30 ± 2.26
2	8.25 ± 2.19
3	6.56 ± 2.68
4	6.91 ± 2.23
5	6.81 ± 2.29
6	6.78 ± 2.34
7	7.07 ± 2.21
8	7.15 ± 2.43
9	6.94 ± 2.25
10	7.03 ± 2.51
11	6.70 ± 2.03
12	8.00 ± 2.45
13	7.69 ± 1.97
14	7.17 ± 1.72

known and  $6.56 \pm 2.68$  for most affected picture is number 3 (Tables 2 and 3).

## DISCUSSION

Printing warning messages on tobacco product packaging is a cost effective approach. This is also referred to in the Tobacco Control Frame Agreement as MPOWER Pack [7, 8]. Smokers and non-smokers see such messages. At the beginning, only pictorials

that referred to problems caused by smoking were printed. This was an appropriate method because it was more efficient. In addition, they caught the attention of illiterate smokers. Pictorial warning messages were first printed on cigarette packs in 2001.

In our study, the two pictorial warnings most recognized by female and male were “Cigarette smoke contains carcinogens such as benzene nitrosamine, formaldehyde, and hydrogen cyanide” and “Smoking causes fatal lung cancer”. With regard to impression, female were most impressed by the message “Protect

your children; do not make them breathe your smoke”, and male were most affected by “Smoking reduces blood flow and causes impotence”.

In a study performed on high school graduates, likewise, male students stated that they were particularly affected by the impotence effect of smoking. Impotence is important for male. Female students mostly refer to the importance of smoking during pregnancy because of its effect on unborn babies. This shows that females and males pay attention to different subjects. On the other hand, both male or female students found the lung cancer warning most striking [9]. Lung cancer is a feared complication due to its fatality rate.

Providing awareness of the detrimental effects of smoking using pictorial warnings is an influential method. Supporting photos carrying clear messages that reflect serious health problems would be a good educational practice. Current pictorials have not been found sufficient by high school students.

In the study by Vardavas *et al.* [10], the pictorial and notice with strongest warning was mostly “Smoking causes fatal lung cancer” with a frequency of 38.0%, followed by “Smoking is detrimental to your unborn baby” at 11.7%, and “Protect your children; do not make them breathe your smoke” with 6.6% (10). In a Turkish study by Bayrak *et al.* [11], the most influential warning message was “Smoking is detrimental to your unborn baby” with a rate of 70.6%, which proves that different pictorials and notes could have differing effects on different social groups.

With regard to tobacco control, cigarette packs could be an efficient tool to transmit information on the detrimental effect of smoking. They will be particularly effective among people with poor literacy and children. The more cigarette packs there are, the better the message is received. The findings to date show that pictorial warnings notify people better about health risks, provide high awareness and visibility between non-smokers and youths, and clarify health risks, as such, they are much more effective than written warnings or notices alone.

Studies also show that regularly updating pictorial warnings on cigarette packs and making them large and striking would make them persuasive, and provide public support, medical information, and motivation to quit smoking [12]. Another study in Mexico found that pictorial warnings had a more positive effect than

written ones [13].

As with our study, another study reported that people with lower education were more prone to addiction. This might be both due to lack of education or assuming cigarette smoking as a relief method while coping with difficulties. In the same study, no differences was observed in Fagerström scores in relation with the participants’ sex [14]. On the contrary, in our study, Female were significantly more dependent than male according to statistical estimations.

## CONCLUSION

Pictorial warnings on the cigarette packs are very influential for the purposes of establishing social awareness in the challenge against smoking. For Turkey, reinforcing written warning messages on cigarette packs with pictorials is an important development. This study is a precursor of detailed research about relation between smoking cessation and pictorial warnings. At the end of this study, the effect of pictures about the decision to quit smoking may be investigated by a qualitative study especially for pictures 1, 2, 4, 6, 7, and 11.

### Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

- [1] Bala MM, Strzeszynski L, Topor-Madry R, Cahill K. Mass media interventions for smoking cessation in adults. *Cochrane Database Syst Rev* 2013;6:CD004704.
- [2] Mackay J, Eriksen M, Shafey O. *The Tobacco Atlas*. 2nd ed.

Brighton, UK: American Cancer Society, 2006.

[3] US Department of Health and Human Services. Preventing tobacco use among young people: a report of the Surgeon General. US.

[4] Hammond D, Fong GT, Borland R, Cummings KM, McNeill A, Driezen P. Communicating risk to smokers: the impact of health warnings on cigarette packages. *Am J Prev Med* 2007;32:202-9.

[5] Tütün Ürünlerinin Zararlarının Önlenmesi Ve Kontrolü Hakkında Kanun. <http://www.mevzuat.gov.tr/Kanunlar.aspx> [Erişim Tarihi: 07.10.2012].

[6] Buzgan T, Çom S, İrmak H, Baykan H, Aydın E, Taner S. MPOWER: Tütün Salgınına Kontrol Etmeye Yönelik Politika Paketi, Sağlık Bakanlığı, Ankara, 2011.

[7] WHO Framework Convention on Tobacco Control, World Health Organization 2003, Geneva.

[8] WHO Report on the Global Tobacco Epidemic, The MPOWER Package, WHO, Geneva, 2008.

[9] Bilir N, Kaplan B, Küçük Biçer B, Ararat E, Akyol M, Arslan A, et al. [Opinions of a group of high school students in Ankara on pictorial warnings on cigarette packages]. *Turk Toraks Derg* 2013;14:127-33.

[Article in Turkish]

[10] Vardavas CI, Connolly G, Karamanolis K, Kafatos A. Adolescents perceived effectiveness of the proposed European graphic tobacco warning labels. *Eur J Public Health* 2009;19:212-7.

[11] Bayrak B, Bilir N, Yardım MS, Gürkan H, Karakullukçuoğlu Z, Kaya A. [Opinions of a group of high school students about the possible impact of combined warnings to be depicted on the cigarette packages]. *Turk Toraks Derg* 2010;11:1-9. [Article in Turkish]

[12] Hammond D. Health warning messages on tobacco products: a review. *Tob Control*. 2011;20:327-37.

[13] Thrasher JF, Perez-Hernandez R, Arillo-Santillan E, Barrientos-Gutierrez I. [Towards informed tobacco consumption in Mexico: effect of pictorial warning labels in smokers]. *Salud Publica Mex* 2012;54:242-53. [Article in Spanish]

[14] Önsüz MF, Topuzoğlu A, Algan A, Soydemir E, Aslan İ. [Evaluation of the relationship between perception of tobacco packaging warning messages and the nicotine addiction levels of smoker]. *Marmara Med J* 2009;22;111-22. [Article in Turkish]



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Needlestick and sharps injuries among nurses at Atatürk university research hospital and their practices after injury

Elif Okşan Çalikoğlu<sup>ORCID</sup>, Banu Bedir<sup>ORCID</sup>, Hilal Betül Akçay<sup>ORCID</sup>, Ali Gümüş<sup>ORCID</sup>

Department of Public Health, Atatürk University School of Medicine, Erzurum, Turkey

DOI: 10.18621/eurj.404827

## ABSTRACT

**Objective:** Exposure to needlestick and sharps injuries (NSI) is among the major occupational risks of health workers. Yearly 385,000 NSI are reported by health workers. In this study, we aimed to evaluate the frequency of NSI among nurses at Atatürk University Research Hospital together with the elaboration of the utilization of effective preventive measures used for infection control as well as the affecting factors.

**Methods:** All 562 nurses working at Atatürk University Research Hospital during September-November 2016 were invited to fill a questionnaire with 27 items. Questions were asked about the sociodemographic characteristics, having experienced NSI, usage of protective equipment, and hepatitis B vaccination status. A total of 555 (98.7%) nurses volunteered to participate. Verbal consent was taken from the participants.

**Results:** Of the participants, 425 (76.6%) were females, and 130 (23.4%) were males. Their mean age was  $27.5 \pm 7.4$  years. 52.6% (n = 293) of the participants were in the surgical clinics while 47.4% (n = 262) were in the medical clinics. Of the participants, 21.6% (n = 120) stated that they experienced a needlestick or sharps injury within the last one year. Of those injuries, 16.7% (n = 20) happened while removing the needle tip from the syringe, 29.2% (n=35) while trying to reattach the needle cap, 16.7% (n = 20) while filling the syringe, and 12.5% (n = 15) while drawing blood from the patient.

**Conclusion:** Health workers should be trained on injuries and all other occupational risks with cutting and puncturing tools, and they should be instructed on the use of protective equipment.

**Keywords:** needlestick injuries, sharps injuries, occupational health, nurses

*Received: March 12, 2018; Accepted: April 5, 2018; Published Online: April 9, 2018*

Exposure to needlestick and sharps injuries (NSI) is among the major occupational risks of health workers. According to the Centers for Disease Control and Prevention (CDC) estimates, yearly 385,000 NSI are reported by health workers. On the other hand, it has been shown that 50% or more of the NSI was not reported [1]. There is the particular importance of NSI contaminated with body fluids in the transmission of more than 20 pathogens, especially HIV, Hepatitis B, and Hepatitis C to health workers [2]. NSI refer to

medical or laboratory equipment (needles, shredded intravenous cannulation devices, broken glass fragments, lancets, pipettes or ampules, and injectors) that can cause skin penetration injury when held by hand [3]. According to the International Labor Organization (ILO), the most exposed occupation to needle injuries among health professionals are nurses [4]. The insufficient number of nurses and the intense and long working hours brings many occupational risks that involve members of this group, including



Address for correspondence: Banu Bedir, MD., Atatürk University School of Medicine, Department of Public Health, Erzurum, Turkey  
E-mail: banubedir89@hotmail.com

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>



NSI [5]. Injuries with cutting and needling tools are fundamental problems for healthcare workers in the sense of spreading infections [6]. Transmission mainly occurs by percutaneous or the mucosal route. Percutaneous spread happens through deep cuts, cutting with sharp tools, puncturing with needles, burning or peeling, while transmission via mucosal route occurs by contact with the nose, eyes, oral mucosa, blood, or body fluids [7]. The best method to protect health personnel is to prevent their contact with blood [8]. Means of protection from bloodborne infections are compliance with universal precautions, barriers, cleaning of used devices, gloves, and other equipment, as well as waste disposal, immunization, and protective measures after exposure [9]. The Patient and Employee Security Department of the Ministry of Health is valuable from this perspective [10]. Despite the decrease in percutaneous injuries parallel to the preference of disposable medical devices, blood drawing with vacuum tubes, and appropriate disposal of cutting and needling tools, the current rate of NSI remains still high in Turkey [11].

In this study, we aimed to evaluate the frequency of NSI among nurses at Atatürk University Research Hospital together with elaboration of the utilization of effective preventive measures used for infection control as well as the affecting factors.

## METHODS

The population of this descriptive-cross-sectional study was nurses working at Atatürk University Research Hospital. A questionnaire with 27 items was applied to the participants who accepted to join. Items in the questionnaire were: Questions on the sociodemographic characteristics of participants such as age, gender, marital status, department, and duration of work. The second section of the questionnaire consisted of questions on the experience with NSI such as the practice causing injury (drawing venous blood, cannulation, drug administration, etc.), the injuring instruments (needles, lancets, bottles, etc.), usage of protective equipment, and hepatitis B vaccination status. The population under study consisted of 562 nurses. The study was conducted between September-November 2016. Before the study, approval was obtained from Atatürk University

Faculty of Medicine Ethics Committee (decision no. 01, date 28.01.2016). All nurses in the population were invited to join the study; 555 (98.7%) volunteered to participate. Verbal consent was taken from the participants.

## Statistical Analysis

The SPSS 22.0 for Windows software (SPSS Inc., Chicago, IL, USA) was used for data analysis. Descriptive statistics for all variables were given as n, percentage, mean, and standard deviation (SD). The Chi-square test was used for the bivariate analysis of categorical variables and Student t test or Mann-Whitney U test for numerical variables. A  $p$  - value < 0.05 was accepted as statistically significant.

## RESULTS

A total of 555 nurses (98.7%), including 425 (76.6%) females and 130 (23.4%) males, participated in the survey. Their mean age was  $27.5 \pm 7.4$  years.

**Table 1.** Demographic characteristics of the participants

Characteristics	Data n (%)
<b>Age (years)</b>	
17-24	245 (44.1%)
25-29	145 (26.1%)
30 and above	165 (29.7%)
<b>Sex</b>	
Male	130 (23.4%)
Female	425 (76.6%)
<b>Marital Status</b>	
Married	225 (40.5%)
Single	320 (57.7%)
Divorced	10 (1.8%)
<b>Employed Department</b>	
Surgical Disciplines	292 (52.6%)
Medical Disciplines	263 (47.4%)
Intensive Care	355 (64.0%)
Laboratory	30 (5.4%)
Outpatients	60 (10.8%)
Emergency Ward	5 (0.9%)
Dialysis	20 (3.6%)
Inpatient Nurse	85 (15.3%)
<b>Years in the Profession</b>	
0-3 years	185 (33.3%)
4-6 years	135 (24.3%)
7-9 years	100 (18.0%)
10 years and above	135 (24.3%)

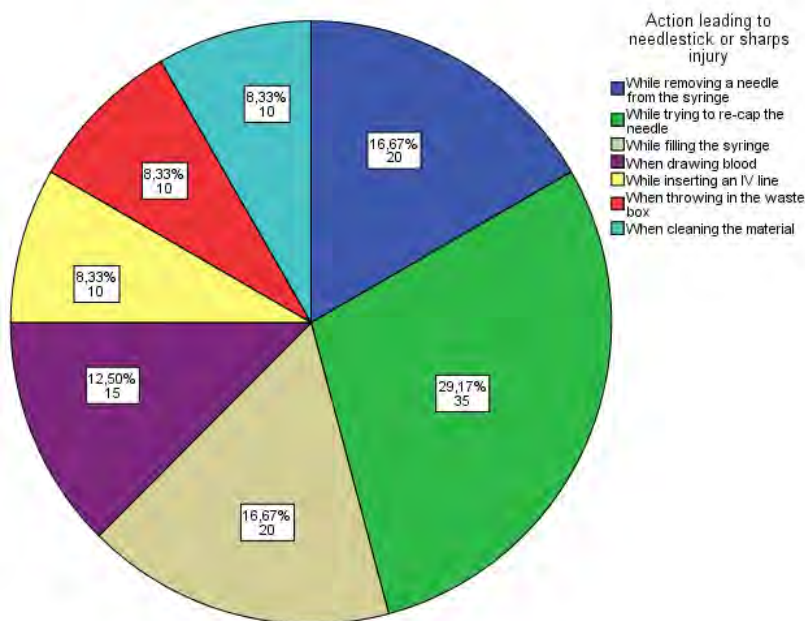


Figure 1. Distribution of actions leading to needlestick and sharps injuries.

52.6% (n = 293) of the participants were in the surgical clinics while 47.4% (n = 262) were in the medical clinics. The mean weekly working time of the participants was 40.1 ± 7.9 hours. 185 (33.3%) participants were working in the nursing profession for 0-3 years, 135 (24.3%) for 4-6 years, 100 (18.1%) for 7-9 years and 135 (24.3%) for more than ten years. Participant characteristics are presented in Table 1. Of the participants, 37.8% (n = 210) were satisfied with their work and 60.4% (n = 335) indicated that their work was too hard. Only 14.4% (n = 80) of those surveyed stated that they could take a break from work. 60.4% of those surveyed (n = 335) stated that they felt tired when they started work. The proportion of in-service training in the last year was 69.4% (n = 385). Of the surveyed, 13.5% (n = 75) stated that they were afraid of being criticized when reporting a needlestick and sharps injury, while 73.9% (n = 410) said that they did not have such a worry. 42.3% (n = 235) of the participants mentioned that employee safety was not a priority the employer, 46.8% (n = 260) stated that adequate measures were not taken against their occupational risks in their institutions, and only 35.1% (n = 195) thought that their institutions provided all equipment to protect them from work accidents. 89% (n = 494) of the survey participants stated that they used protective equipment

during patient interventions.

Of the participants, 21.6% (n = 120) stated that they experienced a needlestick or sharps injury within the last one year. Of those injuries, 16.7% (n = 20) happened while removing the needle tip from the syringe, 29.2% (n = 35) while trying to reattach the needle cap, 16.7% (n = 20) while filling the syringe, and 12.5% (n = 15) while drawing blood from the patient (Figure 1). Of the surveyed, 26.1% (n = 145) reported having hepatitis B vaccination. Only 48.6% (n = 260) of those surveyed knew that they had to fill out the 'Contaminated Needlesticks, Sharps, or Splash Exposures Follow-up Form' after injury, and 12.5% (n = 69) of the injured notified their authorities by filling out the follow-up form.

The mean age of those who stated that they had been injured in the last year (26.6 ± 6.0 years) was found to be significantly lower (t = -2.123; p = 0.034) compared with the uninjured (28.3±8.1 years). Female nurses (23.5%; n = 100) had significantly higher injury rates when compared to males (11.5%; n = 15) (Chi-square = 9.343; p = 0.009). There was no significant difference between the nurses working in the surgical (20.5%; n = 60) or medical wards (20.9; n = 55) concerning injuries (Chi-square = 1.369; p = 0.504). There was a significant difference between injuries with needlestick or sharps of people with different

weekly working hours. Mean duration of working hours was shorter in those with experience of injury within the last year compared to non-exposed ( $39.8 \pm 6.5$  vs.  $40.4 \pm 8.1$  respectively; Mann-Whitney U test;  $Z = -2.567$ ;  $p = 0.010$ ). There was a significant difference in the injury proportions concerning the duration of work in the profession (Chi-square = 54.302;  $p < 0.001$ ). Participants with 0-3 years, 4-6 years, 7-9 years, and 10 or more years' experience had 24.3% ( $n = 45$ ), 22.2% ( $n = 30$ ), 5.0% ( $n = 5$ ), and 25.9% ( $n = 35$ ) NSI; respectively. Those participants reporting the possibility of giving breaks at work experienced less injury compared to the others (Chi-square = 69.294;  $p < 0.001$ ). No significant differences in NSI were observed with regard to having received (23.4%;  $n = 90$ ) or not received (18.2%;  $n = 20$ ) in-service trainings (Chi-square = 1.444;  $p = 0.486$ ).

## DISCUSSION

The proportion of participants, who had at least one needlestick or sharps injury within the last year, was 21.6%. A similar study conducted in Muğla revealed a ratio of 42% [12]. Another study conducted in İzmir showed a proportion of 65.8% [13], while in a study done in Isparta, this rate was 36.2% [14]. In the latter investigation, according to the latest injuries remembered, the proportion of NSI was 30.4%. In various studies, it was determined that most of the injuries were caused by injector needles [15, 16]. In the survey conducted by the CDC, 5,000 percutaneous injuries were identified during the five-year follow-up period, out of which 62% were due to syringe needles [17].

In our study, the mean age of those who had been injured in the last year was found to be significantly lower than those uninjured. In one research, it was stated that being under the age of 24, having an experience of four years or less, working in surgical or intensive care units, and working more than 8 hours a day, were factors that increased needlestick and sharps injuries [16]. According to the literature, those working in surgical and intensive care units, having mixed shifts or more extended working hours, nurses with less experience, reloading needles, and those who do not use protective gloves while holding needles are more likely to be injured [18, 19].

In our study, although the number of nurses in the surgical units who had NSI was higher than nurses working in medical wards, the difference was not statistically significant. The literature provides ambiguous information on this issue. Among the reasons for the higher number of injuries in the surgical units may be the relatively higher frequency of parenteral applications and procedures in these wards. Many studies have shown that healthcare workers in the emergency and surgical departments had more penetrating puncture injuries than in other units [2, 11, 20].

The proportion of vaccination against hepatitis B in our study was 73.9%. The probability of infection after percutaneous injuries in the form of needle puncture is 30% for Hepatitis B 3-4% for Hepatitis C [21], and 0.3% for HIV [14]. These rates indicate that percutaneous injuries are a significant risk for Hepatitis B in particular. The practical way of protection from hepatitis B is vaccination. All healthcare providers should be included in the Hepatitis B vaccination program [22]. However, also the immunity status of post-vaccination persons should continuously be monitored.

It was determined that 51.4% of the participants in the study were not informed about the form to be filled after a needlestick or sharps injury. Usage of the follow-up form in the event of any injury was found to be 11.7%. In another study conducted in İzmir [13], 13.8% reported the injury while 34.8% did not do so, and 5.8% stated that they were not aware of the regulations about notification. When the reasons for not reporting injury were queried, 15.3% answered "I did not know how to report" and 7.2% mentioned, "I had no time for notification". In another study conducted in Mersin, it was determined that 87.3% of the research group did not report NSI. When the reasons for not reporting the injury were examined, 48.6% of the employees answered: "I did not know that I had to report," 17% responded, "I was not worried," and 16% said, "I did not know the process" [21]. Other studies reported proportions between 32.4% and 96.2%. When all studies are evaluated together, the most reported reasons for not reporting (in decreasing order) are; negligence, fear of perception, fear of warning, lack of knowledge about the reporting procedures, concerns about privacy, and reluctance [23-25].

Fear of being criticized when reporting the injury was 13.5%. In another study conducted in Istanbul, it was stated that especially those who are new to the profession act more timidly in reporting an injury [26]. It was also observed that these people had less knowledge about infectious diseases. Increasing the notification rate is possible by increasing the training of newcomers to the profession [27].

The use of safety devices that cover the needle-tip after hypodermic injection lowers the risk of NSI per HCW by 43.4%-100% compared to conventional devices [28]. The World Health Organization (WHO) recommends the use of safety injection devices and instructs governments to transition to their exclusive use by 2020 [29].

## CONCLUSION

Health workers should be trained on injuries and all other occupational risks with cutting and puncturing tools, and they should be instructed on the use of protective equipment, which must be provided by the employer. Safety-engineered devices should be used for hypodermic injections. Occupational physicians should be assigned to follow up in case of any injury or occupational illness. Not only nurses but all other allied health workers should be provided with for hepatitis B vaccinations and antibody follow-ups, with screening, diagnosis, and treatment support also for other occupational infectious diseases.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

- [1] Centers for Disease Control and Prevention. Workbook for designing, implementing, and evaluating a sharps injury prevention program 2008. Available from: [https://www.cdc.gov/sharpsafety/pdf/sharpsworkbook\\_2008.pdf](https://www.cdc.gov/sharpsafety/pdf/sharpsworkbook_2008.pdf).
- [2] Omaç M, Eğri M, Karaoğlu L. [Evaluation of occupational needlestick-sharp injuries and status of hepatitis B immunization on nurses working at Malatya province hospitals]. İnönü Üniversitesi Tıp Fakültesi Dergisi 2010;17:19-25. [Article in Turkish]
- [3] Korkmaz M. [Needlestick and sharp injuries in health workers] Fırat Sağlık Hizmetleri Dergisi 2008;3:17-37. [Article in Turkish]
- [4] Elmihyeh B, Whitaker I, James M, Chahal C, Galea A, Alshafi K. Needle-stick injuries in the National Health Service: a culture of silence. J R Soc Med 2004;97:326-7.
- [5] Yıldırım A, Özpulat F. [The knowledge and awareness levels on professional risks of nursing students in a medical vocational high school in Turkey]. Sürekli Tıp Eğitimi Dergisi 2015;24:18-29. [Article in Turkish]
- [6] İlhan MN, Durukan E, Aras E, Türkçüoğlu S, Aygün R. Long working hours increase the risk of sharp and needlestick injury in nurses: the need for new policy implication. J Adv Nurs 2006;56:563-8.
- [7] Hatzakis A, Wait S, Bruix J, Buti M, Carballo M, Cavaleri M, et al. The state of hepatitis B and C in Europe: report from the hepatitis B and C summit conference. J Viral Hepat 2011;18 Suppl 1:1-16.
- [8] Cardo DM, Bell DM. Bloodborne pathogen transmission in health care workers. Risks and prevention strategies. Infect Dis Clin North Am 1997;11:331-46.
- [9] Özvarış ŞB. [Protecting health workers from infections]. Sürekli Tıp Eğitimi Dergisi 1999;9:12. [Article in Turkish].
- [10] TC. Sağlık Bakanlığı Sağlık Hizmetleri Genel Müdürlüğü Sağlıkta Kalite ve Akreditasyon Daire Başkanlığı.
- [11] Ayrancı U, Kosgeroğlu N. Needlestick and sharps injuries among nurses in the healthcare sector in a city of western Turkey. J Hosp Infect 2004;58:216-23.
- [12] Eğri M, Perlivan E. [Epidemiology of needlestick and sharps injuries in health care workers at Turgut Özal Medical Center]. Sağlık ve Toplum 2000;10:35-9. [Article in Turkish]
- [13] Samancıoğlu S, Ünlü D, Durmaz Akyol A. [The evaluation of needlestick and sharp injuries among intensive care nurses]. Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi 2013;16:43-9. [Article in Turkish]
- [14] Kişioğlu AN, Öztürk M, Uskun E, Kırbyık S. [In a medical hospital's health workers incisive and perforating injury epidemiologies and prevention behaviours and attitudes]. Türkiye Klinikleri J Med Sci 2002;22:390-6. [Article in Turkish]
- [15] Cheng F, Ford W, Cheng S, Weber M, Kerndt P. Occupational risk of acquiring HIV infection through needlestick injuries. Clin Perform Qual Health Care 1995;3:147-50.
- [16] Rakickene J, Barkowska T, Caplinskas S. [Occupational HIV infection. Medical workers and HIV prevention]. Zh Mikrobiol, Epidemiol, Immunobiol 2000;4:73-4. [Article in Russian]
- [17] CDC. Sharp injury prevention program workbook 2008, 2008. Available from: <http://www.cdc.gov/Sharpsafety/pdf/sharpsworkbook>
- [18] Salehi AS, Garner P. Occupational injury history and universal precautions awareness: a survey in Kabul hospital staff. BMC Infect Dis 2010;10:19.
- [19] Nsubuga FM, Jaakkola MS. Needle stick injuries among nurses in sub-Saharan Africa. Trop Med Int Health 2005;10:773-81.
- [20] Shiao J, Guo L, McLaws ML. Estimation of the risk of bloodborne pathogens to health care workers after a needlestick injury in Taiwan. Am J Infect Control 2002;30:15-20.
- [21] Altrok M, Kuyurtar F, Karaçorlu S, Ersöz G, Erdoğan S. [Healthcare workers experiences with sharps and needlestick injuries and precautions they took when injuring]. Maltepe Üniversitesi Hemşirelik Bilim ve Sanatı Dergisi 2009;2:70-9.
- [22] Türkistanlı E, Şenuzun FE, Karaca BS, San AT, Aydemir G. [The state of the immunization of the health workers who have working in Ege university research hospital]. Ege Tıp Dergisi 2000;39:29-32. [Article in Turkish]
- [23] Souza-Borges FR, Ribeiro LA, Oliveira LC. Occupational exposures to body fluids and behaviors regarding their prevention and

post-exposure among medical and nursing students at a Brazilian public university. *Rev Inst Med Trop São Paulo* 2014;56:157-63.

[24] Prasuna J, Sharma R, Bhatt A, Arazoo A, Painuly D, Butola H, et al. Occurrence and knowledge about needle stick injury in nursing students. *J Ayub Med Coll Abbottabad* 2015;27:430-3.

[25] Yang YH, Liou SH, Chen CJ, Yang CY, Wang CL, Chen CY, et al. The effectiveness of a training program on reducing needlestick injuries/sharp object injuries among soon graduate vocational nursing school students in southern Taiwan. *J Occup Health* 2007;49:424-9.

[26] Merih YD, Kocabey MY, Çırpı F, Bolca Z, Celayir AC. [Epidemiology and preventive measurements of sharps injuries in a state

hospital during the last three years]. *Zeynep Kamil Tıp Bülteni* 2009;40:11-5. [Article in Turkish]

[27] Ede G, Kaptan D. Injury experiences and precautions taken by nurses working in pediatric wards towards penetrative/incisive tools. *Int J Caring Sci* 2016;9:569-78.

[28] Cooke CE, Stephens JM. Clinical, economic, and humanistic burden of needlestick injuries in healthcare workers. *Med Devices (Auckl)* 2017;10:225-35.

[29] World Health Organization. WHO guideline on the use of safety-engineered syringes for intramuscular, intradermal and subcutaneous injections in health-care settings. Geneva, Switzerland. 2015.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Emotional and behavioral problems in infants and preschool children: prevalence and sociodemographic risk factors

Çağatay Uğur<sup>1</sup>, Esra Yürümez<sup>2</sup>, Yasemin Yilmazer<sup>3</sup>

<sup>1</sup>Department of Child and Adolescent Psychiatry, Ankara Dışkapı Pediatric Hematology Oncology Training and Research Hospital, Ankara, Turkey

<sup>2</sup>Department of Child and Adolescent Psychiatry, Ankara University School of Medicine, Ankara, Turkey

<sup>3</sup>Department of Child and Adolescent Psychiatry, Child Development Unit, Ankara Dışkapı Pediatric Hematology Oncology Training and Research Hospital, Ankara, Turkey

DOI: 10.18621/eurj.379887

## ABSTRACT

**Objective:** To determine the prevalence of behavioral disorders and the relationship between sociodemographic, environmental and family factors among infants and preschool children applied to psychiatry clinic.

**Methods:** The sample comprised 355 children between 20-59 months of age and showing normal developmental pattern. After psychiatric assessments, the patients were referred to the child development unit for developmental assessment, support and psychoeducation. Ankara Developmental Screening Inventory (ADSI) was applied to all participants.

**Results:** The mean age was significantly higher among the children applied to the clinic due to limit setting problems (LSP) than that of the children applied due to the other problems. The children with speech delay were the group applied to the clinic at the earliest age. Speech delay rates were higher among boys compared with girls. Sibling jealousy was more common among girls than boys. In the group with LSP, fathers' education levels were lower than that of the group without LSP. There was no difference between children in terms of the number of siblings, birth order and family size.

**Conclusion:** The findings indicate that limit setting was by far the most common problem among children applied to our clinic. Consequently, the utility of results to raise intervention strategies within limit setting should be developed and intervened earlier.

**Keywords:** Infant, preschool children, limit-setting, emotional problems, behavioral problems

*Received: January 17, 2018; Accepted: March 28, 2018; Published Online: April 7, 2018*

Bagner *et al.* [1] stated that emotional and behavioral problems are highly prevalent in early childhood and are important focal points for child psychiatrists. While psychiatric disorders traditionally are not diagnosed in children younger than two years of age, studies conducted in the recent past have demonstrated the appropriateness of assessing

emotional and behavioral problems during infancy. Family, environmental and sociodemographic factors have been associated with higher risk for behavioral, developmental and mental disorders in infants and preschool children [2, 3].

Experts note that the home environment is the main context in which children grow up and develop



**Address for correspondence:** Esra Yürümez, MD., Ankara University School of Medicine, Department of Child and Adolescent Psychiatry, Cebeci Hospital, Mamak Street, Altındağ, 06230 Ankara, Turkey  
E-mail: esrayurumez@gmail.com, Tel. +90 312 5957108

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

[4-6]. This being the case, it has a significant influence on the development of behavioral problems. In a family, the interactions between family members have an effect on other family members through the quality of their relationships and personal risk factors which can ultimately spill over and impact on the relationships with other people [7].

A number of studies have shown that low level of parental education, young maternal age, experience of stressful life events and low socio-economic background are associated with increased risk of developing attention, externalizing and internalizing problems among children [4, 8].

A number of studies have been conducted on the prevalence of childhood behavioral problems in different countries [9-11]. A review of related studies published in 20 countries revealed prevalence of behavioral problems ranging from 1 to 51% [12]. Among preschool aged children (between 1-6 years old), the overall prevalence rate was found to be 10% according to the review. Another review conducted by Brauner and Stephens [13] reported that among children aged less than five, the prevalence rate for behavioral and emotional problems ranged from 9.5 to 14.2%.

In Turkey, studies on the prevalence of behavioral and mental health problems among infants and preschool age children are insufficient. Furthermore, although links between sociodemographic, environmental and family attributes and children's mental health have been established in several studies [1-4], a few studies have been conducted in this area. This study aims to determine the prevalence of behavioral disorders and the link between socio-demographic, environmental and family factors among infants and preschool children applied to an outpatient clinic in Ankara, Turkey.

## METHODS

For the study, the data review of the patients applied to our clinic between April 2016 and January 2017 was conducted. The sample of the study included the patients who applied to the child and adolescent psychiatry clinic and whose semi-structured psychiatric interviews were completed before being

referred to the child development unit for developmental support, monitoring and family education.

### Participants

The sample comprised 355 young children between 20 and 59 months of age and their mothers or fathers who applied to an outpatient child development and monitoring unit of a training and research hospital. Children with chronic medical or neurological disease, intellectual and developmental delay (except for those who only have speech delay), uncorrected visual and auditory problems were excluded.

### Procedure

The research protocol was approved by the local ethic committee. The procedures of the study were in accordance with the Declaration of Helsinki, as well as local laws and regulations. The developmental stages of the children were assessed using the Ankara Developmental Screening Inventory (ADSI), and the children who showed normal developmental pattern were included in the study.

### Measures

#### *Sociodemographic form*

A questionnaire comprised queries on the perinatal and developmental history of child, age, education levels, occupation, number of children, physical and mental illnesses, marital status (married, divorced or widowed) of parents, social support of the family and other family members was used.

#### *Ankara Developmental Screening Inventory (ADSI)*

The ADSI is a 154-item scale based on a parental report for the assessment and evaluation of social, cognitive and communicative levels of children between 0-6 years of age [14]. The five subscales of the inventory are language-cognitive, fine motor, gross motor, social interaction skills and self-care abilities. The internal consistency of the scale was .99-.80 and the test-retest reliability values were .99-.80 for three age groups (0-12, 13-44 and 45-72 months).

### Statistical Analysis

SPSS 17.0 was used for analyses. Categorical variables were pointed out with frequency (n) and

percentages (%). Continuous variables were highlighted by mean, median, standard deviation and range. Chi-square and Fisher’s exact test, t-test were used where appropriate. The value of  $p < 0.05$  was accepted as statistically significant.

## RESULTS

A total of 355 subjects were included in the study. Among all children, 126 (35.4%) were in early childhood (20-36 months) and 229 (64.5%) were in preschool age (36-59 months).

The mean age of the participants was  $40 \pm 10$  months. The mean age of the children with speech delay was  $35 \pm 9.6$  months. The children with speech delay were the group who applied to the clinic at the earliest age. In all participants, 208 patients (58.5%) were males and 147 (41.4%) were females. Mothers’ mean age was  $30.9 \pm 5.1$  years, and fathers’ mean age was  $34.6 \pm 5.4$  years. The maternal and paternal average education durations were  $10.2 \pm 3.5$  and  $11.8 \pm 3.1$  years, respectively.

### The frequency of causes of admission

Patients included in the study had various reasons for referring to the hospital. The main reason of admission was limit setting problems (229 children,

64.5%). The frequency distributions of causes of admission were shown in Table 1.

### Gender comparisons

As a reason for referring to the hospital, the speech delay was more common among boys than girls (21.2% vs. 10.4%). Sibling jealousy was a significantly more frequent reason among girls than boys (9.8% vs. 4.8%) as shown in Table 1.

### Number of siblings

The family sizes and number of siblings were analyzed, 140 (39.4%) children had no sibling whereas 156 (43.9%) had only one, and 59 (16.7%) had at least two siblings. Analyzing the relationship between behavioral problems and number of siblings, it was found that prevalence of toilet problems (67.56%) were higher among children who had no siblings, than that of children with siblings and this association was statistically significant ( $p < 0.05$ ). It was also found that children without siblings had higher prevalence of eating (9.2%) and sleeping problems (10.7%) but these associations were statistically not significant ( $p > 0.05$ ). The children having one sibling had higher prevalence of limit setting problems (43.73%), sibling jealousy (75.86%), nail eating(14.1%) speech disorder (6.6%) and masturbation problems (7.5%) compared with

**Table 1.** Frequency and gender comparison of complaints caused application to the clinic.

	Boys (n = 208)	Girls (n = 147)	Total (n = 355)	X <sup>2</sup>	p value
Limit setting problems	135 (64.9%)	94 (48.7%)	229 (64.5%)	1.853	0.470
Speech delay	44 (21.2%)	20 (10.4%)	64 (18.0%)	1.068	<b>0.045</b>
Toilet habit problems	23 (11.1%)	14 (7.3%)	37 (10.4%)	1.641	0.389
Sibling jealousy	10 (4.8%)	19 (9.8%)	29 (8.2%)	1.006	<b>0.006</b>
Sleep problems	10 (4.8%)	11 (5.7%)	21 (5.9%)	1.293	0.204
Eating problems	11 (5.3%)	10 (5.2%)	21 (5.9%)	1.551	0.353
Nail biting	8 (3.9%)	7 (3.6%)	15 (4.2%)	1.673	0.433
Anxiety	7 (3.4%)	5 (2.6%)	12 (3.4%)	1.985	0.603
Speech disorder	6 (2.9%)	3 (1.5%)	9 (2.5%)	1.618	0.446*
ADHD signs	4 (1.9%)	2 (1.0%)	6 (1.7%)	1.205	0.197
Divorcing	3 (1.4%)	2 (1.0%)	5 (1.4%)	1.949	0.659
Masturbation	2 (1.0%)	2 (1.0%)	4 (1.1%)	1.726	0.550*
Loss of parents	1 (0.5%)	2 (1.0%)	3 (0.8%)	1.372	0.372*
Autism	1 (0.5%)	1 (0.5%)	2 (0.6%)	1.805	0.657*
Delectation	0	1 (0.5%)	1 (0.3%)	1.234	0.414*

Data are shown as number (%). ADHD = Attention Deficit Hyperactivity Disorder, \* = Fisher’s exact test



**Table 2.** Demographical and clinical findings of children with limit setting problems

Variables	Children with LSP (n = 229)	Children without LSP (n = 126)	Total (n = 355)	X <sup>2</sup>	p value
<b>Children</b>					
Age (months)	41 ± 9.8 (20-59)	38.3 ± 10.2 (22-59)	40 ± 10 (20-59)	2.434	<b>0.015</b>
<b>Gender</b>				1.853	0.470
Boys	135 (59%)	73 (57.9%)	208 (58.6%)		
Girls	94 (41%)	53 (42.1%)	147 (41.4%)		
<b>Mothers</b>					
age (years)	31.1 ± 5.3 (19-49)	30.8 ± 4.8 (18-42)	31 ± 5.1 (18-49)	1.446	0.505
education (years)	10.4 ± 3.3 (5-15)	10.3 ± 3.2 (5-15)		1.446	0.505
<b>Fathers</b>					
age (years)	34.9 ± 5.6 (20-65)	34.3 ± 5.1 (25-55)	34.7 ± 5.5 (20-65)	1.446	0.284
education (years)	9.3 ± 3.1 (5-15)	10.1 ± 3.1 (5-15)		1.446	<b>&lt; 0.001</b>

Data are shown as mean ± standard deviation (minimum-maximum) or number (%). LSP = Limit Setting Problems

children without sibling or with more than one sibling. Only sibling jealousy was statistically significant (*p* < 0.05).

**Marital status**

The number of parents divorced was 32 (9%) and widowed was 6 (1.7%). The number of children whose parents were married was 310 (87.3%) and children with parents in prison were 7 (2%). There was found no significant association between marital status and the frequency of reasons for admission (*p* > 0.05).

**Family type**

The family types were assessed as nuclear (comprised of parents and children) and extended (including other relatives like grandparents living with family) ones. The number of nuclear families was 282 (79.4%) and extended families was 73 (21.6%). There was found no significant relationship between family type and problems causing the admission to the clinic (*p* > 0.05).

**Results in children with limit setting problems**

A statistical evaluation has also been carried out for the limit setting problems which constitutes more than half of the complaints caused the admission to the hospital.

At this stage, the participants were divided into two groups according to the presence of limit setting problems. Mean age of the children with and without

limit setting problems were 41 ± 9.8 and 38.3 ± 10.2 months, respectively. There was found a significant difference between groups in respect to age at the time of admission (*p* = 0.015).

Among the children with limit setting problems, 135 (58.9%) patients were males and 94 (41.1%) were females. In the other group, 73 (57.9%) patients were males and 53 (42.1%) were females. There was no significant difference between the two groups in terms of distribution of gender (*p* > 0.05).

Mothers’ mean age was 31.1 ± 5.3 years, and fathers’ mean age was 34.9 ± 5.6 years. The average education duration of mothers and fathers were 10.7 and 11.3 years respectively. There was found significant difference between groups in fathers’ education durations. The education durations of fathers were significantly lower in the group with limit setting problems than the group without limit setting problems (*p* < 0.001) (see Table 2). Sociodemographic features of children were shown in Table 2.

There was found no significant difference between groups with and without limit setting problems in terms of being an only child, birth order and overall family size (*p* < 0.05).

**DISCUSSION**

**Prevalence of behavioral problems**

The findings of this study indicate that limit

setting problems, speech delay, toilet habit problems, jealousy of siblings, sleep problems, eating problems, nail eating/finger sucking, anxiety problems, divorce-related issues, and speech disorder were the most prevalent behavioral problems among infants and preschool children. Limit setting was by far the most common problem among children and followed by speech delay, toilet habit problems, sibling jealousy, and sleep problems. The participants of the current study were composed of patients presented to the clinic. Thus, the results of community screening may differ. On the other hand, these results are widely consistent with those found in past studies. Petersen *et al.* [15] reported that the prevalence of developmental and behavioral disorders in children (6 months to 17 years) was 33.5%.

Several studies have shown that prevalence rates for insomnia in the United States and Caucasian countries vary from 20 to 30% [16, 17]. The frequency of sleep problems was found as 6.0% in our population. Different from the studies investigating the prevalence of sleep problems specifically, the participants were not assessed in terms of sleep patterns and problems separately. Sleep problems are known to be expressed inadequately if they have not been asked specifically and the frequency of sleep problems may have seen less [18].

In Taiwan, Chou [19] revealed a prevalence of limit setting problems of 70% and sleep problems of 66%. The prevalence rates for constipation and toilet habit problems in children worldwide stands at between 0.3 to 28% [20, 21]. The definition and perception of behavioral problems may differ according to sociocultural environment but generally these results are showing consistency.

### Age and Gender

The average age of children with limit setting problems was statistically older than that of the group without limit setting problems. In addition, most of children with limit setting problems were admitted to the clinic at preschool age. The reason for late admission to the clinic may be normalization of behavioral problems by parents related with cultural norms and approaches in the way of limit setting. Additionally, some parents' may fail to recognize the emotional and behavioral problems until the involvement of children to a structured social

environment. Parenting with appropriate limit setting strategies positively influences self-regulation and compliance skills of children [22]. This is related to awareness of social approval or disapproval. Children between 36-60 months are expected to be more compliant by their parents [23]. Starting kindergarten, at the age of 36 months, promotes socialization by an imitative process. Most children will learn to deal with social rules of people who are not family members. They are expected to regulate themselves and meet changing situational demands. The maladaptation of children to parental limit setting may prompt the need for professional intervention in preschool.

In the current study, the children who applied to the clinic due to speech disorders were the youngest group. It is not surprising as speech delay is one of the most worrying and noticeable problems for families. According to the results of this study, female gender is associated with jealousy of siblings. This finding contradicts with a study [24] that showed jealousy of siblings, as expressed in the form of sibling victimization, was more prevalent in boys compared to girls. On the issue of gender effect on sibling jealousy, results of studies are inconsistent. There are studies suggesting that aggressive behaviors of boys and anxious responses of girls increase based on sibling jealousy [25, 26]. The aggressive behaviors may not be interpreted as the signs of sibling jealousy by parents but it may be easier to link the symptoms like withdrawal, regression, anxiety to jealousy and to seek professional help.

Gender was also found to be associated with speech delay with higher prevalence among boys. This result is consistent with the findings of a study [27] that associated male gender, family history, and low parental education with speech delay problems in children aged five and younger. The findings are also consistent with several previous studies that showed consistent advantage for infant and preschool girls with regard to different aspects of learning including vocabulary size, syntax complexity, vocabulary growth and morphosyntactic growth [28-30]. The advantage that girls enjoy with regard to language learning according to Nelson [31] may be attributed to the fact that they are "left brain dominant learners and therefore analyze speech streams into individual phonetic elements and words". Boys on the other hand, tend to be right brain dominant learners and

focus more on the overall sound of the language and how it is used.

### Parental Age and Education

In the study, in all children, both the mothers and fathers of children with behavioral and emotional problems were roughly corresponding to young adults. Several studies indicate that children whose parents (mostly mothers) are older, show lower risk of behavioral problems [32]. Other studies, though supporting the link between parental age and disorders, note that for other psychiatric illnesses, this relationship is either unconvincing or inconsistent. Maternal age has a complex link with several psychosocial variables.

Parental education is closely linked to family socio-economic status to the extent that low parental education most often translates to low socio-economic family status and strain on family resources [33]. In the group with limit setting problems, the level of education of the fathers was statistically significantly lower than that of the group without limit setting problems. In terms of maternal education, there was found no significance between two groups but average education level of all mothers which is known to be a risk factor for emerging of psychopathology among children [34] were relatively low in our study. Taking into account that most of the mothers in these families are not being in a job and having a regular income, the socio-economic status of these families may not be high.

### Being an Only Child

The study found an insignificant association between being an only child in the family and having toilet problems. Children who were an only child in their family experienced higher prevalence of divorce-related problems compared to their counterparts who had siblings. The findings of the study also indicate that children from families with more than three children tended to experience lower prevalence of behavioral problems. Besides that, children without siblings tend to show higher prevalence of toilet habit problems, eating, sleeping, ADHD, speech delay and divorce-related problems. The frequency of emotional and behavioral problems among children without a sibling may be related with experiencing more common parental psychopathology, marital conflicts

and separation of parents during growing up. Those who came from families with two children, on the other hand, have higher prevalence of limit setting problems, sibling jealousy, nail eating, speech disorder and masturbation problems. These findings seem to suggest that large families serve as a protective factor against behavioral problems. The results of this study are congruent with the findings of a study [35] that showed higher prevalence of behavioral problems among “only children” and lowest prevalence among large families with at least 3 children. Larger families generally tend to provide children with an environment for socializing which is beneficial for child development [36].

### Family Type

An association (but not significant) was found between family type and eating and divorce-related problems. Children who came from nuclear families had higher prevalence of behavioral disorders compared to their counterparts from extended family. These findings are well in line with the findings of several studies. A study by Taanila and colleagues [35] revealed, for example, that single parent families were associated with increased risk of emotional problems among girls. McLanahan and Sandefur [38] noted that children from single parent families are more likely to experience behavioral problems compared to the children who come from families with two parents. Families with single parents may not provide the stimulating environment for exploration and learning which are necessary for child development. Furthermore, parental stress and depression may affect the child leading to loss of appetite and other eating disorders.

### Others

Contrary to expectation, the study found no significant association between overall family size, parents' marital status traditionally thought to be risk factors for mental and behavioral problems [4, 8]. Several studies have associated parental marital status with behavioral problems to the extent that children coming from families in which the parents are married and more educated show less prevalence of behavioral disorders [39-41]. This situation could be attributed the quality of relationship that parents have with each other and their child consistent with family systems

theory. The situation could also be explained by the effect of environmental and socio-economic factors such as poverty, unemployment and low parental education.

### Limitations

The relatively large sample size and inclusion of children at normal developmental stages are the strong aspects of our study. On the other hand, one of the limitations of current study is the absence of a control group comprised of healthy children have not applied to a clinic. As rapid improvement or impairments may occur in developmental stages of the preschool age, including a follow up period could give more clear findings.

