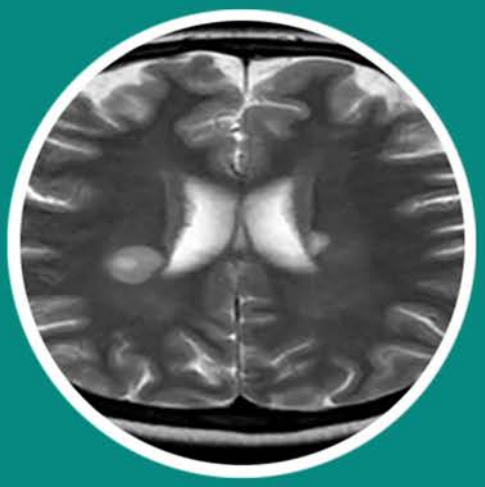
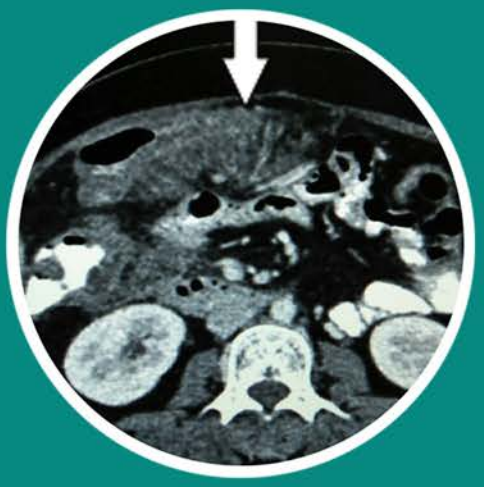
Volume 5 Issue 4 July 2019

e-ISSN: 2149-3189

The European Research Journal





The Association of Health Research & Strategy I www.dergipark.org.tr/eurj

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), EMBASE, ProQuest Central, ROAD, SciLit, MIAR, J-Gate, SHERPA/RoMEO, BASE, EZB, CrossRef, JournalTOCs, WorldCat, TURK MEDLINE, Turkish Citation Index.

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/

e-ISSN: 2149-3189

Editorial Board

INTERNATIONAL EDITORIAL BOARD MEMBERS

Table of Contents

Original Articles

Reviews

Case Report

Letter to the Editor

The European Research Journal 2019;5(4):576-581 ORIGINAL ARTICLE

Is there a difference in 25-hydroxyvitamin D levels between female university students with and without joint hypermobility?

Filiz Tuna[1], Hande Özdemir[2], Derya Demirbağ Kabayel[2], Zeynep Banu Doğanlar[3]

[1]Department of Physical Therapy and Rehabilitation, Trakya University School of Health Sciences, Edirne, Turkey
[2]Department of Physical Therapy and Rehabilitation, Trakya University School of Medicine, Edirne, Turkey
[3]Department of Medical Biology, Trakya University School of Medicine, Edirne, Turkey

DOI: 10.18621/eurj.411056

ABSTRACT

Objectives: Individuals with joint hypermobility (JH) constitute a sensitive group with regard to musculoskeletal problems. This study aimed to investigate whether females with generalized joint hypermobility (GJH) are at risk of hypovitaminosis D compared with non-GJH female participants and whether there is a relationship between vitamin D levels, Beighton score and musculoskeletal complaints.

Methods: In this cross-sectional, descriptive and case-control study, 76 female participants aged 18-25 years were included. The Beighton score with a cut-off of 4/9 was applied for defining GJH. In addition, serum biochemical (the enzymatic colorimetric method) and hormonal (the electrochemiluminescence method) parameters were evaluated.

Results: The mean serum 25-hydroxyvitamin D (25[OH]D) levels of GJH (n = 38) and non-GJH (n = 38) groups were 15.70 ± 7.96 ng/mL and 16.80 ± 5.45 ng/mL, respectively. There was no statistically significant difference between the groups in terms of biochemical and hormonal parameters. We found vitamin D deficiency in 89.5% of participants with GJH, and 84.2% of controls. There was no correlation between vitamin D, Brighton criteria, and musculoskeletal complaints.

Conclusion: The female participants with GJH showed similar frequency of musculoskeletal complaints and similar low level of 25(OH)D in relation to controls.