### CONCLUSION

In terms of assessing the common reasons that infants and preschool children are admitted to the clinic, our study revealed some inferences. The findings indicate that limit setting was by far the most common problem. Insufficient materials assessing parental limit setting problems, inadequate education and training approaches, and lack of studies complicate the development of new intervention strategies in this area. Consequently, the utility of results to produce different approaches, including psychoeducation and supports to the parents with limit setting, should be developed and intervention provided earlier.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

### REFERENCES

[1] Bagner D, Rodríguez G, Blake C, Linares D, Carter A. Assessment of behavioural and emotional problems in infancy: a systematic review. *Clin Child Fam Psychol Rev* 2012;15:113-28.  
 [2] National Research Council and Institute of Medicine. Preventing mental, emotional, and behavioural disorders among young people:

progress and possibilities, The National Academic Press: Washington, 2009.  
 [3] Evans G, Kim P. Childhood poverty, chronic stress, self-regulation, and coping. *Child Dev Perspect* 2013;7:43-8.  
 [4] Santos LMD, Queirós FC, Barreto ML, Santos DND. Prevalence of behaviour problems and associated factors in preschool children from the city of Salvador, state of Bahia, Brazil. *Rev Bras Psiquiatr* 2016;38:46-52.  
 [5] Wamboldt M, Cordaro A, Clarke D. Parent-child relational problem: field trial results, changes in DSM-5, and proposed changes for ICD-11. *Fam Process* 2015;54:33-47.  
 [6] Bernet W, Wamboldt M, Narrow W. Child affected by parental relationship distress. *J Am Acad Child Adolesc Psychiatry* 2016;55:571-9.  
 [7] Coley R, Hernandez D. Predictors of paternal involvement for resident and nonresident low-income fathers. *Dev Psychol* 2006;42:1041-56.  
 [8] Ellajosyula R, Narayanan J. Sociodemographic factors, clinical features and course in frontotemporal dementia: a large cohort study from South India. *Neurology* 2017;88 (16 Supplement):P4.188.  
 [9] Matijasevich A, Murray E, Stein A, Anselmi L, Menezes AM, Santos IS, et al. Increase in child behaviour problems among urban Brazilian 4-year olds: 1993 and 2004 Pelotas birth cohorts. *J Child Psychol Psychiatry* 2014;55:1125-34.  
 [10] Vitolo YL, Fleitlich-Bilyk B, Goodman R, Bordin IA. Parental beliefs and child-rearing attitudes and mental health problems among school children. *Rev Saude Publica* 2005;39:716-24.  
 [11] Moren-Cross JL, Wright DR, LaGory M, Lanzi RG. Perceived neighborhood characteristics and problem behaviour among disadvantaged children. *Child Psychiatry Hum Dev* 2005;36:273-94.  
 [12] Roberts R, Attkisson C, Rosenblatt A. Prevalence of psychopathology among children and adolescents. *Am J Psychiatry* 1998;155:715-25.  
 [13] Brauner C, Stephens B. Estimating the prevalence of early childhood serious emotional/behavioural disorders: challenges and recommendations. *Public Health Rep* 2006;121:303-10.  
 [14] Savaşır I, Sezgin N, Erol N. [Handbook of Ankara Developmental Screening Test]. Ankara, Turkey: Ankara University School of Medicine; 1994. [Book in Turkish]  
 [15] Petersen M, Kube D, Whitaker T, Graff J, Palmer F. Prevalence of developmental and behavioural disorders in a pediatric hospital. *Pediatrics* 2009;123:e490-5.  
 [16] Calhoun SL, Fernandez-Mendoza J, Vgontzas AN, Liao D, Bixler EO. Prevalence of insomnia symptoms in a general population sample of young children and preadolescents: gender effects. *Sleep Med* 2014;15:91-5.  
 [17] Fricke-Oerckermann L, Plück J, Schredl M, Heinz K, Mitschke A, Wiater A, et al. Prevalence and course of sleep problems in childhood. *Sleep* 2007;30:1371-7.  
 [18] Mindell JA, Moline ML, Zendell SM, Brown LM, Fry JM. Pediatricians and sleep disorders: training and practice. *Pediatrics* 1994;94:194-200.  
 [19] Chou Y. Survey of sleep in infants and young children in northern Taiwan. *Sleep Biol Rhythms* 2007;5:40-9.  
 [20] Catto-Smith A. Constipation and toileting issues in children. *Med J Aust* 2005;182:242-6.  
 [21] Xinias I, Mavroudi A. Constipation in childhood. An update on evaluation and management. *Hippokratia* 2015;19:11-9.  
 [22] Bryant BK, Crockenberg SB. Correlates and dimensions of prosocial behaviour: A study of female siblings with their mothers. *Child Dev* 1980:529-44.  
 [23] Stipek D, Recchia S, McClintic S. Self-evaluation in young children. *Monogr Soc Res Child Dev* 1992;57:1-98.  
 [24] Tucker C, Finkelhor D, Shattuck N, Turner H. Prevalence and

- correlates of sibling victimization types. *Child Abuse Negl* 2013;37:213-23.
- [25] Shaw DS, Keenan K, Vondra JI. Developmental precursors of externalizing behaviour; Ages 1 to 3. *Dev Psychol* 1994;30:355-64.
- [26] Zahn-Waxler C, Shirtcliff EA, Marceau K. Disorders of childhood and adolescence: Gender and psychopathology. *Annu Rev Clin Psychol* 2008;4:275-303.
- [27] Wallace IF, Berkman ND, Watson LR, Coyne-Beasley T, Wood CT, Cullen K, et al. Screening for speech and language delay in children 5 years old and younger: a systematic review. *Pediatrics* 2015;136:e448-62.
- [28] Hadley PA, Rispoli M, Fitzgerald C, Bahnsen A. Predictors of morphosyntactic growth in typically developing toddlers: contributions of parent input and child sex. *J Speech Lang Hear Res* 2011;54:549-66.
- [29] Simonsen H, Kristoffersen K, Bleses D, Wehberg S, Jergensen R. The Norwegian Communicative Development Inventories: Reliability, main developmental trends and gender differences. *First Language* 2014;34:3-23.
- [30] Westerlund M, Lagerberg D. Expressive vocabulary in 18-month-old children in relation to demographic factors, mother and child characteristics, communication style and shared reading. *Child Care Health Dev* 2008;34:257-66.
- [31] Nelson K. The nominal shift in semantic-syntactic development. *Cogn Psychol* 1975;7:461-79.
- [32] Tearne J. Older maternal age and child behavioural and cognitive outcomes: a review of the literature. *Fertil Steril* 2015;103:1381-91.
- [33] Ryan RM, Claessens A, Markowitz AJ. Associations between family structure change and child behaviour problems: The moderating effect of family income. *Child Dev* 2015;86:112-27.
- [34] Biedel DC, Turner SM. At risk for anxiety: I. Psychopathology in the offsprings of anxious parents. *J Am Acad Child Adolesc Psychiatry* 1997;36:918-24.
- [35] Taanila A, Ebeling H, Kotimaa A, Moilanen I, Järvelin MR. Is a large family a protective factor against behavioural and emotional problems at the age of 8 years?. *Acta Paediatr* 2004;93:508-17.
- [36] Carlson M, Corcoran M. Family structure and children's behavioural and cognitive outcomes. *J Marriage Fam* 2001;63:779-92.
- [37] Lawson D, Mace R. Siblings and childhood mental health: evidence for a later-born advantage. *Soc Sci Med* 2010;70:2061-9.
- [38] McLanahan S, Sandefur G. *Growing Up with a Single Parent. What Hurts, What Helps.* Harvard University Press: Cambridge, 1997.
- [39] Campbell S, Shaw D, Gilliom M. Early externalizing behaviour problems: toddlers and preschoolers at risk for later maladjustment. *Dev Psychopathol* 2000;12:467-88.
- [40] Tremblay R, Nagin D, Seguin J, Zoccolillo M, Zelazo P, Boivin M, et al. Physical aggression during early childhood: trajectories and predictors. *Pediatrics* 2004;114:e43-50.
- [41] Cote S, Vaillancourt T, LeBlanc J, Nagin D, Tremblay E. The development of physical aggression from toddlerhood to pre-adolescence: a nationwide longitudinal study of Canadian children. *J Abnorm Child Psychol* 2006;34:71-85.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Wrongs known as right in thyroid scintigraphy and uptake study

Serdar Savaş Gül 

Department of Nuclear Medicine, Gaziosmanpaşa University School of Medicine, Tokat, Turkey

DOI: 10.18621/eurj.410060

## ABSTRACT

**Objectives:** Thyroid scintigraphy using  $^{99m}\text{Tc}$ -pertechnetate is commonly used to study function and structure of thyroid gland. Pin-hole collimator is generally preferred in thyroid scintigraphy and uptake studies. The purpose of the present study was to determine actual radiopharmaceutical uptake value in an experimental  $^{99m}\text{Tc}$ -pertechnetate thyroid scintigraphy and uptake model.

**Methods:** Thyroid hyperactive and hypoactive nodule models were created using 4 mCi (148 MBq)  $^{99m}\text{Tc}$ -pertechnetate. In the experimental model, 4 mm, 6 mm and 8 mm diameter pin-hole collimators, and 5 cm, 7 cm and 10 cm object-to-pinhole distances were investigated.

**Results:** In thyroid hyperactive nodule model, despite the same activity value, uptake at 7 cm object-to-pinhole distance was higher compared to 10 cm distance (122% and 103%, respectively). In the patient with Graves' disease, despite the same activity value, uptake at 5 cm object-to-pinhole distance was higher compared to 10 cm distance (8% and 4%, respectively). In thyroid hypoactive nodule model, 4 mm, 6 mm and 8 mm diameters pin-hole collimators were imaged at 5 cm, 10 cm and 15 cm object-to-pinhole distances. The resolution differences between the images were evaluated.

**Conclusion:** It was determined that imaging using 10 cm object-to-pinhole distance and 4 mm diameter pin-hole collimator was best in terms of image resolution and optimum  $^{99m}\text{Tc}$ -pertechnetate uptake level.

**Keywords:**  $^{99m}\text{Tc}$ -pertechnetate, thyroid, scintigraphy, uptake

*Received: March 27, 2018; Accepted: August 13, 2018; Published Online: November 23, 2018*

Thyroid scintigraphy and uptake examination is a simple, non-invasive and safe method for evaluation of thyroid gland function and structure. For a standard estimation of thyroid hormone synthesis in clinical practice, radiopharmaceuticals (i.e.,  $^{131}\text{I}$ iodine,  $^{123}\text{I}$ iodine,  $^{99m}\text{Tc}$ Technetium) have been commonly quantified for thyroid gland uptake through determining the degree of trapping or organification in the thyroid gland for more than five decades [1, 2].

Use of  $^{131}\text{I}$ iodine in thyroid scintigraphy and uptake

studies have major disadvantage of high radiation impact on gland (1-3 rad/mCi administered) due to longer half-life and beta particle emission of  $^{131}\text{I}$ iodine [3].  $^{123}\text{I}$ iodine has major limitations of high cost and unavailability due to complex production in a cyclotron [4]. Thyroid scintigraphy and uptake studies also use  $^{99m}\text{Tc}$ Technetium ( $^{99m}\text{Tc}$ ), in the chemical form of pertechnetate [1, 2, 5].  $^{99m}\text{Tc}$ -pertechnetate is concentrated in thyroid gland, gastric mucous membrane, lachrymal and salivary glands [6]. Thyroid gland up-



Address for correspondence: Serdar Savaş Gül, MD., Gaziosmanpaşa University School of Medicine, Department of Nuclear Medicine, Tokat, Turkey  
E-mail: gopnukleertip@gmail.com

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

takes  $^{99m}\text{Tc}$ -pertechnetate because of its volume and charge similarities with iodide.  $^{99m}\text{Tc}$ -pertechnetate has been commonly used to evaluate thyroid function because it has shorter half-life (six hours) and shorter retention time in the gland and does not involve beta radiation. As a result, its dosimetry load on thyroid gland and on whole body is 10,000 times less than what is caused by  $^{131}\text{I}$ odine. It has gamma photon of 140 keV, which is ideal for imaging with scintillation cameras. Besides, it is costless and is easily available [7].

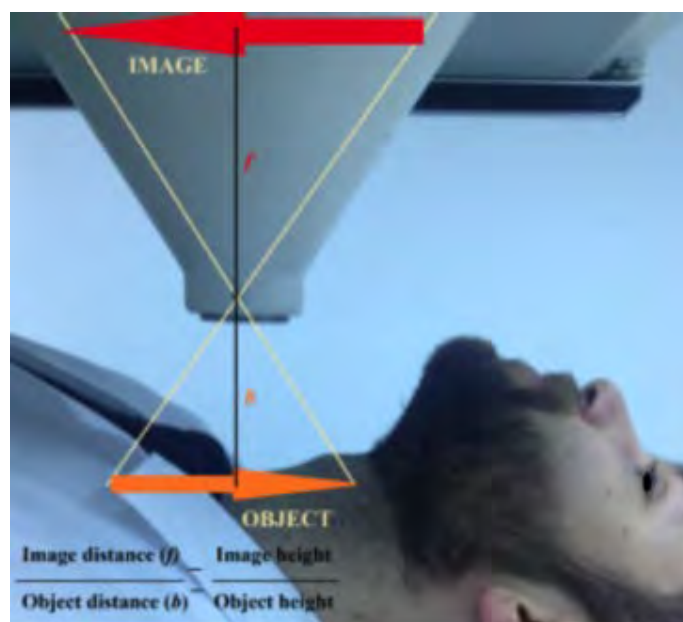
Thyroid scintigraphy and uptake studies generally employ a pin-hole or a parallel-hole collimator. It is used together with rotating gamma cameras which have large crystal areas to augment the sensitivity for emission and transmission computed tomography when used with small organs such as the thyroid, brain or heart [8]. For thyroid imaging, scintillation gamma cameras with pin-hole collimator are preferred [9, 10]. Thyroid gland has low absolute  $^{99m}\text{Tc}$ -pertechnetate uptake, which ranges from 0.3 to 3.0% depending upon the method employed [11]. Because of semi-quantitative parameters used, higher inter- and intra-observer variability has been reported for  $^{99m}\text{Tc}$ -pertechnetate uptake [12].

The aim of the present study was to determine actual radiopharmaceutical uptake value in an experimental  $^{99m}\text{Tc}$ -pertechnetate thyroid scintigraphy and uptake model. Uptake value and image resolution effects were investigated using different pin-hole collimator diameters and object-to-pinhole distances.

## METHODS

### Study Design

Effects of 4, 6 and 8 mm diameter pin-hole collimators, and 5cm and 10cm object-to-pinhole distances were evaluated in the present study. Hyperactive and hypoactive thyroid nodule models were created using 4 mCi (148 MBq)  $^{99m}\text{Tc}$ -pertechnetate. Scintigraphic hot areas represent hyperactive nodules, while cold areas represent hypoactive nodules. Width of the circular object field was determined by moving the source across the widest part of the field. Detector-to-pinhole and the object-to-pinhole distances were measured. Magnification factor was determined and verified by



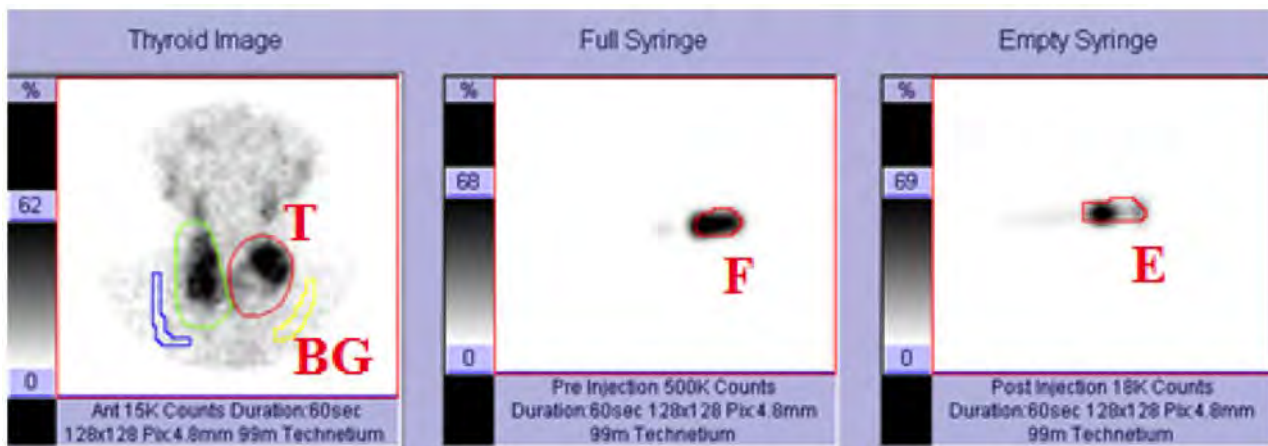
**Figure 1.** Geometry of the pin-hole collimator. The size of the image depends on the distance between object and image.

both using these field widths and using the camera and object distances to the pinhole. A scintillation gamma camera (Siemens E-CAM, Germany) equipped with a low-energy, pin-hole collimator was used. Images were obtained on a  $128 \times 128$  matrix and at zoom 1. For uptake calculation, images of the injector were obtained before and after radiopharmaceutical injection. Images of the syringe were obtained for 1 minutes and of the anterior neck for 100,000 counts. Images were taken from the source directly under pin-hole collimator with a 140 keV and 20% energy window for 1 minutes at a distance of 5 cm, 7 cm and 10 cm. Peak counts were measured and full width was determined using half of the maximum distance. Operating principle of the pin-hole collimator is shown in Figure 1.

$^{99m}\text{Tc}$ -pertechnetate thyroid uptake was calculated semi-quantitatively from regions of interest in thyroid tissue and background activity values as shown in Figure 2 using the formula: Thyroid Uptake (%): “T-BG/F-E” [Full (F) and empty injector (E), anterior neck region thyroid (T) and background (BG) activity values] [13].

## RESULTS

For thyroid hyperactive nodule model, full and

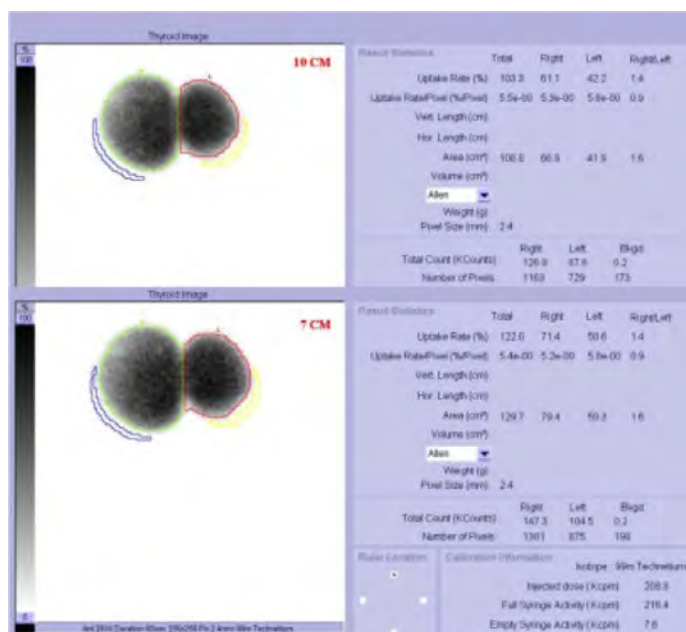


**Figure 2.** Parameters used in thyroid uptake study [Full (F) and empty injector (E), anterior neck region thyroid (T) and background (BG)].

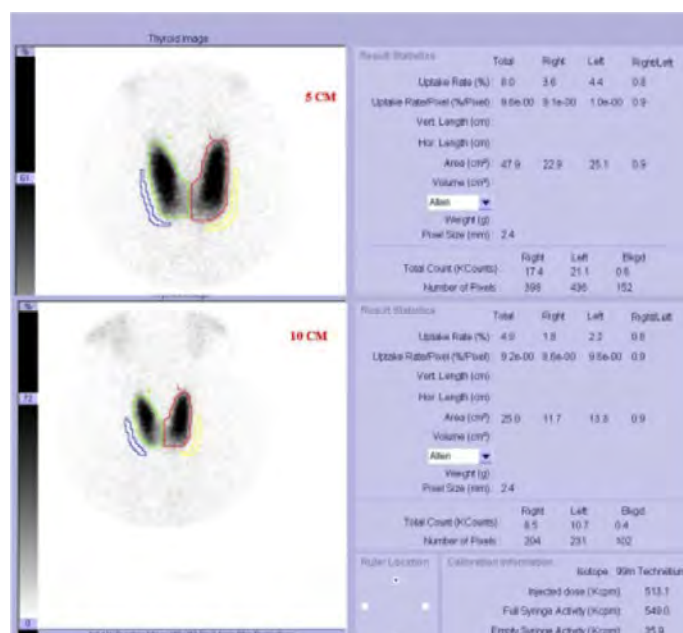
empty injector counts were taken before and after injection of <sup>99m</sup>Tc-pertechnetate radioactivity. Radiopharmaceutical uptake measurements were performed at 7 cm and 10 cm object-to-pinhole distances using a 4 mm diameter pin-hole collimator. Although activity values were the same, uptake at 7 cm object-to-pinhole distance was higher than that of 10 cm (122% and 103%, respectively) (Figure 3). In diffusely increased uptake, thyroid uptake values in our patients for <sup>99m</sup>Tc-pertechnetate at 5 cm and 10 cm

object-to-pinhole distances were 8% and 4%, respectively (Figure 4).

In thyroid hypoactive nodule model, images were taken from 4 mm, 6 mm and 8 mm diameter pin-hole collimators at 5 cm, 10 cm and 15 cm object-to-pinhole distances. The resolution differences in images from different parameters were evaluated. It was found out that the best images were obtained from 10 cm object-to-pinhole distance and using 4 mm pin-hole collimator (Figure 5).

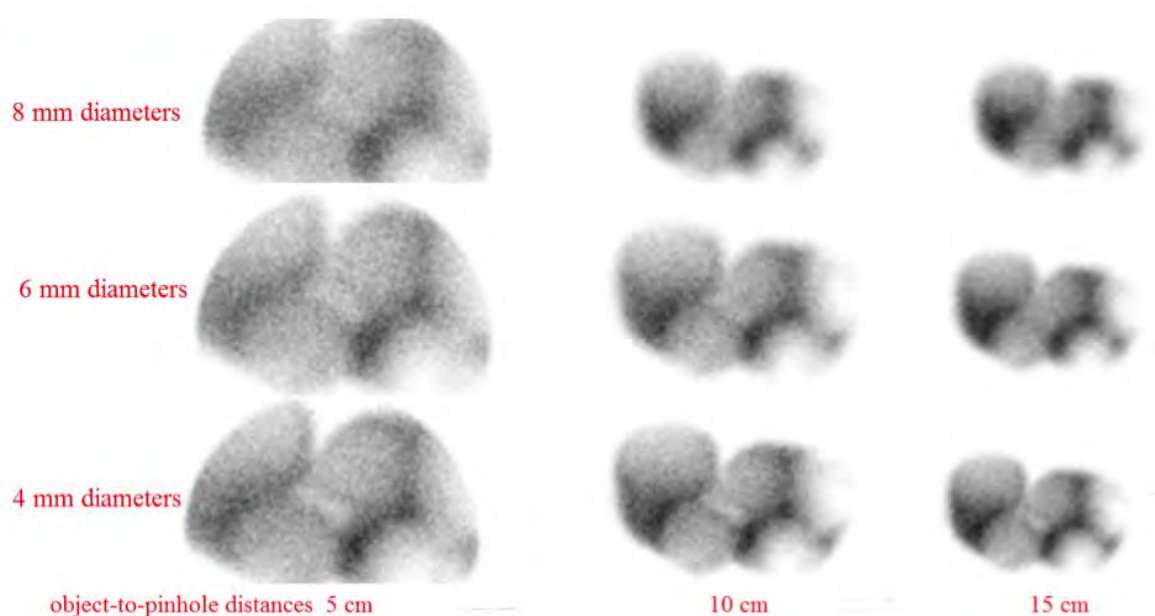


**Figure 3.** Different uptake values of the thyroid hyperactive nodule model at 7 cm and 10 cm object-to-pinhole distances.



**Figure 4.** Different uptake values of patient with Graves' disease at 5 cm and 10 cm object-to-pinhole distances.





**Figure 5.** Image quality of the thyroid hypoactive nodule model at 5 cm, 10 cm and 15 cm object-to-pinhole distances using 4 mm, 6 mm and 8 mm diameter pin-hole collimators.

## DISCUSSION

Thyroid uptake and scintigraphy scans have been commonly used in diagnosis and management of thyroid diseases [14-16]. They are an important practice in nuclear medicine [17, 18]. Similar to radioiodine,  $^{99m}\text{Tc}$ -pertechnetate enters into thyroid follicular cells through a sodium-iodide symporter. Thus, uptake of  $^{99m}\text{Tc}$ -pertechnetate in thyroid can be used to evaluate thyroid function [19, 20]. A pin-hole collimator is generally used in thyroid scintigraphy [21]. Thyroid uptake is calculated using gland images and syringe counts before and after radiopharmaceutical injection, and is simplified for use in routine nuclear medicine [5]. The mistakes made in the uptake operation are affecting the result. In our study, we investigated the parameters required for the uptake of the most accurate results. In the presents study, thyroid uptake of  $^{99m}\text{Tc}$ -pertechnetate was evaluated using different object-to-pinhole distances and different pin-hole collimator diameters. Radioactive iodine uptake test is mainly used to determine the etymology of hyperthyroidism and to help decide appropriate  $^{131}\text{I}$  rate for the treatment of hyperthyroidism [22, 23].  $^{131}\text{I}$  complexes with pharmaceutical substrates enable imaging other organs. However, it had a limited use, and its high

gamma energy and beta emission lowered the activity of radiopharmaceuticals used, which leads to long acquisition periods and lower quality images.  $^{99m}\text{Tc}$ -pertechnetate, which emits only gamma radiation of 140 keV and has a half-life of only six hours, is a better radionuclide and can be used for imaging of numerous organs in the body. However, due to shorter half-life,  $^{99m}\text{Tc}$ -pertechnetate delivered weekly by radiopharmaceutical companies [24, 25].

It has been reported that normal thyroid uptake of  $^{99m}\text{Tc}$ -pertechnetate ranges from 0.3 to 3% in high iodine-consuming countries and from 1.2 to 7.0% in low iodine-consuming ones [2, 11]. On the other hand, thyroid uptake of radioiodine is much higher, ranging from 6 to 35% in 4-24 hours after radioiodine administration [6]. Due to absence of an organification mechanism for  $^{99m}\text{Tc}$ -pertechnetate and its resulting leakage from thyroid, thyroid uptake of  $^{99m}\text{Tc}$ -pertechnetate is usually measured at the plateau phase of 15 to 30 min after injection. One of the reasons why  $^{99m}\text{Tc}$ -pertechnetate thyroid uptake test is considered unreliable compared to radioiodine test is this unstable retention. Heterogeneity of the  $^{99m}\text{Tc}$ -pertechnetate thyroid uptake protocol constitutes another reason for its unreliability [26]. It was shown in the present study that smaller object to pinhole distance during thyroid uptake study results in higher  $^{99m}\text{Tc}$ -pertechnetate

uptake values than it actually is.

<sup>99m</sup>Tc-pertechnetate thyroid uptake test can be carried out using different parameters such as hardware (thyroid uptake system or planar gamma camera), software (thigh or mediastinum for background activity correction, syringe activity or separate standard source for injected dose determination), injection dose (37-370 MBq = 1-10 mCi) and measurement time and duration. Because of its suboptimal reliability, <sup>99m</sup>Tc-pertechnetate thyroid uptake test is useful only for differential diagnosis to distinguish conditions with extremely altered thyroid function, such as Grave's disease from destructive thyroiditis [27]. In the present study, it was shown that the results could be different depending upon object-to-pinhole distances during <sup>99m</sup>Tc-pertechnetate and thyroid uptake.

### Limitations

The main limitation of the present study to demonstrate the reproducibility of <sup>99m</sup>Tc-pertechnetate and thyroid uptake is employment of a single model of thyroid probe device in a single institution. It could have been beneficial to evaluate the test in different institutions with different equipment, with use of isotope of iodine, and with different staffs, patient populations, and protocols. Nonetheless, the present study is the first attempt to measure the reproducibility of the test. This highlights the importance for each institution to measure their own practice-specific values. Significant deviation from norm should prompt a review of equipment and technique used including radioiodine dosage, probe characteristics, and technologists' expertise [12, 28].

### CONCLUSION

In conclusion, thyroid uptake studies are frequently used in clinical practice. Use of <sup>99m</sup>Tc-pertechnetate to assess thyroid structure and function provides a simple, fast and efficient method which could easily become a part of the routine studies in nuclear medicine laboratories. However, <sup>99m</sup>Tc-pertechnetate thyroid uptake has an inter- and intra-observer variability, which must be standardized before its routine use. Optimum distance in pin-hole collimators deserve special attention for imaging

quality. Effects of patient's object-to-pinhole distance on collimation, image quality and uptake value were investigated in the present study. It was found out that 10 cm object-to-pinhole distance with 4 mm-diameter pin-hole collimator gave the best result for optimum imaging in <sup>99m</sup>Tc-pertechnetate thyroid uptake test.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

### Acknowledgements

The author is grateful to nuclear medicine technician Abdulsamet Yalçınkaya of Nuclear Medicine Department of Gaziosmanpaşa University Medical School for his invaluable help in the gamma camera shots.

### REFERENCES

- [1] Higgins HP, Ball D, Eastham S. 20-Min <sup>99m</sup>Tc thyroid uptake: a simplified method using the gamma camera. *J Nucl Med* 1973;14:907-11.
- [2] Schneider PB. Simple, rapid thyroid function testing with <sup>99m</sup>Tc-pertechnetate thyroid uptake ratio and neck/thigh ratio. *Am J Roentgenol* 1979;132:249-353.
- [3] Becker D, Charkes ND, Dworkin H, Hurley J, McDougall IR, Price D, et al. Procedure guideline for thyroid uptake measurement: 1.0. Society of Nuclear Medicine. *J Nucl Med* 1996;37:1266-8.
- [4] Ziessman HA, Fahey FH, Gochoco JM. Impact of radiocontaminants in commercially available iodine-123: dosimetric evaluation. *J Nucl Med* 1986;27:428-32.
- [5] Ramos CD, Zantut-Wittmann DE, Tambascia MA, Assumpcao L, Etchebere EC, Camargo EE. Thyroid suppression test with L-thyroxine and [<sup>99m</sup>Tc] pertechnetate. *Clin Endocrinol (Oxf)* 2000;52:471-7.
- [6] Anjos DA, Etchebere EC, Santos AO, Lima MC, Ramos CD, Paula RB, et al. Normal values of [<sup>99m</sup>Tc] pertechnetate uptake and excretion fraction by major salivary glands. *Nucl Med Commun* 2006;27:395-403.
- [7] Smith JJ, Croft BY, Brookeman VA, Teates CD. Estimation of 24-hour thyroid uptake of I-131 sodium iodide using a 5-minute uptake of technetium-99m pertechnetate. *Clin Nucl Med* 1990;15:80-3.
- [8] Gullberg GT, Zeng GL, Datz FL, Christian PE, Tung CH,

- Morgan HT. Review of convergent beam tomography in single photon emission computed tomography. *Phys Med Biol* 1992;37:507-34.
- [9] Anger K, Feine U, Kaiser E. Improved quality of thyroid scintigrams by using a gamma camera with pin-hole collimator. *Rofo* 1981;135:188-92.
- [10] Tai YC, Wu H, Pal D, O'Sullivan JA. Virtual-Pinhole PET. *J Nucl Med* 2008;49:471-9.
- [11] Selby JB, Buse MG, Gooneratne NS, Moore DO. The Anger camera and the pertechnetate ion in the routine evaluation of thyroid uptake and imaging. *Clin Nucl Med* 1979;4:233-7.
- [12] Volckaert V, Vandermeulen E, Duchateau L, Saunders JH, Peremans K. Inter- and intraobserver variability of (semi-) quantitative parameters commonly used in feline thyroid scintigraphy. *Res Vet Sci* 2016;105:87-91.
- [13] Ramos CD, Zantut Wittmann DE, Etchebehere EC, Tambascia MA, Silva CA, Camargo EE. Thyroid uptake and scintigraphy using <sup>99m</sup>Tc pertechnetate: standardization in normal individuals. *Sao Paulo Med J* 2002;120:45-8.
- [14] Sarkar SD. Benign thyroid disease: what is the role of nuclear medicine? *Semin Nucl Med* 2006;36:185-93.
- [15] Clerc J. Imaging the thyroid in children. *Best Pract Res Clin Endocrinol Metab* 2014;28:203-20.
- [16] Biassoni L, Easty M. Paediatric nuclear medicine imaging. *Br Med Bull* 2017;123:127-48.
- [17] Alimanovic-Alagic R, Brkovic A, Kucukalic-Selimovic E. Evaluation of thyroid diseases in nuclear medicine. *Med Arh* 2008;62:303-6.
- [18] Töre G, Karayaçın B, Esen B, Türkmen C, Yüksel D, Varoğlu E, et al. Tiroit sintigrafisi uygulama kılavuzu. *Turk J Nucl Med* 2003;12:178-80.
- [19] Chung JK. Sodium iodide symporter: its role in nuclear medicine. *J Nucl Med* 2002;43:1188-200.
- [20] Chung JK, Youn HW, Kang JH, Lee HY, Kang KW. Sodium iodide symporter and the radioiodine treatment of thyroid carcinoma. *Nucl Med Mol Imaging* 2010;44:4-14.
- [21] Ogawa K, Hashimoto J, Kubo A, Hashimoto S, Suzuki K, Ruike T. Development of a converging collimator for thyroid scintigraphy. *Kakuigaku* 1990;27:303-11.
- [22] Meier DA, Kaplan MM. Radioiodine uptake and thyroid scintiscanning. *Endocrinol Metab Clin North Am* 2001;30:291-313.
- [23] Franklyn JA. What is the role of radioiodine uptake measurement and thyroid scintigraphy in the diagnosis and management of hyperthyroidism. *Clin Endocrinol (Oxf)* 2010;72:11-2.
- [24] Green CH. Technetium-99m production issues in the United Kingdom. *J Med Phys* 2012;37:66-71.
- [25] Shapiro B, Zanin DE, Schipper R. Reference-free thyroid uptake measurement. *Nucl Med Commun* 2014;35:382-90.
- [26] Meier DA, Brill DR, Becker DV, Clarke SE, Silberstein EB, Royal HD, et al. Procedure guideline for therapy of thyroid disease with (131) iodine. *J Nucl Med* 2002;43:856-61.
- [27] Lee H, Kim JH, Kang YK, Moon JH, So Y, Lee WW. Quantitative single-photon emission computed tomography/computed tomography for technetium pertechnetate thyroid uptake measurement. *Medicine (Baltimore)* 2016;95:e4170.
- [28] Pelletier-Galarneau M, Martineau P, Klein R, Henderson M, Zuckier LS. Reproducibility of radioactive iodine uptake (RAIU) measurements. *J Appl Clin Med Phys* 2018;19:239-42.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Comparison of effects of melatonin, pentoxifylline and dimethyl sulfoxide in experimental liver ischemia-reperfusion injury by three different methods

Zeliha Türkyılmaz<sup>1</sup>, Ahmet Hatipoğlu<sup>2</sup>, Mahmut Yüksel<sup>3</sup>, Nurettin Aydoğdu<sup>4</sup>, Gülara Hüseyinova<sup>5</sup>

<sup>1</sup>Department of General Surgery, Edirne 1. Murat State Hospital, Edirne, Turkey

<sup>2</sup>Department of General Surgery, Trakya University School of Medicine, Edirne, Turkey

<sup>3</sup>Department of Nuclear Medicine, Altınbaş University Medical Park Bahçelievler Hospital, İstanbul, Turkey

<sup>4</sup>Department of Physiology, Trakya University School of Medicine, Edirne, Turkey

<sup>5</sup>Department of Pathology, Trakya University School of Medicine, Edirne, Turkey

DOI: 10.18621/eurj.421296

## ABSTRACT

**Objectives:** Liver transplantation is increasingly being used in the treatment of end-stage liver disease. Ischemia-reperfusion injury is one of the major problems encountered in transplantation. In this study, we aimed to compare the effects of melatonin, pentoxifylline, and dimethyl sulfoxide (DMSO), in hepatic ischemia-reperfusion injury with different methods such as biochemical/ultrastructural changes and hepatobiliary scintigraphy.

**Methods:** Thirty rabbits were used in the Laboratory of Experimental Animals of Trakya University under appropriate conditions. Sham laparotomy and only ischemia reperfusion group were planned. They were used melatonin, pentoxifylline, and DMSO after I-R in the other three groups. 6 rabbits were randomly selected for each group. Rabbits in all groups were subjected to liver scintigraphy. Following scintigraphy, 2 cm<sup>2</sup> of liver tissue was removed to examining for liver antioxidant enzyme levels (superoxide dismutase [SOD] and glutathione peroxidase [GPx]) and for liver electron microscopy.

**Results:** Pentoxifylline and melatonin protected significantly uptake and excretion functions in liver scintigraphy. When the effects of all three substances were examined by electron microscopy, it was found that the three substances protected the liver from the effects of ischemia-reperfusion damage at varying rates. All three agents were found to protect SOD and GPx from falling in various amounts.

**Conclusions:** Studies to prevent ischemia-reperfusion injury, which may develop as a result of the Pringle maneuver applied to liver transplantations as well as to liver resections or liver injuries, still maintain their popularity. In our study, the effects of agents were identified in three different ways. Ischemia-reperfusion injury-reducing effect of pentoxifylline gave parallel results with three methods.

**Keywords:** Pentoxifylline, melatonin, dimethyl sulfoxide, ischemia, reperfusion

Received: May 5, 2018; Accepted: July 4, 2018; Published Online: November 14, 2018



Address for correspondence: Zeliha Türkyılmaz, MD., Edirne 1. Murat State Hospital, Department of General Surgery, Edirne, Turkey  
E-mail: turkyilmazz@yahoo.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

**L**iver transplantation is increasingly being used in the treatment of end-stage liver disease, and as a consequence, any problem of transplantation is becoming popular for researchers. The Pringle maneuver, commonly practiced in liver surgery and first described by Hogarth Pringle in 1908, is the clamping of the portal triad [1]. Hepatic ischemia-reperfusion (I-R) damage is common due to Pringle maneuver applied in liver transplantations and liver resections. Ischemia-reperfusion injury may also occur in sepsis and hemorrhagic shock. Studies have shown that oxygen free radicals (OFRs) are released by ischemia-reperfusion injury. Experimental studies have investigated the activity and mechanisms of many molecules thought to have therapeutic effects in ischemia-reperfusion injury [2-4].

Melatonin is one of the strongest known scavengers of both hydroxyl radicals and other oxygen radicals. Melatonin not only enhances antioxidant enzyme activity but also inhibits some pre-oxidative enzymes. The phosphodiesterase inhibitor, pentoxifylline, is a vasodilator and at the same time has the property of reducing blood viscosity. It is known to increase tissue oxygenation. Pentoxifylline has been shown to protect the liver against normothermic ischemia-reperfusion injury. There are studies indicating that dimethyl sulfoxide (DMSO) is known to be associated with radioprotective and cytoprotective effects, as well as protective effects of ischemia-reperfusion injury [5-7].

In this study, we wanted to determine in different ways whether melatonin, pentoxifylline and DMSO had protective effect on ischemia reperfusion. We aimed to compare the biochemical parameters (superoxide dismutase [SOD] and glutathione peroxidase [GPx]), electron microscopic examination of hepatic tissue and hepatobiliarscintigraphy for the effects of all three agents.

## METHODS

A total of 30 rabbits weighing 1750-2150 g, which were properly cared in the Experimental Animal Laboratory of Trakya University School of Medicine, were used in the study. The rabbits were randomly assigned into 5 groups, with 6 rabbits in each group.

## Groups

Group A: Sham laparotomy (control group)

Group B: Only ischemia-reperfusion (I-R) injury

Group C: 10 mg/kg melatonin (Sigma M5250) before I-R

Group D: 50 mg/kg pentoxifylline (PTX) (Sigma P1784) before I-R

Group E: 1 g/kg DMSO (Sigma D8779) before I-R

The rabbits were starved for 12 hours before surgical intervention. Before the operation, the abdominal area was shaved, and the skin was cleaned with povidone-iodine. They were anesthetized with i.m. Ketamin (10mg/kg) and i.m. Rompum (1 ml/kg). Group A underwent sham laparotomy, and then HBS was performed after closure of the abdominal wall. Following scintigraphy, 2 cm<sup>2</sup> of hepatic tissue was removed to determine hepatic antioxidant enzyme levels and for electron microscopy of the liver from the free edge of the right lobe of the liver. In the rabbits of Groups B, C, D and E, the hepatoduodenal ligament was dissected and then was occluded with microvascular clamps, and the Pringle maneuver was applied for 30 minutes. Group B received no any agent before the operation, Group C received 10 mg/kg intravenous (i.v.) melatonin before the operation, Group D received 50 mg/kg pentoxifylline before the operation, and Group E received 1 g/kg (90%) DMSO before the operation. Microvascular clamps were opened after 30 minutes, and then reperfusion was ensured. Hepatobiliary Scintigraphy (HBS) was performed after intravenous injection of a radiopharmaceutical at 15 minutes of reperfusion. Hepatic tissue was removed to determine hepatic antioxidant enzyme levels and electron microscopy of the liver at all other groups as in the sham laparotomy group.

## Hepatobiliary Scintigraphy (HBS)

It was performed by obtaining 45 minutes dynamic images, immediately after 37 MBq Tc99m-Br IDA was administered intravenously via the ear vein of the rabbits at 15 minutes of reperfusion in the Department of Nuclear Medicine, Trakya University School of Medicine. Dynamic images were recorded by the single-head gamma camera equipped with a low energy, high resolution collimator, so that there

would be 12 images in the first 5 minutes and 1 image/2 minutes in the next 40 minutes. A region of interest (ROI) was drawn on the liver parenchyma except for the major biliary ducts and intestines in the right upper quadrant on the obtained dynamic images. Thus, the time-activity curves of the liver parenchyma were obtained. The peak time of liver involvement (Liver PT) and the half-life of the peak activity in the liver (Liver T<sub>1/2</sub>) were calculated from the obtained curves.

### Electron Microscopy

To examine cell organelle damage in the liver, 2 cm<sup>2</sup> of hepatic tissue which was removed from the free edge of the right lobe of the liver of the rabbits in all groups 60 minutes after reperfusion was used. The obtained tissues were first fixed with 2.5% phosphate buffered osmium tetroxide (OsO<sub>4</sub>). They were dehydrated in 30% and 100% alcohols, respectively. The specimens were blocked with Epon 812 after the application of propylene oxide. The blocks which were cut using Raychert ultramicrotome were stained with uranyl acetate. The stained sections were examined using Zeiss-EM-9 and JEM-100B electron microscopes by a pathologist blind to the groups and scintigraphic data in the Department of Pathology, Trakya University School of Medicine.

### Biochemical Analysis

Biochemical parameters were studied by a researcher blind to the groups in the Research Laboratories of Department of Chemistry, Faculty of Science and Letters, Trakya University. For the measurement of SOD and GPx values, the liver tissues from each subject were washed with isotonic solution in a standard manner, and then they were dried and stored at -70°C in the eppendorf tubes. Each of the materials removed to be studied were weighed, and the protein values of the tissues were calculated by the Lowry method after homogenization. Using SOD kit (Randox-Ransod SD125-8092H), the baseline and 3 min values of SOD enzyme activity for each tissue were detected by JenWay 6105 UV/visible spectrophotometer. For each tissue, the SOD values were divided by the protein values, and results were expressed as U/mg protein. Using Glutathione peroxidase kit (Randox- Ransel RS504-1315F), it was studied in a similar manner with SOD.

### Statistical Analysis

Statistical analysis: The data of our study was obtained using the MiniBit package program (SOO64 minitab release 13) (License No: wcp. 1331.00197) in Trakya University Information Processing Center. All parameters are shown as mean ± standard deviation. *p* values < 0.05 were considered to be statistically significant.

## RESULTS

### Hepatobiliary Scintigraphy Findings

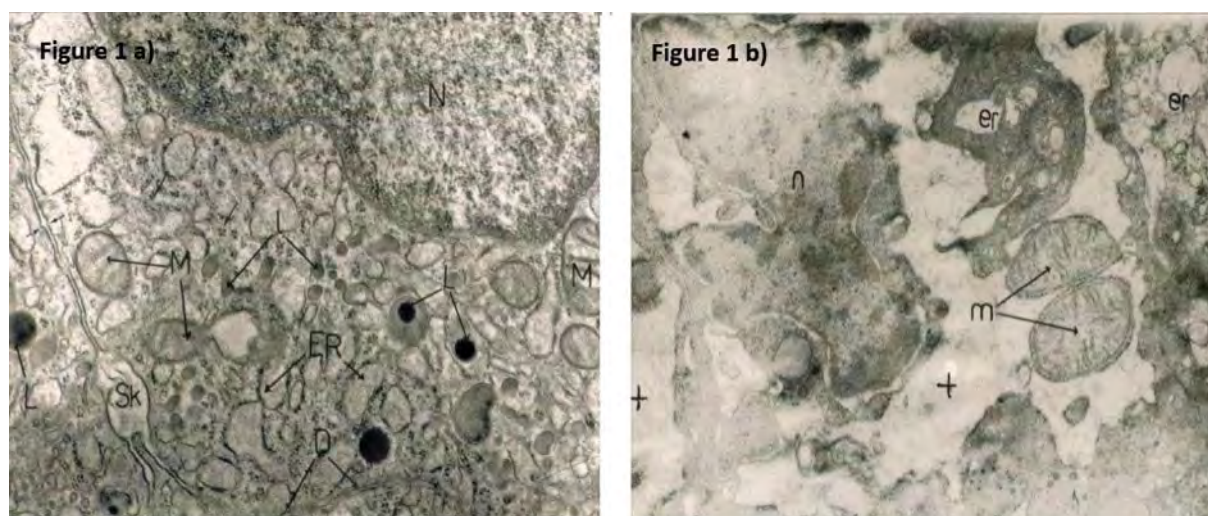
The HBS data of all groups are given in Table 1. The mean Liver PT value statistically significantly higher in Group B compared to Group A (2.73 ± 0.84 min vs 9.45 ± 4.26 min; *p* = 0.004). The mean Liver PT value statistically significantly higher in Groups C, D, and E compared to Group A (2.73 ± 0.84 min vs 5.25 ± 1.36 min, 4.67 ± 0.30 min, and 5.63 ± 1.06 min, for Groups C, D, and E respectively; *p* < 0.05). The mean Liver PT value was statistically significantly lower in Groups C and D, compared to Group B (9.45 ± 4.26 min vs 5.25 ± 1.36 min, 4.67 ± 0.30 min, for Groups C and D respectively; *p* < 0.05). There was no statistically significant difference in mean Liver PT value between Group E and B (9.45 ± 4.26 min vs 5.63 ± 1.06 min; *p* > 0.05). There was no statistically significant difference in mean Liver PT value between Group C, D, and E (5.25 ± 1.36 min vs 4.67 ± 0.30 min, and 5.63 ± 1.06 min, for Groups D and E respectively; *p* > 0.05). The mean Liver PT value of Group D was closest to that of Group A. There was a statistically significant difference in mean Liver PT value between Groups D and E (4.67 ± 0.30 min vs 5.63 ± 1.06 min; *p* = 0.03).

While the mean Liver T<sub>1/2</sub> value was 4.43 ± 1.36

**Table 1.** Hepatobiliary scintigraphy findings

Groups	Liver PT (min)	Liver T <sub>1/2</sub> (min)
Group A	2.73 ± 0.84	4.43 ± 1.36
Group B	9.45 ± 4.26	26.98 ± 12.54
Group C	5.25 ± 1.36	14.45 ± 7.15
Group D	4.67 ± 0.30	12.53 ± 3.03
Group E	5.63 ± 1.06	13.28 ± 3.36

Data are shown as mean ± standard deviation. Liver PT = the peak time of liver involvement, Liver T<sub>1/2</sub> = the half-life of the peak activity in the liver



**Figure 1.** a) Electron microscopy image of Group A. The hepatocytes, sinusoids, space of Disse, bile ducts and other structures were normally observed. b) Electron microscopy image of Group B. Major destructive and degenerative changes in the hepatocytes. The nucleus was pyknotic and the cytoplasm was edematous. glycogen granules decreased, mitochondrial swelling, mitochondrial crystals were destroyed and degenerated. sinusoid and space of Disse extensively expanded, erythrocytes were clustered.

min in Group A, it was  $26.98 \pm 12.54$  min in Group B. The mean Liver T<sub>1/2</sub> value statistically significantly higher in Group B compared to Group A ( $p = 0.004$ ). The mean Liver T<sub>1/2</sub> value statistically significantly higher in Group C, D and E compared to Group A. ( $4.43 \pm 1.36$  min vs  $14.45 \pm 7.15$  min,  $12.53 \pm 3.03$  min, and  $13.28 \pm 3.36$  min; for Groups A, C, D, and E respectively;  $p < 0.05$ ). The mean Liver T<sub>1/2</sub> value was statistically significantly lower in Groups C, D and E compared to Group B ( $26.98 \pm 12.54$  min,  $14.45 \pm 7.15$  min,  $12.53 \pm 3.03$  min,  $13.28 \pm 3.36$ ; for Groups B, C, D and E respectively;  $p < 0.05$ ).

These data suggest that the uptake and excretion functions were significantly preserved in those treated with melatonin and pentoxifylline in comparison with the I-R group. The uptake times were reduced in those treated with DMSO in comparison with the I-R group, there was no statistically significant difference between the two groups. It was found that the uptake time of those treated with pentoxifylline was statistically significantly lower than that of those treated with DMSO. Despite Liver PT prolong in the DMSO group, Liver T<sub>1/2</sub> time was maintained as in the pentoxifylline and melatonin groups.

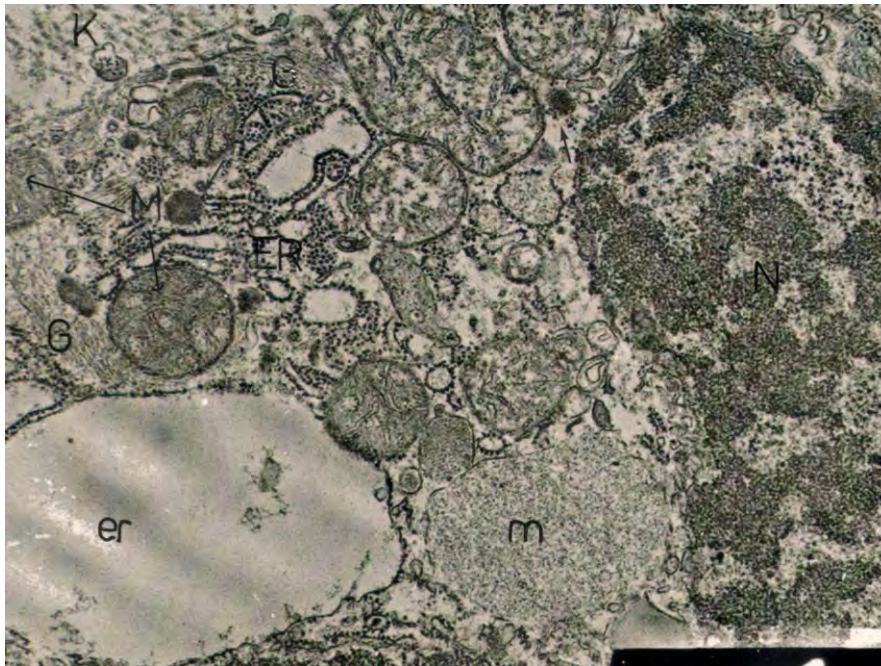
### Ultrastructural Findings

When Group A was examined by electron microscopy, the hepatocytes, sinusoids, space of

Disse, bile ducts and other structures were normally observed (Figure 1a).

When Group B was examined by electron microscopy, there were the major destructive and degenerative changes in the majority of hepatocytes. It was remarkable that the nucleus was pyknotic and the cytoplasm was edematous. It was seen that the glycogen granules were reduced, the mitochondrial swelling occurred, the mitochondrial crystals were destructed and degenerated, and the endoplasmic reticulum were expanded and disappeared in some places. Moreover, the degeneration and lysis of other organelles were observed. Depending on ischemia-reperfusion injury, it was seen that the sinusoid and space of Disse extensively expanded and the erythrocytes were clustered in it. Macrophage activity was present in the cytoplasm of Kupffer cells and outside the cell. Increased vacuoles and microvesicles were observed. Phagocytosed materials were seen in the cytoplasm (Figure 1b).

When Group C was examined by electron microscopy, it was observed that the majority of organelles in the cytoplasm of hepatocytes were normal. However, it was remarkable that the mitochondria, endoplasmic reticulum and other organelles were destructed in some places. In addition, it was seen that there was an increase in collagen fibrils around hepatocytes. In Group C, it was



**Figure 2.** Electron microscopy image of Group C. The majority of organelles in the cytoplasm were normal. However, it was remarkable that the mitochondria, endoplasmic reticulum and other organelles were destructed in some places microscopy.

observed that the erythrocytes were clustered in the lumen of the large vessels, and there were numerous fibroblasts and secreted collagen fibrils around them in the liver parenchyma (Figure 2).

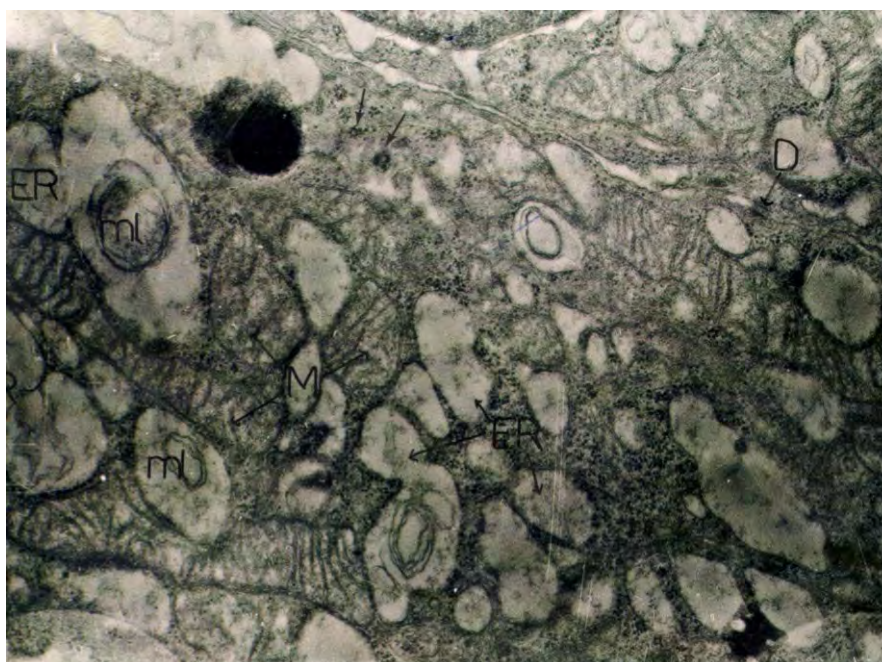
In generally, when Group D was examined by

electron microscopy, normal hepatocytes were observed. The expansions in the space of Disse and bile ducts were remarkable. The outer membranes of hepatocytes and the microvilli of the bile ducts were preserved. There was mild intracellular edema at the



**Figure 3.** Electron microscopy image of Group D. The outer membranes of hepatocytes and the microvilli of the bile ducts were preserved. The double-layered outer membranes and the crystals of the mitochondria were preserved. Other organelles also were normal.





**Figure 4.** Electron microscopy image of Group E. Mitochondria in hepatocytes swollen, but the outer membranes and the crystals did not deteriorate.

large magnification. The double-layered outer membranes and the crystals of the mitochondria were preserved. Other organelles were normal (Figure 3).

When Group E was examined by electron microscopy, it was observed that the mitochondria in hepatocytes were swollen, but the outer membranes and the crystals did not deteriorate. It was seen that there were endoplasmic reticulum expansion and myelin-like membrane structures in the ER lumen. It was observed that there were abnormal, swollen mitochondria and enlarged ER and other organelles in hepatocyte cytoplasm at the large magnification. Besides, there were irregularities in mitochondrial structures and myelin-like membrane structures in the ER lumen. There was also a proliferation of ribosomes and glycogen granules (Figure 4).

**Table 2.** SOD and GPx values of groups

Experimental Groups	SOD (U/mg protein)	GPx (U/mg protein)
Group A	7.44 ± 2.17	0.96 ± 0.17
Group B	3.53 ± 0.47	0.40 ± 0.071
Group C	5.47 ± 0.64	0.73 ± 0.005
Group D	5.70 ± 0.63	0.75 ± 0.01
Group E	5.91 ± 0.84	0.77 ± 0.087

Data are shown as mean ± standard deviation. SOD = superoxide dismutase, GPx = glutathione peroxidase

### Biochemical Findings

The mean SOD and GPx values of all groups are given in Table 2. The mean SOD value was statistically significantly lower in Group B compared to Group A ( $p = 0.004$ ). The mean SOD value was statistically significantly lower in Group C compared to Group A ( $p = 0.004$ ). However, the mean SOD value was not statistically significantly lower in Groups D and E compared to Group A. It was determined that the mean SOD value was significantly preserved in Groups C, D, and E compared to Group B ( $p = 0.004$ ). And also, there was no statistically significant difference between Groups C, D, and E in terms of mean SOD value.

The mean GPx value was statistically significantly lower in Group B compared to Group A ( $0.96 \pm 0.17$  vs  $0.40 \pm 0.071$ ,  $p = 0.004$ ). The mean GPx value was statistically significantly lower in Group C compared to Group A ( $0.96 \pm 0.17$  vs  $0.73 \pm 0.005$ ,  $p = 0.06$ ). However, the mean GPx value was not statistically significantly lower in Groups D and E compared to Group A ( $0.96 \pm 0.17$  vs  $0.75 \pm 0.01$  and  $0.77 \pm 0.087$ ;  $p = 0.6$ ). It was determined that the mean GPx value was significantly preserved in Groups C, D, and E compared to Group B ( $p = 0.004$ ). Moreover, there was no statistically significant difference between Groups C, D, and E in terms of mean GPx value.

## DISCUSSION

Studies to prevent I-R injury, which may develop as a result of the Pringle maneuver applied to liver transplantations as well as to liver resections or liver injuries, still maintain their popularity. Studies have been conducted for a long time to preserve the liver under in vitro conditions [3, 5-7]. Liver cells may be resistant to ischemia for 30 to 60 minutes, but irreversible cell damage is usually seen over a longer period of time. After 60 minutes of ischemia, SORs begin to increase at 5 minutes of reperfusion and then peak at 15 minutes of reperfusion [8]. SORs, which occur due to I-R injury, cause damage to both liver parenchyma and other liver cells [2]. The resource of SORs is that the concentration of O<sub>2</sub> suddenly increases in the medium due to reperfusion. The increased amount of SORs interacts with cell membrane lipids, resulting in the formation of arachidonic acid. Inflammatory markers such as prostaglandins (PG) and leukotrienes (LT) are released from arachidonic acid by the activation of lipoxygenase and cyclooxygenase pathways. They contribute to cell damage by disrupting cell membrane permeability. SORs are destroyed by cellular defense mechanisms. When SORs are destroyed, enzymatic pathways such as SOD, GPx, and catalase (Cat) are activated [8-14]. Numerous substances, which are thought to be effective by enzymatic or non-enzymatic pathways, have been experimentally tested in order to reduce ischemic reperfusion injury in the liver and other tissues, but there are not still products that have been actively applied for treatment [3, 5, 6].

Melatonin, a hormone released from the pineal gland, is a strong scavenger for hydroxyl radicals and other oxygen radicals that are toxic in vivo and in vitro. Its passage to the tissues is quite good due to its lipophilic nature, and it is particularly effective on the hydroxyl radical, which is the most toxic radical [15-17]. Some studies have reported that melatonin acts by capturing the superoxide of an indole-derived metabolite and also enhances SOD mRNA expression. Melatonin both stimulates important antioxidant enzymes such as intracellular superoxide dismutases (CuZnSOD and MnSOD) and selenium-containing glutathione peroxidase and catalase (CAT). And also inhibits some pre-oxidative enzymes (such as myeloperoxidase). Because of all of them, many

studies have reported that it reduces lipid peroxidation and protects cells and DNA against oxidative damage [15, 17-19]. Sewerynek *et al.* [20] showed in the mouse model of liver ischemia-reperfusion injury that melatonin reduced leukocyte infiltration and lipid peroxidation products and also increased glutathione reductase (GR) activity. In mice treated with melatonin, less apoptotic (TUNEL positive) cells and DNA fragmentation were observed than only I-R constructed mice. These results show that melatonin reduces the level of apoptotic pathway and oxidative stress and, as a result, improves hepatocytes which are exposed to I-R [21]. Aktöz *et al.* [22] found that SOD and GPx values, which decreased after I-R in rats undergoing renal ischemia reperfusion injury, were significantly preserved in melatonin-treated group. Baykara *et al.* [18] found that there were swollen and vacuolated mitochondria, dilated bile ducts, and several hepatocyte nuclei with heterochromatic and apoptotic appearance in rat liver undergoing I-R injury. They stated that hepatocyte nuclei and mitochondria appeared to be normal in melatonin-treated group. In ultrastructural evaluation of our study, although the majority of organelles in the cytoplasm of hepatocytes were normal in the melatonin-treated group, it was remarkable that the mitochondria, endoplasmic reticulum and other organelles were destructed in some places. In addition, it was seen that there was an increase in collagen fibrils around hepatocytes. Moreover, SOD and GPx values were preserved when compared with the group undergoing only I-R injury. And also, it was observed that the uptake and excretion functions in HBS were significantly preserved in the melatonin-treated group compared to the group undergoing only I-R injury.

Pentoxifylline, a methylxanthine derivative, is a phosphodiesterase inhibitor. Unlike other peripheral vasodilators, it reduces blood viscosity and increases tissue oxygenation. It increases erythrocyte flexibility, as well as reduces platelet aggregation. It increases microvascular blood flow. It has been stated that it selectively directs blood flow to tissues with a disturbed microcirculation in reperfusion [23, 24]. Dinçkan *et al.* [25] revealed that pentoxifylline has protective effect on pneumoperitoneum-induced oxidative stress in rats. There are studies showing that it is effective in I-R injury by decreasing the release of TNF- $\alpha$ , IL-1-, IL-6, SORs and proteases especially

from Kupffer cells [23]. In an experimental study of I-R injury performed using pentoxifylline by El-Ghoneimi *et al.* [7], they reported that it reduced serum levels of TNF- $\alpha$  by providing inhibition of TNF-alpha gene expression. Some studies found that pentoxifylline reduced malondialdehyde and myeloperoxidase activity [26, 27]. Pentoxifylline, a methylxanthine derivative, is a phosphodiesterase inhibitor. Unlike other peripheral vasodilators, it reduces blood viscosity and increases tissue oxygenation. It increases erythrocyte flexibility, as well as reduces platelet aggregation. It increases microvascular blood flow. It has been stated that it selectively directs blood flow to tissues with a disturbed microcirculation in reperfusion [23, 24]. Dinçkan *et al.* [25] revealed that pentoxifylline has protective effect on pneumoperitoneum-induced oxidative stress in rats. There are studies showing that it is effective in I-R injury by decreasing the release of TNF- $\alpha$ , IL1-, IL-6, SORs and proteases especially from Kupffer cells [23]. In an experimental study of I-R injury performed using pentoxifylline by El-Ghoneimi *et al.* [7], they reported that it reduced serum levels of TNF- $\alpha$  by providing inhibition of TNF-alpha gene expression. Some studies found that pentoxifylline reduced malondialdehyde and myeloperoxidase activity [26, 27]. In a clinical trial conducted in 101 noncirrhotic patients by Petrowsky *et al.* [28], they found that PTX which was administered at 12 hours before surgery and at 72 hours after surgery in patients undergoing major liver surgery provided a positive contribution to regeneration in remnant liver tissue. In our study, pentoxifylline has been found to significantly maintain SOD and GPx values in liver I-R injury compared to the group B that undergoing only I-R injury. The electron microscopy findings also confirm these values. Moreover, the HBS findings also showed us the protective feature of pentoxifylline by objective values. HBS has never been studied in identifying changes in liver functions in previous experimental models performed using pentoxifylline. It has been first used in our study. HBS reveals like elektron microcopy an objective finding that shows the efficacy of pentoxifylline.

Some studies have reported that DMSO has protective effect on I-R injury by reducing SORs. DMSO scavenges the hydroxyl radical, which is one

of the most toxic superoxide radicals. In the past decade, there have been studies showing the protective effects of DMSO on liver I-R injury by biochemical parameters as well as histopathological findings [6, 29]. However, the popularity of this agent has decreased due to its nephrotoxic effects [30]. Şahin *et al.* [31] found that DMSO reductions in I-R injury at non-toxic doses and in slow release. In an experimental study conducted by Hatipoğlu *et al.* [6], I-R group and the I-R group after DMSO were compared; hepatic peak time and the half-life of hepatic activity were significantly higher only in the I-R group. In our study, the SOD and GPx values were significantly preserved in the DMSO-treated group compared to the group undergoing only I-R injury. Electron microscope showed that the mitochondria in hepatocytes were swollen, but the outer membranes and the crystals were not deteriorated. There were myelin-like membrane structures in enlarged ER and ER lumens. In HBS, the DMSO group had shorter uptake and excretion times than the I-R group. However, unlike the previous study, the Liver PT was not well protected in the DMSO group. On the other hand, in our study, Liver T1/2 time was preserved in this group.

Today, HBS is sometimes used to assess liver function after transplantation [32]. HBS provides both quantitative and visual appearances when assessing hepatic uptake and excretory functions [6, 33]. HBS as more practical and useful method has been tried to replace serial biopsies to recognize tissue rejection after transplantation. <sup>99m</sup>Tc iminodiacetic acid (IDA) analogues, first presented by Ekman *et al.* [34], are now the most commonly used agents in the application of hepatobiliaryscintigraphy. Since HBS shows hepatocyte functions and bile duct dynamics, it is used in bile leaks that occur in liver operations, in partial or complete biliary obstructions, and in post-transplant patients [33-35]. Functional status of the liver affects the uptake of IDA and its derivatives. HBS shows hepatic uptake and excretion [36]. Because of this feature, it is considered to be an important non-invasive alternative in assessing liver I-R injury. Brunot *et al.* [37] found that early biopsy results were consistent with liver uptake functions. However, studies have shown that HBS is a good method for detecting liver complications after transplantation, while it was not found to be safe in distinguishing

tissue rejection from biliary complications [38]. In a study of Tagge *et al.* [39], the effects of ischemia-reperfusion injury on pig liver transplants has been investigated using <sup>99m</sup>Tc-diphenyl, and it was found that median transit time of the pharmaceutical agent was prolonged in ischemia. It has also been determined that this condition is associated with duration of ischemia [39]. In a study of Kuni *et al.* [40], liver biopsies were compared by quantitative HBS, and it was shown that the mean damage scores of patients with normal and abnormal uptake were significantly different. In the same study, it was also found that the uptake criteria were insufficient to distinguish pure hepatic damage from cholestasis [40].

In our study, it was found that pentoxifylline and melatonin agents significantly protect uptake and excretion functions in liver scintigraphy, but the uptake functions of the DMSO-treated group were not significantly protected compared to the I-R group. Furthermore, when the scintigraphic parameters were considered, it was found that the protective effect of pentoxifylline was better at a statistically significant level than DMSO. Although there was no statistically significant difference between pentoxifylline and melatonin, uptake and excretion results of pentoxifylline were better. In our study, the effects of all three agents were examined by electron microscopy, it was found that the liver was largely protected from the effects of I-R injury, but the EM findings in the pentoxifylline-treated group were more normal. In particular, the mitochondria and other organelles were observed to be preserved prominently in use of pentoxifylline. Considering only the electron microscopic findings in our study, it can be said that pentoxifylline is more effective in reducing I-R damage than the other two agents. It was determined that these three agents maintained significantly the SOD and GPx values when compared with the I-R group. There was no significant difference between these three agents.

## CONCLUSION

When all methods are evaluated in this study, pentoxifylline, melatonin and DMSO have been found to be effective in protecting the hepatic ischemia reperfusion injury. Although there was no difference

between pentoxifylline and DMSO according to biochemical parameters, pentoxifylline was more effective when electron microscopy findings and HBS parameters were taken into consideration. This suggests that it would be safer for the cytoprotective effect of a substance to be assessed in more than one way rather than as a single method. In our study, I-R injury-reducing effect of pentoxifylline, which gives parallel results with three methods, gives more confidence. Reducing I-R injury confirmed by all three ways, provide this agent with confidence and After the experimental works has been replicated, we foresee that it may be used to be in the future in pre-transplant and shock situations.

### *Authorship declaration*

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### *Author contributors*

All authors contributed to the design of the study. ZT: performed surgical intervention; wrote the manuscript and contributed design of the study and analysis and interpretation of the data; gives final approval for the submitted version to be published, AH: contributed substantially to the conception and design of the study and analysis and interpretation of the data. MY: contributed design of the study; performed hepatobiliarscintigraphy and interpreted of the hepatobiliarscintigraphy data. NA: studied biochemical parameters and interpreted of the biochemical data. GH: interpreted of the electron microscopy.

### *Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### *Ethics approval*

Medical Faculty Ethics Committee of Trakya University.

### *Acknowledgements*

The authors would like to thank the TUBAP Scientific Research Project of Trakya University (TUBAP-428).

## REFERENCES

- [1] Pringle JG. Notes on the arrest of hepatic hemorrhage due to trauma. *Ann Surg* 1908;48:541-9.
- [2] Park SW, Lee SM. Antioxidant and prooxidant properties of ascorbic acid on hepatic dysfunction induced by cold ischemia-reperfusion. *Eur J Pharmacol* 2008;580:401-6.
- [3] Grossine E, Pollesello P, Bellofatto K, Siguado L, Farruggio S, Origlia V, et al. Protective effects elicited by levosimendan against liver ischemia/reperfusion injury in anesthetized rats. *Liver Transpl* 2014;20:361-75.
- [4] Lee SM, Park MJ, Cho TS, Clemens MG. Hepatic injury and lipid peroxidation during ischemia and reperfusion. *Shock* 2000;13:279-84.
- [5] Reiter RJ, Tan DX, Galano A. Melatonin: exceeding expectations. *Physiology* 2014;29:325-33.
- [6] Hatipoglu AR, Temiz E, Yuksel M, Hoscoskun Z, Coskun I, Huseyinova G. The comparison of electron microscopy and scintigraphy in determining the protective effect of DMSO on ischemia/reperfusion injury in rats. *Hepatogastroenterology* 2001;48:798-802.
- [7] El-Ghoneimi A. Inhibition of tumor necrosis factor alpha gene transcription by pentoxifylline reduces normothermic liver ischemia-reperfusion injury in rats. *Transplant Proc* 2007;39:1761-4.
- [8] Wang WY, Taki Y, Monimoto T, Nishihira T, Yokoo N, Jikko A. Effects of partial ischemia and reflow on mitochondrial metabolism in rat liver. *Eur Surg Res* 1988;20:181-9.
- [9] Halliwell B. Oxidative stress, nutrition health, experimental strategies for optimization of nutritional antioxidant intake in humans. *Free Radic Res* 1996;25:57-74.
- [10] Valko M, Jomova K, Rhodes CJ, Kuca K, Musilek K. Redox- and non-redox-metal-induced formation of free radicals and their role in human disease. *Arch Toxicol* 2016;90:1-37.
- [11] Barber DA, Harris SR. Oxygen free radicals and antioxidants: a review. *Am Pharm* 1994;34:26-35.
- [12] Romani F, Vertamati M, Frangi M, Aseni P, Monti R, Codeghini A, et al. Effects of superoksid dismutase on liver ischemia reperfusion injury in the rat: a biochemical monitoring. *Eur Surg Res* 1988;20:335-40.
- [13] Jaeschke H. Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. *Am J Physiol Gastrointest Liver Physiol* 2003;284:15-21.
- [14] McCord JM, Edeas MA. SOD, oxidative stress and human pathologies: a brief history and a future vision. *Biomed Pharmacother* 2005;59:139-42.
- [15] Hatipoglu A, Turkyilmaz Z, Mert S. The effects of melatonin on postoperative intraabdominal adhesion formation. *Yonsei Med J* 2007;48:659-64.
- [16] Tan DX, Chen LD, Poeggeler B, Manchester LC, Reiter RJ. Melatonin: a potent, endogenous hydroxyl radical scavenger. *Endocr J* 1993;1:57-60.
- [17] Reiter RJ. Melatonin: lowering the high price of free radicals. *News Physiol Sci* 2000;15:246-50.
- [18] Baykara B, Tekmen I, Pekcetin C, Ulukus C, Tuncel P, Sagol O, et al. The protective effects of carnosine and melatonin in ischemia-reperfusion injury in the rat liver. *Acta Histochem* 2009;111:42-51.
- [19] Tan DX, Manchester LC, Reiter RJ, Qi WB, Karbownik M, Calvo JR. Significance of melatonin in the antioxidative defense system: reactions and products. *Biol Signals Recept* 2000;9:137-59.
- [20] Sewerynek E, Reiter RJ, Melchiorri D, Ortiz GG, Lewinski A. Oxidative damage in the liver induced by ischemia-reperfusion: protection by melatonin. *Hepatogastroenterology* 1996;43:898-905.
- [21] Kim SH, Lee SM. Cytoprotective effects of melatonin against necrosis and apoptosis induced by ischemia/reperfusion injury in rat liver. *J Pineal Res* 2008;44:165-71.
- [22] Aktöz T, Aydoğdu N, Alagol B, Yalçın O, Hüseyinova G, Atakan IH. The protective effects of melatonin and vitamin E against renal ischemia-reperfusion injury in rats. *Ren Fail* 2007;29:535-42.
- [23] Adams GA, Dhar A, Shukla SD, Silver D. Effects of pentoxifylline on tissue injury and platelet activating factor production during ischemia-reperfusion injury. *J Vasc Surg* 1995;21:742-8.
- [24] Genoves P, Garcia D, Cejalvo D, Martin A, Zaragoza C, Toledo AH, et al. Pentoxifylline in liver ischemia and reperfusion. *J Invest Surg* 2014;27:114-24.
- [25] Dinçkan A, Sahin E, Oguz M, Emek K, Gumuslu S. The effect of pentoxifylline on oxidative stress in CO<sub>2</sub> pneumoperitoneum. *Surg Endosc* 2009;23:534-8.
- [26] Hammerman C, Goldschmidt D, Caplan MS, Eidelman AY, Branki D, Hochman A. Amelioration of ischemia-reperfusion injury in rat intestine by pentoxifylline-mediated inhibition of xanthine oxidase. *J Pediatr Gastroenterol Nutr* 1999;29:69-74.
- [27] Inal M, Kanbak G, Adali M. Prevention of ischemia-reperfusion-induced oxidative injury in liver by allopurinol and pentoxifylline. *Transplantationsmedizin* 2006;18:29-32.
- [28] Petrowsky H, Breitenstein S, Slankamenac K, Vetter D, Lehmann K, Heinrich S, et al. Effects of Pentoxifylline on liver regeneration: A double-blinded, randomized; controlled trial in 101 patients undergoing major liver resection. *Ann Surg* 2010;252:813-22.
- [29] Akyurek N, Kafali EM, Muhtaroglu S. The effects of dimethylsulfoxide on experimental hepatic ischemia. *Swiss Surg* 2000;6:23-7.
- [30] Nishihara G, Sakemi T, Ikeda Y. Multiple organ failure associated with dimethyl sulfoxide and hydroxyethylstarch in autologous blood stem cell transplantation. *Nephron* 1996;72:356-7.
- [31] Sahin M, Avsar FM, Ozel H, Topalaoglu S, Yilmaz B, Pasaoglu H, et al. The effects of dimethyl sulfoxide on liver damage caused by ischemia-reperfusion. *Transplant Proc* 2004;36:2590-2.
- [32] Loken MK, Ascher NL, Boudreau RJ, Najarian JS. Scintigraphic evaluation of liver transplant function. *J Nucl Med* 1986;27:451-9.
- [33] Graaf W, Bennink R, Vetelainen R, Guulik T. Nuclear imaging techniques for the assessment of hepatic function in liver surgery and transplantation. *J Nucl Med* 2010;51:742-52.
- [34] Ekman M, Fjalling M, Holmberg S, Person H. IODIDA

clearance rate: a method for measuring hepatocyte uptake function. *Tranplant Proc* 1992;24:387-8.

[35] Vetelainen RL, Bennink RJ, De Bruin K, Van Vliet A, Van Gulik TM. Hepatobiliary function assessed by 99mTc-mebrofenin cholescintigraphy in the evaluation of severity of steatosis in a rat model. *Eur J Nucl Med Mol Imaging* 2006;33:1107-14.

[36] Kurzawinski TR, Selves L, Farouk M, Dooley J, Hilson A, Buscombe JR, et al. Prospective study of hepatobiliary scintigraphy and endoscopic cholangiography for the detection of early biliary complications after orthotopic liver transplantation. *Br J Surg* 1997;84:620-3.

[37] Brunot B, Petras S, Germain P, Vinee P, Constantinesco A.

Biopsy and quantitative hepatobiliary scintigraphy in the evaluation of liver transplantation. *J Nucl Med* 1994;35:1321-7.

[38] Kim JS, Moon DH, Lee SG, Lee YJ, Park KM, Hwang S, et al. The usefulness of hepatobiliary scintigraphy in the diagnosis of complications after adult-to-adult living donor liver transplantation. *Eur J Nucl Med Mol Imaging* 2002;29:473-9.

[39] Tagge EP, Champbell D Jr, Reichie R. Quantitative hepatic scintigraphy to evaluate ischemic-reperfusion injury in porcine liver transplantation. *Tranplant Proc* 1987;1:1095-7.

[40] Kuni CC, Engeler CM, Nakhieh RE, Du Cret RP, Boudreau RJ. Correlation of technetium-99m-DISIDA hepatobiliary studies with biopsies in liver transplant patients. *J Nucl Med* 1991;32:1545-7.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Effect of lipid parameters on carotid artery disease progression in patients undergoing carotid endarterectomy and unoperated patients with non-severe carotid artery stenosis

Kadir Kaan Özsin<sup>ORCID</sup>, Umut Serhat Sanrı<sup>ORCID</sup>, Faruk Toktaş<sup>ORCID</sup>, İbrahim Burak Şeker<sup>ORCID</sup>, Şenol Yavuz<sup>ORCID</sup>

Department of Cardiovascular Surgery, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

DOI: 10.18621/eurj.444384

## ABSTRACT

**Objectives:** We aim to evaluate the relationship between serum lipid indices and carotid artery stenosis (CAS).

**Methods:** This retrospective observational study included patients who underwent carotid endarterectomy (CEA) and unoperated patients who have CAS less than 50%. CAS was diagnosed with history and physical examination followed by doppler ultrasonography, coronary and carotid angiography. All data retrieved retrospectively from the hospital medical files. Non-high-density lipoprotein-cholesterol (non-HDL-C) level was calculated by removing HDL-C from total cholesterol. In addition, low-density lipoprotein-cholesterol (LDL-C)/HDL-C ratio, non-HDL-C/HDL-C ratio, and triglyceride (TG)/HDL-C ratio were assessed.

**Results:** CEA group (77.5% male, mean age:  $71.35 \pm 8.35$  years) included 40 patients who underwent CEA, and there were 32 patients who have less than 50% CAS in unoperated group (68.8% male, mean age:  $63.94 \pm 9.92$  years). The development of CAS was not significantly correlated with LDL-C/HDL-C ratio ( $p = 0.119$ ), non-HDL-C/HDL-C ratio ( $p = 0.227$ ) and TG/HDL-C ratio ( $p = 0.768$ ). Advanced age and presence of coronary artery disease were identified as an independent predictor of the development of CAS. For predicting development of CAS, there were 50.0% sensitivity and 65.6% specificity for LDL-C/HDL-C ratio and non-HDL-C/HDL-C ratio (area under the curve [AUC]: 0.592, log rank  $p = 0.183$ , AUC: 0.583, log rank  $p = 0.227$ , respectively).

**Conclusions:** We found that lipid ratios were not an independent predictors of the development of CAS. But, we think that AUC values which were above 0.5 for lipid ratios are may be important development of CAS.

**Keywords:** Carotid artery stenosis, lipid levels, disease progression

*Received: July 16, 2018; Accepted: August 8, 2018; Published Online: September 7, 2018*

Carotid artery stenosis (CAS) is a serious vascular problem for whole population and also an important cause of strokes particularly in the elderly people [1]. In order to prevent these complications, it is necessary to intervene in symptomatic patients who have severe CAS [2]. In asymptomatic CAS, the incidence of stroke increases by 0.35-5%, and also the incidence

and mortality of acute cardiovascular disease significantly increase [3].

Atherosclerosis is related to the inflammation and immunity and it is the main reason for CAS [4]. Traditionally, in the pathogenesis of atherosclerosis, there is accumulation of plasma lipids in the vascular wall, which contributes to the formation of an unstable



Address for correspondence: Kadir Kaan Özsin, MD., University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Cardiovascular Surgery, Bursa, Turkey  
E-mail: kkozsin@gmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

plaque, which can be ruptured [5]. Framingham study showed that extracranial carotid artery atherosclerosis associated with increased plasma concentrations of total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) and also there is an association with decreased plasma concentration of high-density lipoprotein-cholesterol (HDL-C) [6].

Based on this balance, the usage of ratios of the serum lipid levels measurement can maintain the assessment of plaque burden. Consequently, we aim to evaluate relationship of serum lipid levels between patients who underwent carotid endarterectomy (CEA) and unoperated patients who have less than 50% CAS.

## METHODS

### Patients

This retrospective observational study included patients who underwent CEA and unoperated patients who have less than 50% CAS. This study was performed between 2017 and 2018 at Department of Cardiovascular Surgery, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey. The study was approved by the local institutional Ethical Committee of University of Health Sciences.

Carotid artery stenosis was diagnosed with history and physical examination followed by doppler ultrasonography, coronary and carotid angiography. All analyzed data were retrospectively taken from hospital medical records.

All patients were operated under local anesthesia. The exclusion criteria were level of triglyceride (TG) above 400 mg/dL, combined coronary artery bypass and CEA surgery, familial hyperlipidemia, and chronic renal failure. Eventually, 40 patients undergoing CEA were included in the CEA group, and 32 patients who have less than 50% CAS in unoperated group.

All data were recorded as age, gender, comorbidities (hypertension, diabetes mellitus, and cerebrovascular accident [CVA]), smoking, the presence of coronary artery disease (CAD), statin usage, and body mass index.

### Laboratory measurements

Fasting blood samples were taken from an antecubital vein of each patient. Levels of TC, TG, and

HDL-C were measured using chemistry analyzer (Beckman Coulter AU5800, CA, USA). The LDL-C was estimated by the method of Friedewald's formula (TG <400 mg/dl) [7]. Non-HDL-C level was calculated by removing HDL-C from total cholesterol. In addition, LDL-C/HDL-C ratio, non HDL-C/HDL-C ratio, and TG/HDL-C ratio were assessed.

### Statistical Analysis

Statistical analysis data were analyzed with the Statistical Package for the Social Sciences (IBM SPSS Statistic Inc. version 21.0, Chicago, IL, USA). Continuous and ordinal variables were expressed as mean  $\pm$  standard deviation and nominal variables were expressed as frequency and percentage. Kolmogorov-Smirnov test and Shapiro-Wilk tests of normality were used to identify distribution of variables. Student's *t* test was used to compare two groups for continuous variables with normal distribution. Chi Square test was used to compare two groups for nominal variables. Mann-Whitney U test was used to compare two groups for continuous variables without normal distribution. Predictors of disease progression were identified by using binary logistic regression analysis. For all tests, a *p* value of < 0.05 was considered statistically significant. Receiver-operating characteristic (ROC) curve was applied for the prediction of disease progression and the area under the curve (AUC) was calculated for LDL-C/HDL-C ratio, non HDL-C/HDL-C ratio, and TG/HDL-C ratio.

## RESULTS

A total number of 40 patients in the CEA group (77.5% male, mean age:  $71.35 \pm 8.35$  years) and 32 patients in the unoperated group (68.8% male, mean age:  $63.94 \pm 9.92$  years) were recorded in this study. The demographic and clinical characteristics of the patients are summarized in Table 1. There were statistically difference between two group in terms of age ( $p = 0.001$ ), presence of hypertension ( $p = 0.035$ ), previous CVA ( $p = 0.001$ ), presence of CAD ( $p = 0.001$ ) and statin therapy ( $p = 0.032$ ) (Table 1).

The comparison of laboratory findings are shown in Table 2. Both CEA group and unoperated group were similar to each other regards to laboratory findings. In addition, non-HDL-C level, LDL-C/HDL-



**Table 1.** Demographic and clinical characteristics of the patients

	CEA group (n = 40)	Unoperated group (n = 32)	p value
Age (years)	71.4 ± 8.4	63.9 ± 9.9	<b>0.001<sup>#</sup></b>
Male gender, n (%)	31 (77.5)	22 (68.8)	0.403 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	27.54 ± 4.1	26.96 ± 4.1	0.552 <sup>*</sup>
Hypertension, n (%)	25 (62.5)	12 (37.5)	<b>0.035<sup>a</sup></b>
Diabetes mellitus, n (%)	15(37.5)	18 (56.3)	0.113 <sup>a</sup>
Previous CVA, n (%)	20 (50)	4 (12.5)	<b>0.001<sup>a</sup></b>
CAD, n(%)	26 (65)	8 (25)	<b>0.001<sup>a</sup></b>
Smoking <sup>†</sup> , n(%)	17 (42.5)	11 (34.4)	0.482 <sup>a</sup>
Statin therapy, n(%)	17 (42.5)	6 (18.8)	<b>0.032<sup>a</sup></b>

CEA = Carotid endarterectomy, BMI = Body mass index, CVA = Cerebrovascular accident, CAD = Coronary artery disease, <sup>†</sup>Current or former smoking, <sup>a</sup>Pearson Chi- Square, <sup>#</sup> Mann-Whitney U test, <sup>\*</sup> Student's-t test

C ratio, non-HDL-C/HDL-C ratio and TG/HDL-C ratio were not significantly different between the groups ( $p = 0.432$ ,  $p = 0.119$ ,  $p = 0.227$  and  $p = 0.768$ ; respectively) (Table2).

Factors related to the development of CAS were included univariate logistic regression analysis. In unadjusted univariate logistic regression analysis, the development of CAS was significantly correlated with

advanced age (OR [odds ratio]: 0.913, 95% CI [confidence interval]: 0.860-0.969,  $p = 0.003$ ), hypertension (OR: 0.360, 95% CI: 0.138-0.940,  $p = 0.037$ ) and presence of CAD (OR: 0.179, 95% CI: 0.064-0.503,  $p = 0.001$ ) but was not correlated with diabetes mellitus, smoking, non-HDL-C level, LDL-C/HDL-C ratio, non-HDL-C/HDL-C ratio and TG/HDL-C ratio (Table 3). In addition, advanced age

**Table 2.** Laboratory findings

	CEA group (n = 40) (mean ± SD)	Unoperated group (n = 32) (mean ± SD)	P value
Hematocrit (%)	38.9 ± 5.6	39.1 ± 7.7	0.907 <sup>*</sup>
Hemoglobin (g/dL)	12.8 ± 1.9	13.4 ± 1.9	0.201 <sup>*</sup>
White blood cell (10 <sup>3</sup> /μL)	8.3 ± 2.6	8.9 ± 2.1	0.252 <sup>*</sup>
Platelet (10 <sup>3</sup> /μL)	248.6 ± 65.2	243.7 ± 71.1	0.760 <sup>*</sup>
Red cell distribution width (%)	14.7 ± 1.3	14.3 ± 1.6	0.229 <sup>*</sup>
Mean platelet volume (fL)	8.6 ± 1.4	8.7 ± 1.6	0.959 <sup>#</sup>
NLR	3.7 ± 1.9	3.1 ± 1.8	0.080 <sup>#</sup>
HbA1c (%)	6.5 ± 1.5	6.8 ± 1.5	0.236 <sup>#</sup>
Creatinine (mg/dL)	1.0 ± 0.3	1.0 ± 0.8	0.398 <sup>#</sup>
Ca (mg/dL)	9.2 ± 0.6	9.2 ± 0.6	0.933 <sup>*</sup>
Mg (mg/dL)	1.8 ± 0.2	1.8 ± 0.3	0.671 <sup>*</sup>
C-reactive protein (mg/dL)	7.5 ± 9.8	7.9 ± 7.1	0.782 <sup>#</sup>
Total protein (g/dL)	6.9 ± 0.5	6.9 ± 0.7	0.967 <sup>*</sup>
Albumin (g/dL)	3.7 ± 0.5	3.8 ± 0.5	0.878 <sup>#</sup>
Fibrinogen (μg/ml)	402.3 ± 91.2	407.7 ± 84.2	0.910 <sup>#</sup>
Total cholesterol (mg/dL)	199.1 ± 59.3	191.7 ± 47.5	0.572 <sup>*</sup>
LDL-C (mg/dL)	123.4 ± 45.6	115.8 ± 39.9	0.457 <sup>*</sup>
HDL-C (mg/dL)	39.5 ± 7.6	42.1 ± 8.2	0.207 <sup>#</sup>
Non-HDL-C (mg/dL)	159.6 ± 59.0	149.6 ± 44.5	0.432 <sup>*</sup>
TG (mg/dL)	191.6 ± 137.2	186.9 ± 80.1	0.441 <sup>#</sup>
LDL-C/HDL-C	3.2 ± 1.3	2.8 ± 0.9	0.119 <sup>*</sup>
Non-HDL-C/HDL-C	4.2 ± 1.9	3.6 ± 1.1	0.227 <sup>#</sup>
TG/HDL-C	5.2 ± 4.9	4.7 ± 2.5	0.768 <sup>#</sup>

CEA = Carotid endarterectomy, NLR = Neutrophil to lymphocyte ratio, LDL-C = Low-density lipoprotein-cholesterol, HDL-C = High-density lipoprotein-cholesterol, TG = Triglyceride, <sup>#</sup> Mann-Whitney U test, <sup>\*</sup> Student's-t test, SD = Standard deviation

**Table 3.** Binary Logistic regression analysis to identify predictors of disease progression

Variables	Univariate analysis			Multivariate analysis		
	<i>p</i>	Exp(B) Odds Ratio	95% C.I. Lower-Upper	<i>p</i>	Exp(B) Odds Ratio	95% C.I. Lower-Upper
Age	<b>0.003</b>	.913	.860-.969	<b>0.003</b>	.902	.842-.967
HT	<b>0.037</b>	.360	.138-.940	0.528	.691	.219-2.179
DM	0.115	2.143	.831-5.526			
CAD	<b>0.001</b>	.179	.064-.503	<b>0.002</b>	.143	.042-.489
Smoking	0.483	.709	.271-1.854			
Non-HDL-C	0.428	.996	.987-1.005			
LDL-C / HDL-C	0.123	.709	.458-1.098			
Non HDL-C / HDL-C	0.133	.763	.536-1.086			
TG / HDL-C	0.583	.965	.850-1.096			
NLR	0.154	.814	.614-1.080			

HT = Hypertension, DM = Diabetes mellitus, LDL-C = Low-density lipoprotein-cholesterol, HDL-C = High-density lipoprotein-cholesterol, TG = Triglyceride, NLR = Neutrophil to lymphocyte ratio

and presence of CAD were identified as an independent predictor of development of CAS in multivariate analysis (OR: 0.902, 95% CI: 0.842-0.967, *p* = 0.003; OR: 0.143, 95% CI: 0.042-0.489, *p* = 0.002) (Table 3).

Additionally, in ROC curve analysis, for LDL-C/HDL-C ratio it was determined a cut-off level of 3.1 for predicting progression of CAD (AUC: 0.592, 95% CI: 0.460-0.723, log rank *p* = 0.183), for non-HDL-C/HDL-C ratio it was determined as a cut-off level of 4.4 for predicting progression of CAS (AUC: 0.583,

95% CI: 0.452-0.715, log rank *p* = 0.227) and for TG/HDL-C ratio, it was determined as a cut-off level of 4.4 for predicting progression of CAS (AUC: 0.480, 95% CI: 0.346-0.614, log rank *p* = 0.768) (Table 4). In the measurements above their cut-off values, there were 50.0% sensitivity and 65.6% specificity for LDL-C/HDL-C ratio, 50.0% sensitivity and 65.6% specificity for non HDL-C/HDL-C ratio, and 47.5% sensitivity and 53.1% specificity for TG/HDL-C ratio (Figure 1).