Keywords: female, joint hypermobility, musculoskeletal complaints, 25-hydroxyvitamin D deficiency

Received: March 30, 2018; Accepted: May 19, 2018; Published Online: September 15, 2018

Joint hypermobility or laxity is having a range of motion beyond the limits of normal joint. It can affect one or more joints. Beighton scoring (BS), where in nine joints are evaluated, is used to define JH and BS 4-6/9 is reported as generalized joint hypermobility (GJH) [1, 2]. Hypermobility brings with it many problems as musculoskeletal or systemic manifestations. Musculoskeletal manifestations are traumas, degenerative joint and bone diseases, disturbed proprioception, muscle weakness and musculoskeletal traits. Systemic manifestations are cardiovascular involvements, skin, mucosae, fascia involvement, and nervous system involvement [2]. These manifestations were included easily under the umbrella named hypermobility syndrome or hypermobile Ehlers-Danlos syndrome (hEDS) with Brighton criteria until the 2017

Address for correspondence: *Filiz Tuna, MD., Trakya University School of Health Sciences, Department of Physical Therapy and Rehabilitation, Edirne, Turkey*
E-mail: drftuna@hotmail.com

e-ISSN: 2149-3189

International Classification of EDS that were based on strict criteria [3].

According to updated classification hEDS is a connective tissue disorder simultaneously comprised; 1) Beighton score ≥ 5/9, 2) At least two of of feature A (at least 5 meets of a 12 systemic features of a connective tissue), feature B (positive family history) and feature C (at least one existence of three musculoskeletal complications), and 3) Exclusion of extraordinary skin fragility, further connective tissue disorders, and another diseases with JH. However, feature B was accepted enough for the diagnosis [3].

Although Vitamin D is a hormone that is essential for functioning of muscles, as well as bone mineralization [4], until now, no study has reported vitamin D levels in GJH and its correlation with musculoskeletal complaints. Hypermobile EDS with GJH is reported as risk for chronic pain, fatigue [5], low bone density, osteoporosis, and fractures [6, 7]. While management suggestions include considering 25-hydroxyvitamin D (25[OH]D) deficiency, there is no enough data on levels of 25(OH)D in EDS groups as well as GJH [8-11]. Considering the possibility that individuals with GJH differ from controls in mean of level of 25(OH)D and some biochemical parameters (sodium, potassium, chlorine, alkaline phosphatase, calcium, phosphorus, magnesium, iron, and iron binding capacity levels) we aimed to evaluate them and comprise with controls.

METHODS

Patients

For the aims of this study, we selected females with definition of GJH according to the Beighton scoring, aged between 18-25 years. Participants were selected from a total of 221 female students from the Health Sciences Faculty of Trakya University (Edirne, Turkey). A group of students with Beighton score ≤ 3/9 and no any genetic disorder, chronic drug use and chronic disease of locomotor system was selected as control. All participant were selected from the same sources. Controls were matched by age and sex with individuals with GJH. Participants with a Beighton score of ≥ 4/9 were included in the GJH group and those with a score ≤ 3/9 were included in the control group (non-GJH) [12]. Exclusion criteria were male sex, drug use, and the presence of a known disease in both groups (Figure 1). Based on the mean 25(OH)D vitamin level 26.3 in the control group [13] and minimum difference between groups of 25%, an α error of 5%, SD of 10%, and power 80% we defined a sample of 38 participants for each group. This observational, cross-sectional (between February 2017 and July 2017), controlled, quantitative study was approved by the Ethics Committee of the Trakya University Medical Faculty (TÜTF-BAEK-2016/105) and written informed consent was obtained from each participants.

Edirne is city in the Marmara Region of Turkey, latitudes 40°30-42°00 North l and 26°00-27°00 East. Average maximum temperatures range between 6.5°C in winter and 31.7°C in summer, with annual average of 19.6°C [14].

Clinical Evaluation

A total of 221 female students from Health Science Faculty of Trakya University (Edirne, Turkey) underwent an initial clinical interview and Beighton scoring. Beighton scoring was performed by evaluating nine joints and the following items:

I- Placement of hands flat on the floor without bending the knees

II- Hyperextension of the elbow to ≥ 10°

III- Hyperextension of the knee to ≥ 10°

IV- Opposition of the thumb to the volar aspect of the ipsilateral forearm

V- Passive dorsiflexion of the fifth metacarpophalangeal joint to ≥ 90° [15]. During physical examination, we investigated the presence of features used in the diagnosis of hEDS according to the 2017 International Classification of EDS [3]. Data collected included age, sex, height, weight, BMI, clothing style, and history of musculoskeletal complaint. To evaluate history of the musculoskeletal complaint, participants were questioned aboutthe joint pain, widespread musculoskeletal pain and soft tissue injuries. Clothing style of the participants was registered by researchers based on their observations as veiled or not.

Laboratory Evaluation

After 10-12 h fasting, venous blood samples fromthe antecubital area were taken from all participants between 08.30 and 9.00 in the morning

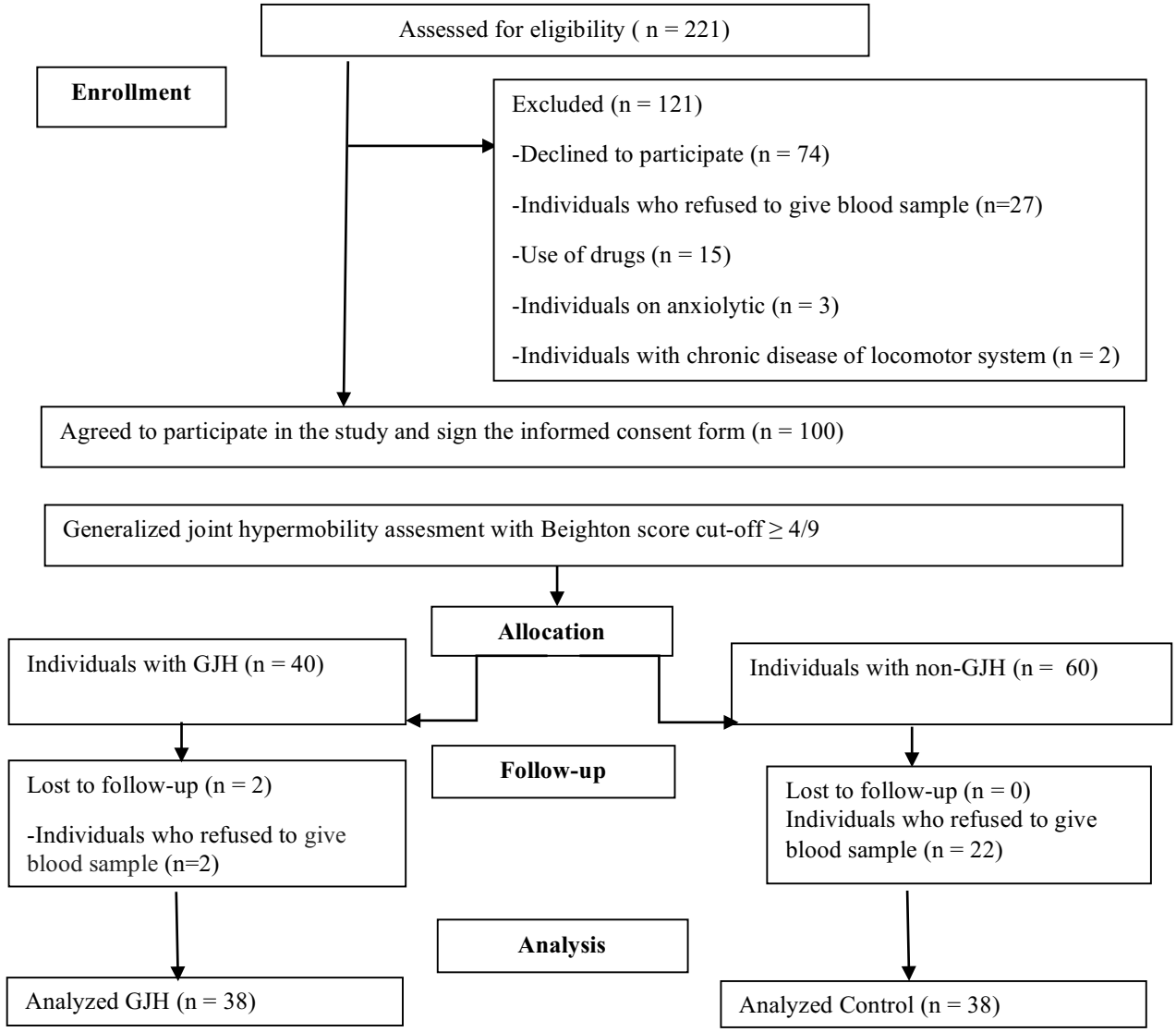


Figure 1. Flow diagram of the progress.

from April 2017 to May 2017. Serum sodium, potassium, chlorine, alkaline phosphatase, calcium, phosphorus, magnesium, iron, and iron binding capacity levels were measured using the enzymatic colorimetric method (Beckman Coulter AU 5800), and serum 25(OH)D, folic acid, and ferritin levels were evaluated using the electrochemiluminescence method (Beckman Coulter UniCelDxI 600). 25(OH)D levels of participants were classified according to the Endocrine Society asdeficiency (< 20 ng/mL), insufficiency (21-29 ng/mL), normallevels (30-39 ng/mL), and preferred levels (40-60 ng/mL) [16].

Statistical Analysis

Statistical evaluation was performed by the IBM SPSS version 20.0 statistics software package (IBM Corporation, Armonk, NY, USA). Descriptive variables were reported within groups according to frequency, means, standard deviation, and percentages. Normal distribution were evaluated by the Shapiro-Wilk test. T test was used for normally distributed data. Spearman's rho correlation analysis test was used to assess correlations between variables. A p value of < 0.05 was considered statistically significant.