**Table 4.** Result of ROC curve analysis

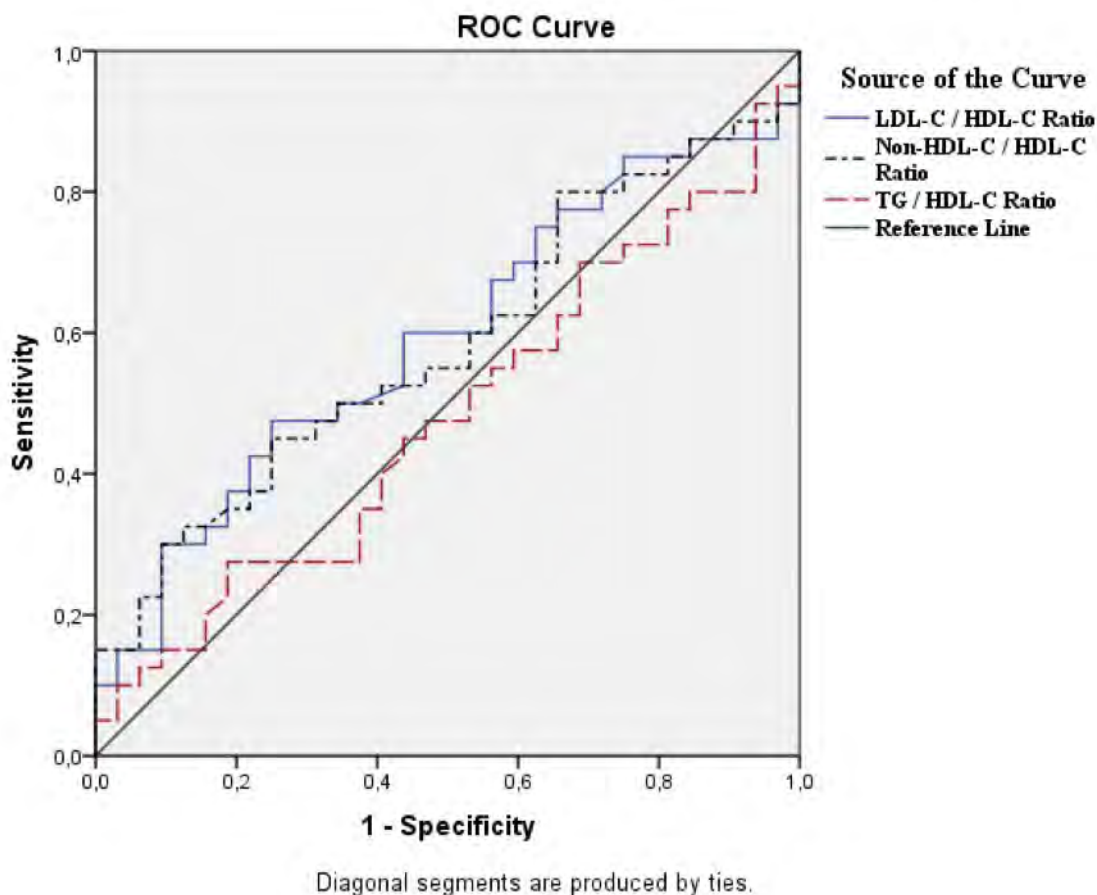
Test Result Variable(s)	AUC	Sensitivity	Specificity	Cut-off value	<i>p</i> value	Asymptotic 95% Confidence Interval	
						Lower	Upper
LDL-C / HDL-C Ratio	<b>.592</b>	50%	65.6%	3.1	.183	.460	.723
Non HDL-C / HDL-C Ratio	<b>.583</b>	50%	65.6%	4.4	.227	.452	.715
TG / HDL-C Ratio	.480	47.5%	53.1%	4.4	.768	.346	.614

ROC = Receiver operating characteristic, AUC = Area under the curve, LDL-C = Low-density lipoprotein-cholesterol, HDL-C = High-density lipoprotein-cholesterol, TG = Triglyceride

## DISCUSSION

In our study, we assessed the effect of LDL-C/HDL-C ratio, non HDL-C/HDL-C ratio and TG/HDL-C ratio in the development of CAS. In univariate logistic regression analysis, we found significant correlation among advanced age, hypertension and presence of CAD with the

development of CAS. In multivariate logistic regression analysis, advanced age and presence of CAD were detected as independent predictors for the development of CAS. Additionally, in ROC curve analysis, we found that AUC of measured ratios were above 0.5 except from TG/HDL-C ratio (Table 4). However, in our study, all measured indexes were not independent predictors for the development of CAS.



**Figure 1.** ROC curve and AUC for predicting progression of carotid artery stenosis of LDL-C/HDL-C ratio, non HDL-C/HDL-C ratio, and TG / HDL-C ratio. ROC = Receiver operation characteristic, AUC =Area under the curve, LDL-C = Low-density lipoprotein-cholesterol, HDL-C = High = density lipoprotein-cholesterol, TG = Triglyceride

In a systematic review of 17 studies that examined carotid artery intima-media thickness (cIMT), including 10,124 healthy subjects free from cardiovascular disease risk factors, a strong positive relationship has been found between age and cIMT [8]. This study also suggested that cIMT progressed strongly and linearly to advanced age. In the few previous studies, there is strong evidence that middle-aged and elderly people have a higher cIMT than younger adults [9, 10]. Our study was not a study investigating the relationship between cIMT thickness and the age, but we found that the mean age was higher in CEA group than in the unoperated group ( $p = 0.001$ ). In addition, in our study, in logistic regression analysis, advanced age was defined as an independent predictor of CAS development. Additionally, in logistic regression analysis, we detected that advanced age was an independent

predictor of CAS development.

Hyperlipidaemia is a well-documented risk factor in cardiovascular disease assessment. High HDL-C level is related inversely proportional to CAD, ischemic stroke and carotid atherosclerosis [11]. In many previous studies while HDL-C is accepted as an antiatherogenic agent, it has reported that LDL-C is a classical atherogenic lipoprotein [12]. Even though, the LDL-C level has been considered as the primary target of lipid-lowering therapy, non-HDL-C has been recommended as the secondary target of lipid lowering treatment, especially for patients with high TG levels [12]. In some studies, non-HDL-C has found as a more precious predictive value for atherosclerosis and CVD than LDL-C [13]. Furthermore, TC/HDL-C and LDL-C/HDL-C ratios have been considered as better predictors for atherosclerosis than each independent lipid parameter in other studies [14, 15]. Previous

studies have stated that TG/HDL-C ratio is one of the main indicators for cardiovascular diseases, insulin resistance and metabolism syndrome [16, 17]. Formerly published epidemic analysis have shown that non-HDL-C is a bit better than LDL-C as the predictor for CVD risk [13, 18]. Another meta-analysis including more than 300,000 people has demonstrated that the predictive value of non-HDL-C for CVD risk is similar with LDL-C (both measured and calculated) [19].

TC, LDL-C and non-HDL-C have precious predictive values for intima-media thickness and the presence of carotid plaque compared with other lipid parameters. Among these, TC has the greatest predictive value for the presence of carotid plaque. The value of non-HDL-C is not lower than LDL-C for foresight of cIMT and plaque [20]. Non-HDL-C has several advantages as a risk predictor of atherosclerosis. Firstly all potential atherogenic lipid particles included in its structure and it can be calculated in the non-fasting state; lastly, it can be calculated in the presence of hypertriglyceridemia [20].

Siemlink *et al.* [21] revealed in their study including 1,443 CEA patients, that plasma lipid levels were not associated with the carotid atherosclerotic plaque composition. They tried to explain this result to the presence of atherosclerotic disease and comorbid disease in the patients included in the study and to the fact that the majority of the patients took lipid-lowering drugs. They also noted that with respect to plasma lipids, only a preoperative measurement was made and plasma lipid concentrations could change significantly over time. Accordingly, a recent meta-analysis has shown that statin therapy leads to regression of carotid plaques by improving inflammation, not lipid levels [22].

In our study, we detected that LDL-C/HDL-C ratio, non-HDL-C/HDL-C ratio and TG/HDL-C ratio were not significantly different between the groups (Table 2) and in logistic regression analysis (Table 3) we revealed that the progression of CAS was not correlated with LDL-C/HDL-C ratio, non-HDL-C/HDL-C ratio, and TG/HDL-C ratio. Our results are similar with the study of Siemlink *et al.* [21]. In our study, atherosclerotic disease ( $p = 0.001$ ), hypertension as a comorbidity ( $p = 0.035$ ) and statin therapy ( $p = 0.032$ ) were statistically different in the

CEA group. This may explain that, why in our study lipid ratios are not statistically significant with carotid artery disease.

On the other hand, in ROC curve analysis, we found that there were 50.0% sensitivity and 65.6 % specificity for LDL-C/HDL-C ratio (AUC: 0.592, log rank  $p = 0.183$ ) and were 50.0% sensitivity and 65.6% specificity for non HDL-C/HDL-C ratio (AUC: 0.583, log rank  $p = 0.227$ ) (Table 4, Figure 1). We think that in present study AUC values which were above 0.5 are not pointless values for LDL-C/HDL-C ratio and non HDL-C/HDL-C ratio. However, more studies are needed in this regard.

## CONCLUSION

In conclusion, many factors contribute to the development of CAS. Many studies have been done regarding the effect of lipid parameters on CAS. Although our results were not statistically significant, we concluded that high lipid ratios may be a factor in the development of CAS. Therefore, there is a need for studies involving patients who are free of atherosclerotic risk factors and who do not use lipid-lowering agents.

### Authorship contributions

Concept-Design: KKÖ, USS, ŞY; Data collection: KKÖ, USS, İBŞ; Analysis: KKÖ, FT; Literature search: KKÖ, FT, İBŞ; Writing: KKÖ, USS, ŞY; Critical review: ŞY.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

- [1] Boulos NM, Gardin JM, Malik S, Postley J, Wong ND. Carotid plaque characterization, stenosis, and intima-media thickness according to age and gender in a large registry cohort. *Am J Cardio* 2016;117:1185-91.
- [2] Toktas F, Goncu T, Surer S, Yumun G, Ozsin KK, Erdolu B, et al. Carotid endarterectomy: a comparison on general and local

anesthesia. *Eur Res J* 2015;1:39-43.

[3] Divya KP, Sandeep N, Sarma S, Sylaja PN. Risk of stroke and cardiac events in medically treated asymptomatic carotid stenosis. *J Stroke Cerebrovasc Dis* 2015;24:2149-53.

[4] Wong BW, Meredith A, Lin D, McManus BM. The biological role of inflammation in atherosclerosis. *Can J Cardiol* 2012;28:631-41.

[5] Anitschkow N, Chalator S, Pelias, Mary Z. Classics in arteriosclerosis research: On experimental cholesterol steatosis and its significance in the origin of some pathological processes. *Arteriosclerosis* 1983;3:178-82.

[6] Fine-Edelstein JS, Wolf PA, O'Leary DH, Poehlman H, Belanger AJ, Kase CS, et al. Precursors of extracranial carotid atherosclerosis in the Framingham study. *Neurology* 1994;44:1046-50.

[7] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499-502.

[8] Van den Munckhof ICL, Jones H, Hopman MTE, de Graaf J, Nyakayiru J, van Dijk B, et al. Relation between age and carotid artery intima-medial thickness: a systematic review. *Clin Cardiol* 2018;41:698-704.

[9] Youn YJ, Lee NS, Kim JY, Lee JW, Sung JK, Ahn SG, et al. Normative values and correlates of mean common carotid intima-media thickness in the Korean rural middle-aged population: the Atherosclerosis Risk of Rural Areas in Korea General Population (ARIRANG) study. *J Korean Med Sci* 2011;26:365-71.

[10] Engelen L, Ferreira I, Stehouwer CD, Boutouyrie P, Laurent S. Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors. *Eur Heart J* 2013;34:2368-80.

[11] Yokokawa H, Yasumura S, Tanno K, Ohsawa M, Onoda T, Itai K, et al. Serum low-density lipoprotein to high-density lipoprotein ratio as a predictor of future acute myocardial infarction among men in a 2.7-year cohort study of a Japanese northern rural population. *J Atheroscler Thromb* 2011;18:89-98.

[12] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood

cholesterol in adults (adult treatment panel III) final report. *Circulation* 2002;106:3143-421.

[13] Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, et al. Non-high density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med* 2001;161:1413-9.

[14] Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA* 2005;294:326-33.

[15] Kinosian B, Glick H, Garland G. Cholesterol and coronary heart disease: predicting risks by levels and ratios. *Ann Intern Med* 1994;121:641-7.

[16] Zhou M, Zhu L, Cui X, Feng L, Zhao X, He S, et al. The triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio as a predictor of insulin resistance but not of  $\beta$  cell function in a Chinese population with different glucose tolerance status. *Lipids Health Dis* 2016;15:104.

[17] Kiyosue A. Nonfasting TG/HDL-C ratio seems a good predictor of MACE in CAD patients with statin therapy. Could it be a treatment target? *J Cardiol* 2018;71:8-9.

[18] Bittner V, Hardison R, Kelsey SF, Weiner BH, Jacobs AK, Sopko G. Non-high-density lipoprotein cholesterol levels predict five-year outcome in the bypass angioplasty revascularization investigation (BARI). *Circulation* 2002;106:2537-42.

[19] Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993-2000.

[20] Hou Q, Li S, Gao Y, Tian H. Relations of lipid parameters, other variables with carotid intima-media thickness and plaque in the general Chinese adults: an observational study. *Lipids Health Dis* 2018;17:107.

[21] Siemelink MA, van der Laan SW, van Setten J, de Vries JP, de Borst GJ, Moll FL, et al. Common variants associated with blood lipid levels do not affect carotid plaque composition. *Atherosclerosis* 2015;242:351-6.

[22] Ibrahimi P, Jashari F, Bajraktari G, Wester P, Henein MY. Ultrasound assessment of carotid plaque echogenicity response to statin therapy: a systematic review and meta-analysis. *Int J Mol Sci* 2015;16:10734-47.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Coenzyme Q10 deficiency in elderly: Can nutritional supplementation play a role? Mini review

Angelo Michele Carella<sup>✉</sup>, Teresa Marinelli<sup>✉</sup>, Michele Di Pumpo<sup>✉</sup>, Giovanni Modola<sup>✉</sup>, Angelo Benvenuto<sup>✉</sup>

Department of Internal Medicine, "T. Masselli-Mascia" Hospital, San Severo (Foggia), Italy

DOI: 10.18621/eurj.411682

## ABSTRACT

Coenzyme Q10 (CoQ10), an important mitochondrial redox component, plays a pivotal role in cellular energy production; moreover, it is the only lipid-soluble antioxidant endogenously synthesized in humans. Given its function and physiological importance, it is not surprising that CoQ10 deficiency may result in several diseases. With aging, humans begin to lose the ability to synthesize CoQ10 from food, resulting in reduced serum levels of CoQ10 and contributing to aging-associated symptoms. Poor eating habits, infections, stress and also some drugs, as beta blockers, antihypertensive agents and statins, may reduce serum levels of CoQ10. Dietary supplementation has been proposed as key strategy to increase CoQ10 availability, improving health status in elderly; however CoQ10 is not approved by U.S. Food and Drug Administration for the treatment of any medical condition and it is sold only as a dietary supplement. Aim of the study was to examine the latest relevant evidences on potential benefits of CoQ10 nutritional supplement and its implication in improving health status in elderly. There is evidence that, in elderly, oral administration of CoQ10 reduces oxidative stress and inflammatory markers and reduces cardiovascular mortality; in diabetics CoQ10 treatment improves insulin sensitivity and decreases glycated hemoglobin. Therapeutic benefit from CoQ10 supplementation has also been obtained in neurodegenerative diseases as Parkinson's, Alzheimer's and Huntington's diseases. CoQ10 supplements could be useful in several aging-related clinical conditions; however, well standardized long-term and larger further studies are needed

**Keywords:** coenzyme Q10, elderly, supplementation

*Received: April 1, 2018; Accepted: May 2, 2018; Published Online: May 19, 2018*

Coenzyme Q10 (CoQ10) is an important mitochondrial redox component that plays a pivotal role in cellular energy production as essential cofactor in oxidative phosphorylation. CoQ10 is present in all the biological membranes, mostly in the phospholipid membrane of the mitochondria, where it also acts as cell membrane stabilizing and potent intracellular scavenger of free radicals [1].

Organs with utmost energy needs as brain, heart, kidney and liver have the highest concentrations of

CoQ10 and its omnipresence throughout the body gave alternate name, Ubiquinone [1, 2]. Moreover, this enzyme is the only lipid-soluble antioxidant endogenously synthesized in humans [2]; however, the endogenous production of CoQ10 begin to progressively decrease after the age of 20 [3], so that with aging humans lose the ability to synthesize CoQ10 from food, resulting in reduced serum levels of this important antioxidant factor [4]. Poor eating habits, infections, stress and also some drugs, as beta



Address for correspondence: Angelo Michele Carella, MD., "T. Masselli-Mascia" Hospital, Department of Internal Medicine, San Severo (Foggia), Italy  
E-mail: mic.carella@virgilio.it

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

blockers, antihypertensive agents and statins, may reduce serum levels of CoQ10 [5-7]. In humans, the daily requirement for CoQ10 is 3-6 mg, derived primarily from meat, particularly organ meats as kidney, liver, heart and beef; fish as sardines and mackerel; soy oil and peanuts are also rich source of dietary CoQ10 [8].

CoQ10 is gaining popularity in cosmetic and anti-ageing industries [9-12] but, given its function and physiological importance, it is not surprising that CoQ10 deficiency contributes to aging-associated symptoms and may result in several diseases [4]. For this reason, dietary supplementation has been proposed as a key strategy to increase CoQ10 availability, improving health status in elderly [6]; however CoQ10 is not approved by U.S. Food and Drug Administration for the treatment of any medical condition and it is sold only as a dietary supplement. Yet, although CoQ10 deficiency is more relevant in elderly, there was poor interest in researchers regarding to potential benefits that CoQ10 dietary supplements could have in older people. Aim of this research was to examine the latest relevant evidences on potential benefits of CoQ10 nutritional supplement and its implication in improving health status in elderly.

## METHODS

A review of recent literature has been carried out via Pub Med database, using these search term: coenzyme Q10, elderly, supplementation. Search was not limited by language or human subjects. All the found items, published in the last five years, from January 2013 to December 2017, were analysed. Article types was determined using filters available on PubMed database. Additional articles were selected from the bibliographies of the quoted references. Other data were deduced from retrospective analysis and by careful assessment of the obtained items and their references.

## RESULTS

Eighty items were obtained: 59 were clinical studies/trials, including 55 randomized controlled

trials, 4 multicenter studies, 5 comparative studies; 3 reviews and 4 case reports were also found. Five studies were conducted in animal models. Observational studies were not found, neither meta-analysis nor guidelines nor consensus. Remaining items were prevalently other journal articles or other publication types.

In summary, the analysis of obtained data primarily showed that, in elderly, oral administration of CoQ10 reduces oxidative stress, inflammatory markers and cardiovascular mortality; positive effects of CoQ10 supplementation on oxidative stress were also observed in subjects with chronic kidney disease. Moreover in diabetic patients CoQ10 treatment improves insulin sensitivity and decreases glycated hemoglobin. Therapeutic benefit from CoQ10 supplementation has also been obtained in neurodegenerative diseases as Parkinson's, Alzheimer's and Huntington's. Lastly, there is some evidence that, in patients with breast and other types of cancer, CoQ10 supplementation seems associated with improvement of cancer-related fatigue. Generally, no toxicity was observed with varying doses of CoQ10 used in the different studies.

## DISCUSSION

There is promising evidence that oral administration of CoQ10 improves health status in elderly and slows the deterioration in health-related quality of life [13, 14]. Increasing evidence were found particularly in patient with cardiac diseases; the heart muscle uses more energy than any other tissue and normally it has the highest concentration of CoQ10, so it is very sensitive to CoQ10 deficiency [15].

In the past, it has been observed that nutritional supplements of CoQ10 make improvements of heart muscle function in patients with chronic heart failure [16]. In healthy elderly subjects higher serum levels of ubiquinol were found associated with lower serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker for chronic heart failure [17]. Moreover, in a cohort of community-dwelling elderly, long-term supplementation of CoQ10 and selenium has reduced NT-proBNP levels and cardiovascular mortality [18]; the same results were also achieved in

a 5-year prospective randomized double-blind placebo- controlled trial, carried out among elderly Swedish citizens [19]. Reduced cardiovascular mortality, in subjects receiving nutritional supplements of CoQ10, was confirmed in other studies among healthy elderly [20], also after a 10-year follow-up period [21], and in patients with chronic heart failure [15].

There is evidence that in patients with coronary artery disease, CoQ10 supplementation is able to reduce oxidative stress and inflammatory markers as Interleukin-6, increasing antioxidant enzyme activity [22, 23]; this benefit was also found in type 2 diabetic patients with stable coronary heart disease [24] and in veterans with stenosis of one major coronary artery during statins therapy [25].

Benefits for cardiovascular patients could also be related to other effects of CoQ10: it has been shown that long-term CoQ10 supplementation improves endothelium-dependent vasodilation in senescent rats, enhancing arterial relaxation and lowering blood pressure [26]; in humans, oral doses of CoQ10, varying from 75 to 600 mg daily, allowed to reduce the need to multidrug antihypertensive regimens [27]. Even in hypertensive patients daily supplementation of CoQ10 can be effective in decreasing some pro-inflammatory factors, such as Interleukin-6 and high-sensitivity-C reactive protein [28]. In some studies dietary supplementation with CoQ10 was also associated with improvement in lipid pattern of hypercholesterolemic patients [29-31], although in these studies CoQ10 was not administered alone, but in combination with other nutraceuticals. Some studies have also shown that CoQ10 supplementation effectively reduced statin-related muscular symptoms [32, 33]; nevertheless, other studies revealed no significant effects of CoQ10 on statin-induced myopathy and rhabdomyolysis, compared with placebo [34, 35].

With age, there is a decline in renal function and the incidence of kidney failure increases in elderly; in addition, given the high burden of risk factors for kidney disease in the middle-aged population, the high prevalence of chronic kidney disease in the elderly is not surprising [36, 37]. Compared with younger adults, older adults with advanced kidney disease have multiple comorbidities and a higher risk of death [38]; moreover, in patients with chronic renal failure and in

those receiving maintenance hemodialysis for end-stage renal disease there is an increased risk of cardiovascular disease, attributable to excess of oxidative stress [39, 40]. The effect of CoQ10 supplementation on oxidative stress was also assessed in subjects with chronic kidney disease and in hemodialysis patients, but conflicting as well as non unique results were found in our search [41-43].

The effects of CoQ10 were also investigated in diabetic patients: positive effects of a nutraceutical combination, including CoQ10, on lipid profile and glucose plasma levels were reported in a systematic review of randomized controlled trials [44]. Few studies have investigated the effects of coenzyme Q10 supplementation in elderly diabetics, predominantly in type2 diabetic patients: it has been shown that CoQ10 supplementation can decrease glycosylated hemoglobin in overweight and obese patients with type 2 diabetes [45], but the effect on glycemic control was discordant [46, 47]; however, there is evidence that oral administration of CoQ10 counteracts oxidative stress in type 2 diabetics [46] and reduces circulating levels of reactive oxygen species in patients with nonproliferative diabetic retinopathy [48]. Lastly, in patients with metabolic syndrome oral coenzyme Q10 administration can have beneficial effects on serum insulin levels, homeostasis model of assessment-insulin resistance, homeostatic model assessment-beta cell function and plasma total antioxidant capacity concentrations when compared with placebo group [49]. Coenzyme Q10 has been considered for improving glycemic control through various mechanisms, including a decrease in oxidation stress and improvement in beta cell function, insulin sensitivity and endothelial function [44].

For at least 20 years, potential benefits from CoQ10 supplementation in the treatment of neurodegenerative diseases were investigated in animal models [50-53] and in humans [50, 54-56]. Parkinson's disease is a typical age-related neurodegenerative disease characterized by degeneration and progressive loss of dopaminergic neurons in the substantianigra leading to several clinic manifestations including tremors, bradykinesia, akinesia, abnormal postural reflexes, rigidity and, in the advanced stage of the disease, cognitive impairment and dementia [57]. It has been suggested that oxidative stress can play a role in the etiology and



progression of Parkinson's disease and pathological studies in animal models suggest that mitochondrial dysfunction can be a key pathological mechanism in Parkinson's disease [58]. It has been demonstrated that, in mice, CoQ10 can protect against striatal lesions produced by the mitochondrial toxins malonate and 3-nitropropionic acid and it also protects against 1-methyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity [50, 59, 60]. Some studies [55, 56, 61, 62] have shown beneficial effects of oral CoQ10 supplementation in Parkinson's patients, while in other studies [63, 64] CoQ10 showed no evidence of clinical benefit. However, a recent review [65] has established that the supplementation with CoQ10 does not slow functional decline nor provide any symptomatic benefit for patients with Parkinson's disease; moreover, data from a subsequent meta-analysis of randomized controlled trials [66] performed to assess the efficacy of CoQ10 supplementation in the treatment of Parkinson's disease, have confirmed that CoQ10 is not superior to placebo in terms of motor symptoms, although it has been shown safe and well tolerated. Then, at present, CoQ10 supplements appear to have a limited role in the prevention or treatment, as primary or adjunctive therapy, of Parkinson's.

Increasing evidence suggests that Alzheimer's disease is associated with oxidative damage that is caused in part by mitochondrial dysfunction which has been identified as an early event in Alzheimer's pathogenesis [67]. In vitro and in vivo analysis have suggested the neuroprotective potentials of CoQ10 in Alzheimer disease [68, 69]. It is assumed that the antioxidant capacity of this compound can slow down neurodegeneration and improve cognitive functions and functional decline by facilitating ATP synthesis and counteracting mitochondrial dysfunction. Clinical studies for the evaluation of neuroprotective effect, safety and tolerability of CoQ10 in mild to moderate Alzheimer patients will be required.

Huntington's disease is a rare genetic neurodegenerative disorder, characterized by progressive death of striatal and cortex neurons. Typically, the onset of symptoms is in middle-age, but this disorder can manifest at any time between infancy and senescence. Main clinical manifestation of Huntington's disease are hyperkinetic movements, behavioural difficulties, weight loss and progressive cognitive decline leading to death 15 to 20 years after

the onset of symptoms [70]. Various lines of evidence have produced the involvement of mitochondrial dysfunction in the pathogenesis of Huntington's disease [71] and some studies have dashed hopes that CoQ10 could have disease-modifying properties and play a therapeutic role in Huntington's disease [51, 52, 54]. In this regard, in our search we have found poor and weak clinical evidences [72, 73], then further studies will be needed.

Oxidative stress and resulting cellular DNA damage have been suggested to play a role in the etiology of several chronic diseases, including cancer [74-76] and decreased levels of CoQ10 were found in plasma of women with breast cancer [77] and cervical cancer [78] as well as in melanoma patients [79]. We have found some evidence in which CoQ10 supplementation seems associated with beneficial effect on DNA damage via p53-dependent DNA repair machinery in elderly subjects [80-82]. Moreover, in the past, few small studies have reported the ability of CoQ10 supplementation in ameliorating cardiotoxicity, liver toxicity and tolerability of cancer treatments, particularly in patients receiving chemotherapy with anthracyclines [83, 84]. Lastly, CoQ10 was often used in patients with breast and other cancers to improve tumor-related fatigue [85]. Unfortunately, at present, clinical investigations in older cancer patients are too limited; in our research we have found only a randomized, double-blind, placebo controlled study of CoQ10 in women (median age 52 years) with breast cancer and planned adjuvant chemotherapy, in which CoQ10 supplementation did not result in improved self-reported fatigue or quality of life [86]. In summary, although there are several evidences supporting potential benefits of CoQ10 supplementation in cancer patients, clinical results seem too weak and not very effective; hence, even in this field further studies will be needed.

With regard to safety and tolerability of CoQ10 dietary supplements, from our data it has emerged that CoQ10, generally, was well tolerated and no toxicity was observed; nevertheless, some adverse effects, mainly gastrointestinal, were observed with very high intake. Other potential side effects are rashes and headaches; yet, another aspect to consider is that the structure of CoQ10 is similar to vitamin K, therefore CoQ10 should be used with caution and accurate coagulation monitoring in patients taking oral

anticoagulant therapy, to avoid potential drug interactions [87-89].

Finally, CoQ10 is fat-soluble, so it is better absorbed when taken with a meal that contains oil or fat. Unfortunately, because of its hydrophobicity and large molecular weight, the absorption of dietary CoQ10 from the gastrointestinal tract is limited and its in vivo bioavailability is known to be poor. It was found that bioavailability of CoQ10 was significantly different depending on the formulations and dissolution could be one of the important factors affecting CoQ10 absorption; then, bile and the solubilized formulation are essential for absorption of CoQ10 [90]. Several novel formulations of CoQ10 have been developed to improve absorption and bioavailability of CoQ10 in an attempt to enhance its water solubility [91, 92]; solubilize formulations of CoQ10 proved to be clearly superior to oily dispersions and crystalline CoQ10 in their overall bioavailability [93], but also CoQ10 lipid-based formulations with a novel colloid delivery system, known as "colloidal-Q10", have been shown to improve the enteral absorption and the bioavailability of CoQ10 [94].

In summary, our data analysis leads to some considerations: 1) most clinical trials evaluating potential benefits of CoQ10 supplementation in elderly are small and short-term studies; the most significant data were obtained from various arms and sub-analysis of a 4-year double-blind randomized placebo-controlled intervention trial, carried out among 443 Swedish citizens with long-term follow-up from 5 to 10 years [19-21]; 2) in several studies enrolled patients were not evermore homogeneous by age and health status; 3) in many studies CoQ10 was co-administered with other nutraceuticals or dietary supplements, particularly selenium but also n-3 fatty acids, monacolin K, policosanol, vitamins, folic acid, resveratrol and others; 4) although most commonly used CoQ10 dosage was 100-200 mg daily, in the different studies CoQ10 supplements were administered in considerably variable dosing regimens, from 20 mg up to 1800 mg daily and more; lower doses were used in studies involving co-administration of CoQ10 with other dietary supplements; 5) Ubiquinol, a reduced form of CoQ10 with increased polarity and better intestinal absorption

and bioavailability, was the most used in clinical trials but not evermore.

## CONCLUSION

Our data confirm the evidence that oral supplementation of CoQ10 can improve several aging-related clinical conditions and slow the deterioration in health-related quality of life; CoQ10 benefits seem linked primarily to its antioxidant properties. Therefore CoQ10 nutritional supplement could be useful in improving health status in elderly, but main limit to its efficacy seems linked to its oral absorption and relative low bioavailability. Dietary supplements of CoQ10 seem well tolerated and no toxicity was observed though some adverse effects, largely gastrointestinal, were observed with very high intake. Unfortunately, the clinical evidences are often poor and weak as well as conflicting, so that well standardized long-term and larger further studies will be needed, also to establish the most effective dosage and the most bioavailable formulation.

### *Authorship declaration*

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### *Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### *Financing*

The authors disclosed that they did not receive any grant during conduction or writing of this study.

## REFERENCES

- [1] Littarru GP, Tiano L. Bioenergetic and antioxidant properties of coenzyme Q10: recent developments. *Mol Biotechnol* 2007;37:31-7.
- [2] Kawamukai M. Biosynthesis of coenzyme Q in eukaryotes. *Biosci Biotechnol Biochem* 2016;80:23-33.
- [3] Kalen A, Appelkvist EL, Dallner G. Age-related changes in the lipid compositions of rat and human tissues. *Lipids* 1989;24:579-84.
- [4] Saini R. Coenzyme Q10: the essential nutrient. *J Pharm Bioallied Sci* 2011;3:466-7.

- [5] Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: a systematic review. *J Am Coll Cardiol* 2007;49:2231-7.
- [6] Garrido-Maraver J, Cordero MD, Oropesa-Ávila M, Fernández Vega A, de la Mata M, Delgado Pavón A, et al. Coenzyme q10 therapy. *Mol Syndromol* 2014;5:187-97.
- [7] Braillon A. Coenzyme Q10 and statin-induced myopathy--II. *Mayo Clinic Proc* 2015;90:420.
- [8] Pravst I, Zmitek K, Zmitek J. Coenzyme Q10 contents in foods and fortification strategies. *Critical Rev Food Sc iNutr* 2010;50:269-80.
- [9] Žmitek K, Pogačnik T, Mervic L, Žmitek J, Pravst I. The effect of dietary intake of coenzyme Q10 on skin parameters and condition: results of a randomised, placebo-controlled, double-blind study. *Biofactors* 2017;43:132-40.
- [10] De Luca C, Mikhal'chik EV, Suprun MV, Papacharalambous M, Truhanov AI, Korkina LG. Skin antiageing and systemic redox effects of supplementation with marine collagen peptides and plant-derived antioxidants: a single-blind case-control clinical study. *Oxid Med Cell Longev* 2016;2016:4389410.
- [11] Rona C, Vailati F, Berardesca E. The cosmetic treatment of wrinkles. *J Cosmet Dermat* 2004;3:26-34.
- [12] Chiu A, Kimball A. Topical vitamins, minerals and botanical ingredients as modulators of environmental and chronological skin damage. *Br J Dermatol* 2003;149:681-91.
- [13] Johansson P, Dahlström Ö, Dahlström U, Alehagen U. Improved health-related quality of life, and more days out of hospital with supplementation with selenium and coenzyme Q10 combined. Results from a double blind, placebo-controlled prospective study. *J Nutr Health Aging* 2015;19:870-7.
- [14] González-Guardia L, Yubero-Serrano EM, Delgado-Lista J, Perez-Martinez P, Garcia-Rios A, Marin C, et al. Effects of the Mediterranean diet supplemented with coenzyme q10 onmetabolomic profiles in elderly men and women. *J Gerontol A Biol Sci Med Sci* 2015;70:78-84.
- [15] Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, et al. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure. *JACC Heart Fail* 2014;2:641-49.
- [16] Sander S, Coleman CI, Patel AA, Kluger J, White CM. The impact of coenzyme Q10 on systolic function in patients with chronic heart failure. *J Card Fail* 2006;12:464-72.
- [17] Onur S, Niklowitz P, Jacobs G, Lieb W, Menke T, Döring F. Association between serum level of ubiquinol and NT-proBNP, a marker for chronic heart failure, in healthy elderly subjects. *Biofactors* 2015;41:35-43.
- [18] Johansson P, Dahlström Ö, Dahlström U, Alehagen U. Effect of selenium and Q10 on the cardiac biomarker NT-proBNP. *Scand Cardiovasc J* 2013;47:281-8.
- [19] Alehagen U, Johansson P, Björnstedt M, Rosén A, Dahlström U. Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzymeQ10 supplementation: a 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. *Int J Cardiol* 2013;167:1860-6.
- [20] Alehagen U, Alexander J, Aaseth J. Supplementation with selenium and coenzyme Q10 reduces cardiovascular mortality in elderly with low selenium status. A secondary analysis of a randomised clinical trial. *PLoS One* 2016;11:e0157541.
- [21] Alehagen U, Aaseth J, Johansson P. Reduced cardiovascular mortality 10 years after supplementation with selenium and coenzyme Q10 for four years: follow-up results of a prospective randomized double-blind placebo-controlled trial in elderly citizens. *PLoS One* 2015;10:e0141641.
- [22] Lee BJ, Huang YC, Chen SJ, Lin PT. Coenzyme Q10 supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with coronary artery disease. *Nutrition* 2012;28:250-5.
- [23] Lee BJ, Huang YC, Chen SJ, Lin PT. Effects of coenzyme Q10 supplementation on inflammatory markers (high-sensitivity C-reactive protein, interleukin-6, and homocysteine) in patients with coronary artery disease. *Nutrition* 2012;28:767-72.
- [24] Mirhashemi SM, Najafi V, Raygan F, Asemi Z. The effects of coenzyme Q10 supplementation on cardiometabolic markers in overweight type 2 diabetic patients with stable myocardial infarction: a randomized, double-blind, placebo-controlled trial. *ARYA Atheroscler* 2016;12:158-65.
- [25] Lee BJ, Tseng YF, Yen CH, Lin PT. Effects of coenzymeQ10 supplementation (300 mg/day) on antioxidation and anti-inflammation in coronary artery disease patients during statins therapy: a randomized, placebo-controlled trial. *Nutr J* 2013;12(1):142.
- [26] Lonrot K, Porsti I, Alho H, Wu X, Hervonen A, Tolvanen JP. Control of arterial tone after long-term coenzyme Q10 supplementation in senescent rats. *Br J Pharmacol* 1998;124:1500-6.
- [27] Langsjoen H, Langsjoen P, Willis R, Willis R, Folkers K. Usefulness of coenzyme Q10 in clinical cardiology: a long-term study. *Mol Aspects Med* 1994;15Suppl:s165-75.
- [28] Bagheri Nesami N, Mozaffari-Khosravi H, Najarzadeh A, Salehifar E. The Effect of Coenzyme Q10 Supplementation on Pro-Inflammatory Factors and Adiponectin in Mildly hypertensive patients: a randomized, double-blind, placebo-controlled trial. *Int J Vitam Nutr Res* 2015;85:156-64.
- [29] Cicero AF, Morbini M, Rosticci M, D'Addato S, Grandi E, Borghi C. Middle-Term dietary supplementation with red yeast rice plus coenzyme Q10 improves lipid pattern, endothelial reactivity and arterial stiffness in moderately hypercholesterolemic subjects. *Ann Nutr Metab* 2016;68:213-9.
- [30] Barrat E, Zair Y, Ogier N, Housez B, Vergara C, Maudet C, et al. A combined natural supplement lowers LDL cholesterol in subjects with moderate untreated hypercholesterolemia: a randomized placebo-controlled trial. *Int J Food Sci Nutr* 2013;64:882-9.
- [31] Hobbs T, Caso R, McMahon D, Nymark M. A novel, multi-ingredient supplement to manage elevated blood lipids in patients with no evidence of cardiovascular disease: a pilot study. *Altern Ther Health Med* 2014;20:18-23.
- [32] Skarlovnik A, Janić M, Lunder M, Turk M, Šabovič M. Coenzyme Q10 supplementation decreases statin-related mild-to-moderate muscle symptoms: a randomized clinical study. *Med Sci Monit* 2014;20:2183-8.
- [33] Fedacko J, Pella D, Fedackova P, Hänninen O, Tuomainen P, Jarcuska P, et al. Coenzyme Q(10) and selenium in statin-associated myopathy treatment. *Can J Physiol Pharmacol* 2013;91:165-70.
- [34] Taylor BA, Lorson L, White CM, Thompson PD. A randomized trial of coenzyme Q10 in patients with confirmed statin myopathy. *Atherosclerosis* 2015;238:329-35.
- [35] Bogsrud MP, Langslet G, Ose L, Arnesen KE, SmStuen MC, Malt UF, et al. No effect of combined coenzyme Q10 and selenium supplementation on atorvastatin-induced myopathy. *Scand Cardiovasc J* 2013;47:80-7.
- [36] Zhou XJ, Rakheja D, Yu X, Saxena R, Vaziri ND, Silva FG. The aging kidney. *Kidney Int* 2008;74:710-20.
- [37] O'Sullivan ED, Hughes J, Ferenbach DA. Renal Aging: causes and consequences. *J Am Soc Nephrol* 2017;28:407-20.
- [38] O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol* 2007;18:2758-65.
- [39] Cottone S, Lorito MC, Riccobene R, Nardi E, Mulè G, Buscemi S, et al. Oxidative stress, inflammation and cardiovascular disease in chronic renal failure. *J Nephrol* 2008;21:175-9.
- [40] Dounousi E, Papavasiliou E, Makedou A, Ioannou K, Katopodis KP, Tselepis A, et al. Oxidative stress is progressively enhanced with advancing stages of CKD. *Am J Kidney Dis* 2006;48:752-60.

- [41] Gokbel H, Turk S, Okudan N, Atalay H, Belviranli M, Gaipov A, et al. Effects of coenzyme Q10 supplementation on exercise performance and markers of oxidative stress in hemodialysis patients: a double-blind placebo-controlled crossover trial. *Am J Ther* 2016;23:e1736-43.
- [42] Yeung CK, Billings FT 4th, Claessens AJ, Roshanravan B, Linke L, Sundell MB, et al. Coenzyme Q10 dose-escalation study in hemodialysis patients: safety, tolerability, and effect on oxidative stress. *BMC Nephrol* 2015;16:183.
- [43] Barden A, O'Callaghan N, Burke V, Mas E, Beilin LJ, Fenech M, et al. n-3 fatty acid supplementation and leukocyte telomere length in patients with chronic kidney disease. *Nutrients* 2016;8:175.
- [44] Pirro M, Mannarino MR, Bianconi V, Simental-Mendía LE, Bagaglia F, Mannarino E, et al. The effects of a nutraceutical combination on plasma lipids and glucose: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res* 2016;110:76-88.
- [45] Mehrdadi P, Kolahdouz Mohammadi R, Alipoor E, Eshraghian MR, Esteghamati A, Hosseinzadeh-Attar MJ. The Effect of coenzyme Q10 supplementation on Circulating levels of novel adipokine adipolin/CTRP12 in overweight and obese patients with type 2 diabetes. *Exp Clin Endocrinol Diabetes* 2017;125:156-62.
- [46] Moazen M, Mazloom Z, Ahmadi A, Dabbaghmanesh MH, Roosta S. Effect of coenzyme Q10 on glycaemic control, oxidative stress and adiponectin in type 2 diabetes. *J Pak Med Assoc* 2015;65:404-8.
- [47] Kolahdouz Mohammadi R, Hosseinzadeh-Attar MJ, Eshraghian MR, Nakhjavani M, Khorami E, Esteghamati A. The effect of coenzyme Q10 supplementation on metabolic status of type 2 diabetic patients. *Minerva Gastroenterol Dietol* 2013;59:231-6.
- [48] Domanico D, Fragiotta S, Cutini A, Carnevale C, Zompatori L, Vingolo EM. Circulating levels of reactive oxygen species in patients with nonproliferative diabetic retinopathy and the influence of antioxidant supplementation: 6-month follow-up. *Indian J Ophthalmol* 2015;63:9-14.
- [49] Raygan F, Rezavandi Z, Dadkhah Tehrani S, Farrokhan A, Asemi Z. The effects of coenzyme Q10 administration on glucose homeostasis parameters, lipid profiles, biomarkers of inflammation and oxidative stress in patients with metabolic syndrome. *Eur J Nutr* 2016;55:2357-64.
- [50] Beal MF. Coenzyme Q10 administration and its potential for treatment of neurodegenerative diseases. *Biofactors* 1999;9:261-6.
- [51] Galpern WR, Cudkovic ME. Coenzyme Q treatment of neurodegenerative diseases of aging. *Mitochondrion* 2007;7Suppl:S146-53.
- [52] Beal MF. Coenzyme Q10 as a possible treatment for neurodegenerative diseases. *Free Radic Res* 2002;36:455-60.
- [53] Wadsworth TL, Bishop JA, Pappu AS, Woltjer RL, Quinn JF. Evaluation of coenzyme Q as an antioxidant strategy for Alzheimer's disease. *J Alzheimers Dis* 2008;14:225-34.
- [54] Shults CW. Coenzyme Q10 in neurodegenerative diseases. *Curr Med Chem* 2003;10:1917-21.
- [55] Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, et al. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Arch Neurol* 2002;59:1541-50.
- [56] Müller T, Büttner T, Gholipour AF, Kuhn W. Coenzyme Q10 supplementation provides mild symptomatic benefit in patients with Parkinson's disease. *Neurosci Lett* 2003;341:201-4.
- [57] Thomas B, Beal MF. Parkinson's disease. *Hum Mol Genet* 2007;16 Spec No.2:R183-94.
- [58] Henchcliffe C, Beal MF. Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. *Nat Clin Pract Neurol* 2008;4:600-9.
- [59] Sutachan JJ, Casas Z, Albarracín SL, Stab BR 2nd, Samudio I, Gonzalez J, et al. Cellular and molecular mechanisms of antioxidants in Parkinson's disease. *Nutr Neurosci* 2012;15:120-6.
- [60] Beal MF. Therapeutic approaches to mitochondrial dysfunction in Parkinson's disease. *Parkinsonism Relat Disord* 2009;15Suppl3:S189-94.
- [61] Yoritaka A, Kawajiri S, Yamamoto Y, Nakahara T, Ando M, Hashimoto K, et al. Randomized, double-blind, placebo-controlled pilot trial of reduced coenzyme Q10 for Parkinson's disease. *Parkinsonism Relat Disord* 2015;21:911-6.
- [62] Li Z, Wang P, Yu Z, Cong Y, Sun H, Zhang J, et al. The effect of creatine and coenzyme q10 combination therapy on mild cognitive impairment in Parkinson's disease. *Eur Neurol* 2015;73:205-11.
- [63] Parkinson Study Group QE3 Investigators, Beal MF, Oakes D, et al. A randomized clinical trial of high-dosage coenzyme Q10 in early Parkinson disease: no evidence of benefit. *JAMA Neurol* 2014;71:543-52.
- [64] Storch A, Jost WH, Vieregge P, Spiegel J, Greulich W, Durner J, et al. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q(10) in Parkinson disease. *Arch Neurol* 2007;64:938-44.
- [65] Negida A, Menshawy A, El Ashal G, Elfouly Y, Hani Y, Hegazy Y, et al. Coenzyme Q10 for patients with Parkinson's disease: a systematic review and meta-analysis. *CNS Neurol Disord Drug Target* 2016;15:45-53.
- [66] Zhu ZG, Sun MX, Zhang WL, Wang WW, Jin YM, Xie CL. The efficacy and safety of coenzyme Q10 in Parkinson's disease: a meta-analysis of randomized controlled trials. *Neurol Sci* 2017;38:215-24.
- [67] Shoshan-Barmatz V, Nahon-Crystal E, Shteinifer-Kuzmine A, Gupta R. VDAC1, mitochondrial dysfunction, and Alzheimer's disease. *Pharmacol Res* 2018;131:87-101.
- [68] Ishrat T, Khan MB, Hoda MN, Yousuf S, Ahmad M, Ansari MA, et al. Coenzyme Q10 modulates cognitive impairment against intracerebroventricular injection of streptozotocin in rats. *Behav Brain Res* 2006;171:9-16.
- [69] Choi H, Park HH, Koh SH, Choi NY, Yu HJ, Park J, et al. Coenzyme Q10 protects against amyloid  $\beta$ -induced neuronal cell death by inhibiting oxidative stress and activating the P13K pathway. *Neurotoxicology* 2012;33:85-90.
- [70] Ha AD, Fung VS. Huntington's disease. *Curr Opin Neurol* 2012;25:491-8.
- [71] Jodeiri Farshbaf M, Ghaedi K. Huntington's disease and mitochondria. *Neurotox Res* 2017;32:518-29.
- [72] Huntington Study Group. A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. *Neurology* 2001;57:397-404.
- [73] McGarry A, McDermott M, Kieburtz K, de Blicke EA, Beal F, Marder K, et al. A randomized, double-blind, placebo-controlled trial of coenzyme Q10 in Huntington disease. *Neurology* 2017;88:152-9.
- [74] Bartsch H, Nair J. Chronic inflammation and oxidative stress in the genesis and perpetuation of cancer: role of lipid peroxidation, DNA damage, and repair. *Langenbecks Arch Surg* 2006;391:499-510.
- [75] Akinobu T, Kazuhide Y. Control of oxidative stress in hepatocellular carcinoma: Helpful or harmful? *World J Hepatol* 2015;7:968-79.
- [76] Leufkens AM, van Duijnhoven FJ, Woudt SH, Siersema PD, Jenab M, Jansen EH, et al. Biomarkers of oxidative stress and risk of developing colorectal cancer: a cohort-nested case-control study in the European Prospective Investigation Into Cancer and Nutrition. *Am J Epidemiol* 2012;175:653-63.
- [77] Jolliet P, Simon N, Barre J, Pons JY, Boukef M, Paniel BJ, et al. Plasma coenzyme Q10 concentrations in breast Cancer; prognosis and therapeutic consequences. *Int J Clin Pharmacol Ther* 1998;36:506-9.
- [78] Palan PR, Mikhail MS, Shaban DW, Romney SL. Plasma concentrations of coenzyme Q10 and tocopherols in cervical intraepithelial neoplasia and cervical cancer. *Eur J Cancer Prev* 2003;12:321-6.

- [79] Rusciani L, Proietti I, Rusciani A, Paradisi A, Sbordoni G, Alfano C, et al. Low plasma coenzyme Q10 levels as an independent prognostic factor for melanoma progression. *J Am Acad Dermatol* 2006;54:234-41.
- [80] Gutierrez-Mariscal FM, Perez-Martinez P, Delgado-Lista J, Yubero-Serrano EM, Camargo A, Delgado-Casado N, et al. Mediterranean diet supplemented with coenzyme Q10 induces postprandial changes in p53 in response to oxidative DNA damage in elderly subjects. *Age (Dordr)* 2012;34:389-403.
- [81] Kantor ED, Ulrich CM, Owen RW, Schmezer P, Neuhouser ML, Lampe JW, et al. Specialty supplement use and biologic measures of oxidative stress and DNA damage. *Cancer Epidemiol Biomarkers Prev* 2013;22:2312-22.
- [82] Gutierrez-Mariscal FM, Yubero-Serrano EM, Rangel-Zúñiga OA, Marín C, García-Rios A, Perez-Martinez P, et al. Postprandial activation of p53-dependent DNA repair is modified by Mediterranean diet supplemented with coenzyme Q10 in elderly subjects. *J Gerontol A Biol Sci Med Sci* 2014;69:886-93.
- [83] Iarussi D, Auricchio U, Agretto A, Murano A, Giuliano M, Casale F, et al. Protective effect of coenzyme Q10 on anthracycline cardiotoxicity: control study in children with acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Mol Aspects Med* 1994;15(suppl):S207-S212.
- [84] Roffe L, Schmidt, K, Ernst E. Efficacy of coenzyme Q10 for improved tolerability of cancer treatments; a systematic review. *J Clin Oncol* 2004;22:4418-24.
- [85] Hill GJ, Shriver BJ, Arnett DB. Examining intentions to use CoQ10 amongst breast cancer patients. *Am J Health Behav* 2006;30:313-21.
- [86] Lesser GJ, Case D, Stark N, Williford S, Giguere J, Garino LA, et al. A randomized, double-blind, placebo-controlled study of oral coenzyme Q10 to relieve self-reported treatment-related fatigue in newly diagnosed patients with breast cancer. *J Support Oncol* 2013;11:31-42.
- [87] Spigset O. Reduced effect of warfarin caused by ubiquinol. *Lancet* 1994;344:1372-3.
- [88] Zhou Q, Zhou S, Chan E. Effect of coenzyme Q10 on warfarin hydroxylation in rat and human liver microsomes. *Curr Drug Metab* 2005;6:67-81.
- [89] Shalansky S, Lynd L, Richardson K, Ingaszewski A, Kerr C. Risk of warfarin-related bleeding events and supratherapeutic international normalized ratios associated with complementary and alternative medicine: a longitudinal analysis. *Pharmacotherapy* 2007;27:1237-47.
- [90] Bhagavan HN, Chopra RK. Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radic Res* 2006;40:445-53.
- [91] Zmitek J, Smidovnik A, Fir M, Prosek M, Zmitek K, Walczak J, et al. Relative bioavailability of two forms of a novel water-soluble coenzyme Q10. *Ann Nutr Metab* 2008;52:281-7.
- [92] Bhagavan HN, Chopra RK. Plasma coenzyme Q10 response to oral ingestion of coenzyme Q10 formulations. *Mitochondrion* 2007;7 Suppl:S78-88.
- [93] Schulz C, Obermüller-Jevic UC, Hasselwander O, Bernhardt J, Biesalski HK. Comparison of the relative bioavailability of different coenzyme Q10 formulations with a novel solubilizate (Solu Q10). *Int J Food Sci Nutr* 2006;57:546-55.
- [94] Liu ZX, Artmann C. Relative bioavailability comparison of different coenzyme Q10 formulations with a novel delivery system. *Altern Ther Health Med* 2009;15:42-6.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Myocysticercosis: an unusual presentation in sternocleidomastoid muscle diagnosed by high frequency ultrasonography

Mohd Ilyas<sup>ORCID</sup>, Arshad Bhat<sup>ORCID</sup>

Department of Radiodiagnosis, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India

DOI: 10.18621/eurj.384825

## ABSTRACT

Myocysticercosis is rare disorder and in particular the involvement of the neck muscles is much rarer. A rare case of myocysticercosis involving the right sternocleidomastoid muscle is presented with ultrasonographic demonstration of the nidus and associated edema.

**Keywords:** myocysticercosis, sternocleidomastoid muscle, high frequency ultrasonography

*Received: January 27, 2018; Accepted: May 2, 2018; Published Online: May 29, 2018*

Cysticercosis is caused by the larval form of the pork tapeworm, *Taenia solium*. The most common sites involved are brain, spinal cord, soft tissues, orbit and skeletal muscles. Although muscular involvement is not that uncommon but the involvement of neck muscles especially isolated involvement of sternocleidomastoid is a rare and uncommon presentation.

## CASE PRESENTATION

A 26-year-old male patient was referred for high frequency ultrasonography for soft tissue swelling in the right sternocleidomastoid muscle (SCM) region. The patient's blood profile didn't reveal any abnormality. There was no history of fever and malaise. On clinical examination, the swelling was firm, separate from the skin and not separate from SCM muscle. Clinically the differentials included lipoma, sebaceous cyst, abscess, hematoma,

neurofibroma, pseudotumor, parasitic cyst and enlarged lymph node. Using 12 MHz transducer, the swelling was scanned which revealed a hyperechoic focus suggestive of nidus and hypo to isoechoic in the middle of right SCM muscle with surrounding hypoechoic fluid echogenicity area suggestive of edema (Figures 1 and 2) (Video 1). The radiological differentials included myocysticercosis, and cystic peripheral nerve sheath tumour. The radiological study helped to rule out abscess, lipoma, hematoma (additionally there was no history of trauma) and other differentials as each of these conditions has a peculiar radiological appearance. The left SCM muscle was also evaluated using high frequency sonography but no abnormality was found. CT head was done (to rule out neurocysticercosis) which didn't reveal any abnormality. Preliminary diagnosis of isolated SCM myocysticercosis was made and patient referred for fine needle aspiration cytology (FNAC). The FNAC results showed polymorphonuclear infiltrate with occasional giant cells and palisading histiocytes with



Address for correspondence: Mohd Ilyas, MD., Sher-i-Kashmir Institute of Medical Sciences, , Department of Radiodiagnosis, Srinagar, India  
E-mail: ilyasmir40@gmail.com, Tel: +91 941 9561234

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>



Figure 1. USG image depicting hyperechoic nidus and surrounding edema and scolex.

a part of scolex. The patient was given albendazole for 4 weeks and repeat scan done which showed marked resolution of edema.

**DISCUSSION**

Cysticercosis is caused by the encysted (metacestode) larvae of the tapeworm *T. solium*, which

develop after ingestion of eggs in undercooked pork or faeco-oral transmission between humans. Larvae are disseminated by hematogenous spread to neural, muscular and ocular tissues. Humans act as definitive host while the pigs act as intermediate host. The disease is endemic in virtually all developing countries, in Central and South America, Asia and Africa with the exception of Muslim countries where pork is not consumed. The perpetuation of this

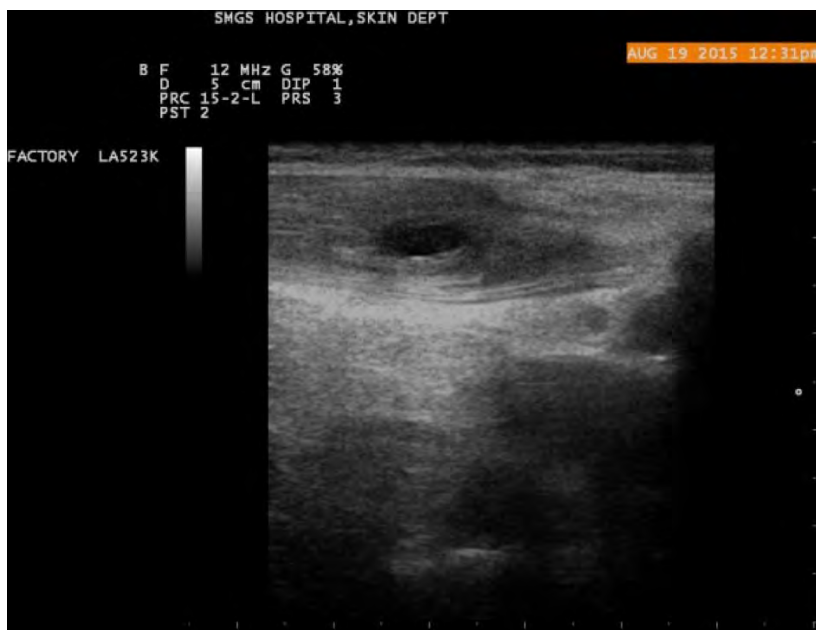
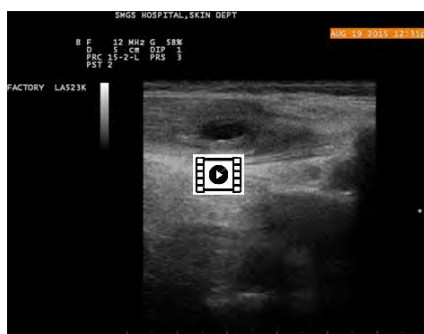


Figure 2. Demonstration of the associated edema.



**Video 1.** Video recording showing the surrounding normal structures and vessels and cysticercus focus.

parasitic disease is related to poor hygiene and sanitation [1]. Cysticercosis is the most common parasitic infection of the soft tissues and muscles. It can affect various other organs including the brain, spinal cord, orbit, muscle, subcutaneous tissue and heart [2]. If the eggs contaminate food sources upon ingestion they develop into larvae and result in cysticercosis. Hence, even people who doesn't consume pork, including vegetarians can develop cysticercosis. Muscular cysticercosis is uncommon in head and neck region with exception of orbital cysticercosis. It may present clinically with myalgia, pseudotumor, mass or as pseudohypertrophy which may be misdiagnosed as lipoma, epidermoid cyst, abscess, pyomyositis, tubercular lymphadenitis, neuroma, neurofibroma, sarcoma, myxoma, ganglion or fat necrosis [3]. High frequency ultrasonography is the initial and most reliable diagnostic modality for a soft tissue swelling [4]. CT scan and MRI can also be used for the diagnosis but due to expensiveness, especially in developing countries people can't afford. Imaging methods CT and USG are equally effective in identifying the cyst and the scolex [5]. The treatment of myocysticercosis depends upon location. Surgical excision is done for isolated skeletal muscle cysticercosis associated with abscess but those not associated with abscess can be treated with antihelminthic drugs with a follow-up USG at 3 weeks to check for resolution. Three types of USG presentation can be there [6];

- a. Cyst with scolex without surrounding edema (most common).
- b. Cyst with scolex and surrounding edema (as in the present case).
- c. Irregular cyst with no scolex and with surrounding edema (least common).

In the present case, as there was no abscess formation, antihelminthic was prescribed and follow-up USG done at 4 weeks post-treatment wherein marked resolution of the edema was seen.

## CONCLUSION

Although myocysticercosis is a common manifestation but involvement of muscles (sternocleidomastoid in the present case) is a rare presentation. All the three presentations on USG should be kept in mind whenever a soft tissue swelling is evaluated by USG. Cysticercosis should always be part of the differential diagnosis of subcutaneous and intramuscular swellings in endemic countries like India. USG is a good modality, inexpensive and easily available tool for diagnosis of myocysticercosis. Whenever dealing with a neck swelling, the parasitic aetiology should be always kept in mind.

### Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### Informed consent

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

### Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.



## REFERENCES

- [1] Hawk MW, Shahlaia K, Kim KD, Theis JH. Neurocysticercosis: a review. *Surg Neurol* 2005;63:123-32.
- [2] Mittal A, Das D, Aiyer N, Nagaraj J, Gupta M. Masseter cysticercosis - a rare case diagnosed on ultrasound. *Dentomaxillofac Radiol* 2008;37:113-6.
- [3] Jhankaria BG, Chauhan GB, Krishnan P, Jhankaria B. MRI and ultrasound in solitary muscular and soft tissue cysticercosis. *Skeletal Radiol* 2005;34:722-6.
- [4] Smiti S, Sripathi H, Naik L. Unusual location of cysticercus lesions in soft tissue - report of three cases. *Indian J Radiol Imaging* 2003;13:157-8.
- [5] Kraft R. Cysticercosis: an emerging parasitic disease. *Am Fam Physician* 2007;76:91-6.
- [6] Naik D, Srinath MG, Kumar A. Soft tissue cysticercosis-ultrasonographic spectrum of the disease. *Indian J Radiol Imaging* 2011;21:60-2.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Cornual heterotopic pregnancy after *in vitro* fertilization: management by laparoscopic repair

Nur Dokuzeylül Güngör<sup>ORCID</sup>, Tuğba Gürbüz<sup>ORCID</sup>

Department of Gynecology and Obstetrics, Medical Park Göztepe Hospital, İstanbul, Turkey

DOI: 10.18621/eurj.376498

## ABSTRACT

The incidence of heterotopic pregnancy has risen dramatically with the widespread use of assisted reproductive technology. The risk factors for this pathology include tubal infertility, cleavage stage embryo transfer and frozen embryo transfer. Herein we report two cases with cornual heterotopic pregnancy after *in vitro* fertilization/embryo transfer. They managed by laparoscopic cornual repair or salpingectomy. Early diagnosis and appropriate management of heterotopic pregnancy may lead to a favorable prognosis.

**Keywords:** Cornual heterotopic pregnancy, *in vitro* fertilization, laparoscopic cornual repair

*Received: January 9, 2018; Accepted: February 22, 2018; Published Online: May 26, 2018*

**E**ctopic pregnancy is still a leading cause of maternal mortality in the first trimester of pregnancy. The co-existence of an ectopic pregnancy with a viable intrauterine pregnancy is known as heterotopic pregnancy affecting about 1% of patients during assisted conception [1, 2].

Cornual pregnancy is a rare entity, representing 2% of ectopic pregnancy. Its management is difficult and manipulated according to clinical situation. A history of tubal infertility, pelvic inflammatory disease and specific aspects of embryo transfer technique are the most significant risk factors for heterotopic pregnancy [1]. Recent advances in imaging modalities have led to the early and accurate diagnosis of non-tubal ectopic pregnancy. The combination of ultrasound (USG) and serum beta human chorionic gonadotrophin ( $\beta$ -hCG) is the most reliable tool for diagnosis.

Herein we presented two cases of cornual pregnancy coexisting with intrauterine pregnancy.

## CASE PRESENTATION

### Case 1

A 32-year-old primipara, who had two previous intrauterine inseminations (IUI) and two intracytoplasmic sperm injection (ICSI) at another clinic was referred to our clinic for a second opinion. She had loss of two pregnancies before 8<sup>th</sup> week of gestation. She had been undergoing infertility treatment for nine years. Clinical information received from the previous clinic included: semen analysis, within normal limits hysterosalpingography (HSG), patent left Fallopian tube and peritubal adhesions on right side. Serum hormone levels were within normal limits (On Day 3, follicle-stimulating hormone: 8.3 IU/L, luteinizing hormone: 2.5 IU/L, prolactin: 16.3 ng/ml; On Day 21, progesterone: 15.6 ng/ml, AMH: 2.4 ng/ml). She had hypothyroidism, and was taking anti-thyroid drugs for six years. Chromosomal analysis was normal for the couple. Before the ICSI,



Address for correspondence: Tuğba Gürbüz, MD., Medical Park Göztepe Hospital, Department of Gynecology and Obstetrics, İstanbul, Turkey  
E-mail: drtgurbuz@hotmail.com, Tel: +90 532 3283523

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>



**Figure 1.** USG appearance of the first case.

we decided to perform laparoscopy and hysteroscopy to rule out any mechanical obstacle for implantation.

During laparoscopy there was a hydrosalpinx on right side and we did cornual blockage. Hysteroscopy was normal. The patient underwent ICSI in our clinic. The ovarian stimulation was performed with antagonist protocol initiated with 225 IU recombinant FSH/day. Six ova were harvested, and all were fertilized via ICSI. Although semen analysis was previously reported as normal, ICSI was performed during the *in vitro* fertilization (IVF)/ICSI cycle due to a low motility (< 22%) found during that cycle.

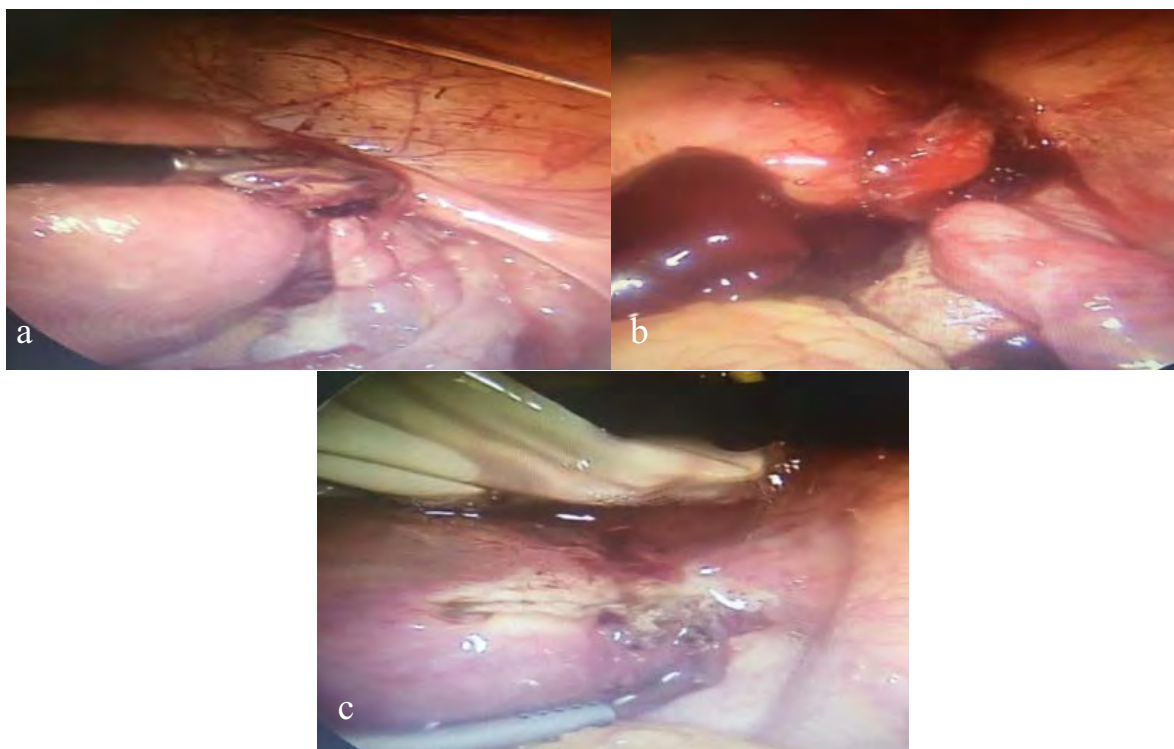
On day 5, two embryo transfers were done under ultrasound guidance with a soft-tipped catheter. The endometrial thickness was 11 mm, and the embryos were expelled into the uterine cavity approximately 1 cm from the uterine fundus with good visualization. A subsequent pregnancy test was positive, and the serum  $\beta$ -HCG was 75 IU/L at 4 weeks 0 days of gestation from embryo transfer (post-OPU 14 days). Two days later we checked the serum  $\beta$ -HCG level again which was 151 IU/L.

USG was performed and a gestational sac (GS) was located in the uterus at sixth week of gestation. One week later, she came to our clinic with vaginal bleeding and abdominal discomfort. Intraabdominal bleeding was diagnosed during USG. Also there was an intrauterine 7 weeks of pregnancy with heartbeat, and a cornual pregnancy was detected (Figure 1). We performed laparoscopic cornual repair (Figure 2a-c).

Intrauterine pregnancy has continued and she gave a live birth at term by cesarean section.

### Case 2

A 40-year-old multipara who had four previous ICSI at another clinic was referred to our clinic for a new trial due to male infertility. She had an 8 years old boy with motor mental retardation because of a perinatal asphyxia and a 2-years old healthy girl achieved by ICSI. She has two cesarean sections previously. Hormone profile and HSG were normal. We give antagonist protocol and picked up 7 oocytes. Under ultrasound guidance, we gave 2 embryos on day 4.  $\beta$ -hCG was 38 IU/L after oocyte pick up on 14<sup>th</sup> day. Two days later it increased 157 IU/L. We saw the patient at 6<sup>th</sup> week of gestation and detected intrauterine pregnancy with heartbeat. At 11<sup>th</sup> week of gestation she admitted to hospital with severe abdominal pain and hypotension. During USG there was an intraabdominal bleeding and a gestational sac with fetal heart beat on the left corn. Laparoscopy was performed on vital indication with excision of the ruptured hemorrhagic left cornual pregnancy. There was no problem during the postoperative course. The intrauterine pregnancy viability was confirmed postoperatively, and she was discharged on her first postoperative day. The intrauterine pregnancy continued uneventfully. A healthy girl was delivered by cesarean section.



**Figure 2.** Laparoscopic appearances of the case (a, b and c).

## DISCUSSION

The literature review demonstrates that cornual pregnancy is a very rare condition and more likely when additional risk factors for ectopic pregnancies are present, such as hydrosalpinges, blocked tubes, endometriosis, fibroids or prior tubal ectopic pregnancies.

Cornual pregnancy occurs in an area in which a rich blood supply is provided by the vascular anastomosis of the uterine and ovarian arteries [3]. Because of this mortality and morbidity occur more frequently [4].

Recently, the diagnosis of ectopic pregnancy has been possible before rupture because of improvements in USG and early sensitive serum  $\beta$ -hCG measurements [5]. Heterotopic pregnancy diagnosis is sometimes very difficult for clinicians because of widely, varying clinical features. Although timely diagnosis of heterotopic pregnancy must be done urgently, it remains challenging. Clinical manifestations of heterotopic pregnancy include abdominal pain and vaginal bleeding, and are also observed in intrauterine pregnancy. Treatment options

of heterotopic pregnancy are surgery, medical treatment, and expectant management for maintaining intrauterine pregnancy.

Most women with heterotopic pregnancy present with hemodynamic instability because of rupture. Therefore, surgery could be the first option with these patients. Laparoscopic suturing is a controversial issue for cornual pregnancies. If a myometrial gap results from evacuation of the cornual pregnancy, the gap requires suture closure to minimize the risk of uterine rupture with intrauterine pregnancy [6].

The main concern with laparoscopic treatment of cornual pregnancy is the subsequent risk of uterine rupture and recurrence of the cornual ectopic pregnancy [7]. A number of uneventful pregnancies have been reported in addition to instances where uterine rupture or subsequent heterotopic pregnancy have occurred [8-11].

Careful individualized antenatal care and planned cesarean delivery at term (>37 weeks) appear to be the safest approach in these cases during future pregnancies [12].

It is advisable that a transvaginal USG should be performed at 5 to 6 weeks gestation in the subsequent

pregnancy to rule out a recurrence of cornual pregnancy [13].

It is difficult to discover an ectopic pregnancy during a spontaneous pregnancy, but, for a patient who presents regularly at a hospital during early gestation, early diagnosis is facilitated.

First case was very likely to be misdiagnosed as an intrauterine normal (75 IU/L). However, the literature contains a report of a ruptured ectopic pregnancy with an  $\beta$ -hCG level of <10 IU/L [14]. Thus, we must keep the possibility of an ectopic pregnancy in mind at all times, even if the  $\beta$ -hCG titer is very low. The bleeding 7 days after the diagnosis of pregnancy was misdiagnosed as threatened abortion via a telephone conversation; however, it was actually due to cornual pregnancy. This situation can often occur during a normal pregnancy. An intrauterine gestational sac was detected when the patient presented at our clinic 12 days after the first positive  $\beta$ -hCG level. Based on the day of transfer, a yolk sac has been observed within the echogenic area. The risk of heterotopic pregnancy after IVF/ICSI is increased by the number of embryos [15, 16].

As a mechanism for heterotopic pregnancy by IVF/ICSI, aspects of the transfer that may increase the risk of ectopic pregnancy include a large volume of transfer media, induction of abnormal uterine contractions, and the location of the embryo transfer in relation to the uterine fundus [5]. The endometrial thickness was also linked to an increased risk of ectopic pregnancy [17]. Thus, it may be that heterotopic pregnancy may occur when some factors are present at the same time.

However, no gold standard has yet been defined and data regarding recurrence of cornual pregnancies in subsequent pregnancies after different treatments are sparse [18].

## CONCLUSION

These two cases were a rare occurrence, and can occur even in cases where the index of suspicion would be theoretically low. The incidence of heterotopic pregnancy has risen dramatically with the widespread use of assisted reproductive technology. Early diagnosis and appropriate management of heterotopic pregnancy may lead to a favorable prognosis.

Laparoscopic cornual repair appears to be an effective treatment in this condition.

### Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### Informed consent

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

### Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Talbot K, Simpson R, Price N, Jackson SR. Heterotopic pregnancy. *J Obstet Gynaecol* 2011;31:7-12.
- [2] Felekis T, Akrivis C, Tsirkas P, Korkontzelos I. Heterotopic triplet pregnancy after *in vitro* fertilization with favorable outcome of the intrauterine twin pregnancy subsequent to surgical treatment of the tubal pregnancy. *Case Rep Obstet Gynecol* 2014;2014:356131.
- [3] Ehrenberg-Buchner S, Sandadi S, Moawad NS, Pinkerton JS, Hurd WW. Ectopic pregnancy: role of laparoscopic treatment. *Clin Obstet Gynecol* 2009;52:372-9.
- [4] Berretta R, Merisio C, Dall'Asta A. Conservative treatment for interstitial monochorionic twin pregnancy. *J Obstet Gynaecol Res* 2014;40:829-32.
- [5] Refaat B, Dalton E, Ledger WL. Ectopic pregnancy secondary to *in vitro* fertilisation-embryo transfer: pathogenic mechanisms and management strategies. *Reprod Biol Endocrinol* 2015;13:30.
- [6] Moawad NS, Mahajan ST, Moniz MH. Current diagnosis and treatment of interstitial pregnancy. *Am J Obstet Gynecol* 2010;202:15-29.
- [7] Ng S, Hamontri S, Chua I, Chern B, Siow A. Laparoscopic management of 53 cases of cornual ectopic pregnancy. *Fertil Steril* 2009;92:448-52.
- [8] Vilos GA. Laparoscopic resection of a heterotopic cornual pregnancy followed by term vaginal delivery. *J Am Assoc Gynecol Laparosc* 1995;2:471-3.
- [9] Sagiv R, Golan A, Arbel-Alon S, Glezerman M. Three conservative approaches to treatment of interstitial pregnancy. *J Am Assoc Gynecol Laparosc* 2001;8:154-8.
- [10] Weissman A, Fishman A. Uterine rupture following conservative surgery for interstitial pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1992;44:237-9.
- [11] Downey GP, Tuck SM. Spontaneous uterine rupture during subsequent pregnancy following non-excision of an interstitial ectopic gestation. *Br J Obstet Gynaecol* 1994;101:162-3.
- [12] Radwan F, Martin S. Management of corneal (interstitial)

pregnancy. *Obstet Gynecol* 2007;9:249-55.

[13] Moawad NS, Mahajan ST, Moniz MH, Taylor SE, Hurd WW. Current diagnosis and treatment of interstitial pregnancy. *Am J Obstet Gynecol* 2010;202:15-29.

[14] Fu J, Henne MB, Blumstein S, Lathi RB. Rupture of ectopic pregnancy with minimally detectable beta-human chorionic gonadotropin levels: a report of 2 cases. *J Reprod Med* 2007;52:541-2.

[15] Bu Z, Xiong Y, Wang K, Sun Y. Risk factors for ectopic pregnancy in assisted reproductive technology: a 6-year, single-center study. *Fertil Steril* 2016;106:90-4.

[16] Yanaihara A, Yorimitsu T, Motoyama H, Ohara M, Kawamura T. Clinical outcome of frozen blastocyst transfer; single vs. double transfer. *J Assist Reprod Genet* 2008;25:531-4.

[17] Rombauts L, McMaster R, Motteram C, Fernando S. Risk of ectopic pregnancy is linked to endometrial thickness in a retrospective cohort study of 8120 assisted reproduction technology cycles. *Human Reprod* 2015;30:2846-52.

[18] Egger E. Recurrent interstitial pregnancy: a review of the literature. *Geburtsh Frauenheilk* 2017;77:335-9.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Things to keep in mind after cardiopulmonary resuscitation: bilateral severe and widespread subcutaneous emphysema together with unilateral pneumothorax

Timuçin Alar<sup>ORCID</sup>, İsmail Ertuğrul Gedik<sup>ORCID</sup>

Department of Thoracic Surgery, Onsekiz Mart University School of Medicine, Çanakkale, Turkey

DOI: 10.18621/eurj.396685

## ABSTRACT

Cardiopulmonary resuscitation (CPR) can cause severe complications such as rib and sternal fracture, pneumothorax or hemothorax. In this article, we report a case of widespread and severe bilateral subcutaneous emphysema and unilateral iatrogenic pneumothorax that does not correlate with the severity of the emphysema that occurred after active CPR.

**Keywords:** Cardiopulmonary resuscitation, pneumothorax, emphysema

*Received: February 19, 2018; Accepted: June 3, 2018; Published Online: June 20, 2018*

Cardiopulmonary resuscitation (CPR) is a life-saving maneuver but it can also damage the chest wall and cause severe complications. The incidence of rib fractures during CPR varies between 13-97%. In addition, it is known that the incidence of sternal fracture changes between 1 and 43% during CPR [1]. Pneumothorax, which is a known complication of rib fractures, has also been reported among the complications of CPR [1, 2].

In this article, we report a case of widespread and severe bilateral subcutaneous emphysema and unilateral iatrogenic pneumothorax that does not correlate with the severity of the emphysema that occurred after active CPR.

## CASE PRESENTATION

A 79-year-old female patient has presented to a medical center with the complaint of palpitation.

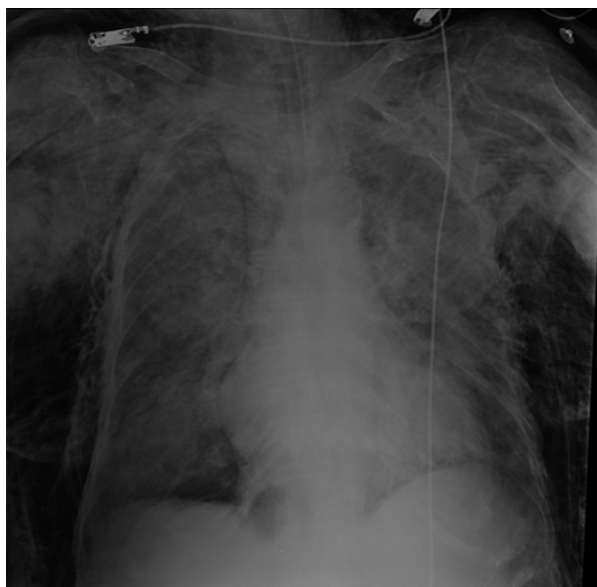
During initial physical examination, she has developed cardiopulmonary arrest. Active CPR has been performed for 20 minutes and the patient responded to CPR. She has been re-examined during the post-CPR period and referred to our hospital with the finding of extensive subcutaneous emphysema. The patient developed cardiopulmonary arrest again in our emergency department and active CPR was applied for 10 minutes. The patient responded to the second CPR as well and was consulted to our clinics. On the physical examination, the patient was unconscious and her pupils were dilated. She had widespread subcutaneous emphysema on the eyelids, around the neck, frontal wall of the chest and abdomen. Her lung auscultation revealed diminished respiratory sounds on the right lung. Postero-anterior chest X-ray and chest computed tomography (CT) revealed minimal pleural effusion bilaterally, fractures of the 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> ribs on the right, 2<sup>nd</sup> and 3<sup>rd</sup> ribs on the left, bilateral common subcutaneous emphysema with



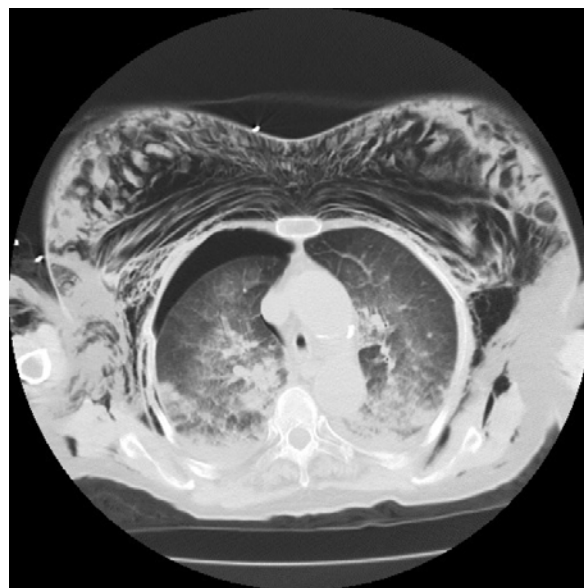
**Address for correspondence:** Timuçin Alar, MD., Assoc. Prof., Onsekiz Mart University School of Medicine, Department of Thoracic Surgery, Çanakkale, Turkey  
E-mail: timucinalar@gmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>



**Figure 1.** Chest X-ray showing bilateral multiple ribs fractures and widespread subcutaneous emphysema.



**Figure 2.** Computed tomography scan showing bilateral widespread subcutaneous emphysema with pneumothorax of the right lung and bilateral ribs fractures with bilateral pleural effusion

pneumothorax of the right lung (Figures 1 and 2). The patient underwent urgent tube thoracostomy through the intersection of second intercostal space and mid-clavicular line on the right with 28 Fr drain. There was plenty of air and 100 cc sero-hemorrhagic drainage. After the procedure, the patient who was planned to be hospitalized in the intensive care unit (ICU) was referred to another center by ambulance due to lack of unoccupied ICU rooms.

## DISCUSSION

It is argued that in order for an active CPR to be effective, approximately 5-6 cm of chest compression should be applied and 100-120 compressions should be performed per minute [3]. Thus, patients who had CPR are exposed to intense forces on the chest and are severely traumatized. For this reason, physicians should not overlook the possibility that complications of chest trauma such as rib fractures and hemo-pneumothorax can also be seen after active CPR. There are also publications supporting this argument [3, 4]. It is also reported that especially elderly and women are more susceptible to CPR-related injuries [5]. Our case is compatible with these publications in terms of age and the development of unilateral multiple rib fractures.

Although there are not many publications about the development of pneumothorax after CPR, this condition has been reported as a complication of CPR [6, 7]. This complication can be developed with or without rib fractures. Pneumothorax, without rib fractures, may develop due to chest compressions or barotrauma resulting from mechanical ventilation during or after endotracheal intubation. Similarly, pneumothorax secondary to CPR may be accompanied by subcutaneous emphysema [8]. However, in our case, bilateral subcutaneous emphysema was quite widespread and severe compared to the pneumothorax that was detected on the right. When the scientific literature is reviewed, only one case with severe subcutaneous emphysema incompatible with pneumothorax secondary to CPR was found [9]. If the developmental mechanism is examined, displacement of fractured rib fragments causes visceral pleura and pulmonary parenchymal laceration. Thus, some of the air that escapes to the pleura with the developing pneumothorax passes through the intercostal muscle lacerations caused by displaced ribs and finally reach subcutaneous space. The air that enters the subcutaneous space due to high frequency active chest compressions and positive pressure mechanical ventilation are trapped because of the fact that the ruptured intercostal muscles operate as a one-way valve system during the passive



decompression period. We think that bilateral severe subcutaneous emphysema incompatible with the volume of pneumothorax developed with this mechanism in our case.

## CONCLUSION

As a result, it should never be forgotten that CPR is a serious cause of chest trauma. Patients responding to CPR should be investigated as soon as possible for chest trauma and its complications that are a potential source of morbidity and mortality.

### *Informed consent*

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

### *Conflict of interest*

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### *Acknowledgement*

This paper presented at 8<sup>th</sup> National Thoracic Surgery

Congress, April 23-26, Antalya, Turkey.

## REFERENCES

- [1] Hoke R S, Chamberlain D. Skeletal chest injuries secondary to cardiopulmonary resuscitation. *Resuscitation* 2004;63:327-38.
- [2] Sirmali M, Türüt H, Topçu S, Gülhan E, Yazici U, Kaya S, et al. A comprehensive analysis of traumatic rib fractures: morbidity, mortality and management. *Eur J Cardiothorac Surg* 2003;24:133-8.
- [3] Kim MJ, Park YS, Kim SW, Yoon YS, Lee KR, Lim TH, et al. Chest injury following cardiopulmonary resuscitation: A prospective computed tomography evaluation. *Resuscitation* 2013;84:361-4.
- [4] Karmy-Jones R, Jurkovich GJ. Blunt chest trauma. *Curr Probl Surg* 2004;41:211-380.
- [5] Beom JH, You JS, Kim MJ, Seung MK, Park YS, Chung HS, et al. Investigation of complications secondary to chest compressions before and after the 2010 cardiopulmonary resuscitation guideline changes by using multi-detector computed tomography: a retrospective study. *Scand J Trauma Resusc Emerg Med* 2017;25:8.
- [6] Krischer JP, Fine EG, Davis JH, Nagel EL. Complications of cardiac resuscitation. *Chest* 1987;92:287-91.
- [7] Oschatz E, Wunderbaldinger P, Sterz F, Holzer M, Kofler J, Slatin H, et al. Cardiopulmonary resuscitation performed by bystanders does not increase adverse effects as assessed by chest radiography. *Anesth Analg* 2001;93:128-33.
- [8] Vinay B, Venkataramaiah S, Sriganesh K, Rao M. Pneumothorax with subcutaneous emphysema following cardio-pulmonary resuscitation. *Minerva Anesthesiol* 2013;79:824-5.
- [9] Bekeredjian R, Meyer FJ, Frey N, Radeleff B. Massive tissue emphysema after cardiopulmonary resuscitation. *Am J Emerg Med* 2007;25:101-2.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# *Datura stramonium* poisoning: a case report and review of the literature

Muhammet Furkan Korkmaz<sup>1</sup>, Muharrem Bostanci<sup>1</sup>, Hatice Onur<sup>1</sup>, Eren Çağan<sup>2</sup>

<sup>1</sup>Department of Pediatrics, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

<sup>2</sup>Department of Pediatric Infectious Diseases, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

DOI: 10.18621/eurj.392041

## ABSTRACT

*Datura stramonium* is a widespread annual, leafy herbaceous plant that is a powerful hallucinogen. It can cause severe anticholinergic poisoning after inappropriate and unconscious usage. We would like to present an approach, accompanied by literature, to the poisoning case for a 6-year-old child who initially presented with altered mental status, abnormal/incoherent speech and agitation, and had an only response to physostigmine. It is essential to consider anticholinergic plant-based ingestions in the differential diagnosis of children presenting with altered mental state, hallucination, and agitation. Health care workers and parents should be aware of toxicities and potential risks of these plants.

**Keywords:** Anticholinergic syndrome, emergency medicine, toxicology

Received: February 8, 2018; Accepted: April 29, 2018; Published Online: June 7, 2018

*Datura stramonium*, which is commonly called Thorn Apple, Jimson Weed, Angel's Trumpet, is a wild growing plant that is entirely toxic. *Datura stramonium* seeds are flat, disk-shaped, brown, nearly three millimeters in diameter, and appear similar to tomato seeds [1]. All parts of the plant contain a variety of alkaloids including atropine, hyoscyamine, and scopolamine having hallucinogenic and anticholinergic effects [2, 3]. Many people use *Datura* in herbal medication to manage common illnesses such as asthma, chronic bronchitis, flu symptoms and pain [4]. Especially by teenagers it is widely used for its hallucination properties, and the favored way is smoking its leaves [1].

This report presents an unusual case of *Datura stramonium* poisoning occurring after accidental ingestion in a 6-year-old child who initially introduced

with altered mental status, abnormal/incoherent speech and agitation, and had an only response to physostigmine.

## CASE PRESENTATION

A 6-year-old boy was brought to our pediatric department by his parents with complaints of incoherent talks, visual hallucination, and irrational behavior. According to his history, these complaints which were observed within the hour following accidental ingestion of unknown plant. The patient did not have any pathologic medical history or allergic reaction. On the initial physical examination, his vital signs were: blood pressure 125/75 mm Hg, temperature 37.3 °C, pulse rate 118 beats/min,



Address for correspondence: Muhammet Furkan Korkmaz, MD., Bursa Yüksek İhtisas Training and Research Hospital, Department of Pediatrics, Yildırım, Bursa, Turkey  
E-mail: korkmazmfurkan@gmail.com, Tel: +90 224 294 40 00 - 4418, Fax: +90 224 294 44 99

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

respiratory rate 23 breaths/min, and oxygen saturation 98% on room air. He had dry mouth and dilated reactive pupils bilaterally. He was agitated and aggressive with purposeless movements. He had no focal neurological signs, and other systemic examination findings were normal. There was sinus tachycardia in his ECG. Complete blood count, serum electrolytes, liver-renal function tests, acute phase markers and urinalysis were normal.

The patient was diagnosed with anticholinergic poisoning initially. It was asked parents to bring an example from that plant. The sample was studied in our pharmacology laboratory and defined as DS. Gastric decontamination with nasogastric lavage and activated charcoal (1gr/kg) was rapidly performed within the second hour of ingestion. Intravenous fluids and midazolam (0.2 mg/kg) were administered. The patient continued to be agitated after the second dose of midazolam. 0.02 mg/kg physostigmine intravenous infusion (i.v.) was administered in several minutes (max 0.5 mg/min). He was able to recognize familiar people within five minutes. Repeated neurological examination revealed. A gradual improvement was observed in his state of consciousness with the disappearance of tachycardia, mydriasis, and agitation. On the second day of hospitalization, he became fully conscious, communicating intelligently, and was discharged home.

## DISCUSSION

*Datura* was named as Jimson weed (a shortened version of Jamestown weed) after the first inscribed accidental ingestion happened in Jamestown, Virginia (USA), in 1676. DS seeds which contain the most alkaloid and flowers appear from May to September. The spinous pod includes between 50 and 100 brown-black seeds. The seeds comprise the equivalent of approximately 6 mg of atropine which may be fatal [5].

Adolescents are the most prevalent age group for poisoning with *Datura stramonium*. Intentional abuse is common by eating seeds, drinking tea or smoking cigarettes [6]. Since *Datura stramonium* is not known for its hallucinogenic or euphoric effect between adolescents in our region, *datura* seeds or leaves are

generally consumed accidentally by children (as our case).

*Datura stramonium* ingestion results in the classic picture of atropine poisoning. Usual symptoms are sinus tachycardia, hyperthermia, dry mouth-skin, or redding of skin, sluggish intestinal sounds, urinary retention, visual defect, drowsiness, speech disorder, agitation, disorientation, and hallucination. The symptoms generally occur within 1-4 hours and may continue 24-48 hours depending on gastric depletion [1]. Respiratory failure and cardiovascular collapse may have been observed in severe forms. Rhabdomyolysis and fulminant hepatitis have also been reported rarely. Since children have a marked irritability to atropine toxicity, even a small amount may produce severe central nervous system manifestations [7].

The treatment protocol in this condition is mainly supportive care and observation. Especially within the first hour of ingestion, gastric lavage and activated charcoal were critical and recommended. Benzodiazepines are used to control agitation. Thus, hyperthermia, rhabdomyolysis, and traumatic injuries are seen less frequently [8].

Physostigmine is a prototypical therapeutic cholinesterase inhibitor that crosses the blood-brain barrier and reverses both central and peripheral anticholinergic effects. It is suggested when the patient has peripheral anticholinergic signs, seizures and hemodynamically unstable dysrhythmias, unmanageable agitation, and coma with respiratory depression, malign hypertension, or hypotension. The initial dose for children is 0.5 to 2.0 mg i.v. over 5 minutes. This dose can be repeated as needed. But there are some contraindications, such as; cardiovascular disease, bronchospasm, intestinal obstruction, heart block, peripheral vascular disease, and bladder obstruction [9, 10]. In our patient, gastric lavage and activated charcoal were performed after admission. However, a rapid improvement of the neurological manifestations was obtained. Intravenous fluids and midazolam (0.2 mg/kg) were administered. But the patient continued to be agitated after 12-hours of observation and the second dose of midazolam. Thus physostigmine intravenous infusion was administered. He could only be discharged after 48-hours hospitalization.

## CONCLUSION

Hallucinogenic, euphoric and other anticholinergic effects of *Datura stramonium* are not well known in some countries. *Datura stramonium* may be accidentally used as a food ingredient. It is important to consider anticholinergic plant-based ingestions in the differential diagnosis of children presenting with altered mental state, hallucination, and agitation. Since its harmful effects are not known well in some countries, people should be informed about toxicities and potential risks of these plants.

### *Informed consent*

Written informed consent was obtained from the patient's family for publication of this case report.

### *Conflict of interest*

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Disel NR, Yılmaz M, Kekec Z, Karanlık M. Poisoned after diner: Dolma with *Datura stramonium*. Turk J Emerg Med 2016;15:51-5.
- [2] Yılmaz MS, Kavalcı C, Kavalcı G, Ongar M, Özlem M. [*Datura stramonium* abuse: a case report]. J Clin Anal Med 2013;4:479-81. [Article in Turkish]
- [3] Trancă SD, Szabo R, Cociş M. Acute poisoning due to ingestion of *Datura stramonium* -- a case report. Rom J Anaesth Intensive Care 2017;24:65-8.
- [4] Adegoke SA, Alo LA. *Datura stramonium* poisoning in children. Niger J Clin Pract 2013;16:116-8.
- [5] Wiebe TH, Sigurdson EC, Katz LY. Angel's trumpet (*Datura stramonium*) poisoning and delirium in adolescents in Winnipeg, Manitoba: summer 2006. Paediatr Child Health 2008;13:193-6.
- [6] Amini M, Khosrojerdi H, Afshari R. Acute *stramonium* poisoning in East of Iran -- a case series. Avicenna J Phytomed 2012;2:86-9.
- [7] Bouziri A, Hamdi A, Borgi A, Bel Hadj S, Fitouri Z, Menif K, et al. *Datura stramonium* L. poisoning in a geophagous child: a case report. Int J Emerg Med 2011;4:31.
- [8] Wax PM, Young AC. Anticholinergics. In: Tintinalli JE, Stapczynski JS, Ma OJ, Cline DM, Cydulka RK, Meckler GD, editors. Tintinalli's emergency medicine: a comprehensive study guide. 7th ed. New York: McGraw-Hill; 2011:1305-8.
- [9] Sever M, Cekin M. Anticholinergic intoxication due to *Datura stramonium*: three pediatric cases. Akademik Acil Tıp Dergisi 2007;5:28-30.
- [10] Rakotomavo F, Andriamasy C, Rasamoelina N, Raveloson N. *Datura stramonium* intoxication in two children. Pediatr Int 2014;56:14-6.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# An unusual cause of hemorrhagic shock: gastric Dieulafoy's lesion

Ahmet Erdoğan<sup>1</sup>, Murat Ferhat Ferhatoğlu<sup>2</sup>, Hikmet Pehlevan<sup>3</sup>, Osman Yıldırım<sup>3</sup>, Kazım Şenol<sup>4</sup>

<sup>1</sup>Department of General Surgery, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey

<sup>2</sup>Department of General Surgery, Okan University School of Medicine, İstanbul, Turkey

<sup>3</sup>Department of General Surgery, Ankara Numune Training and Research Hospital, Ankara, Turkey

<sup>4</sup>Department of General Surgery, Bursa State Hospital, Bursa, Turkey

DOI: 10.18621/eurj.384720

## ABSTRACT

Dieulafoy's lesion (DL) related massive gastrointestinal bleeding is a rare and mortal health condition. DL is a superficial vascular lesion of the gastric mucosa that is mostly located in the proximal part of the stomach which is difficult to diagnose. Endoscopy is a safe and effective method for diagnosis and treatment. However, emergency surgery should be essential for diagnosis and treatment. Here we present a successful clinical and surgical management of a case with massive gastrointestinal bleeding related to gastric DL.