Table 1. Characteristics of participants with GJH and controls

	Groups	n	Mean ± SD	*p* value
Age, year	GJH	38	19.87 ± 1.45	0.239
	Control	38	20.26 ± 1.44	
	Total	76	20.07 ± 1.45	
Height, m	GJH	38	1.65 ± 0.05	0.464
	Control	38	1.64 ± 0.04	
	Total	76	1.64 ± 0.05	
Weight, kg	GJH	38	56.31 ± 6.29	0.643
	Control	38	57.05 ± 7.45	
	Total	76	56.68 ± 6.86	
BMI, kg/m^2	GJH	38	20.63 ± 1.75	0.304
	Control	38	21.14 ± 2.44	
	Total	76	20.88 ± 2.13	
Veiled clothing style, %	GJH	9	23.7	0.079
	Control	7	18.4	
	Total	16	21.1	
History of musculoskeletal complaint, %	GJH	14	43.8	0.486
	Control	18	56.3	
	Total	32	42.1	
25 (OH)D level, ng/ml	GJH	38	15.73 ± 7.97	0.496
	Control	38	16.80 ± 5.46	
	Total	76	16.26 ± 6.81	

GJH = generalized joint hypermobility, BMI = body mass index

RESULTS

Complete laboratory data were obtained for 76 female participants, of whom 38 had GJH and 38 did not. Total Beighton score range were 0-9/9. The average ages of GJH and control groups were 19.87 ± 1.45 and 20.26 ± 1.44 years, respectively. Participants' age, height, weight, BMI, clothing style, and history of musculoskeletal pain parameters were normally distributed. The mean serum 25(OH)D levels of GJH and control groups were found no statistically different (Table 1). Laboratory data of sodium, potassium, chlorine, alkaline phosphatase, calcium, phosphorus, magnesium, and iron, were obtained for 73 participants, of whom 38 had GJH and 35 did not. There was no statistically significant difference between the GJH and control groups with respect to the biochemical and hormonal levels. Significant positive correlation was found between weight and 25(OH)D levels (Table 2). Neither in the GJH nor in the control group hEDS was identified.

Table 2. Correlations of parameters with statistically significance

		r	*p* value
Age	Chlorine	-0.277	0.020
	Phosphorus	0.287	0.014
	Hyperextension of right elbow	-0.229	0.046
	Hyperextension of right knee	-0.264	0.021
	Hyperextension of left knee	-0.252	0.028
Weight	Calcium	0.267	0.023
	Height	0.485	<0.001
	BMI	0.847	<0.001
25(OH)D levels	Weight (kg)	0.303	0.008
	Potassium	0.265	0.022
	Hyperextension of right elbow	-0.340	0.003
	Hyperextension of left elbow	-0.244	0.034

Distribution of participants according to 25(OH)D calassifications among the GJH and control groups was showed in Table 3. Only one of participants had preferred level of vitamin D.No correlation was found between the Beighton scores, musculoskeletal manifestations, and serum 25(OH)D levels. No correlation was found between the clinical parameters (Beighton scoring parameters) of participants with GJH and 25(OH)D levels, except for a statistically significant negative correlation between the 25(OH)D levels and the hyperextension of right and left elbow (Table 2).

Table 3. Distribution of 25(OH)D classifications among the groups

		n (% within groups)		
		GJH	**Control**	**Total**
25 (OH) D classification	Deficiency	34 (89.5)	32 (84.2)	66 (86.8)
	Insufficiency	2 (5.3)	4 (10.5)	6 (7.9)
	Normal	1 (2.6)	2 (5.3)	3 (3.9)
	Preferred	1 (2.6)	0 (0.0)	1 (1.3)
Total		38 (100)	38 (100)	76 (100)

GJH = generalized joint hypermobility

DISCUSSION

Present study shows that mean 25(OH)D levels are low, but not statistically different in females with GJH. We also found no statistically significant association between Beighton scoring and neitherhistory of musculoskeletal complaint nor 25(OH)D levels. While GJH is widely known as predisposing to musculoskeletal pain, neither vitamin D deficiency nor insufficiency is not sufficiently researched in this population. Significant positive correlation was found between weight, BMI and 25(OH)D levels. These results are not consistent with previous studies reporting negative correlation between BMI and vitamin D in healthy adults [17]. This wasprobably due to both groups having normal mean BMI.