**Keywords:** Dieulafoy's lesion, hemorrhagia, shock

*Received: January 26, 2018; Accepted: March 27, 2018; Published Online: May 30, 2018*

Dieulafoy's lesion (DL) is a rare cause of gastrointestinal bleeding that prolonged diagnosis usually presents with life-threatening health conditions. It was identified by Gallard for the first time in 1884 and was named by the French surgeon Georges Dieulafoy in 1898 [1]. DL is described as a large arteriolar lesion protruding from the mucosal defects by erosion in the submucosa which may cause massive bleeding. DL is observed especially in male (Male/Female: 2/1) and elderly patients presenting with multiple co-morbidities including, hypertension, cardiovascular disease, chronic kidney disease and diabetes [2]. In regard to these co-morbidities, non-steroidal anti-inflammatory drugs, aspirin and warfarin use have also been linked to DL [3]. The effects of smoking and alcohol consumption in DL are controversial [4].

DL presents with recurrent massive bleeding attacks and clinical manifestation varies between obvious and obscure hematemesis and/or melena findings [5]. Therefore, intermittent clinical course of DL complicates the initial diagnosis and appropriate treatment. Gastrointestinal endoscopy, angiography, scintigraphy and surgery are diagnostic and therapeutic options in DL. Definitive diagnosis and treatment of DL is challenging and depends on the clinicians' experience.

This article is aimed to provide a review of diagnostic and therapeutic approaches to the DL presented with hemorrhagic shock during hospitalization and a clinical perspective for clinicians even in challenging diagnosis with complicated clinical courses.



**Address for correspondence:** Murat Ferhat Ferhatoğlu, MD., Okan University School of Medicine, Department of General Surgery, Aydınlı Yolu Cad., Okan Üniversitesi Hastanesi, Tuzla, İstanbul, Turkey  
E-mail: ferhatferhatoglu@yahoo.co.uk, Tel: +905553214793

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

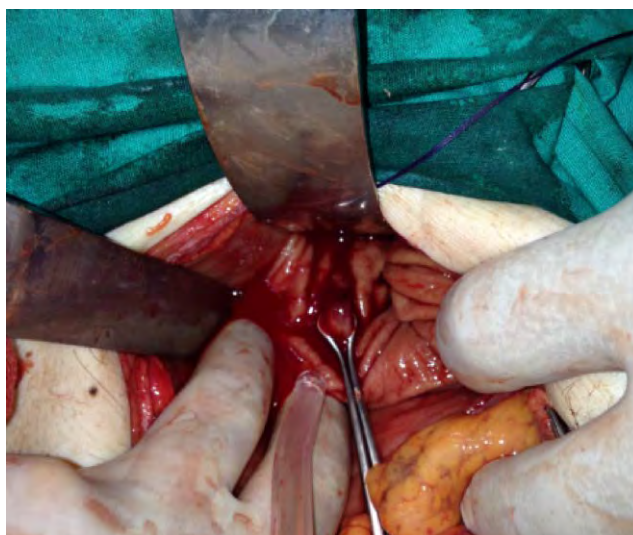
## CASE PRESENTATION

A 62-year-old male patient was admitted to the emergency room with black, tarry defecation for three days and skin paleness. His past medical records demonstrated several admissions to the emergency room with gastrointestinal bleeding symptoms. He had no remarkable history of alcohol and tobacco consumption and non-steroidal anti-inflammatory drug use. He was hypotensive (80/60 mmHg), tachypneic (18 counts/min.) and in poor general condition. Physical examination was normal except for melena at rectal examination. Complete blood count test revealed severe anemia with hemoglobin level 7.8 g/dl and hematocrit level 21.8%. The patient's oral intake was stopped, and proton pump inhibitor infusion was started. Hemodynamic status was stabilized with intravenous hydration and two units of erythrocyte suspensions. Emergency esophagogastroduodenoscopy showed no evidence of such lesion with active bleeding. In colonoscopy signs of bleeding was observed but an active bleeding was not observed. To localize the hemorrhage, technetium 99m-labeled red blood cell scintigraphy was performed but no extravasations of radionuclide were observed into the gastrointestinal tract. On the third day of hospitalization, patient's general status was unexpectedly deteriorated and hemoglobin levels were reduced to 6.1 mg/dl. Patient was consulted to the general surgery department and emergency surgery was planned. At the operation theatre, patient was in

hemorrhagic shock with blood pressure of 60/20 mmHg, pulse of 120 beat/min and hemoglobin level of 3.9 mg/dl. Midline laparotomy evidenced massively dilated stomach with a possible gastric bleeding. Gastrotomy was performed and 2000 cc hemorrhagic fluid was aspirated. Further evaluation of the gastric mucosa demonstrated an active bleeding submucosal artery protruding to the mucosa at the proximal part of the corpus close to the lesser curvature (Figure 1). Wedge resection and primary closure with interrupted sutures were performed. Nasogastric and abdominal drains were inserted. Intraoperatively, patient had four units of erythrocyte suspensions and transferred to the intensive care unit for close monitoring. Postoperative follow-up was uneventful. Nasogastric and abdominal drains were removed on postoperative fourth day. Patient was discharged on postoperative 11<sup>th</sup> day without any complications.

## DISCUSSION

In the literature 1-2% of all gastrointestinal bleedings were associated with DL. Almost 80% of DL occurs in upper part of the stomach within 6 cm of the gastroesophageal junction, most commonly in the small curvature. Other extragastric localizations are duodenum (14%), colon (5%), Billroth II anastomoses (5%), jejunum (1%) and esophagus (1%)(6). Initial gastrointestinal endoscopy evaluates 70% of the lesions effectively, but two or more



**Figure 1.** Peroperative pathognomonic view of pulsatile bleeding Dieulafoy's lesion with erosion of mucosa.

endoscopies may be required with 6% of patients to establish the diagnosis [1]. Endoscopy is recommended as the first line treatment option for bleeding control. Various techniques have been described including, epinephrine injection and sclerotherapy, thermal-electrocoagulation, heater probe or argon coagulation, elastic band ligation, hemoclips, or combination of them. Hemostasis can be achieved with these methods up to 90% of bleeding lesions. Advances in endoscopic management has decreased the mortality rates from 80% to 8.6% [7]. However, the risk of recurrence in mono-therapy is documented 9-40% more than compared to patients undergoing combined methods [8]. Recurrences are observed mostly during hospitalization and are associated with epinephrine monotherapy, arterial bleeding demonstrated at endoscopy and contralateral circulation or incomplete embolisation of the feeding artery after embolization therapy [9, 10]. Therefore, the choice of technique depends on the patient, lesion type, localization and the experience of the clinician [11].

Surgical treatment of DL is significantly decreased in time due to efficient therapeutic role of endoscopic management with satisfactory clinical outcomes. Recent studies have demonstrated that surgical treatment is required only in 4-8% of patients [12]. Nowadays, surgery is required for recurrent lesions after angiographic and endoscopic treatment failure. Surgery is also recommended for extra-gastric localized DL especially in lower gastrointestinal tract. The suggested surgical treatment for gastric DL is laparotomy with extensive gastrotomy and resection of the entire lesion including the thick submucosal artery. Laparoscopic management of DL with accurate endoscopic diagnosis preoperatively has been demonstrated in few cases [13, 14], but has not been widely accepted.

## CONCLUSION

Our case demonstrated a rare clinical presentation of DL with acute hemorrhagic shock during hospitalization. In such cases, gold standard diagnostic tools, endoscopy and scintigraphy are unable to detect the pathognomonic findings of DL. Patients presenting with intermittent gastrointestinal bleeding episodes

with high clinical suspicion of DL, should be hospitalized immediately and evaluated with short-term endoscopic monitoring to avoid life-threatening complication of DL.

### *Authors' contributions*

AE, HP and OY collected the information, reviewed the literature and wrote the manuscript. MFF, KŞ critically reviewed the manuscript and approved the final form. All authors read and approved the final manuscript.

### *Informed consent*

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

### *Conflict of interest*

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Baxter M, Aly EH. Dieulafoy's lesion: current trends in diagnosis and management. *Ann R Coll Surg Eng* 2010;92:548-54.
- [2] Norton ID, Petersen BT, Sorbi D, Balm RK, Alexander GL, Gostout CJ. Management and long-term prognosis of Dieulafoy lesion. *Gastrointest Endosc* 1999;50:762-7.
- [3] Chaer RA, Helton WS. Dieulafoy's disease. *J Am Coll Surg* 2003;196:290-6.
- [4] Veldhuyzen van Zanten SJ, Bartelsman JF, Schipper ME, Tytgat GN. Recurrent massive haematemesis from Dieulafoy vascular malformations--a review of 101 cases. *Gut* 1986;27:213-22.
- [5] al-Mishlab T, Amin AM, Ellul JP. Dieulafoy's lesion: an obscure cause of GI bleeding. *J R Coll Surg of Edinb* 1999;44:222-5.
- [6] Strong RW. Dieulafoy's disease--a distinct clinical entity. *Aust N Z J Surg* 1984;54:337-9.
- [7] Romaozinho JM, Pontes JM, Lérias C, Ferreira M, Freitas D. Dieulafoy's lesion: management and long-term outcome. *Endoscopy* 2004;36:416-20.
- [8] Lee YT, Walmsley RS, Leong RW, Sung JJ. Dieulafoy's lesion. *Gastrointest Endosc* 2003;58:236-43.
- [9] Jamanca-Poma Y, Velasco-Guardado A, Pinero-Perez C, Calderon-Begazo R, Umana-Mejia J, Geijo-Martinez F, et al. Prognostic factors for recurrence of gastrointestinal bleeding due to Dieulafoy's lesion. *World J Gastroenterol* 2012;18):5734-8.
- [10] Alshumrani G, Almuaikael M. Angiographic findings and endovascular embolization in Dieulafoy disease: a case report and literature review. *Diagn Interv Radiol* 2006;12:151-4.
- [11] Ding YJ, Zhao L, Liu J, Luo HS. Clinical and endoscopic analysis of gastric Dieulafoy's lesion. *World J Gastroenterol* 2010;16:631-5.
- [12] Beyazit Y, Dişibeyaz S, Suvak B, Purnak T, Torun S, Parlak E. [Evaluation of treatment results among patients with acute

gastrointestinal bleeding due to Dieulafoy's lesion admitted to the emergency department] Ulus Travma Acil Cerrahi Derg 2013;19:133-9. [Article in Turkish]

[13] Hoffman A, Kunert A, Lahat A, Volkov A, Zmora O, Rosin D. Laparoscopic resection of gastric Dieulafoy lesion following

preoperative tattooing. Isr Med Assoc J 2011;13:187-8.

[14] Sai Prasad TR, Lim KH, Lim KH, Yap TL. Bleeding jejunal Dieulafoy pseudopolyp: capsule endoscopic detection and laparoscopic-assisted resection. J Laparoendosc Adv Surg Tech A 2007;17:509-12.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.



# Cecal diverticulitis mimicking acute appendicitis

Cihan Bedel 

Department of Emergency Medicine, Antalya Training And Research Hospital, Antalya, Turkey

DOI: 10.18621/eurj.378652

## ABSTRACT

Cecal diverticulitis is a rare cause of acute abdomen and is often confused with appendicitis because of physical examination findings that suggest appendicitis. Here I present a case of an 48-year-old female with cecal diverticulitis who was medically treated. This study aimed to create awareness for cecal diverticulitis and help avoid unnecessary surgical procedures for medically treatable pathologies.

**Keywords:** Cecum, diverticulitis, emergency department

*Received: January 14, 2018; Accepted: March 11, 2018; Published Online: May 23, 2018*

Cecal diverticulitis is a rare clinical problem in the Western world, more commonly seen in the descending and sigmoid colon [1]. The disease is often misdiagnosed at the time of its occurrence. The symptoms and signs of the disease similar to acute appendicitis with right sided abdominal tenderness, nausea, vomiting, fever and leukocytosis [2]. In the past, It is extremely difficult to distinguish patients with cecal diverticulitis preoperative from acute appendicitis and such distinction is usually made in the operating room [3, 4]. This study aimed to create awareness for cecal diverticulitis and help avoid unnecessary surgical procedures for medically treatable pathologies.

## CASE PRESENTATION

A 48-year-old female with abdominal pain persisting for 2 day admitted to the emergency service. Physical examination revealed tenderness in the right lower quadrant and right lateral side of the umbilicus. The patient had experienced neither nausea nor vomiting. The laboratory test results on admission

were within the normal limits except White blood cell count was slightly elevated at 11700/ml, with C-reactive protein raised to 89 mg/l (normal: 0-3mg/l). Minimal collection was present in the pericecal region on ultrasonography. Computed tomography (CT) scan of the abdomen showed diverticulitis in 1 cm size with fecalite and contamination of fatty tissue in the lateral wall of the stain (Figure 1a and 1b). The patient was hospitalized in the general surgery clinic. Oral intake was discontinued. Intravenous fluid support, a cefuroxime axetil (Cefaks iv; Deva, İstanbul, Turkey) and ornidazole (Orniject iv; Tüm-Ekip, İstanbul, Turkey) were administered. Abdominal pain was relieved on the second day of hospitalization. No collection was present in the pericecal region in ultrasonography made 5 days of hospitalization. The patient was discharged on the seventh day after hospitalization. The patient was discharged after prescribing antibiotics and antiinflammatory drugs.

## DISCUSSION

Cecal diverticulitis is a rare clinical problem in the



Address for correspondence: Cihan Bedel, MD., Antalya Training and Research Hospital, Department of Emergency Medicine, 07100 Muratpaşa, Antalya, Turkey  
E-mail: cihanbedel@hotmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>



**Figure 1.** Axial (a) and coronal view of the cecal diverticulitis with pericolic fat stranding (white arrow)

Western world, more commonly seen in the descending and sigmoid colon [1]. Most patients with right side diverticula are asymptomatic. Their clinical presentation is well known to nearly mimic acute appendicitis and the correct diagnosis of cecal diverticulitis is most commonly made intra-operatively during exploration for suspected appendicitis [2].

Ultrasonography evaluation can be used as first modality in right lower abdominal pain. Right-sided colonic diverticulitis should be considered if ultrasonography findings show local wall thickening

of the colon ( $> 4$  mm), regional pericolic fat thickening, oval-shaped or rounded hypoechoic or nearly anechoic structure protruding from segmentally thickened cecal or ascending colonic walls [5]. In study conducted by Chou *et al.* [5], abdominal ultrasonography was shown to diagnose acute uncomplicated right colonic diverticulitis in 23 cases among 934 patients with indeterminate acute right lower abdominal pain. They demonstrated high sensitivity (91.3%) and specificity (99.8%) of ultrasonography for diagnosis of diverticulitis [5].

Previous studies have reported several pitfalls and

limitations that lowered diagnostic accuracy of ultrasonography examinations, such as obesity and excessive bowel gas. It may be logical for very obese patients suspected of having right-sided colonic diverticulitis in differential diagnosis of right lower quadrant pain to be sent directly to CT because of difficulty in penetrating tissue with ultrasonography [6, 7]. Diverticulitis is diagnosed more confidently with CT than abdominal ultrasonography [7]. CT scan may also be useful to show up other diseases responsible for lower right abdominal pain, such as neoplastic disease, acute appendicitis, ileitis, inflammatory bowel disease [8].

Treatment of cecal diverticulitis is still controversial, varying from conservative therapy to aggressive surgery, such as right hemicolectomy [9]. Conservative management of cecal diverticulitis may be an effective treatment modality in cases diagnosed with imaging techniques. Surgical treatment may be necessary for diverticular bleeding unresponsive to conservative management, or recurrent and/or complicated diverticulitis in cases with perforation, abscess formation, intestinal obstruction, or fistula [10, 11]. In this study, symptoms completely resolved with a conservative treatment.

## CONCLUSION

As a result, cecal diverticulitis should be considered in the differential diagnosis of patients complaining of right iliac fossa pain. If uncomplicated diverticulitis of the right colon is correctly diagnosed with radiological evaluation will prevent unnecessary surgeries.

## Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

## Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Kurer MA. Solitary caecal diverticulitis as an unusual cause of a right iliac fossa mass: a case report. *J Med Case Rep* 2007;1:132.
- [2] Griffiths EA, Bergin FG, Henry JA, Mudawi AM. Acute inflammation of a congenital cecal diverticulum mimicking appendicitis. *Med Sci Monit* 2003;9:107-9.
- [3] Papapolychroniadis C, Kaimakis D, Fotiadis P, Karamanlis E, Stefopoulou M, Kouskouras K, et al. Perforated diverticulum of the caecum. A difficult preoperative diagnosis. Report of two cases and review of the literature. *Tech Coloproctol* 2004;8:S116-8.
- [4] Yardımcı E, Hasbahceci M, İdiz UO, Atay M, Akbulut H. Is surgery necessary to confirm diagnosis of right-sided diverticulitis in spite of relevant clinical and radiological findings? *Ulus Travma Acil Cerrahi Derg* 2017;23:61-5.
- [5] Chou Y-H, Chiou H-J, Tiu C-M, Chen J-D, Hsu C-C, Lee C-H, et al. Sonography of acute right side colonic diverticulitis. *Am J Surg* 2001;181:122-7.
- [6] Komuta K, Yamanaka S, Okada K, Kamohara Y, Ueda T, Makimoto N, et al. Toward therapeutic guidelines for patients with acute right colonic diverticulitis. *Am J Surg* 2004;187:233-7.
- [7] Puylaert JB. Ultrasound of colon diverticulitis. *Digest Dis* 2012;30:56-9.
- [8] Heller MT, Bhargava P. Multi-detector computed tomography of acute cecal conditions. *Emerg Radiol* 2014;21:75-82.
- [9] Mudatsakis N, Nikolaou M, Krithinakis K, Matalliotakis M, Politis N, Andreadakis E. Solitary cecal diverticulitis: an unusual cause of acute right iliac fossa pain-a case report and review of the literature. *Case Rep Surg* 2014;2014:131452.
- [10] Jacobs DO. Diverticulitis. *N Eng J Med* 2007;357:2057-66.
- [11] Hildebrand P, Kropp M, Stellmacher F, Roblick U, Bruch H-P, Schwandner O. Surgery for right-sided colonic diverticulitis: results of a 10-year-observation period. *Langenbecks Arch Surg* 2007;392:143-7.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Rectal resection for Schnitzler's metastasis in a patient presenting with severe rectal stenosis: case report and review of the literature

Semra Doğan<sup>1</sup>, Sezai Demirbaş<sup>1</sup>, Elgun Samadov<sup>2</sup>, Salih Erpulat Öziş<sup>1</sup>, Hatim Yahya Uslu<sup>1</sup>

<sup>1</sup>Department of General Surgery, TOBB Economy and Technology University Hospital, Ankara, Turkey

<sup>2</sup>Department of General Surgery, Tibb Universiteti Nariman Narimanov Baku, Baku, Azerbaijan

DOI: 10.18621/eurj.378526

## ABSTRACT

Rectal metastasis resulting from the hematogenous spread of gastric cancer (Schnitzler's disease) is rarely seen. We report a case of 53-year-old female with rectal metastasis from gastric cancer who presented with abdominal pain, tenesmus, and severe constipation. Digital rectal examination revealed a severe stenosis 5-6 cm from the dentate line. Sigmoidoscopy showed a narrowed lumen at 5 cm up from the dentate line. The evident radiologic finding was circumferential stenosis of the rectum located at the same level. Very low anterior resection and total mesorectal excision with coloanal anastomosis in addition to protective ileostomy were performed. Pathological examination revealed metastatic adenocarcinoma (Schnitzler's metastasis). The patient was discharged on the 9<sup>th</sup> postoperative day with no adverse events. It should be kept in mind that rectal stenosis could be metastasis from gastric carcinoma if consistent with the patient's history.

**Keywords:** Schnitzler's disease, gastric cancer, rectum metastasis

*Received: January 13, 2018; Accepted: March 1, 2018; Published Online: May 28, 2018*

The known routes of distant metastasis after curative gastrectomy include lymphatic spreading (Virchow's node), peritoneal seeding (Krukenberg's tumor or Plummer's rectal shelf) or hematogenous spread (Schnitzler's metastasis) [1-3]. We present a patient with rare Schnitzler's metastasis who lived 42 months after curative treatment of gastric cancer.

## CASE PRESENTATION

A 53-year-old woman presented with constipation, tenesmus, abdominal pain, and weight loss of 8-9 kg over a period of 2 months. Her past medical history

was significant for signet ring cell gastric adenocarcinoma (T2N0M0), for which she underwent total gastrectomy with D2 lymph node dissection 42 months earlier. Pathological examination at that time showed the surgical resection margins to be clear. Twenty-one lymph nodes were harvested, and were found to be tumor-free. In the follow-up period of 42 months after total gastrectomy, she was admitted to our General Surgery Clinic with constipation, tenesmus, and abdominal pain.

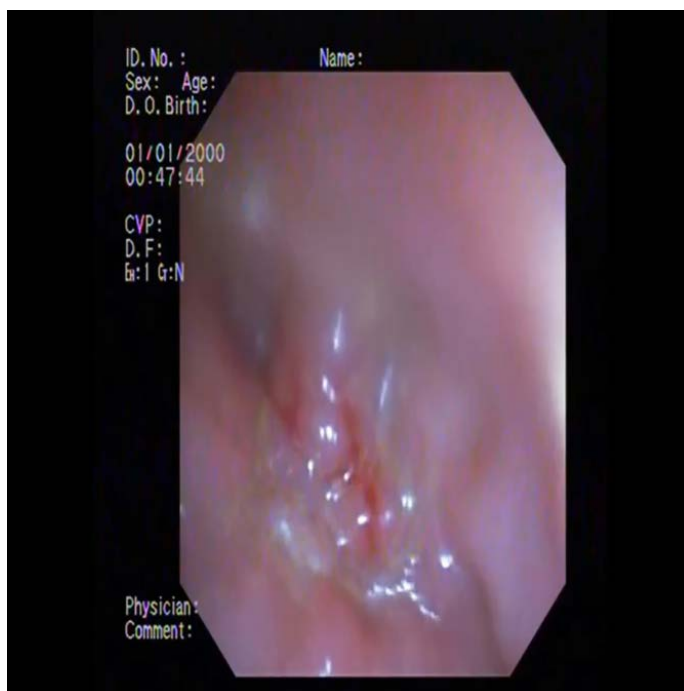
Digital rectal examination revealed severe stenosis 5-6 cm from the dentate line without any mucosal lesion. Blood test results and serum tumor markers were normal. Sigmoidoscopy showed a narrowed



**Address for correspondence:** Semra Doğan, MD., TOBB Economy and Technology University, Department of General Surgery, Yaşam Cad. No:5, Söğütözü, 06510 Ankara, Turkey  
E-mail: opdrsemradogan@yahoo.com, phone: +90 312 292 99 39, fax: +90 312 292 9910

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>



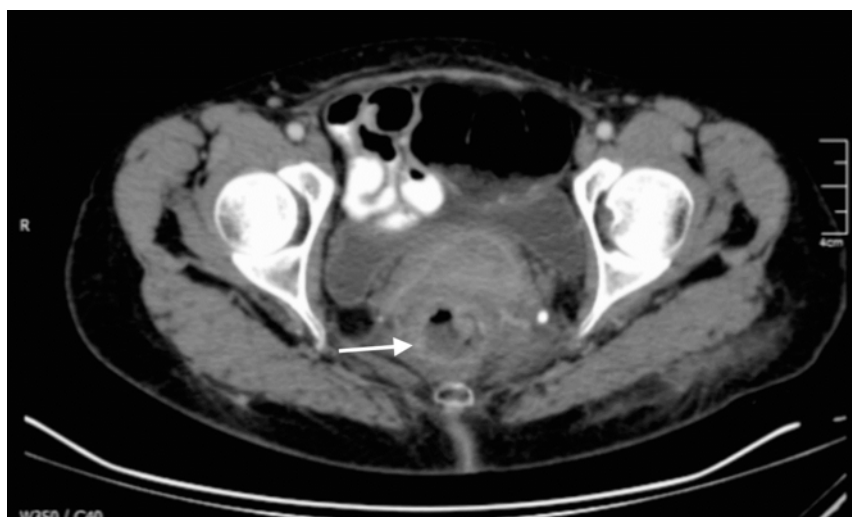
**Figure 1.** Sigmoidoscopy showing the narrowed lumen at 5th cm from the dentate line.

lumen at the 5<sup>th</sup> cm from the dentate line (Figure 1). Histopathological examination of the rectal mucosal biopsy did not find any signs of tumoral involvement.

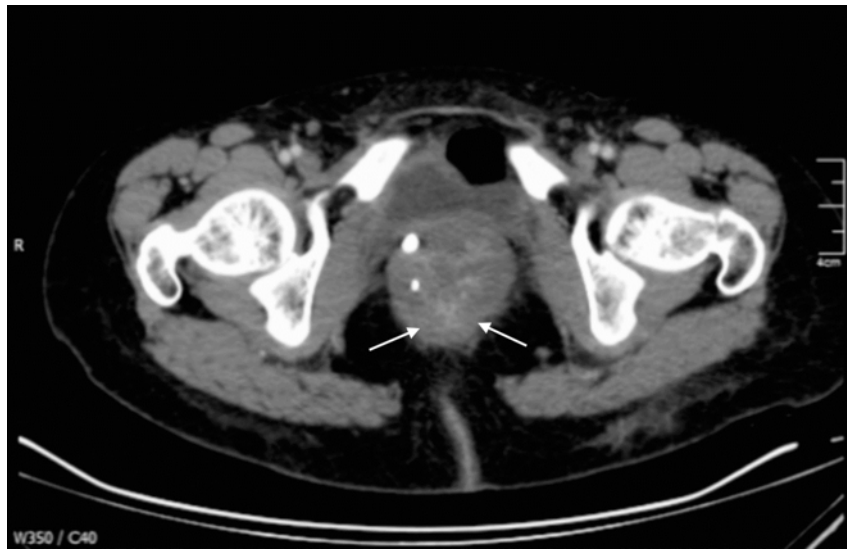
Abdominal and pelvic computed tomography (CT) showed circumferential stenosis of the middle rectum (Figures 2 and 3). There were no signs of metastatic involvement in her pelvic area. At positron emission tomography-computed tomography (PET-CT), a high standardized uptake value (SUV) of 5.8

was detected at the upper-middle rectum (Figure 4). The rectal stenosis was defined as rectal fibrosis on the PET-CT scan. The patient’s past medical history and imaging features made us consider the lesion as metastasis of the rectum from gastric malignancy rather than fibrosis; this possibility was more likely than that of primary malignancy.

Informed consent has been taken from the patient. Very low anterior resection (VLAR) and total



**Figure 2.** Axial CT image showing normal lumen of rectum from the proximal part of rectal stenosis.



**Figure 3.** Axial CT image showing circumferential stenosis of the distal rectum.

mesorectal excision (TME) with pull-through coloanal anastomosis were performed (Figure 5). In addition, protective ileostomy was done. During the operation, frozen section revealed an unclear malignancy with glandular structure. Nevertheless, the entire abdominal exploration gave no evidence of malignant nodular involvement, either in the abdominal spaces or on the pelvic peritoneal surfaces.

Histopathological examination revealed metastatic adenocarcinoma with the lesion originating with histopathology similar to the gastric cancer, which occurred most likely before spreading via the hematologic route.

The patient was discharged on the 9<sup>th</sup> day after surgery without any complications. The patient returned home by flying internationally on



**Figure 4.** At fused PET-CT image, a high standardized uptake value (SUV) of 5.8 at the upper-middle part of rectum is demonstrated.



**Figure 5.** Macroscopic appearance of the resected rectal segment.

postoperative day 11. By that time, she had begun to pass her convalescent period. However, at the early stage of that period, she died. The reason has not been clarified to us by her local physician.

## DISCUSSION

Gastric cancer is the fourth most commonly diagnosed malignancy and the second most common cause of cancer mortality worldwide [4]. The recurrence patterns after curative surgery for gastric cancer have been described as locoregional recurrence, peritoneal recurrence, and distant metastasis. Hematologic (Schnitzler's metastasis) or lymphatic spread from gastric cancer to the rectum is quite rare. We found the lesion of the present patient located in the middle-lower part of the rectum adjacent to the muco-subserosal layer. During the operation we did not determine the presence of any serosal exposure of tumor, or peritoneal or pelvic dissemination, or ascites. These findings supported the idea that this patient's metastatic rectal cancer was due to hematologic or lymphatic dissemination. Therefore, we are reporting this quite unusual case of rectal Schnitzler's metastasis via a hematogenous route of

gastric adenocarcinoma.

Only ten cases, including the present case, have been reported in the English literature of Schnitzler's metastasis to the rectum [5-13]. The mean age of the reported patients was 58.2 years. Seven of these patients were female. Schnitzler's metastasis to the rectum has been encountered synchronously and/or metachronously. Three of these cases in the literature were synchronous and the others, including our case, were metachronous Schnitzler's metastasis to the rectum. In our patient, metachronous Schnitzler's metastasis occurred 42 months after completion of treatment for gastric adenocarcinoma. In the reported cases, the median disease-free survival after gastrectomy was 38 months (range: 18-72 months) for metachronous metastases [5-12]. The disease-free survival of the present patient was 42 months. The cardinal symptoms of the previously reported cases were constipation, abdominal distension and tenesmus; and in the present case, the cardinal symptoms were severe constipation, abdominal distension and excessive weight loss. In these cases, the most prominent finding was stenosis of the rectum, which did not allow the passage of stool due to the metastatic stenosis, as in our case.

Sigmoidoscopy, colonoscopy and CT with

contrast is the most effective diagnostic strategy for reaching a true diagnosis of rectal metastasis. PET-CT can be used to determine whether the rectal lesion is malignant. In a case presented by Lim *et al.* [8], PET-CT showed hypermetabolic activity in the rectum. In the present case, high SUV 5.8 was detected in the upper-middle rectum, and the rectal stenosis was defined as rectal fibrosis.

The endoscopic appearance of luminal metastasis is variable, but the characteristic features are diffuse circumferential wall thickening and stiffness. Rectal biopsy is generally useful for determining metastatic cancer of the rectum. In our case, rectal biopsy did not give any sign of tumoral involvement.

An expandable metallic stent, lateral decompressive left colostomy, extended Hartmann's procedure, low anterior resection, and chemotherapy were chosen as methods of treatment for the patients of the previous reports. For our patient, we decided to perform VLAR and TME with pull-through coloanal anastomosis to remove the rectum completely in accordance with the oncologic resection on evaluation of the findings of CT, pelvic MRI and PET-CT. Closure of the protective ileostomy was planned to be accomplished quite a long time later to allow a second look in the abdominal cavity. But the patient unfortunately died after several days in her convalescent time period after she returned to her home by an international flight.

## CONCLUSION

Rectal metastasis presenting as rectal fibrosis from gastric cancer is very rare. When a patient with a history of gastric cancer presents with symptoms such as change of bowel habits (tenesmus or constipation) and/or rectal stenosis, even if biopsy results are negative for malignancy, it should be kept in mind that rectal stenosis can possibly originate from Schnitzler's metastasis resulting from hematogenous spread of a gastric carcinoma in a patient with a relevant history.

### Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors

are in agreement with the manuscript.

### Informed consent

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

### Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Maehara Y, Hasuda S, Koga T, Tokunaga E, Kakeji Y, Sugimachi K. Postoperative outcome and sites of recurrence in patients following curative resection of gastric cancer. *Br J Surg* 2000;87:353-7.
- [2] Roviello F, Marrelli D, de Manzoni G, Morgagni P, Di Leo A, Saragoni L, et al. Prospective study of peritoneal recurrence after curative surgery for gastric cancer. *Br J Surg* 2003;90:1113-9.
- [3] Niinobu T, Nakagawa S, Itani Y, Nishikawa Y, Amano M, Higaki N, et al. [Rectal stenosis due to Schnitzler metastasis following surgery for gastric cancer -a case successfully treated with TS-1 and CDDP combination chemotherapy]. *Gan To Kagaku Ryoho* 2005;32:1761-4. [Article in Japanese]
- [4] Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006;24:2137-50.
- [5] Yamamoto M, Matsuyama A, Kameyama T, Okamoto M, Okazaki J, Utsunomiya T, et al. [A case of advanced gastric cancer with Schnitzler's metastases effectively treated by combination of paclitaxel and S-1]. *Gan To Kagaku. Ryoho* 2008;35 829-31. [Article in Japanese]
- [6] Olano C, De Simone F, Gonzalez F, Gonzalez N, Tchekmedyan A, Pose A, et al. Stomach cancer presenting with rectal stenosis: Schnitzler's metastasis. *Gastrointest Endosc* 2009;70:809-10.
- [7] Rausei S, Frattini F, Dionigi G, Boni L, Rovera F, Diurni M. Unusual rectal stenosis. *J Surg Oncol* 2010;102:713.
- [8] Lim SW, Huh JW, Kim YJ, Kim HR. Laparoscopic low anterior resection for hematogenous rectal metastasis from gastric adenocarcinoma: a case report. *World J Surg Oncol* 2011;9:148.
- [9] Tural D, Selçukbiricik F, Erçalışkan A, Inanç B, Günver F, Büyükcünal E. Metachronous rectum metastases from gastric adenocarcinoma: a case report. *Case Rep Med* 2012;2012:726841.
- [10] Okugawa T, Oshima T, Ikeo K, Kondo T, Tomita T, Fukui H, et al. Successful self-expandable metallic stent placement for a case of distal rectal stenosis due to gastric cancer metastasis.



Case Rep Gastroenterol 2013;7:214-8.

[11] Derici Z.S, Sokmen S. Gastric carcinoma presenting with severe rectal stenosis: 'Schnitzler's metastasis': case report and review of the literature. Eur Surg 2016;48:246-9.

[12] Uemura N, Kurashige J, Kosumi K, Iwatsuki M, Yamashita K, Iwagami S, et al. Early gastric cancer metastasizing to the rectum, possibly via hematogenous route: a case report and review

of the literature. Surg Case Rep 2016;2:58.

[13] Matsutani T, Sasajima K, Amano H, Egami K, Kan H, Myashita M, et al. A case of expandable metallic stent placement for the stenosis in the sigmoid colon and rectum due to Schnitzler's metastasis from gastric cancer. Gastroenterol Endosc 2005;47:343-7.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Deep vein thrombosis and pulmonary embolism in a patient with acute type B aortic dissection: a case report

Engin Akgül<sup>ORCID</sup>, Gülen Sezer Alptekin Erkul<sup>ORCID</sup>, Sinan Erkul<sup>ORCID</sup>, Ahmet Hakan Vural<sup>ORCID</sup>

Department of Cardiovascular Surgery, Dumlupınar University, Evliya Çelebi Training and Research Hospital, Kütahya, Turkey

DOI: 10.18621/eurj.403641

## ABSTRACT

Acute dissection involving ascending aorta contains high risk of mortality and requires surgical treatment immediately. Venous thrombosis can be manifested as deep vein thrombosis or pulmonary embolism. It may be isolated or complication of another disease. Because of pulmonary thromboembolism risk, treatment of deep vein thrombosis is strongly recommended. A 61-year-old male patient with severe back pain and shortness of breath presented to the emergency service. The findings of the physical examinations, chest x-ray and electrocardiogram were normal. Contrast-enhanced computerized tomography showed an aortic intimal tear that started just below the subclavian artery and extended into the iliac arteries. The patient was hospitalized and the medical treatment started. On the 4<sup>th</sup> day of clinical follow-up, pain and swelling started at his right leg with severe shortness of breath. Venous Doppler ultrasound was performed and there were thrombosis at popliteal, femoral and even at iliac veins. Computed tomography showed pulmonary embolism at pulmonary trunk. Aortic dissection treated with endovascular stent graft firstly to prevent aortic rupture because of anticoagulation and then pulmonary embolism treated with anticoagulant drugs. Hypercoagulation is a self defence of the body for limiting the aortic intimal tear to prevent aortic rupture. So many complications could be seen because of this situation and the physicians should be awakened for this.

**Keywords:** acute aortic dissection, deep vein thrombosis, pulmonary embolism, endovascular stent graft, anticoagulation

*Received: March 9, 2018; Accepted: May 2, 2018; Published Online: June 26, 2018*

Aortic dissection is classified according to the location of the tear [1]. Stanford type A aortic dissection has a high mortality rate and should be promptly directed to surgery whereas Stanford type B aortic dissection can be followed without surgery [2, 3]. However, organ malperfusion may be likely if the dissection flap or intramural hematoma extends distally involving visceral and iliac arteries in type B aortic dissection [4]. On the other hand deep vein thrombosis (DVT) and pulmonary thromboembolism are some of the manifestations of venous

thromboembolism (VTE) [5, 6]. Herein we aimed to discuss a case of acute type B aortic dissection with VTE possibly provoked by the dissection itself or our treatment approach.

## CASE PRESENTATION

A 61-year-old-male patient presented with complaints such as severe back pain that begins two hours before admission. He had a history of



Address for correspondence: Engin Akgül, MD., Dumlupınar University, Evliya Çelebi Training and Research Hospital, Department of Cardiovascular Surgery, Kütahya, Turkey  
E-mail: engin\_akgul@hotmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

hypertension for 10 years. The arterial blood pressure measured 190/130 mm Hg bilaterally. The other findings of physical examination were ordinary as were also electrocardiographic findings and chest x-ray. Contrast-enhanced computerized tomographic angiography (CTA) was performed. It showed an extensive dissection of the aorta arising distal to the left subclavian artery and extending into the common iliac arteries bilaterally. Antihypertensive, analgesic and sedative therapies arranged to stabilize the blood pressure. The pain regressed and the blood pressure controlled with the medical therapy alone. The renal functions were normal and there was not an evidence of organ malperfusion thus surgical treatment was not planned. On the 4th day of clinical follow-up he had pain, swelling, erythema and an increase in the diameter of his right leg with severe shortness of breath although the arterial circulation of the lower extremities was intact with palpable arteries. Venous Doppler ultrasound imaging was performed and it

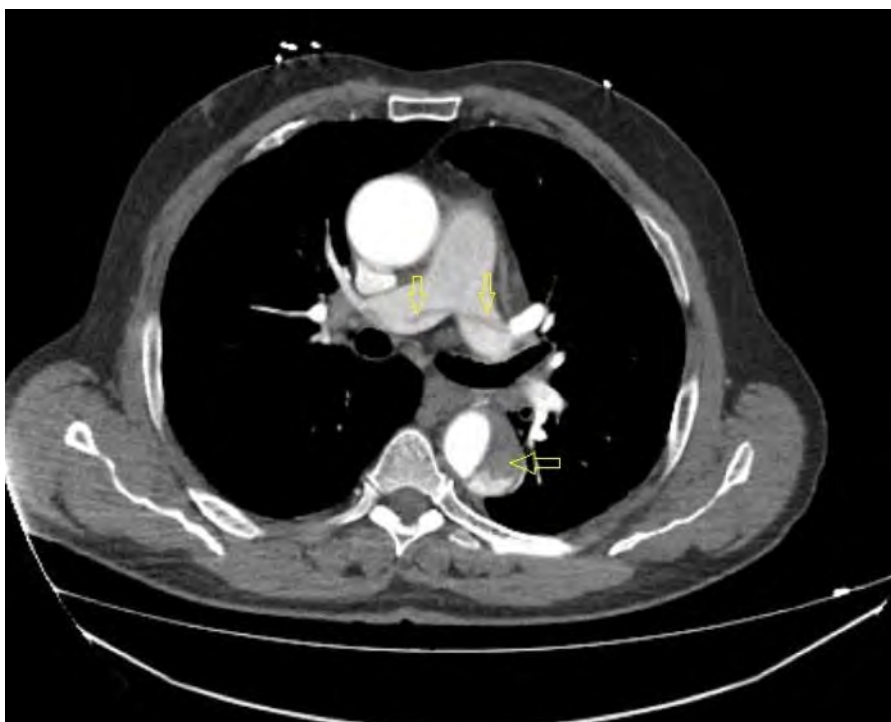
showed the acute thrombosis of the right popliteal, femoral and iliac veins. As the deep vein thrombosis was diagnosed, a CTA performed to evaluate pulmonary thromboembolism (Figure 1). It showed the segmental embolism in the main pulmonary trunk and in the branches of the bilateral pulmonary arteries (Figure 2). An effective dosage of anticoagulant therapy was not applied to avoid the rupture of the aorta. We decided to treat type B aortic dissection with endovascular stenting prominently to apply an adequate anticoagulant therapy soon afterwards. Thoracic endovascular aortic repair (TEVAR) was determined to perform (Figure 3). The left brachial artery used for the guidewire access for entering to the true lumen. Right femoral artery explored via a right femoral incision under local anesthesia. The wire moved forward into the descending aorta towards the right common femoral artery. A transvers arteriotomy made on the right common femoral artery to capture the guidewire with a clamp. Endovascular stent graft (42×42×207 mm, Medtronic, USA) implanted in the descending aorta just below the left subclavian artery and above the fourth thoracic vertebral level. No complication occurred. After TEVAR medical treatment for pulmonary thromboembolism and DVT revised. Anticoagulant treatment (Warfarin sodium) started the day after TEVAR for a target international normalized ratio (INR) level between 2-3. An effective dosage (80 IU/kg, enoxaparin sodium twice a day subcutaneously) of low molecular weight heparin (LMWH) applied from the day of the intervention until reaching the target INR. Shortness of breath and the edema of the leg regressed and the difference in diameter between two legs decreased after TEVAR in several days. The patient discharged on the 10<sup>th</sup> day after TEVAR with an effective dosage regimen of warfarin sodium and acetylsalicylic acid treatment. The symptoms relieved at discharge. Three months after the discharge the patient had no symptom related to either VTE or the aortic dissection.

## DISCUSSION

Type B aortic dissection may be accompanied with rupture, organ malperfusion, aortic aneurysm-dilatation and severe pain [7]. Immediate surgery is one of the treatment options for complicated



**Figure 1.** Edema of the right leg due to deep vein thrombosis.



**Figure 2.** Thrombosis at bilateral pulmonary arteries and the aortic dissection flap were figured with vertical and horizontal arrows respectively.



**Figure 3.** CT angiography image: the endovascular stent graft in the right position.

dissections but many authors recommend TEVAR instead of open surgery as the initial treatment [8]. A conservative approach by pain medication and antihypertensive drugs is a more appropriate treatment option for the uncomplicated type B aortic dissection in many cases [9]. Even though the patients are determined as uncomplicated on admission, a significant majority of them develop severe complications and need further interventions on follow-up [9]. Because of these catastrophic complications, indications of TEVAR for type B aortic dissections should be expanded for some circumstances.

It was suggested that during aortic dissection hypercoagulability may be triggered as a self-defence and this may cause thromboembolism [10]. VTE is a miscellaneous entity in the presence of acute aortic dissection therefore the anticoagulant or the thrombolytic therapy essential for the treatment of VTE may cause recanalization of the false lumen of the aorta. At the meantime the tear may be expanded proximally or distally and the false lumen may turn into a devastating hematoma ending in a poor outcome for the patient [10]. On the other hand in a hypercoagulable circumstance, the pulmonary

thromboembolism with or without DVT is a life threatening status which should be treated promptly. In our case thrombolytic therapy was contraindicated and the convenience for the application of LMWH was uncertain. The vena cava filter should be a treatment option to prevent pulmonary embolism in such cases [10]. However in our case acute pulmonary embolism was present from the time of the DVT diagnosis. Therefore we decided to treat the dissection site first by TEVAR and afterwards to apply an effective dosage of anticoagulant regimen. Three months after the discharge, the all symptoms of the patient were relieved. There are many studies which suggest the correlation of D-Dimer levels with re-dissection and VTE incidence among the patients with type B aortic dissection [11]. Although we couldn't find any recommendation for the treatment of VTE concomitant with aortic dissection in the literature considering it is a rare and an individual circumstance. However we think that it was life saving to treat aortic dissection prominently with an endovascular therapy option in our case.

## CONCLUSION

Hypercoagulation is a self defence of the body for limiting the aortic intimal tear to prevent aortic rupture. Therefore the thromboembolism of the other vessels may be observed concomitantly. The patients should be evaluated individually and the endovascular treatment options should be kept in mind for such miscellaneous circumstances.

### *Informed consent*

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

### *Conflict of interest*

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Pape L, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, et al. Presentation, diagnosis and outcomes of acute aortic dissection: 17-year trends from the International Registry of Acute Aortic Dissection. *J Am Coll Cardiol* 2015;66:350-8.
- [2] Yavuz S. Alternative cannulation techniques in surgical repair for acute type A aortic dissection. *Eur Res J* 2016;2:1-6.
- [3] Nienaber CA, Kische S, Rousseau H, Eggebrecht H, Rehders TC, Kundt G, et al. Endovascular repair of type B aortic dissection: long-term results of the randomized investigation of stent grafts in aortic dissection trial. *Circ Cardiovasc Interv* 2013;6:407-16.
- [4] Grimm JC, Magruder JT, Crawford TC, Sciortino CM, Zehr KJ, Mandal K, et al. Differential outcomes of type A dissection with malperfusion according to affected organ system. *Ann Cardiothorac Surg* 2016;5:202-8.
- [5] Tapson VF. Acute pulmonary embolism. *N Engl J Med* 2008;358:1037-52.
- [6] Yavuz S, Toktas F, Goncu T, Eris C, Gucu A, Ay D, et al. Surgical embolectomy for acute massive pulmonary embolism. *Int J Clin Exp Med* 2014;7:5362-75.
- [7] Appoo JJ, Bozinovski J, Chu MW, El-Hamamsy I, Forbes TL, Moon M, et al. Canadian Cardiovascular Society/Canadian Society of Cardiac Surgeons/Canadian Society for Vascular Surgery Joint Position Statement on Open and Endovascular Surgery for Thoracic Aortic Disease. *Can J Cardiol* 2016;32:703-13.
- [8] Fattori R, Cao P, De Rango P, Czerny M, Evangelista A, Nienaber C, et al. Interdisciplinary expert consensus document on management of type B aortic dissection. *J Am Coll Cardiol* 2013;61:1661-78.
- [9] Sher A, Tadros RO. Is there a role for expanding the indication for TEVAR in acute type B aortic dissections? A further classification of uncomplicated dissections. *J Vasc Endovasc Surg* 2016;1:3.
- [10] Kagawa Y, Ota S, Hoshino K, Yamada N, Nakamura M, Ito M. Acute pulmonary thromboembolism and deep vein thrombosis during the medical treatment of acute aortic dissection was successfully treated by the combination of inferior vena cava filter installation and anticoagulant therapy: a case report. *Ann Vasc Dis* 2015;8:36-9.
- [11] Jo Y, Anzai T, Ueno K, Kaneko H, Kohno T, Sugano Y et al. Re-elevation of D-dimer as a predictor of re-dissection and venous thromboembolism after Stanford type B acute aortic dissection. *Heart Vessels* 2010;25:509-14.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Kikuchi-Fujimoto disease mimicking hematological malignancy: a case report

Hakan Yarkıcı<sup>1</sup>, Faruk Elyiğit<sup>1</sup>, Ahmet Peker<sup>1</sup>, Dudu Solakoğlu Kahraman<sup>2</sup>, Nilgün Erbil<sup>2</sup>, Harun Akar<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, University of Health Sciences, Tepecik Training and Research Hospital, İzmir, Turkey

<sup>2</sup>Department of Clinic of Pathology, University of Health Sciences, Tepecik Training and Research Hospital, İzmir, Turkey

DOI: 18621/eurj.404127

## ABSTRACT

Kikuchi-Fujimoto disease or histiocytic necrotizing lymphadenitis is a benign histopathological condition and a rare cause of lymphadenopathies. This disease which is seen in women around the age of 30 in the far east countries is generally presented with lymphadenopathy, fever, weight loss, and myalgia symptoms. In this article, we would like to present a case of Kikuchi-Fujimoto disease in the histopathology of the lymph node excision, which was examined in terms of lymphadenopathy.

**Keywords:** Kikuchi-Fujimoto disease, histiocytic necrotizing lymphadenitis, benign, lymphadenopathy

*Received: March 11, 2018; Accepted: June 6, 2018; Published Online: June 21, 2018*

**K**ikuchi-Fujimoto disease (KFD) was initially described in Japan. This disease is also known as histiocytic necrotizing lymphadenitis and the underlying pathogenesis of this disease is unclear. This disease which is seen in women around the age of 30 is generally presented with lymphadenopathy, fever, weight loss, and myalgia. In addition, it also affects men and it has wide age limits. It manifests with diffuse lymphadenopathy, especially in the head and neck region. Mediastinal lymphadenopathy, hepatosplenomegaly can also be seen in some patients. Rarely, skin lesions such as diffuse erythema and urticaria can be seen in the body. There is no specific laboratory test used to diagnose Kikuchi-Fujimoto disease. Increases in erythrocyte sedimentation rate and C-reactive protein (CRP) levels and mild leucopenia can be seen in these cases. Lactate dehydrogenase (LDH) levels and anti-nuclear antibody (ANA) titers may increase in complicated

patients [1]. It is important to distinguish between infectious, rheumatologic, and malignant conditions as they are in differential diagnosis. In differential diagnosis, lymphoma, adenocarcinoma metastasis, tuberculosis, toxoplasmosis, cat scratch disease, human immunodeficiency virus disease (HIV), parvovirus and systemic lupus erythematosus (SLE) should be considered [2]. The exact diagnosis of the disease is made by lymph node biopsy. We wanted to present a case of Kikuchi-Fujimoto disease, which was diagnosed via lymph node excision.

## CASE PRESENTATION

An immigrant 25-year-old male patient with no known history of a disease was hospitalized in our Internal Medicine Clinic to investigate fatigue and high fever ongoing 15 days, weight loss of 8 kg in the



**Address for correspondence:** Ahmet Peker, MD., University of Health Sciences, Tepecik Training and Research Hospital, Department of Internal Medicine, İzmir, Turkey  
E-mail: drahmet88@gmail.com, Tel: +90 538 8502519

e-ISSN: 2149-3189

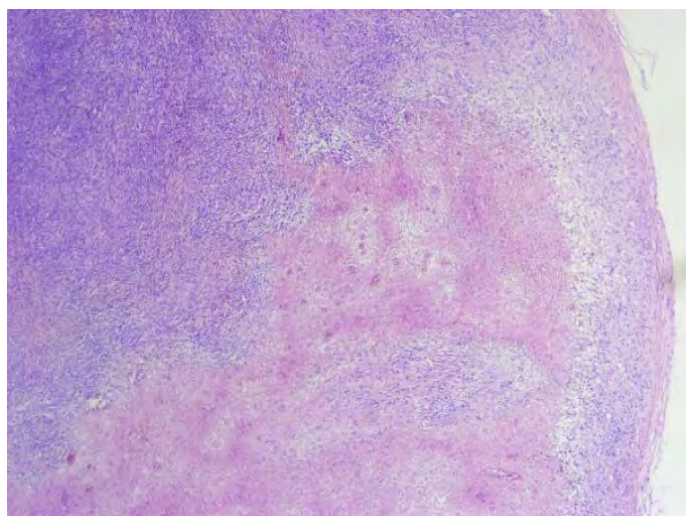
Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

last 3 months, and mediastinal mass etiology on chest X-ray. He hadn't a history of hematological disease, tuberculosis, contact with a case of tuberculosis and history of bite or contact with wild animals. On physical examination, his blood pressure was 120/80 mm Hg, pulse was 85/min, temperature was 36.5°C. Physical examination was normal except for the presence of lymphadenopathies in the bilateral neck, cervical and supraclavicular regions. Laboratory values showed that white blood cell count was 3300/uL, hemoglobin: 11.8 g/dL, thrombocyte count: 313.000/uL, urea: 23 mg/dL, creatinine: 0.9 mg/dL, AST: 23 u/L, lactate dehydrogenase: 347 u/L, total bilirubin: 0.4 mg/dL, direct bilirubin: 0.02 mg/dL, albumin: 3.7 g/dL, sodium: 136 mmol /L, potassium: 4.14 mmol/L and calcium 9.9 mg/dL. The erythrocyte sedimentation rate was 42 mm/h and CRP was 4.2 mg/dl. HIV, antinuclear antibody, anti-ds DNA, rheumatoid factor, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) tests were negative. Computed tomography of the thorax revealed conglomerated mediastinal lymphadenopathies reaching 9×6 cm in size and lymphadenopathies in the left paracardiac areas. Ultrasonography of the neck showed a large number of heterogeneous lymph nodes, which lost their hilar echogenicity, with a size of 45×22 mm in bilateral supraclavicular region. Excision of the right supraclavicular lymph node was performed in the patient whose bone marrow biopsy examination was normal. Patchy fibrinoid necrosis

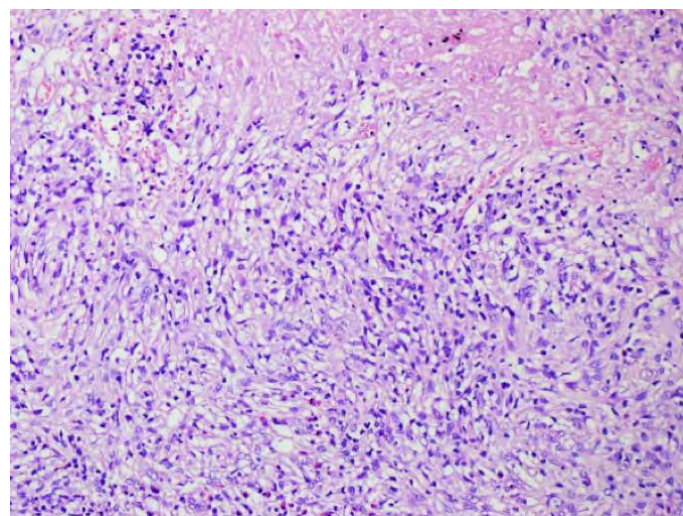
with nuclear fragments in the lymph node, lymphohistiocytic infiltration (Figure 1), caryorectic nuclear debris in necrosis, surrounding histiocytes, lymphocytes and eosinophils (Figure 2) were observed in the biopsy. The biopsy was reported as subacute necrotizing lymphadenitis (Kikuchi-Fujimoto disease). After the diagnosis, the patient's supportive treatment continued. Outpatient controls were planned and he was discharged. Spontaneous regression in lymphadenopathy dimensions and clinical improvement was observed at 6 months follow-up.

## DISCUSSION

Although the pathogenesis of KFD is not fully understood, it has been suggested that KFD is caused by apoptosis with hyperimmune or autoimmune mechanisms initiated by viral or other antigens [3, 4]. Viral or postviral etiologies also have been proposed. There are reports that stated the disease may be concomitant with infectious agents such as EBV, CMV, HHV-6, HIV, and toxoplasmosis and tuberculosis [1]. It has been reported in the literature that patients with SLE can subsequently develop KFD or that patients with KFD can develop SLE [5]. SLE is distinguished from KFH by the presence of hematoxylen-eosin bodies and dense plasma cells in the paracortical region in the histopathological examination [6]. In our case, the tests were negative



**Figure 1.** Lymph node necrosis and lymphohistiocytic infiltration. H & E (×200)



**Figure 2.** Caryorectic nuclear debris in necrosis, surrounding histiocytes.

in terms of CMV, EBV and SLE. He also has a negative family history and a clinic in terms of tuberculosis. Although KFD usually involves the cervical lymph nodes, it may also involve the axillary, thoracic, abdominal, and inguinal lymph nodes [5]. Extranodal involvement has been rarely reported [7]. In our case, besides typical cervical involvement, mediastinal and paracardiac lymphadenopathy involvement was also observed. Although the disease has been reported frequently in Far Eastern countries and women [6], it is interesting that our case is Middle Eastern origin and male. For definitive diagnosis, excisional or incisional lymph node biopsy is required. The sensitivity of lymph node aspiration cytology is 55-60% and is associated with high false positive rates of diagnosis. We diagnosed the disease with excision of the right supraclavicular lymph node in our case. KFD is histopathologically characterized by focal necrotic foci, accompanied by diffuse karyorrhectic and nuclear debris, and histiocytes proliferating around them, locally with plasma cells and T lymphocytes [8]. It is differentiated from the lymphoma by the absence of cellular atypia and the absence of neutrophil leukocytes despite the presence of necrosis [6]. KFD has no specific treatment. In some cases, it is known that steroid therapy has been tested to reduce symptoms [9]. In general, KFD is a self-limited disease within 6 months. The recurrence rate of the disease was 3-4% [10]. We did not perform any specific treatment other than supportive care, and we observed clinical improvement within 6 months.

## CONCLUSION

Histopathologic examination revealed a rare cause of lymphadenopathy in the benign nature of Kikuchi-Fujimoto disease, although the presence of multiple lymphadenopathies in our case suggests a possible preliminary diagnosis of hematologic malignancy on

the first plan. Due to the lack of a specific diagnostic method, histopathologic examination of biopsy materials is regarded as the easiest and reliable way to achieve accurate diagnosis. Thus, early excisional biopsy in the presence of lymphadenopathy can prevent unnecessary investigations, reduce the cost of diagnosis and treatment, and can terminate the concern that the patient is malignant.

## Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

## Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Nikanne E, Ruoppi P, Vornanen M. Kikuchi's disease: report of three cases and an overview. *Laryngoscope* 1997;107:273-6.
- [2] Scully DF, Walsh C, Eskander HF, Kane D. Kikuchi-Fujimoto disease--an unusual mimicker? *N Z Med J* 2013;126:85-8.
- [3]. Bosch X, Guilabert A. Kikuchi-Fujimoto disease. *Orphanet J Rare Dis* 2006;1:18.
- [4] Pandit S, Das A, Choudhury S, Das SK. A rare case of Kikuchi-Fujimoto disease. *J Nat Sci Biol Med* 2013;4:490-2.
- [5] Bhat NA, Hock YL, Turner NO, Das Gupta AR. Kikuchi's disease of the neck (histiocytic necrotizing lymphadenitis). *J Laryngol Otol* 1998;112:898-90.
- [6] Ramiraz AL, Johnson J, Murr AH. Kikuchi-Fujimoto's disease: an easily misdiagnosed clinical entity. *Otolaryngol Head Neck Surg* 2001;125:651-3.
- [7] Tong TR, Chan OW, Lee K. Diagnosing Kikuchi disease on fine needle aspiration biopsy: a retrospective study of 44 cases diagnosed by cytology and 8 by histopathology. *Acta Cytol* 2001;45:953-7.
- [8] Kapadi V, Robinson BA, Angus HA. Kikuchi's disease presenting as fever of unknown origin. *Lancet* 1989;2:1519-20.
- [9] Jang YJ, Park KH, Seok HJ. Management of Kikuchi's disease using glucocorticoid. *J Laryngol Otol* 2000;114:709-11.
- [10] Sousa Ade A, Soares JM, Sá Santos MH, Martins MP, Salles JM. Kikuchi-Fujimoto disease: three case reports. *Sao Paulo Med J* 2010;128:232-5.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.



# A rare complication after inguinal hernia repair: testicular torsion

Yusuf Önder Özsağır<sup>1</sup>, Görkem Akça<sup>1</sup>, Mustafa Ozan Horsanali<sup>2</sup>, Hüseyin Eren<sup>1</sup>, Eyüp Dil<sup>1</sup>

<sup>1</sup>Department of Urology, Recep Tayyip Erdoğan University School of Medicine, Rize, Turkey

<sup>2</sup>Department of Urology, Recep Tayyip Erdoğan University Training and Research Hospital, Rize, Turkey

DOI: 10.18621/eurj.381909

## ABSTRACT

Testicular torsion is the most common urological emergency characterized by reduced blood flow of the testis, often due to spermatic cord torsion occurring in adolescence. A 68-year-old male patient admitted our hospital emergency service with the complaint of acute scrotal pain for a week. On history, he had undergone right inguinal hernia repair with synthetic mesh one week ago. Due to reduced blood flow of right testicular artery on colored doppler ultrasonography, emergent surgery was performed. On intraoperative examination, 360 degree torsion of spermatic cord from distal to the mesh, thrombosis of right testicular artery and necrosis of testicular tissue was observed. After detorsion of right testis, absence of blood supply to the right testis was observed. According to these findings, right inguinal orchiectomy was performed. It should be kept in mind that persistent pain may be a sign of testicular torsion which may develop early after inguinal hernia repair with synthetic polypropylene mesh. In suspicious of testicular torsion because of persistent scrotal pain after inguinal surgery, scrotal colored doppler ultrasonography must be performed immediately and consulted to the urologist. Succeed results may be provided by multidisciplinary approach and early treatment.

**Keywords:** Orchiectomy, testicular torsion, inguinal hernia repair, synthetic polypropylene mesh

*Received: January 20, 2018; Accepted: April 18, 2018; Published Online: June 1, 2018*

**T**esticular torsion is a common surgical emergency among adolescents and adults characterized by a decrease in testicular blood flow which is often occurs due to torsion of spermatic cord. It is one of the most common urological problems in patients admitting to emergency service presenting with acute scrotal pain. There are three types of torsion; extravaginal, intravaginal and torsion of testis appendicularis. Scrotal pain spreading to the lower quadrant of the abdomen may cause symptoms such as nausea and vomiting. The etiology of testicular torsion is mostly idiopathic, and 20% can be traumatic. In one study, the incidence of testicular torsion was

reported as 3.5/100 000 [1]. Although, the risk of encountering inguinal hernia throughout life in men is reported as 27%, it is 3% for women. It is thought that about 20 million hernia repair is performed every year in the world [2].

In case of inguinal hernia repair with synthetic mesh techniques the spermatic cord is potentially affected by chronic inflammatory tissue remodeling that may impair testicular perfusion inducing acute scrotum [3]. Previous studies demonstrated that mesh repair procedure may induce inflammatory response that cause to the encasement of spermatic cord by scar tissue. Although testicular perfusion is not



**Address for correspondence:** Mustafa Ozan Horsanali, MD., Recep Tayyip Erdoğan University Training and Research Hospital, Department of Urology, Rize, Turkey  
E-mail: drozanhorsanali@yahoo.com, Tel: +90 507 9942217

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

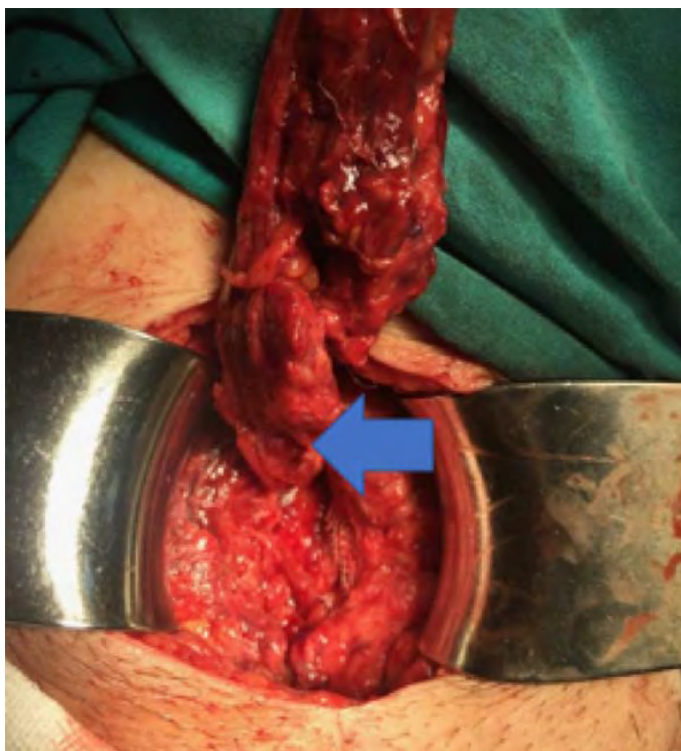
compromised in most of cases, in some cases, a concomitant inflammatory process may impair the blood supply leading to acute scrotum [4, 5]. Testicular torsion causing acute scrotum after inguinal hernia repair is a very rare condition. In our case report, we aimed to present a case of early testicular torsion after inguinal hernia repair with synthetic polypropylene mesh.

## CASE PRESENTATION

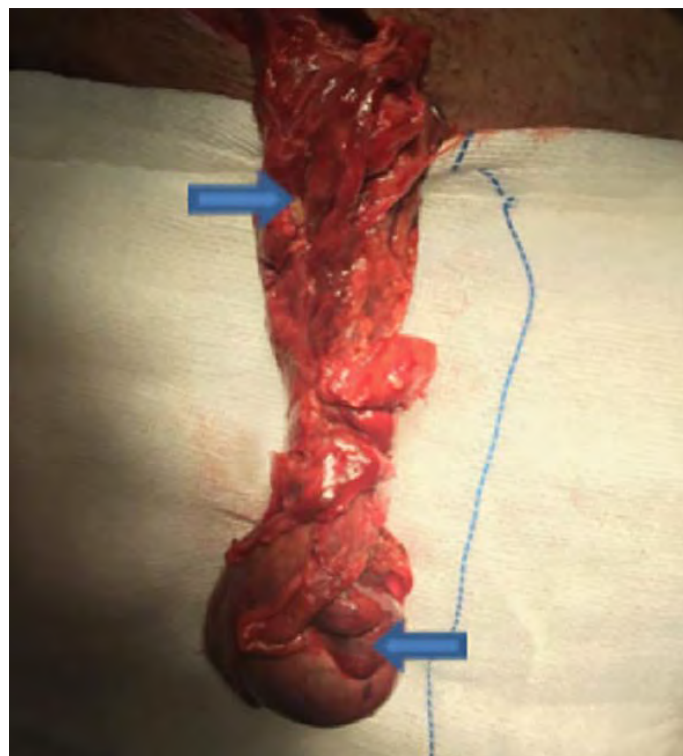
A 68-year-old male patient was admitted to the emergency department with the complaint of persistent right scrotal pain and swelling for a week after operated for right inguinal hernia. On his history, he explained that he went to the general surgeon several times in a week with the same complaint. Patient was consulted to us due to testicular arterial flow were not observed on scrotal doppler ultrasonography evaluation at emergency service.

The vital findings of the patient were stable; he was conscious and cooperative during the application

to the emergency department. On physical examination, right testis was painful with palpation, hyperemic and edematous. Scrotal pain did not decrease when elevation was performed. In the emergency service scrotal doppler ultrasonography was performed. Doppler ultrasonography was revealed that the scrotal skin was thickened and edematous. Blood flow was patents until the distal part of right spermatic cord. However, no flow was detected in the right testis parenchyma, and the parenchyma echo was diffusely reduced compared to the left. According to physical and radiological findings, right testicular torsion was diagnosed and emergent surgical exploration was planned. Right inguinal incision was performed to reach the spermatic cord. Full torsion of right testis distal to inguinal mesh was observed intraoperative. In the previous operation, it was noticed that the synthetic polypropylene mesh was implanted and it was not infected. Then, spermatic cord was detorsioned and general surgeon was invited to the operation and patient consulted intraoperative. Synthetic polypropylene mesh did not remove according to general surgeon's comments. It was



**Figure 1.** Intraoperative imagine of relationship between surgical mesh and spermatic cord. Arrow shows torsion of the spermatic cord.



**Figure 2.** Arrows shows intraoperative necrotic parts of testis and spermatic cord.

observed that the mesh did not compress the spermatic cord. According to the intraoperative findings, mesh independent testicular torsion was considered (Figure 1). Upon this features, tunica vaginalis was opened by incision and it was observed that the right testicular tissue was necrosed (Figure 2). Following the application of warm compress and papaverine injection into the spermatic cord for twenty minutes, the testis was not infused and no improvement was observed in the parenchymal color. According to these findings, inguinal orchiectomy was decided. Spermatic cord clamped and orchiectomy was performed. Patient was discharged after 2 days from operation without complication. Surgical specimen was pathologically evaluated and reported as necrotizing, torsion of testis, inflammatory granulation tissue and congestion.

## DISCUSSION

Testicular torsion is an emergency condition that can be easily diagnosed by physical examination and color doppler ultrasonography in patients admitting emergency service and presenting with an acute scrotum complaint [6]. Torsion of appendices testis, epididymitis, incisional hernia, tumor and trauma should be considered in the differential diagnosis. Testicular torsion peaks at two years of age; extravaginal testicular torsion is common in the prepubertal period, whereas intravaginal testicular torsion is most common in puberty and other advanced ages [7]. Physical examination and scrotal color doppler ultrasonography are the most preferred diagnostic methods. Since scrotal color doppler ultrasonography has a low probability of false positives, surgical exploration is essential for clinically suspected cases of torsion [8].

Inguinal hernia repair with mesh using is a commonly preferred surgical method due to reduced risk of recurrence by 30-50%. Complications after inguinal hernia repair occur in 1.7%-8% of all cases. Recurrence of hernia (0.3%-3.8%) is the most common complication, followed by injury to the vas deferens (1.6%) and injury to the vessels; in particular injury to the spermatic vessels can result in ischemic orchitis and lead to testicular atrophy (0.2%-1.1%). Unusual complications include testicle entrapment in

the inguinal canal, wound infections, ilio-inguinal, ilio-hypogastric and genitofemoral nerve damage [9]. In both experimental and clinical studies reported that, after both open and laparoscopic hernia repair with mesh, causes scar and testicular ischemia are rarely observed. Among the causes of testicular ischemia, acute thrombosis of the pampiniform plexus is considered first of all deduced from arterial thrombosis. Ischemia and necrosis may not observed as there are collateral vessels of arterial flow in acute arterial occlusion [10]. In fact, 33% of the cases with completely obstructed spermatic cord were reported not to have ischemia [11]. Testicular ischemia due to testicular torsion in the early period after inguinal hernia repair using synthetic polypropylene mesh is much more rare condition. In present report, we did not observe the testicular blood flow with scrotal doppler in patient with acute scrotum on the postoperative 7th day after opened inguinal hernia repair using polypropylene synthetic mesh. In the surgical exploration; right testis was torsioned from distal to the synthetic mesh. After detorsion of the right testis, blood flow could not observed and necrotic appearance of the right testis was observed. These features were considered secondary to the right testicular torsion. As a result, right inguinal orchiectomy was performed to the patient.

Because of the increasing elderly population, inguinal hernia repair is one of the most common surgical procedures performed by general surgeons in everyday practice. The acute scrotum associated with testicular torsion is one of the most common emergency surgical conditions in emergency service encountered by urologists. Persistent scrotal pain after inguinal surgeries may be sign of testicular torsion. Because the first patient visits performed by general surgeons after surgery, general surgeons must be awoken in terms of testicular torsion in differential diagnosis. In the study of Holloway including 8 patient who underwent inguinal hernia repair reported testicular infarction with scrotal colored doppler ultrasonography evaluation in 2 patient and absence of testicular blood flow in 1 patient after inguinal hernia repair [12]. In suspicious of testicular torsion after inguinal surgeries, scrotal colored doppler ultrasonography must be performed immediately and patients must consulted to the urologist. Routine examination of blood supply of testis with colored

doppler ultrasonography may facilitate early diagnosis of testicular torsion or infarct and give an opportunity for early treatment. We think good results could be succeeding with multidisciplinary approach of urologist, general surgeon and radiologist in the early period after surgery.

## CONCLUSION

It should be kept in mind that testicular torsion may develop during the early period in patients undergoing inguinal surgery such in our case and urgent surgical decision may be required as soon as possible. Otherwise, adverse events resulting with organ loss may occur and may put surgeons in trouble in terms of legally.

### *Authorship declaration*

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### *Informed consent*

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

### *Conflict of interest*

The authors declared that there are no potential

conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Huang WY, Chen YF, Chang HC, Yang TK, Hsieh JT, Huang KH. The incidence rate and characteristics in patients with testicular torsion: a nationwide, population-based study. *Acta Paediatr* 2013;102:e363-7.
- [2] Kingsnorth A, LeBlanc K. Hernias: inguinal and incisional. *Lancet* 2003;362:1561-71.
- [3] Pepe P, Aragona F. Testicular ischemia following mesh hernia repair and acute prostatitis. *Indian J Urol* 2007;23:323-5.
- [4] Peiper C, Junge K, Klinge U, Strehlau E, Kronen C, Ottinger A, et al. The influence of inguinal mesh repair on the spermatic cord: a pilot study in the rabbit. *J Invest Surg* 2005;18:273-8.
- [5] Shin D, Lipshultz LI, Goldstein M, Barne GA, Fuchs EF, Nagler HM, et al. Herniorrhaphy with polypropylene mesh causing inguinal vasal obstruction: a preventable cause of obstructive azoospermia. *Ann Surg* 2005;241:553-8.
- [6] Akin EA, Khati NJ, Hill MC. Ultrasound of the scrotum. *Ultrasound Q* 2004;20:181-200.
- [7] Arena F, Nicotina P, Scalfari G, Visalli C, Arena S, Zuccarello B, et al. A case of bilateral prenatal testicular torsion: ultrasonographic features, histopathological findings and management. *J Pediatr Urol* 2005;1:369-72.
- [8] Pepe P, Panella P, Pennisi M, Aragona F. Does color Doppler sonography improve the clinical assessment of patients with acute scrotum? *Eur J Radiol* 2006;60:120-4.
- [9] Dellabianca C, Bonardi M, Alessi S. Testicular ischemia after inguinal hernia repair. *J Ultrasound* 2011;14:205-7.
- [10] Fong Y, Wantz G. Prevention of ischemic orchitis during inguinal hernioplasty. *Surg Gynecol Obstet* 1992;174:399-402.
- [11] Heifetz CJ. Resection of the spermatic cord in selected inguinal hernias: Twenty Years of Experience. *Arch Surg* 1971;102:36-9.
- [12] Holloway BJ, Belcher HE, Letourneau JG, Kunberger LE. Scrotal sonography: a valuable tool in the evaluation of complications following inguinal hernia repair. *J Clin Ultrasound* 1998;26:341-4.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Pure spinal extradural arteriovenous malformation in the thoracolumbar region: a case report

Fatih Yakar<sup>1</sup>, Ümit Eroğlu<sup>2</sup>, İhsan Doğan<sup>2</sup>, Hasan Çağlar Uğur<sup>2</sup>

<sup>1</sup>Department of Neurosurgery, Kars Harakani Hospital, Kars, Turkey

<sup>2</sup>Department of Neurosurgery, Ankara University School of Medicine, İbni Sina Hospital, Ankara, Turkey

DOI: 10.18621/eurj.373775

## ABSTRACT

Pure extradural spinal arteriovenous malformations (AVMs) are formed with an epidural artery, a nidus and an arterialized intradural vein in the absence of vertebral cavernous hemangioma and uncommon lesions. The most common extradural tumors are metastasis, lymphomas, benign tumors and malignant bony tumors. Herein, we present a 29-year-old Turkish woman with pure extradural mass that histopathologically diagnosed as AVM. When an extradural spinal compressive mass is detected, neurosurgeons should consider on AVM in differential diagnosis and requirement of selective spinal angiography.

**Keywords:** Arteriovenous malformation, selective spinal angiography, extradural mass

*Received: January 2, 2018; Accepted: May 17, 2018; Published Online: May 22, 2018*

Pure extradural spinal arteriovenous malformations (AVM) are formed with an epidural artery, a nidus and an arterialized intradural vein in the absence of vertebral cavernous hemangioma [1]. The extradural AVMs cause neurological symptoms by increased perimedullary venous pressure and sometimes mimic other spinal pathologies [2]. In this paper, an extradural pure AVM is reported as an uncommon case.

## CASE PRESENTATION

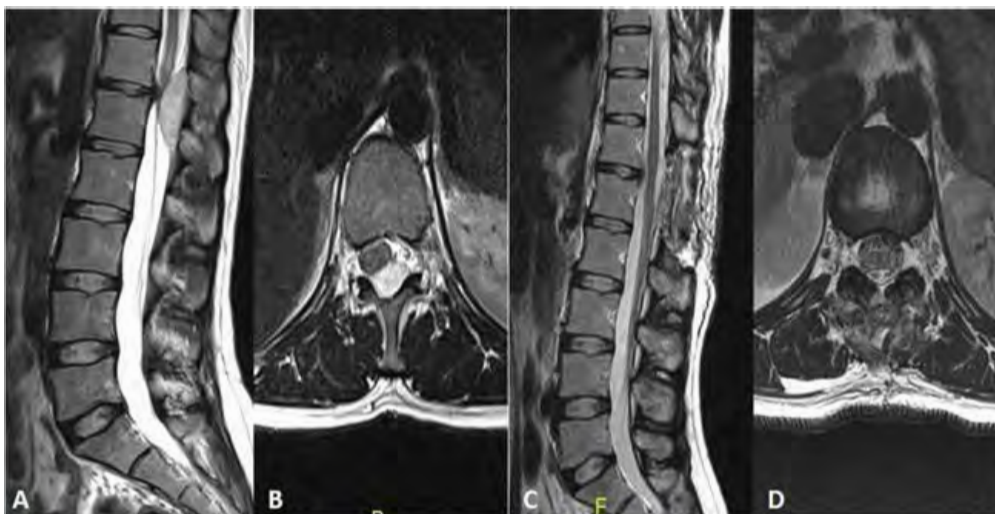
A 29-year-old woman presented with the left leg pain. The pain was aggravated by the rest. Neurological examination on admission revealed straight leg raising was positive on the left leg and no loss of sensation and power. Deep tendon reflex was not reduced. Bilateral Babinski signs were absent.

Magnetic resonance imaging (MRI) showed an extradural compressive mass between the thoracic 12 (T12) and lumbar 1 (L1) vertebra (Figures 1a and 1b). Patient had an anaphylaxis history because of contrast agent allergy so MRI was planned without contrast agent. During the procedure, T12 and L1 partial laminectomy was performed and we noticed a highly hemorrhagic vascular lesion with no adherence to the dura. Arterial feeders were determined and coagulated but drainage vein was not identified (Figures 2a, 2b, and 2c). The dura opened and not found an intradural lesion so it's proved that lesion was a pure extradural lesion (Figure 2d). She had no new additional neurological deficit in the postoperative period. No lesion detected on early postoperative MRI (Figures 1d and 1e). The lesion consists of vascular structures that contain anastomosing, dilatation, congestion, and thrombus organization mixed with fat vacuoles in the microscopic examination (Figures 3a and 3b).



Address for correspondence: Fatih Yakar, MD., Kars Harakani Hospital, Department of Neurosurgery, Kars, Turkey  
E-mail: yakarneurosurgery@gmail.com

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

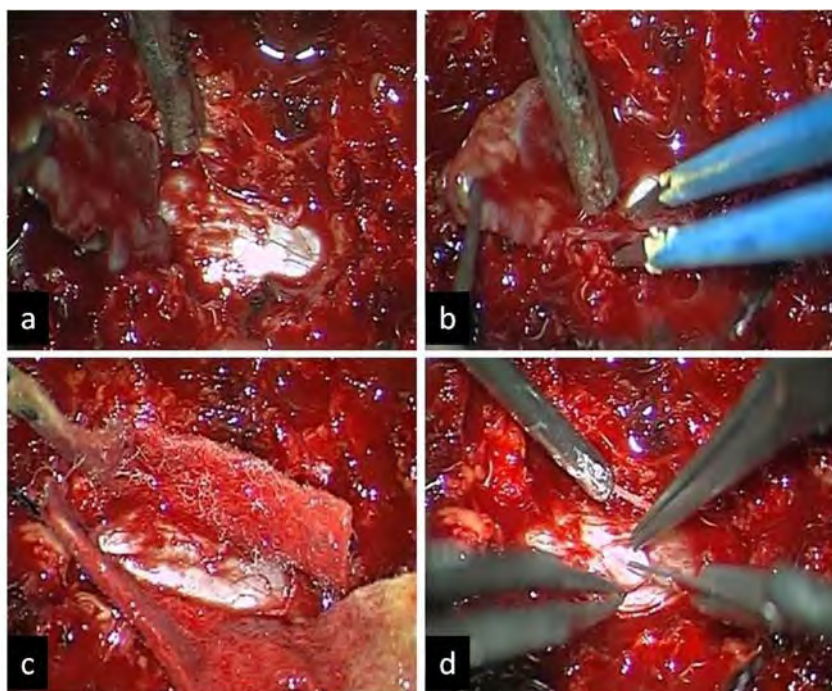


**Figure 1.** Preoperative thoracolumbar MRI showed an extradural mass (a and b), early postoperative MRI (c) sagittal and (d) axial sections.

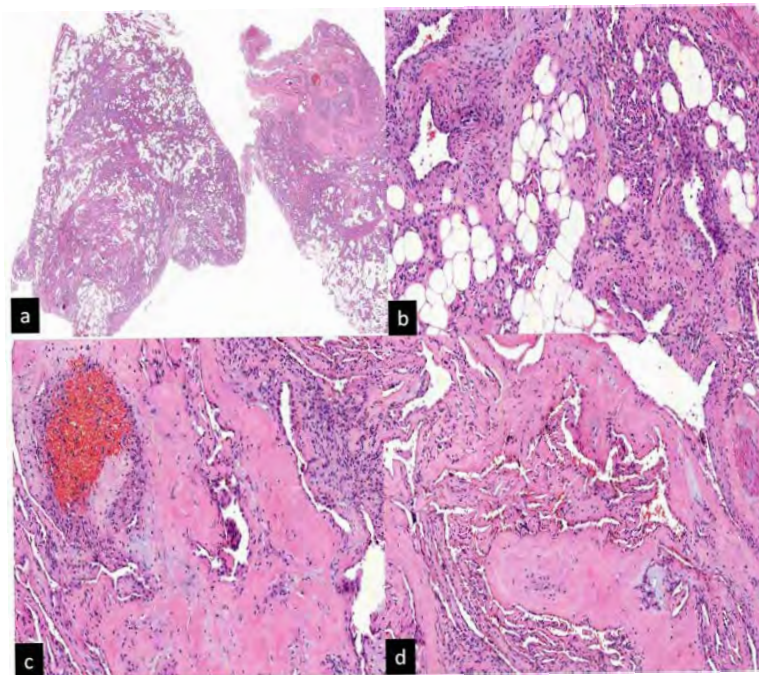
Vascular walls are hyalinized and have focal calcifications and different thickness (Figures 3c and 3d). So it's diagnosed as AVM. At first year follow-up, she had no leg pain and had no motor deficit in both legs. There was no lesion on the first year follow-up MRI (Figures 4a and 4b).

### DISCUSSION

Spinal AVMs were firstly described by Gaupp in 1888 and natural history of spinal AVMs are still unclear [3]. Spinal AVMs are classified into 5 groups: extradural arteriovenous fistulae (AVFs), intradural



**Figure 2.** (a) The intraoperative view of the vascular lesion without an obvious nidus pattern after T12 and L1 partial laminectomy. (b) Bipolar coagulation of arterial feeders. (c) The view of dura after total resection of the lesion. (d) Dura opened and not found intradural lesion so it's evaluated as a pure extradural arteriovenous malformation..



**Figure 3.** Vascular structures with fat cells (a and b) (H&E, x12, x153). Thrombosis and vascular endothelial proliferation in vascular lumens (c and d) (H&E, x153, x127).

AVFs, extradural-intradural AVFs, intramedullary AVMs, and conus medullaris AVM [3]. Fifteen to 20% of spinal vascular anomalies are extradural and cavernous hemangiomas are most common but AVMs are uncommon (3-4% of all intradural spinal cord

mass lesions [3, 4]. AVMs are usually situated intra- and/or perimedullarily [5].

The most common dural spinal AVM is a vertebral body hemangioma that interferes with the extradural spinal canal [6]. Pure extradural spinal AVMs' nidus



**Figure 4.** (a) Sagittal and (b) axial sections of postoperative first year follow up MRI, no lesion was detected

and venous drainage are only extradural without a vertebral body hemangioma, and rarely reported in the literature [1, 7-10].

Tortuous or dilated veins can be detected on the spinal MRI and suspicious of AVM but it is usually not clear [1]. We had no suspicion about AVM in the preoperative MRI. The gold standard of AVM diagnosis is selective spinal angiography [11]. We noticed no hemangioma in the adjacent vertebral body and there was no specific evidence for AVM on MRI and so selective spinal angiography was not performed.

Extradural AVMs can rarely cause spontaneous spinal epidural hematoma and sometimes can mimic Guillain-Barre syndrome [10]. There was no epidural hematoma in our case due to preoperative radiological and intraoperative view. Jonathan *et al.* [12] reported a pediatric extradural spinal AVM and specified that it was mimicking schwannoma. Literature supported us that AVMs may interfere with many lesions [10, 12].

## CONCLUSION

Pure extradural lumbar spinal AVMs in the absence of vertebral body hemangiomas are uncommon in the literature. When an extradural spinal compressive mass is detected, neurosurgeons should consider on AVM in differential diagnosis and requirement of selective spinal angiography.

### *Informed consent*

Written informed consent was obtained from the patient for the publication of this case report.

### *Conflict of interest*

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Marshman LA, David KM, Chawda SJ. Lumbar extradural arteriovenous malformation: case report and literature review. *Spine J* 2007;7:374-9.
- [2] Seung L, Soon K, Young K, In L. Lumbar extradural arteriovenous malformation mimicking intervertebral disc herniation in the lumbar spine. *Korean J Spine* 2008;5:264-6.
- [3] Ozpinar A, Weiner GM, Ducruet AF. Epidemiology, clinical presentation, diagnostic evaluation, and prognosis of spinal arteriovenous malformations. *Handb Clin Neurol* 2017;143:145-52.
- [4] Papo I, Salvolini U, Vecchi A. Extradural spinal hemangioblastomas. *J Neurosurg Sci* 1973;17:184-92.
- [5] Saravanabavaan S, Adrian R, Michael F, Ulrich S, Johannes N, Oliver G. Completely extradural intraspinal arteriovenous malformation in the lumbar spine: a case report. *J Med Case Rep* 2014;8:216.
- [6] Osborn AG. Intracranial vascular malformations. In: Osborn AG, editor. *Diagnostic neuroradiology*. St. Louis, MO: Mosby-Year Book Inc.; 1994:284-329.
- [7] Alexander MJ, Grossi PM, Spetzler RF, McDougall CG. Extradural thoracic arteriovenous malformation in a patient with Klippel-Trenaunay-Weber syndrome. *Neurosurgery* 2002;51:1275-9.
- [8] Gourie-Devi M, Prakash B. Vertebral and epidural hemangioma with paraplegia in Klippel-Trenaunay-Weber syndrome: case report. *J Neurosurg* 1978;48:814-7.
- [9] Han SS, Love MB, Simeone FA. Diagnosis and treatment of a lumbar extradural arteriovenous malformation. *AJNR Am J Neuroradiol* 1987;8:1129-30.
- [10] Paraskevopoulos D, Magras I, Polyzoidis K. Spontaneous spinal epidural hematoma secondary to extradural arteriovenous malformation in a child: a case-based update. *Childs Nerv Syst* 2013;29:1985-91.
- [11] Sugawara T, Hirano Y, Itoh Y, Kinouchi H, Takahashi S, Mizoi K. Angiographically occult spinal dural arteriovenous fistula located using selective computed tomography angiography. *J Neurosurg Spine* 2007;7:215-20.
- [12] Jonathan GE, Nair BR, Joseph V, Mani S, Chacko G. Lumbar extradural arteriovenous malformation mimicking a schwannoma in a child: rarepresentation of neurofibromatosis type-1. *Neurol India* 2017;65:900-2.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.



# Extensive cranial, spinal and abdominal involvement in brucellosis: a case with review of the literature

Ali Murat Koç<sup>1</sup>, Yaprak Ünsal<sup>2</sup>, Hülya Mollamehmetoğlu<sup>1</sup>, Özgür Esen<sup>1</sup>, Rifat Reha Bilgin<sup>2</sup>

<sup>1</sup>Department of Radiology, University of Health Sciences, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey

<sup>2</sup>Department of Neurology, University of Health Sciences, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey

DOI: 10.18621/eurj.378485

## ABSTRACT

Brucellosis is still an endemic disease in certain parts of world. It's clinical and radiological features are crucial for an accurate diagnosis. Although systemic disease in brucellosis shows common typical features, it's also very important to know the uncommon features of multisystemic involvement. Herein we present a case of brucellosis with unique imaging features of extensive cranial, spinal, abdominal involvement in a middle aged woman.

**Keywords:** *Brucella*, spine, multisystemic, magnetic resonance imaging

*Received: January 13, 2018; Accepted: May 2, 2018; Published Online: May 28, 2018*

**B**rucellosis is a multisystemic, granulomatous infection involving several organs or systems of the body. It's mainly seen in endemic areas of the world and transmitted from animals to humans via unpasteurized milk and milk products or direct occupational contact [1]. Systemic dissemination can cause the disease to become recurrent and chronic if it progresses after resolution of acute phase. Osteoarticular system is found to be the most common site of involvement followed by central nervous, genitourinary systems, liver and skin [2]. Although central nervous system involvement is not very common it causes important sequela. Here we present a case of brucellosis with extensive spinal, cranial and abdominal involvement.

## CASE PRESENTATION

A 48-year-old woman admitted to our hospital

with fatigue, abnormal gait, weakness in legs, vertigo and hearing loss complaints. Medical history examination revealed that her symptoms were progressive over the last 18 months. She told that she had worked in a farm with responsibility of animal care. Her general condition was good; she exhibited full consciousness, orientation and cooperation. Neurological examination showed features compatible with pyramidal and sensorineural system involvement. ENT examination also confirmed bilateral sensorineural hearing loss. Laboratory tests, including liver and renal functions, urine and blood biochemical analysis were all within normal limits except mild elevation of serum cholesterol.

MRI examination of brain and spinal cord were performed to evaluate a possible central nervous system pathology. Cranial magnetic resonance imaging (MRI) showed T2-hyperintense cortical nodular lesions with mild perilesional vasogenic edema at the right frontal lobe (Figure 1). Lesions



**Address for correspondence:** Ali Murat Koç, MD., University of Health Sciences, İzmir Bozyaka Training and Research Hospital, Department of Radiology, Saim Çikrikci Cad. No:59, 35170 Karabağlar, İzmir, Turkey  
E-mail: alimuratkoc@gmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>



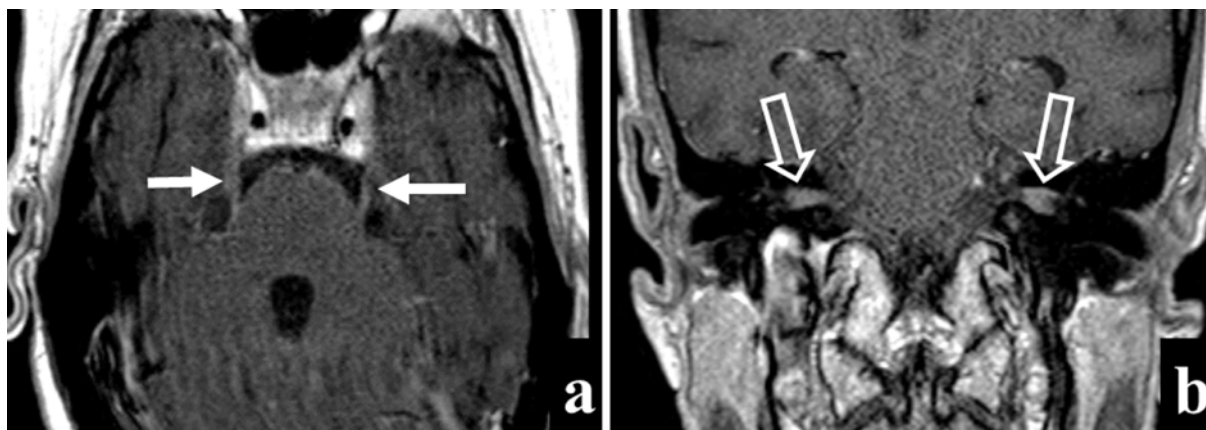
**Figure 1.** Signs of early cerebritis and meningitis in cranial MRI. Enhancing cortical nodular lesions in the right frontal lobe (arrow) with peripheral vasogenic edema (open arrow) can be seen clearly on sagittal post-contrast T1W (a) and FLAIR (b) images. Diffuse meningeal enhancement extending to the spinal cord (short arrows) is also noticed on sagittal post-contrast T1W image (c).

were diffusely enhancing after iv. gadolinium (Gd) injection. There was also diffuse prominent pachymeningeal contrast enhancement extending to the cervical spinal region that is compatible with meningitis (Figure 1). Posterior fossa imaging demonstrated that cisternal parts of bilateral trigeminal, abducens, facial and vestibulocochlear nerves were also thickened and showed diffuse enhancement through their course (Figure 2). Retrospective evaluation of the cranial MRI, which was performed 10 months ago, appeared to be normal besides persistent and stable slight ventriculomegaly.

Spinal MRI examination covering cervical, thoracic and lumbar regions also demonstrated diffuse meningeal enhancement (Figure 3). A longitudinally extending extramedullary soft tissue mass slightly compressing the spinal cord was noticed at the levels

of Th6-7 vertebrae (Figure 3). This lesion showed hypointensity on T2W images and showed diffuse homogenous enhancement. There were also diffuse, poorly delineated increased signal on T2W images effecting the cross section of the spinal cord at the levels of Th1 to Th4 and Th11 to L2 vertebrae. The spinal cord was edematous and showed patchy enhancement after iv. Gd injection at the levels of Th1 to Th4 vertebrae (Figure 3). Findings were thought to be compatible with spinal meningitis, multilevel spinal cord myelitis and extramedullary granuloma. Vertebral column and intervertebral disks did show any specific pathology besides mild degenerative changes.

Chest X-ray, thoracic and abdominal CT imaging were performed to rule out any possible primary malignities and metastatic processes. While X-ray and thorax CT images were unremarkable, abdominal CT



**Figure 2.** Demonstration of cranial nerve involvement in posterior fossa MR images. Diffuse enhancement of bilateral trigeminal (a, arrows), facial and vestibulocochlear (b, open arrows) nerves can be seen in post-contrast coronal (a) and axial (b) T1W images.