The lack of association between 25(OH)D levels and musculoskeletal complaints was probably because of both groups having levels below normal limits. These results are uniform with other studies that also reported no association between these variables. In retrospective multicenter study on patients who applied to physical medicine and rehabilitation outpatient clinics with non-specific muscle pain, vitamin D deficiency was detected in 70.9% of patients (without information about whether patients are hypermobile or not). However, vitamin D deficiency in this population was reported not associated with the severity and duration of pain [18]. Hypermobility, vitamin D deficiency, and female sex are risk factors for idiopathic musculoskeletal pain [11]. Of these, hypermobility and female sex are structural unchanging factors. However, it is possible to misdiagnosed musculoskeletal pain associated with vitamin D deficiency as a pain syndrome associated with joint laxity or vice versa. There are limited number of publications on the role of 25(OH)D in hEDS, defined by the Brighton criteria, where GJH and various symptoms as joint pain are questioned together [6, 9, 19, 20]. Some publications suggest that vitamin D should be observed in painful individuals with hEDS [9, 20]. We found similar serum 25(OH)D levels between the groups and deficiency was found in 89.5% of participants with GJH, and 84.2% of controls. These findings are consistent with low vitamin D levels in eight of 14 cases with vascular type EDS with mean age of 37 ± 16 years [21]. Vitamin D levels < 30 ng/mL were reported to be similar in classical and hypermobility type EDS (86%) and control (82%) groups with a mean age of 40.3 ± 5.9 years. Mean serum 25(OH)D levels of individuals with classical or hypermobility type EDS have been reported as 20.2 ± 12.9 ng/mL [6].

The participants with GJH showed no higher frequency of musculoskeletal complaints in relation to control participants, refusing the profile waited for this population, according to the literature. It was probably due to 25(OH)D in both groups below the recommended levels.

Limitations

A potential limitation of this study was limited number of participants. Current study did not include questionnaires interesting in socioeconomic status and vitamin D intake in the diet. In addition, our study was mainly female student-based and the need to establish knowledge on GJH and hEDS require studies with large population.

CONCLUSION

The female participants with GJH showed similar frequency of musculoskeletal complaints and low 25(OH)D levels in relation to controls. The frequency of deficiency and insufficiency of 25(OH)D in current study is parallel to studies, reporting a high frequency of vitamin D below normal limits, even in places with plenty sunlight.

Conflict of interest

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

Financing

This study was supported by the Trakya University Research Project Foundation (Project Number: TÜBAP-2017/08), Edirne, Turkey.

Acknowledgements

We are particularly grateful to all individuals who volunteered to participate in this study. We also thank Prof. Dr. Necdet Süt, who performed the statistical analysis of the study.

REFERENCES

[1] Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology. Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet 1988;77:31-7.
[2] Castori M, Tinkle B, Levy H, Grahame R, Malfait F, Hakim A. A framework for the classification of joint hypermobility and related conditions. Am J Med Genet C Semin Med Genet C Semin Med Genet 2017;175:148-57.
[3] Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet 2017;175:8-26.
[4] Wintermeyer E, Ihle C, Ehnert S, Stöckle U, Ochs G, de Zwart P, et al. Crucial role of vitamin D in the musculoskeletal system. Nutrients 2016;8. pii:E319.
[5] Rombaut L, Scheper M, De Wandele I, De Vries J, Meeus M, Malfait F, et al. Chronic pain in patients with the hypermobility type of Ehlers–Danlos syndrome: evidence for generalized hyperalgesia. Clin Rheumatol 2015;34:1121-9.
[6] Eller-Vainicher C, Bassotti A, Imeraj A, Cairoli E, Ulivieri FM, Cortini F, et al. Bone involvement in adult patients affected with Ehlers-Danlos syndrome. Osteoporosis Int 2016;27:2525-31.
[7] Gulbahar S, Sahin E, Baydar M, Bircan C, Kizil R, Manisali M, et al. Hypermobility syndrome increases the risk for low bone mass. Clin Rheumatol 2006;25:511-4.
[8] Scheper MC, de Vries JE, de Vos R, Verbunt J, Nollet F, Engelbert RH. Generalized joint hypermobility in professional dancers: a sign of talent or vulnerability? Rheumatology 2013;52:651-8.
[9] Kumar B, Lenert P. Joint hypermobility syndrome: recognizing a commonly overlooked cause of chronic pain. Am J Med 2017;130:640-7.
[10] Engelbert RH, Juul-Kristensen B, Pacey V, de Wandele I, Smeenk S, Woinarosky N, et al. The evidence−based rationale for physical therapy treatment of children, adolescents, and adults diagnosed with joint hypermobility syndrome/hypermobile Ehlers Danlos syndrome. Am J Med Genet C Semin Med Genet 2017;175:158-67.
[11] Joghee S, Dewan V, Chhabra A, Jahan A, Sharma N, Yadav TP. Vitamin D levels in children with idiopathic musculoskeletal pain. Int J Basic Appl Sci 2014;3:21-7.
[12] Juul-Kristensen B, Røgind H, Jensen DV, Remvig L. Inter-examiner reproducibility of tests and criteria for generalized joint hypermobility and benign joint hypermobility syndrome. Rheumatology (Oxford) 2007;46:1835-41.
[13] Kasapoğlu Aksoy M, Altan L, Ökmen Metin B. The relationship between balance and vitamin 25(OH)D in fibromyalgia patients. Mod Rheumatol 2017;27:868-74.
[14] [cited 2018 20/03/2018]; Available from: https://mgm.gov.tr/veridegerlendirme/il-ve-ilceler-istatistik.aspx?m=EDIRNE.
[15] Beighton P, Solomon L, Soskolne C. Articular mobility in an African population. Ann Rheum Dis 1973;32:413-8.
[16] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-30.
[17] Parikh SJ, Edelman M, Uwaifo GI, Freedman RJ, Semega-Janneh M, Reynolds J, et al. The relationship between obesity and serum 1, 25-dihydroxy vitamin D concentrations in healthy adults. J Clin Endocrinol Metab 2004;89:1196-9.
[18] Karahan AY, Hüner B, Kuran B, Sezer N, Çelik C, Salbaş E, et al. [Assessment of the relationship between vitamin D level and non-specific musculoskeletal system pain: a multicenter retrospective study (Stroke Study Group)]. Turk J Osteoporos 2017;23:61-6. [Article in Turkish]
[19] Holick M, Hossein-Nezhad A, Tabatabaei F. Multiple fractures in infants who have Ehlers-Danlos/hypermobility syndrome and or vitamin D deficiency: a case series of 72 infants whose parents were accused of child abuse and neglect. Dermatoendocrinol 2017;9:e1279768.
[20] Busch A, Hoffjan S, Bergmann F, Hartung B, Jung H, Hanel D, et al. Vascular type Ehlers-Danlos syndrome is associated with platelet dysfunction and low vitamin D serum concentration. Orphanet J Rare Dis 2016;11:111.

The European Research Journal 2019;5(4):582-587 ORIGINAL ARTICLE

Bacterial contamination of ultrasound probes and coupling gels in a university hospital in Turkey

Hakan Kıran[1], Murat Aral[2], Gürkan Kıran[1], Salih Serin[1], Deniz Cemgil Arıkan[1], Uğurkan Erkayıran[1], Hasan Çetin Ekerbiçer[3]

[1]Department of Obstetrics and Gynecology, Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey
[2]Department of Microbiology, Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey
[3]Department of Public Health, Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey

DOI: 10.18621/eurj.401327

ABSTRACT

Objectives: Nosocomial outbreaks of infection originating from ultrasound probes and contaminated coupling gels have been reported. It was reported that the ultrasound probe, if cultured after routine scanning of intact skin, may become colonized with skin flora.

Methods: Culture swabs from 22 probes of the 9 ultrasound machines and from the gels in the 10 gel folders were taken. All swabs taken from probe head, probe holder and the coupling gel in the folder at the beginning of the day were cultured. After fifth scanning and after wiping off the gel with a dry, nonsterile paper towel, cultures were again obtained from probe head and probe holder.

Results: A total of 98 culture results were included of which 42.8% were positive for bacterial growth. The rate of bacterial contamination from probes at morning before the start of examination and after scanning were 34.1% and 56.8%, respectively and this difference was statistically significant ($p = 0.023$).

Conclusions: We think that using nonsterile, dry, soft and absorbent paper towel after each procedure, could be inadequate for disinfection of probe head. Especially, good hand hygiene could decrease the rate of growth of bacterial colony at probe handle.

Keywords: Bacterial contamination, ultrasound, coupling gel, nosocomial infections

Received: March 5, 2018; Accepted: August 9, 2018; Published Online: November 6, 2018

A nosocomial infection which means "hospital acquired infection" can be defined as: an infection acquired in hospital by a patient who was admitted for a reason other than that infection [1]. Nosocomial infections are hospital-acquired infections that occur 48 hrs after the admission of the patients to the hospital [2]. They occur worldwide and affect both developed and resource-poor countries. A prevalence survey conducted under the auspices of WHO in 55 hospitals of 14 countries showed an average of 8.7% of hospital patients had nosocomial infections [3].

The hospital environment plays a crucial role in the transmission of organisms associated with nosocomial infections [4]. Nosocomial infections have become an increasingly recognised problem and medical devices can be one of the vehicles for the spread of these infections. Medical equipments including bronchoscopes, gastrointestinal endoscopes, stethoscopes

Address for correspondence: *Uğurkan Erkayıran, MD., Sütçü İmam University School of Medicine, Department of Obstetrics and Gynecology, Kahramanmaraş,Turkey*
E-mail: byugrerk@hotmail.com

e-ISSN: 2149-3189

and electronic thermometer have all been previously implicated in the transmission of nosocomial infections [5-7].

Ultrasonography is a most widely-used diagnostic imaging technique. Staff and patients have been implicated as vectors for the transmission of pathogenic organisms. Ultrasound (US) probes are used by doctors and nurses to assess for clinical evaluation of patients. US probes are reusable instruments, which can act as a reservoir for bacterial pathogens. Nosocomial outbreaks of infection originating from US probes and contaminated coupling gels have been reported [8-10]. The prevalence of US probe contamination after contact with patients' skin during scanning has been found to be as high as 95% with frequent isolation of pathogens such as Staphylococcus aureus [11-13]. It was reported that the ultrasound probe, if cultured after routine scanning of intact skin, may become colonized with skin flora in up to 33% of cases [14].