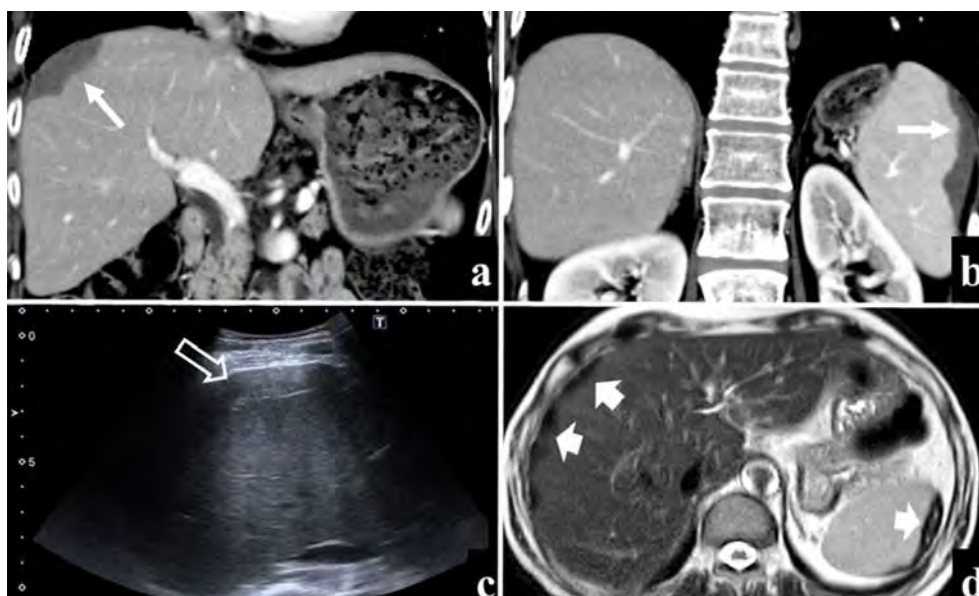


**Figure 3.** Spinal meningitis, transverse myelitis and extramedullary granuloma formation in MR images. Post-contrast sagittal T1W images of servical (a) and thoracic (b) regions show diffuse meningeal enhancement enshasing the whole spinal cord (arrows). Spinal cord is edematous and shows increased signal at the levels of Th1 to Th4 (c) and Th11 to L2 vertebrae (d) in sagittal T2W images (open arrows). There’s also contrast enhancement in spinal cord itself at the upper thoracic region (a, short arrow). Extramedullary soft tissue that’s causing compression of spinal cord at the levels of Th6-7 vertebrae, shows low signal on T2W images (d, dotted arrow) and enhances diffusely after injection of contrast medium (b, dotted arrow).

images showed lobulated, thick, crescent shaped hypodense lesions located at the subcapsular regions of both liver and spleen (Figure 4). Ultrasonographic evaluation confirmed subcapsular collections as hypoechogenic, lobulated collections which have internal septations (Figure 4). Abdominal MRI

examination demonstrated that these lesions also have diffuse hypointense signal on both T1W and T2W images (Figure 4). There were no diffusion restriction and contrast enhancement found in these collections.

Evaluation of these images with clinical findings pointed out a possible granulomatous infection.



**Figure 4.** Hepatosplenic subcapsular collections in abdominal ultrasound, CT and MRI images. Hypodense collections located at the subcapsular regions of liver (a) and spleen (b) can be seen in coronally reformatted post-contrast CT images (arrows). Ultrasound image also shows hypoechogenic subcapsular hepatic collection (c, open arrow). Axial T2W MRI image (d) demonstrates diffuse hypointense signal in these collections (short arrows). It’s importantly noted that neither calcifications (CT and ultrasound images) nor enhancement after injection of contrast medium (CT and MR images) was seen in these collections.

Lumbar puncture was performed to clarify imaging findings. Macroscopic examination of cerebrospinal fluid (CSF) showed decreased viscosity with dark-yellow color change. Laboratory examination showed prominent elevation of protein (4405 mg/dL), elevated leucocytes (109/mm<sup>3</sup>), normal chlorine (109 mEq/L) and normal glucose (62 mg/dL) with concurrent blood glucose also in normal limits (101 mg/dL). Acid-fast bacilli stain and PCR for mycobacterium turned out to be negative and together with non-specific thorax imaging findings, neurotuberculosis and neurosarcoidosis were excluded from differential diagnosis list. Test for *Treponema pallidum* from CSF was also found to be negative. Since the patient had a job history with direct animal contact in a farm and moreover she has been living in an endemic region, laboratory tests for Brucellosis were performed. Rose-Bengal and tube agglutination tests within blood serum and CSF were positive (1/80 and 1/640 in titers, respectively). Although blood cultures did not yield growth for any bacteria, diagnosis of brucellosis was made considering the relatively low sensitivity of cultures for *Brucella* spp. [1]. Patient was then treated with combination of ceftriaxone, rifampicin and doxycycline. Symptoms of fatigue, muscle weakness and hearing loss were found to be partially relieved at control examinations after hospital discharge. Follow-up abdominal ultrasonography and MRI examination performed at 3th month did not show any change in hepatosplenic subcapsular collections.

## DISCUSSION

Hereby we presented a case of brucellosis with extensive, progressive multisystemic involvement. Central nervous system involvement of brucellosis is rare; reported incidences vary between 0.5%-25% in different studies [2-4]. Most common manifestations of neurobrucellosis are meningitis, meningoencephalitis, cerebritis, brain abscess, leukoencephalopathy, demyelinating or vascular diseases [3, 4]. Among those, meningitis and meningoencephalitis are seen in approximately half of the cases [3]. Pseudotumor cerebri together with optic neuritis may cause papilledema. Vestibulocochlear nerve is the most commonly affected nerve causing hearing loss. MRI with contrast is the method of

imaging to evaluate neurobrucellosis. Kizilkilic and Calli [3] indicated that the course of cerebral parenchymal infection in neurobrucellosis resembles to those seen in chronic brain abscesses starting from early cerebritis to well demarcated rim enhancing abscess formation. At the presented case, brain MRI showed diffuse pachymeningeal thickening and enhancement together with nodular, diffusely enhancing, T2 hyperintense lesions located at the right frontal cortex. Findings were determined to be recently developed since the former MRI scan was normal. Together with the findings compatible with meningitis and spinal infection, these cortical lesions appeared to be the components of "early cerebritis" phase of parenchymal infection resembling tuberculomas of neurotuberculosis. Lack of diffusion restriction and peripheral enhancement ruled out classical abscess formations that may be seen in later phases of progressing infectious course. Posterior fossa imaging delicately showed involvement of 8<sup>th</sup> and other cranial nerves which may be only partially seen in routine cranial MRI examinations. Presence of widespread cranial nerve involvement although the patient had symptoms of only vestibulocochlear nerves, emphasizes the benefits of posterior fossa imaging in this group of patients.

Osteoarticular system, including the spinal column is the most common site of focal disease seen in 25%-65% of Brucellosis cases [2, 5]. Disruption of blood brain barrier results in meningitis and also spondylitis. Involvement of spinal cord itself is a very rare entity [5]. Spinal granulomas are also rare complications more commonly seen in tuberculosis and may develop from myelitis. Our case have imaging findings compatible with spinal meningitis, granuloma and multilevel spinal cord lesions compatible with longitudinally extensive transverse myelitis without primary focus of spondylodiscitis. We believe that this might be the first case of brucellosis in the English literature with simultaneous, multilevel, long segment transverse myelitis without spondylitic origin. Only Kirshnan *et al.* [4] presented a case of brucellosis with recurrent episodes of transverse myelitis under controlled treatment. Besides our patient had symptoms over approximately for 1.5 years without any treatment; lack of previous spinal imaging raises doubts about the time of initiation and the synchronicity of spinal cord lesions. We thought that

thick exudate in CSF together with meningeal thickening may have caused focal obstructions in flow resulting in adhesions and loculations. Pooling of CSF in these areas precipitated focal inflammatory processes and resulted in granuloma and myelitis at multiple segments. Low viscosity and very high pleocytosis in CSF also supports this theory.

Reticuloendothelial system is almost always affected in systemic brucellosis. Hepatic and splenic involvement in brucellosis is not rare and reported with varying incidences ranging from 2% to 60% in different series [2, 6]. Presentation may change from mild granulomatous hepatitis to acute/subacute abscesses in both liver and spleen. Cases with hepatitis are generally underdiagnosed because of insidious course. Elevation of liver enzymes may be a clue but not all cases with elevated liver enzymes are can be evaluated as liver involvement of brucellosis. Hepatomegaly, splenomegaly, cholecystitis, pancreatitis, colitis, peritonitis and lymphadenopathy may also be seen [2]. Colmenero *et al.* [6] described rare cases of chronic hepatosplenic abscesses in brucellosis. They identified intraparenchymal and subcapsularly located, hypodense and peripherally enhancing abscess formations in CT examinations that were histopathologically verified. All of the cases presented large central calcifications. Spontaneous splenic rupture (SSR) is also another rare entity that occurs due to several etiological factors. Renzulli *et al.* [7] categorized the etiological factors of SSRs in their systematic review as follows; malignities, infectious disorders, inflammatory disorders, drug-related disorders, mechanical disorders. Dülger *et al.* [8] presented an extremely rare case of atraumatic SSR due to *Brucella* itself. The infectious processes cause some precipitating factors making the spleen more susceptible to hemorrhage and rupture: congestion and dilatation in the sinusoids, capillary thrombosis and focal necrosis in the splenic pulps. At the presented case, subcapsular lesions in both liver and spleen did not enhance in CT and MRI examinations unfavoring expected abscess formations due to brucellosis. Furthermore, lesions were diffusely hypointense on both T1W and T2W images. Granuloma formations also can cause focal hypointense signal changes in MRI due to coarse calcifications. Since CT imaging did not show any sign of calcification, laboratory examinations did not show abnormalities in liver

enzymes and thrombocyte counts, patient did not have a symptom of upper quadrant pain and did not have a history of trauma, follow-up examinations did not show any resolution; these lesions were thought to be either chronic subcapsular hematomas resulting spontaneously from brucellosis or chronic non-calcified granulomatous collections. Liver and spleen sizes were normal and there was no sign of intraabdominal bleeding on CT scan to suspect spontaneous splenic or hepatic rupture at this stage. Any further histopathological confirmation could not be made since the patient did not confirm fine needle aspiration procedure.

## CONCLUSION

Brucellosis is an endemic disease in certain parts of the world. Recognition of the disease and its diverse complications is crucial for a timed treatment to avoid sequela, especially in cases of neurobrucellosis. It's much easier to diagnose brucellosis in a patient with lumbar spondylodiscitis but absence of it should not remove the suspicion of systemic or focal forms of the disease. Differentiation from other granulomatous diseases, vasculitic syndromes, malignancies is also important and can be challenging. Above mentioned spontaneous hepatosplenic subcapsular collections, multilevel transverse myelitis and spinal granulomas are unusual components of the disease that should be kept in mind in evaluation of brucellosis patients.

### Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### Informed consent

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

### Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Inan AS, Ceran N, Erdem I, Engin DO, Senbayrak S, Ozyurek SC, et al. Neurobrucellosis with transient ischemic attack, vasculopathic changes, intracerebral granulomas and basal ganglia infarction: a case report. *J Med Case Rep* 2010;4:340.
- [2] Buzgan T, Karahocagil MK, Irmak H, Baran AI, Karsen H, Evirgen O, et al. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. *Int J Infect Dis* 2010;14:e469-78.
- [3] Kizilkilic O, Calli C. Neurobrucellosis. *Neuroimaging Clin N Am*. 2011;21(4):927-37.
- [4] Krishnan C, Kaplin AI, Graber JS, Darman JS, Kerr DA.. Recurrent transverse myelitis following neurobrucellosis: immunologic features and beneficial response to immunosuppression. *J Neurovirol* 2005;11:225-31.
- [5] Tali ET, Gultekin S. Spinal infections. *Eur Radiol* 2005;15:599-607.
- [6] Colmenero Jde D, Queipo-Ortuno MI, Maria Reguera J, Angel Suarez-Muñoz M, Martín-Carballino S, Morata P. Chronic hepatosplenic abscesses in Brucellosis. Clinico-therapeutic features and molecular diagnostic approach. *Diagn Microbiol Infect Dis* 2002;42:159-67.
- [7] Renzulli P, Hostettler A, Schoepfer AM, Gloor B, Candinas D. Systematic review of atraumatic splenic rupture. *Br J Surg* 2009;96:1114-21.
- [8] Dülger AC, Yılmaz M, Aytemiz E, Bartın K, Bulut MD, Kemik Ö, et al. [Spontaneous splenic rupture and hemoperitoneum due to brucellosis infection: a case report]. *Van Tıp Derg* 2011;18:41-4. [Article in Turkish]



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

# Treatment of the nevus of Ota with the 1064-nm Q-switched Nd: YAG laser

Yeşim Akpınar Kara 

Department of Dermatology, Liv Hospital, Ankara, Turkey

DOI: 10.18621/eurj.392136

## ABSTRACT

Nevus of Ota is a benign hamartoma which presenting as blue-gray hyperpigmented patches on the face and mucous membranes usually within the distribution of first and second branches of the trigeminal nerve. It may occur at birth or during adolescence and the nevus of Ota is very common seen in Japan and east countries. The pigmentation varies and can be dark brown to blue to black-blue. We report a 31-year-old female patient with the nevus of Ota. The Q-switched Nd: YAG laser, had a spot size of 3 mm, an 8 Hz repetition rate, 720 mj/cm<sup>2</sup> fluence. The patient's lesion improved in a rate of 60% with a single session. The Q-switched Nd: YAG laser has a significant effect in treating the nevus of Ota.

**Keywords:** Nevus of Ota, 1064-nm Q-switched Nd: YAG laser, single session

*Received: February 8, 2018; Accepted: August 18, 2018; Published Online: August 27, 2018*

The nevus of Ota, also known as naevus fusco-coeruleus-ophthalmo-maxillaris, was first described by the Japanese dermatologist Ota in 1939 [1]. It is characterized by an increase in pigmentation in the skin and mucous membranes in the regions of the maxillary and ophthalmic branches of the trigeminal nerve [2]. It is melanocytic hamartoma that presents unilateral or bilateral. The nevus of Ota is common in females and it usually appears at birth. In the treatment, cryosurgery, surgical excision, skin grafting and dermabrasion are employed [3]. Since the development of laser technology, several lasers have been introduced into the treatment of benign pigmentary lesions. Notably, Q-switched laser systems have gained popularity in the treatment of the nevus of Ota as they produce less scarring and better outcomes. Nonetheless, the introduction of various treatment options for the nevus of Ota have made it difficult for dermatologists to choose the best solution in practice.

## CASE PRESENTATION

A 31-year-old female patient presented to the hospital with a pigmented patch over on the right side of her forehead that had been present since birth (Figure 1). The case history revealed that this pigmented lesion was asymptomatic and was present since ten years old. She had no history of ocular disease, hearing loss, or use of medications that produce pigmentation. Physical examination revealed a blue-gray, hyperpigmented, poorly defined patch on the right forehead area. There was no pigmentary disturbance of either eye or the oral mucosa. She was diagnosed with the nevus of Ota based on her history.

The local anesthesia was achieved by 15 minutes of pretreatment with topical 5% lidocaine and then cleaned with hydrogen peroxide-sodium-hypochloride. The test shot was placed in a suitable non-exposed area. The patient was initially treated



Address for correspondence: Yeşim Akpınar Kara, MD., Liv Hospital, Department of Dermatology, 1428. Sk. No: 16/8, Cukurambar, Ankara, Turkey  
E-mail: yesim\_akpinar@yahoo.com

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>



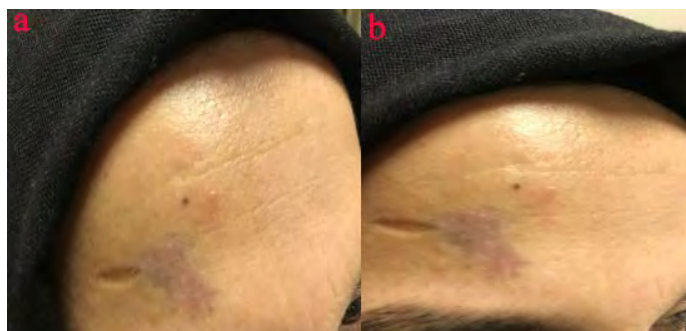
**Figure 1.** Baseline photos of patient with the nevus of Ota.

with 2 sessions of 1064-nm Q-switched Nd: YAG. The entire lesion was then scanned with a 3 mm spotsize at 720mj/cm<sup>2</sup> and 8 Hz. The treatment produced an expected petechial rash (Figures 2a and 2b). Spot hunting” was then performed on the second scan to



**Figure 2.** After laser treatment (a) and after 1 week treatment (b).

treat untreated and skipped areas. An antibiotic ointment (2% fucidic acid) was applied and the treatment area was covered with a sterile gauze pad and kept occluded for 24 hours. The ointment was



**Figure 3.** Four week after laser treatment.

used 3 times a day for the next 7 days without any occlusion. Sun avoidance was recommended. The treatment interval was four week. Since the patient lived outside the country, she could not come to the hospital after the second session of laser therapy. However, the improvement in the color of the nevus of Ota satisfied the patient even after the first session (Figure 3).

## DISCUSSION

The nevus of Ota characterized by a blue-gray color discoloration and originates from dermal melanocytes. The nevus is more common in females, with a male-female ratio of 1:4.8. The nevus present at birth or in the first year of life 36% appear between the ages of 11 and 20 years old [4]. The pigmentation can also involve conjunctiva, cornea, retina, lips, palate, pharynx or nasal mucosa.

The nevus of Ota originates from dermal melanocytes. During embryonic development, melanocytes migrate from the neural crest to the epidermis. It is thought that the nevus of Ota represent melanocytes that have experienced migrational arrest in the dermis. Some have speculated that there is a hormonal influence as well, accounting for the lesions that appear at puberty and the female predominance [5]. Trauma has also been reported as a triggering mechanism.

The Q-switched neodymium-yttrium aluminium-garnet (Q-switched Nd: YAG) laser has been used in the treatment of the nevus of Ota. Q-switched Nd:YAG laser is the least absorbed laser by melanin and has the deepest penetration feature. This laser emits a longer, near infrared ray of 1064-nm, which destroying the dermal melanocytes of the nevus of Ota, by selective photothermolysis [6]. The treatment outcome with Q-switched Nd: YAG laser may vary depending on the depth and density of the melanocytes in the dermis and also the skin types.

In the studies conducted, laser sessions were usually planned as 3-4 session, and the healing rate was found as 80-85% [7]. The treatment effect increases with treatment sessions. If we could complete the treatment sessions in three, we observed that the healing rate would reach 80-90%. Nevertheless, even with a single treatment, it is



possible that the Q-switched Nd: YAG laser is effective in the treatment of the nevus of Ota.

## CONCLUSION

The treatment of the nevus of Ota by Q-switched Nd: YAG laser is safe and effective, with rare complications.

### *Informed consent*

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

### *Conflict of interest*

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ. Fitzpatrick's Dermatology in General Medicine. 7th ed. The Mc Graw-Hill Company, Inc., 2008:632.
- [2] Radmanesh M. Naevus of Ota treatment with cryotherapy. J Dermatolog Treat 2001;12:205-9.
- [3] Ono I, Tateshita T. Efficacy of the ruby laser in the treatment of Ota's nevus previously treated using other therapeutic modalities. Plast Reconstr Surg 1998;102:2352-7.
- [4] Ho SG, Chan HH. The Asian dermatologic patient: review of common pigmentary disorders and cutaneous diseases. Am J Clin Dermatol 2009;10:153-68.
- [5] Kouba DJ, Fincher EF, Moy RL. Nevus of Ota successfully treated by fractional photothermolysis using a fractionated 1440-nm Nd:YAG laser. Arch Dermatol 2008;144:156-8.
- [6] Yongqian C, Li L, Jianhai B, Ran H, Li G, Hao W, et al. A split-face comparison of Q-switched Nd:YAG 1064-nm laser for facial rejuvenation in Nevus of Ota patients. Lasers Med Sci 2017;32:765-9.
- [7] Yan L, Di L, Weihua W, Feng L, Ruilian L, Jun Z, et al. A study on the clinical characteristics of treating nevus of Ota by QS Nd:YAG laser. Lasers Med Sci 2018;33:89-93.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

## Vibration related white finger disease: a case report

Seher Kurtul<sup>ORCID</sup>, Meral Türk<sup>ORCID</sup>

Department of Public Health, Division Occupational Diseases and Health, Ege University School of Medicine, İzmir, Turkey

DOI: 10.18621/eurj.379091

### ABSTRACT

Vibration related white finger disease is frequently observed in workers exposed to hand-arm vibration. The main occupational exposure sources for hand-arm vibration are grinding, road and concrete breaking, using of grinding wheel, rotary saw, high pressure water hose, pneumatic hammer, drill, hammer, hand crusher, lawn mower, road roller. A 38-year-old male patient was admitted to our occupational disease clinic with complaints of pain on both fingertips, swelling on the fingers and occasional whitening of the fingers on both hands. There was a story of pneumatic hammer use in a private firm that produced heat resistant plate for 12 years and also work story in the same company for 2 years in the grinding department. The case was considered to be a white finger disease due to vibration with current findings and work history, and medical treatment for white finger disease was regulated. It has been suggested that the patient should do job change, work in a non-cold environment, and also avoid work that can cause vibration. This case who exposed hand-arm vibrations shows the importance of taking a detailed work history while taking an anamnesis. In screening the health effects of the hand-arm vibration, the complaints of white finger disease should be carefully questioned and examined. Vibration-related white finger disease, as in other occupational diseases, can be protected by taking effective measures at the workplace.

**Keywords:** vibration, occupation, occupational disease, white finger

*Received: January 15, 2018; Accepted: February 11, 2018; Published Online: May 28, 2018*

Vibration; is usually the result of the swinging movements that the tools, equipments and machines in the workplace generate during work and is a physical risk factor that can cause occupational disease. Nowadays, vibration is one of the most studied ergonomic factors affecting human health and job success [1].

The damage of vibration on worker depends on various factor such as individual sensitivity, severity of vibration, exposure frequency, duration (years), level of insulation, grip strength, body part affected by source, maintenance repair of used instruments [2]. It is divided into two parts as whole-body vibration and

hand-arm vibration according to the contact of the body to the vibration source. The main occupational exposure sources for hand-arm vibration are grinding, road and concrete breaking, using of grinding wheel, rotary saw, high pressure water hose, pneumatic hammer, drill, hammer, hand crusher, lawn mower, road roller. Vibration related white finger disease is due to hand-arm vibration; It is a painful disorder in the veins, nerves, muscles and joints that lead to disability [3]. In this article we will present a case of white finger disease due to hand-arm vibration after use of vibrating tools for 12 years.



Address for correspondence: Seher Kurtul, MD., Ege University School of Medicine, Department of Public Health, Division Occupational Diseases and Health, İzmir, Turkey  
E-mail: seherkurtul79@gmail.com, Tel: +90 232 3902075

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

## CASE PRESENTATION

A 38-year-old male patient was admitted to our occupational disease clinic with complaints of pain on both fingertips, swelling on the fingers and occasional whitening of the fingers on both hands (Figure 1). There was a story of pneumatic hammer use in a private firm that produced heat resistant plate for 12 years and also work story in the same company for 2 years in the grinding department. The case was taken from the forging department due to complaints and he was given to the sanding section, but in this section also stated that the complaints continue. there were 20 years-packed cigarette (active) history in his medical history and hypertension in his mother in his family history.

### *Occupational History*

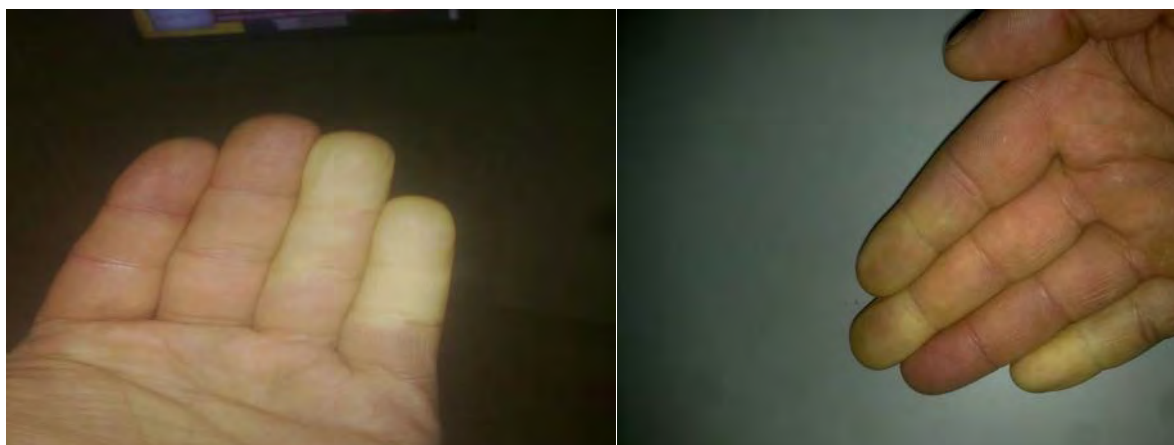
August 2002- currently; In a company that manufactures heat-resistant plaques, he is pouring the mixture of chemicals into big boilers and preparing mud. He is pouring out the prepared mud with a shovel, then stepping up on mud and grinding it with a pneumatic hammer. On average, he is grinding with a pneumatic hammer eight plates per day. For the last 2 years, he has been sanding the burrs of the produced plates.

On physical examination, general condition was good, vital findings were stable, system examinations were usual. Hemogram, routine biochemistry, sedimentation, ANA profiles were within normal limits. The case was consulted in the rheumatology department. Both upper extremity arterial and venous

system doppler USG were observed as usual. The case was considered to be a white finger disease due to vibration with current findings and work history, and medical treatment for white finger disease was regulated. It has been suggested that the patient should do job change, work in a non-cold environment, and also avoid work that can cause vibration.

## DISCUSSION

Vibration is an important risk factor that causes workers to be adversely affected by the working environment and the inadequacy of controlled epidemiological studies on dose-effect relationship makes it difficult to establish this relationship [4]. It has been reported that more than 150 thousands in the Netherlands, more than 0.5 million in the England and more than 0.5 million in the United States are exposed to hand-arm vibrations [5]. Occupational diseases arising from vibration are encountered in SGK statistics. The reason for this is that in our country, the issue of vibration is not well known, employees are not complaining about vibrations in their workplaces [2]. The Raynaud phenomenon associated with hand-arm vibrations is described in 1862. In 1911 Professor Giovanni Loriga described a disease that first appeared on the fingers of workers working with hammer drills in the mines in Italy, with attacks of pallor, cyanosis and chills. This disease started to be called white finger syndrome in the 1970s [6,7]. It is characterized by attacks of vasoconstriction of the finger arteries. Attacks last for minutes, hours and increases with cold



**Figure 1.** Photos taken during attack.

exposure or emotional stress [2].

Nyantumbu *et al.* [8] conducted a cross-sectional study in a gold mine in the Republic of South Africa in order to determine the extent and weight of the hand-arm vibration-induced influence of miners, as well as the tools that caused these impacts. They stated hand-arm vibration is linked to the use of hand-held vibrating tools, and this exposure has indicated that workers may experience pinning, numbness, loss of grip strength, pain, loss of hand skills, and potentially increased risk of occupational accidents. In gold miners exposed to vibration, the prevalence of hand-arm vibrations was found to be 15% and the latent period of 5-6 years was determined for the formation of the disease [8]. In our case, after 12 years using of pneumatic hammer, complaints started in both hands. In a cross-sectional study by Barregard *et al.* [9] in Sweden on car repairers, vibration-associated white fingers were observed in 15% of individual workers exposed to vibration on the average of 3.5 m/s<sup>2</sup> per day for 12 years and this rate increases to 25% in who exposed for 20 years. According to the regulations for protection of employees working in our country against risks related to vibration; for hand-arm vibration [2]. The daily exposure effective value for an 8-hour working period is 2.5 m/s<sup>2</sup>. Vibration-related effects occur for many years, so no significant problem is observed in vibration exposure at high levels.

If the vibrational exposure is lifted in the early stages of the vascular-associated white finger, the development of permanent damage can be avoided and existing findings can be regressed.

Individual vibration measurements must be performed regularly to avoid hand-arm vibrations and necessary technical and engineering precautions should be taken to avoid exceeding the upper limits allowed. Vibrating instrument users should be informed and trained on correct and reliable instrument handling and as it is known that continuous vibration exposure increases the damage, the divided working range should be applied at rest intervals. Necessary medical examination must be carried out before recruitment and clinical examinations should be carried out at regular intervals in workers with vibration exposure. As contact with cold air or cold objects triggers attacks of white finger disease, it can benefit to use gloves to keep fingers and hands warm

and to protect them from injuries. Anti-vibration gloves are also proposed which partially isolate the high frequency components of vibration.

## CONCLUSION

As a result, this case who exposed hand-arm vibrations shows the importance of taking a detailed work history while taking an anamnesis. In screening the health effects of the hand-arm vibration, the complaints of white finger disease should be carefully questioned and examined and more training should be given in order to recognize and evaluate the health effects of hand-arm vibration. Vibration-related white finger disease, as in other occupational diseases, can be protected by taking effective measures at the workplace.

### Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### Informed consent

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

### Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Su BA. Ergonomy. Atılım University Publication No: 5, Engineering Faculty Publication No: 2, Ankara, 2001:p.246.
- [2] Bilir N. Occupational safety and health profile , Turkey. Ministry of Labour and Social Security Publication Number: 62, Ankara: MoLLS, 2016.
- [3] Güven, HNR. [Health effects of vibration on hand-arm vibrating devices]. PhD. Thesis, Hacettepe University, 2002. [Article in Turkish]
- [4] Taylor WA, Wasserman ED. Occupational vibration (Zenz C., Occupational Medicine).3rd Ed., 1994:p.297-303.
- [5] South T. Managing Noise and Vibration at Work: A Practical Guide to Assessment, Measurement and Control. Elsevier Butterworth-Heinemann, UK. 2004.
- [6] Laws J. The hazards of HAVS. Occup Health Saf 1998;67:45-6.

- [7] Noel B. Pathophysiology and classification of the vibration white finger. *Int Arch Occup Environ Health* 2000;73:150-5.
- [8] Nyantumbu B, Barber CM, Ross M, Curran AD, Fishwick D, Dias B, et al. Hand-arm vibration syndrome in South African gold miners. *Occup Med (Lond.)* 2007;57:25-9.
- [9] Barregard L, Ehrenstrom L, Marcus K. Hand-arm vibration syndrome in Swedish car mechanics. *Occup Environ Med* 2003;60:287-94.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

## Bilateral sacroiliitis and left hip arthritis secondary to isotretinoin treatment

Sevgi Kulaklı<sup>1</sup>, Fazıl Kulaklı<sup>2</sup>, İlker İlhanlı<sup>2</sup>, Samet Tatlı<sup>2</sup>, Canan Çelik<sup>2</sup>

<sup>1</sup>Department of Dermatology, Giresun University Prof.Dr.İlhan Özdemir Training and Research Hospital, Giresun, Turkey

<sup>2</sup>Department of Physical Medicine and Rehabilitation, Giresun University Prof.Dr.İlhan Özdemir Training and Research Hospital, Giresun, Turkey

DOI: 10.18621/eurj.421976

Received: May 8, 2018; Accepted: June 11, 2018; Published Online: June 15, 2018

Dear Editor,

Acne vulgaris is a chronic inflammatory disease affecting the pilosebaceous unit in the skin [1]. Isotretinoin is a synthetic vitamin A derivative used in severe cystic acne treatment. Pain and arthralgia are observed in 20% of patients treated with isotretinoin [2]; however sacroiliitis is rare and hip arthritis is even more rare. There was no article in the literature about a patient with sacroiliitis and hip arthritis together.

A 30-year-old male patient who was suffering from severe pain on his left hip and leg for two days admitted to our clinic. His pain was very intense in the evening and the Visual analog scale (VAS) pain score was 8. He experienced morning stiffness for two days and about an hour on his left lower extremity. The patient had no history of inflammatory low back pain, skin lesion, bowel problem or infection. No pathology was found in rheumatologic examination. Family history was normal, however the patient was taking isotretinoin 20 mg/day for acne vulgaris about two months. The patient resorted to the brain surgery department before our clinic, the lumbar magnetic resonance imaging (MRI) was taken and no pathology was detected. The inspection of left leg and other body parts were normal but there was a pronounced skin dryness around the mouth periphery and face. There was mild sensitivity with palpation on left hip but the

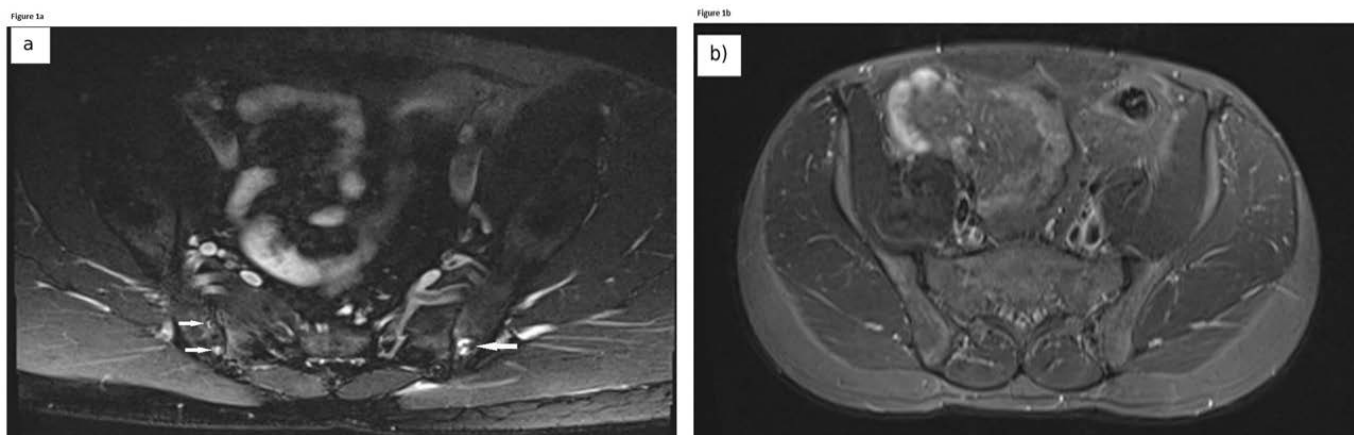
movements were limited and so painful. Flexion, abduction, and external rotation (FABER), flexion, adduction, and internal rotation (FADIR), sacroiliac compression, Mennel and Gaenslen tests were bilateral positive but more painful on left side. Lumbar range of motion was normal and there was no neurological deficit. Erythrocyte sedimentation rate (ESR) (33 mm/hr) and C-reactive protein (CRP) (3.84 mg/L) values were higher in the laboratory tests. Complete blood count, routine biochemical tests and HLA-B27 were negative. Bilateral bone marrow edema on iliac sides of sacroiliac joints and increased joint fluid on left hip was found on MRI (Figures 1a and 2a). As a result of all tests, the patient was diagnosed as bilateral sacroiliitis and left hip arthritis due to isotretinoin. The isotretinoin was ceased and nimesulide 2×100 mg, methylprednisolone 1×16 mg and lansoprazole 1×30 mg was started. A dramatic clinical response was obtained. A significant decrease was observed in the laboratory parameters on the seventh day (CRP: 0.06 mg/L, ESR: 5 mm/hr) and the VAS score was 3. Methylprednisolone was reduced and ceased. A repeat MRI performed five months later showed no evidence of left hip arthritis and sacroiliitis (Figures 1b and 2b) and the examination was completely normal.



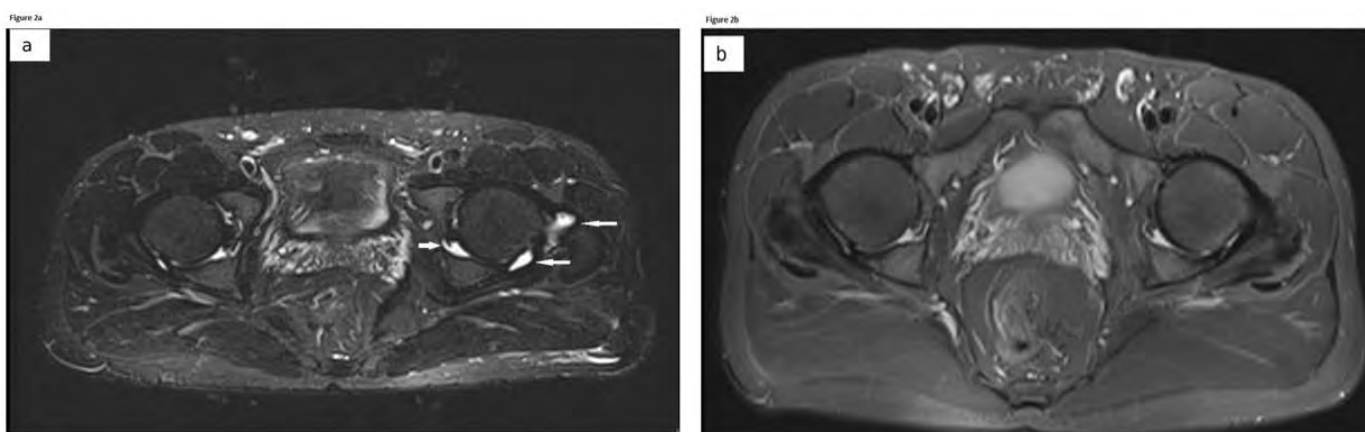
Address for correspondence: Fazıl Kulaklı, MD., Giresun University Prof.Dr.İlhan Özdemir Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Giresun, Turkey  
E-mail: drfz146@gmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>



**Figure 1.** (a) Bilateral bone marrow edema on iliac sides of sacroiliac joints (before treatment), (b) Improved bone marrow edema on sacroiliac joints (five months after treatment).



**Figure 2.** (a) Increased synovial fluid on left hip joint (before treatment), (b) Improved synovial fluid on left hip joint (five months after treatment).

Acne vulgaris is a common skin disease and it does not depend on gender, ethnicity and skin color [1]. Isotretinoin is a synthetic vitamin A derivative using in severe cystic acne treatment. There are many side effects as well as musculoskeletal side effects such as pain, arthritis, arthralgia, myalgia and soft tissue calcification [3]. A small number of cases of sacroiliitis occurring in association with isotretinoin use have been described [3-5]. Isotretinoin-induced peripheral arthritis has also been reported [6-9] and only one of these cases had hip arthritis [8]. A case of peripheral arthritis (bilateral wrist and metacarpophalangeal joints) and subsequent sacroiliitis (unilateral) reported in one study [9]. Unlike these studies, our patient had bilateral sacroiliitis and left

hip arthritis together and no similar case has been seen in the literature. The fact that the patient is a young man and the appearance of sacroiliitis in the MR suggests us primarily ankylosing spondylitis (AS). However, the absence of inflammatory low back pain, HLA B27 negative, rapid onset pain, dramatic response to steroids, and complete resolution of the clinic removed us from AS. In conclusion, we think that our case report will contribute to the literature because of the rarity of the case. Physicians should be aware of this rare cause of acute arthritis and sacroiliitis.

#### *Authorship declaration*

All authors listed meet the authorship criteria

according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

#### *Conflict of interest*

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## REFERENCES

- [1] Kircik LH. Advances in the understanding of the pathogenesis of inflammatory acne. *J Drugs Dermatol* 2016;15(1 Suppl 1):S7-10.
- [2] Kaplan G, Haettich B. Rheumatological symptoms due to retinoids. *Baillieres Clin Rheumatol* 1991;5:77-97.
- [3] Yilmazer B, Coşan F, Çefle A. Bilateral acute sacroiliitis due to isotretinoin therapy: a case report. *Int J Rheum Dis* 2013;16:604-5.
- [4] Dinçer Ü, Çakar E, Kıralp MZ, Dursun H. Can isotretinoin induce sacroiliitis: three cases. *Romatizma* 2008;23:157-9.
- [5] Barbareschi M, Paresce E, Chiaratti A, Ferla Lodigiani A, Clerici G, Greppi F. Unilateral sacroiliitis associated with systemic isotretinoin treatment. *Int J Dermatol* 2010;49:331-3.
- [6] Hughes RA. Arthritis precipitated by isotretinoin treatment for acne vulgaris. *J Rheumatol* 1993;20:1241-2.
- [7] Bewley AP, Rankin EC, Levell NJ, Robinson TW. Isotretinoin causing acute aseptic arthropathy. *Clin Exp Dermatol* 1995;20:279.
- [8] Pedraz T, Martinez A, Pascual E. Acute hip monoarthritis in a patient treated with isotretinoin. *J Clin Rheumatol* 2006;12:105-6.
- [9] Taşdelen ÖY, Yurdakul FG, Duran S, Bodur H. Isotretinoin-induced arthritis mimicking both rheumatoid arthritis and axial spondyloarthritis. *International J Rheum Dis* 2015;18:466-9.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.



# Experience of thrombotic microangiopathy unresponsive to therapeutic apheresis

Hilmi Erdem Sümbül<sup>1</sup>, Onur Taktakoğlu<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Adana Numune Training and Research Hospital, Adana, Turkey

<sup>2</sup>Department of Internal Medicine, Altınkoza Hospital, Adana, Turkey

DOI: 10.18621/eurj.389830

Received: February 3, 2018; Accepted: June 1, 2018; Published Online: June 30, 2018

Dear Editor,

Thrombotic thrombocytopenic purpura (TTP) is a rare disease of unknown etiology characterized by severe thrombocytopenia, microangiopathic hemolytic anemia, fever, renal, neurologic and rarely cardiac involvement [1]. All cases of microangiopathic hemolytic anemia with thrombocytopenia should be considered as TTP and the treatment must be initiated immediately until the contrary is proved [1, 2].

A 48-year-old female patient with the history of diabetes mellitus and hypertension, immunosuppressive drugs user caused by vasculitis, was admitted to our clinic with vasculitis attack. Reference values are summarized in Table 1. Twenty-four hour urine protein was detected as 8 g/day. Renal biopsy findings were consistent with thrombotic microangiopathy. Pulse steroid (1g/day) was administered for 3 days and then 1 mg/kg methylprednisolone was continued. Cyclophosphamide 500 mg/m<sup>2</sup> was applied because of persistent pancytopenia. Peripheral blood smear revealed blister cells, rare normoblasts and schistocytes. Direct Coombs test was negative. TTP was considered because the patient presented both microangiopathic hemolytic anemia with thrombocytopenia. Cyclophosphamide 500 mg/m<sup>2</sup> was administered again because of totally 37 times

unsuccessful therapeutic apheresis therapy and other signs of systemic vasculitis. Rituximab 1000 mg was applied on the on the first and fifteenth days because the low platelets count, refractory microangiopathic hemolytic anemia. Pancytopenia had benefits (Figure 1), proteinuria level decreased to 885 mg/day, the other systemic vasculitis signs (polyneuropathy, pretibial edema) were regressed and the patient was discharged in a healthy condition.

Plasma exchange procedure show a significant effect in treatment of TTP; all adult patients met the diagnostic criteria should be applied plasma exchange [3-5]. Plasma exchange may be effective in immunosuppressive treatment-resistant cases. According to the McDonald *et al.*'s study [5] in London University, rituximab therapy may be more effective in cases of high active ADAMST13 IgG antibodies study then low active ADAMST13 antibodies. It is clear that effective doses, location and maintenance of rituximab therapy should be studied in terms of TTP. All cases of microangiopathic hemolytic anemia with thrombocytopenia should be considered as TTP and the treatment must be initiated immediately like plasmapheresis, steroid, cyclophosphamide, rituximab etc. Even if rituximab is not considered as a first-choice treatment, yet it is a



Address for correspondence: Hilmi Erdem Sümbül, MD., Adana Numune Training and Research Hospital, Department of Internal Medicine, Adana, Turkey  
E-mail: erdemsumbul@gmail.com

e-ISSN: 2149-3189

Copyright © 2019 by The Association of Health Research & Strategy  
Available at <http://dergipark.gov.tr/eurj>

**Table 1.** The reference values on admission

WBC:1,87µl	Hemoglobin:8.2 gr/dl	Hematocrit: 24.6%
Neutrophil: 78.6% (1.47 µl)	MCV:80 fl	RDW: 16.2 %
Lymphocyte: 11.6 % (0.22 µl)	Eosinophil: 0.3%	Platelet:205 µl
LDH: 219 U/L	Sodium:134 mmol/L	BUN:33 mg/dl
CRP:6.54 mg/dl	Potassium:5.1 mmol/L	Creatinine:1.04 mg/dl
Sedimentation: 35	ALT: 15 U/L	Total protein:4.9 g/dl
Rheumatoid factor: 118 I/ml	AST:20 U/L	Albumin:2.8 g/dl

promising drug in treatment of TTP.

#### Authorship declaration

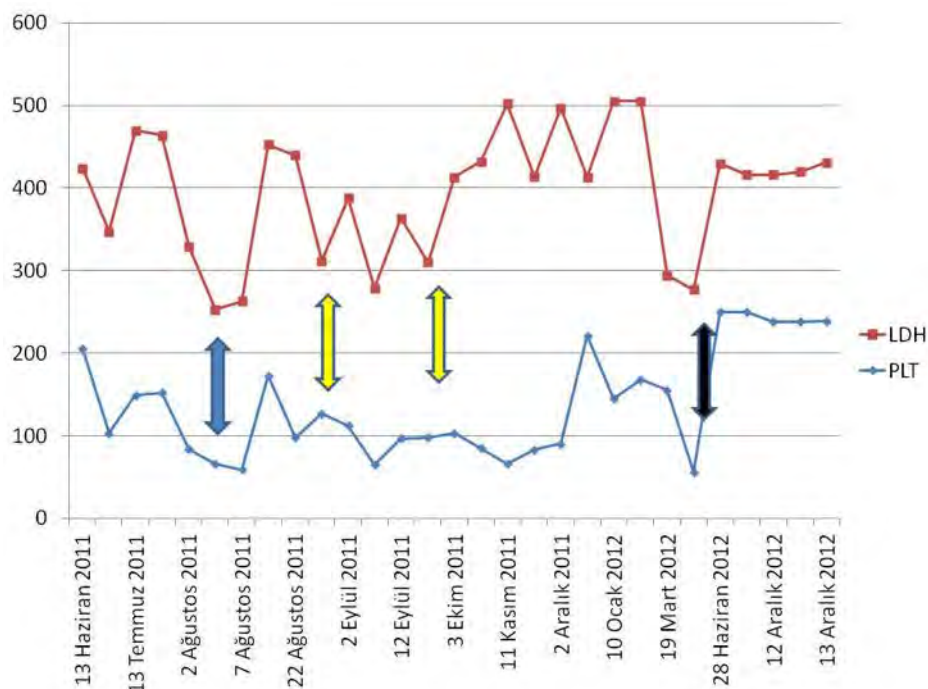
All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

#### Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

#### REFERENCES

- [1] George JN. How I treat patients with thrombotic thrombocytopenic purpura:2010. Blood 2010;116:4060-9.
- [2] Kremer Hovinga JA, Vesely SK, Terrell DR, Lammle B, George JN. Survival and relapse in patient with thrombotic thrombocytopenic purpura. Blood 2010;115:1500-11.
- [3] George JN, Woodson RD, Kiss JE, Kojouri K, Vesely SK. Rituximab therapy for thrombotic thrombocytopenic purpura: a proposed study of the Transfusion Medicine/Hemostasis Clinical Trials Network with a systematic review of rituximab therapy for immune-mediated disorders. J Clin Apher 2006;21:49-56.
- [4] Ling HT, Field JJ, Blinder MA. Sustained response with rituximab in patients with thrombotic thrombocytopenic purpura: a report of 13 cases and review of the literature. Am J Hematol 2009;84:418-21.



**Figure 1.** Course of LDH and PLT. Blue arrow indicates start of plasmapheresis program. Yellow arrow indicates cyclophosphamide therapies and black arrow for Rituximab.

- [5] McDonald V, Manns K, Mackie IJ, Machin SJ, Scully MA. Rituximab pharmacokinetics during the management of acute idiopathic thrombotic thrombocytopenic purpura. *J Thromb Haemost* 2010;8:1201-8.



This is an open access article distributed under the terms of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.



**THE ASSOCIATION OF HEALTH  
RESEARCH AND STRATEGY**