Unclean US probes can potentially transmit pathogens. The prevention of transmission of microorganisms among patients is of great importance, particularly in vulnerable patients who are susceptible to nosocomial infections resulting in increased morbidity, mortality and costs [15]. In this study, the US probes are routinely cleaned after each procedure simply by wiping them until they are visibly clean with a dry, nonsterile, soft, absorbent paper towel. Our purpose was to investigate if this simple cleaning procedure provided adequate probe decontamination to prevent the spread of infection between patients. We studied the potential role for the US probe or coupling gel to serve as a appliance of cross-contamination.

METHODS

A total of 98 culture swabs from 22 probes of the 9 US machines and from the gels in the 10 gel folders were taken by a single investigator. All swabs taken from probe head, probe holder and the coupling gel in the folder at the beginning of the day were cultured. After fifth scanning and after wiping off the gel with a dry, nonsterile paper towel, cultures were again obtained from probe head and probe holder. All samples were tested in a microbiology laboratory. The probes were always used with conducting gel. The US probes used in this study included Hitachi EUB-420, Toshiba Aplio XU, General Electric Vivid 7 Pro, DWL Multidop. X, Aloka Prosound SSD 3500, General Electric Logiq P5, Hitachi EUB 525 and Aloka Prosound 4000. The departments which the study was performed were; radiology, gynecology and obstetry, general surgery, endocrinology, orthopedia, urology, pediatry, neurology and gastroenterology. US coupling gel was first applied to the skin, after which the US probe was placed directly into the skin. Practitioners often did not decontaminate their hands pre- or post-procedure. The US probes are routinely cleaned after each procedure, simply by wiping them until they are visibly clean with a dry, non-sterile, soft, absorbent paper towel. After the final procedure of the day, probes were cleaned with a liquid cleaning solution such as Zefiran, alcohol, hydrogen peroxide, ammonium chloride, non-alcoholic wet tissue or dry towel to remove all traces of coupling gel, which could support the overnight growth of bacteria for any clinic. Patients underwent transvaginal sonography with probes that had been coated with gel and then covered with a latex condom. After the condoms were removed, the probe was wiped with a dry tissue. Condom defects were not detected after the scans by inspection. US probes and gels were chosen randomly and swabs were taken with sterile bouillon-soaked swabs (at least twice; one before clinic opening time, one on the following fifth US scanning), then swabs were cultured in Stuart's transport medium and taken to the laboratory within 3-6 hours. The samples were cultured on blood agar, Sabouraud dextrose agar (SDA) and eozin methylene blue (EMB) agar and incubated in blood and EMB agar at 37°C for 24 hours, or in SDA at 30°C for a week. Conventional microbiological methods were used for identification of the growing microorganisms and for definition of their colony characteristics, such as morphology, Gram stain, catalase, coagulase, oxydase tests and bacitracin and optochin sensitivity tests were done.

Statistical Analysis

All data were expressed as frequency and percentages. Statistic evaluation was performed using Mc Nemar test, and SPSS Ver 15.0. A p value less than 5% ($p < 0.05$) was considered to be statistically significant.

RESULTS

A total of 98 culture results were included of which 42.8% were positive for bacterial growth. The rate of bacterial contamination from probes at morning before the start of examination and after scanning of 5th patient were 34.1% and 56.8%, respectively and this difference was statistically significant ($p = 0.023$). The rates of bacterial contamination at probe head and probe handle were compared at morning before the start of examination and after scanning of 5th patient. The growth of bacterial colony was present in 9 out of 22 probe heads (41%) before the start of examination and in 13 out of 22 probe heads (59.1%) after scanning, the difference was not significant ($p = 0.388$). The growth of bacterial colony was present in 6 out of 22 probe handles (27.2%) before the start of examination and in 12 out of 22 probe handles (54.5%) after scanning and this difference was statistically significant ($p = 0.039$) (Table 1).

Percent positive bacteriological cultures from US probes before and after scanning shown in Figure 1. The growth of bacterial colony was seen in 2 of the gel examples taken from 10 gel folders. The majority of organisms which are found in normal skin and environmental flora were isolated from different parts of the US probes and gels. Of the 98 cultures, 42 (42.8%) were positive; 39 were positive for methicillin-sensitive Staphylococcus aureus (MSSA), 1 was positive for MSSA + Alpha-hemolytic Streptococcus, 1 was positive for MSSA + group A beta-hemolytic streptococcus, and 1 was positive for MSSA + kocuria kristinae. The gels were contaminated with MSSA. At the end of the day all the clinics were using different methods for the disinfection of the probes. No growth of bacterial colony has been detected at the examples taken before the start of examination from the probes that were cleaned with only alcohol after the end of the examinations.

The cleaning methods used at the end of the day and the rate of growth of bacterial colony at these samples are shown in Table 2.

DISCUSSION

Ultrasound probes and transmission gels come into direct contact with the skin of patients and can transmit bacteria between them, which can cause nosocomial infections. US probes may serve as a vector for cross infection particularly in vulnerable patients such as neonates, patients with unhealed wounds, burns and those with haematological malignancies or renal diseases. Thus, detecting bacterial transmission through US equipments is an important factor in the control of infection in hospitals. Nosocomial infections are most commonly caused by

Table1. The results of bacteriological cultures from ultrasound probes before and after scanning

Sampling site	Bacteriological culture	Before scanning (n = 22)	After scanning (n = 22)	*p* value
Probe head	Positive	9	13	0.388
	Negative	13	9	
Probe handle	Positive	6	12	**0.039**
	Negative	16	10	

Table 2. Association with cleaning methods of probes used for routine ultrasonography after the last scan of the day and bacterial contamination. Probes were swabbed before the first examination.

Cleaning methods (n = 44)	Number of swabs (n = 15)	Bacterial contamination	Percentage (%)
Hydrogen peroxide	4	1	25
Alcohol	4	-	0
Benzalkonium chloride	16	4	25
Ammonium chloride	16	7	43.7
Wet tissue	2	1	50
Dry towel	2	2	100

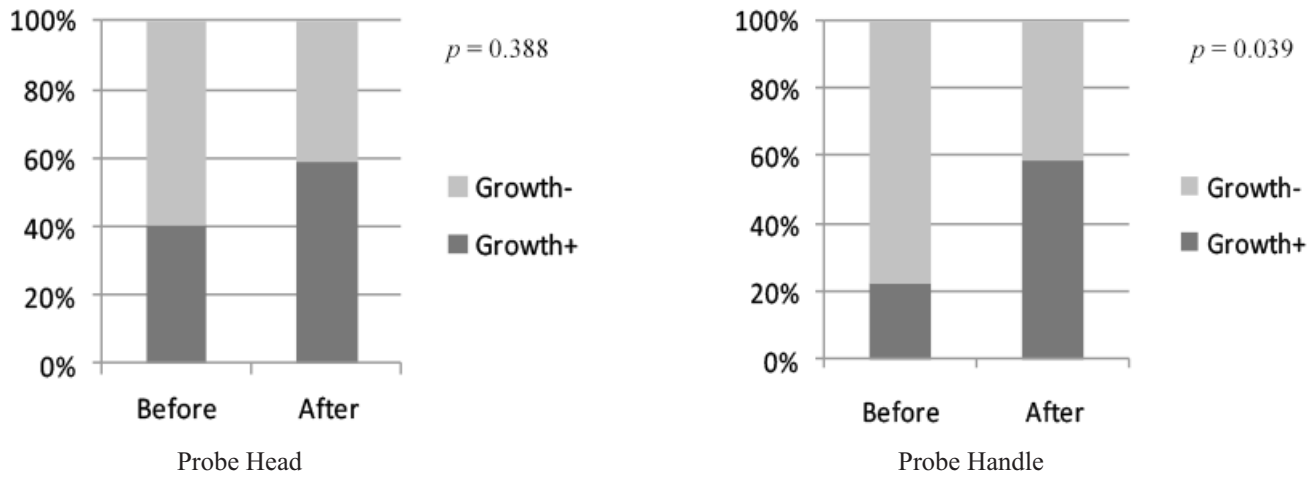


Figure 1. Percent positive bacteriological cultures from ultrasound probes before and after scanning are shown.

MSSA [16]. Other organisms such as *Escherichia coli, Enterococcus spp., Staphylococcus epidermidis, Streptococcus spp., Pseudomonas spp.* and *Candida spp*. are also common in surgical patients [17]. In our study, the prevalence of US probes and gels contamination has been found to be as high as 42.8% with frequent isolation of MSSA.

Sykes *et al*. [18] determined the extent of contamination of US equipment including probe, probe holder, keyboard and gel. The results revealed that 64.5% of the samples were contaminated with environmental organisms, 7.7% with potential pathogens and 27.8% were no growth [18]. Nosocomial outbreaks of infection originating from US probes and contaminated coupling gels have been reported in a French hospital [8]. Ohara *et al*. [19] evaluated whether US instruments are important in the spread of nosocomial staphylococcal infections. Following genomic typing by pulsed-field gel electrophoresis, it was apparent that US procedures transferred colonizing staphylococci from a patient's skin to the US instruments. *Staphylococcus aureus* survived in the transmission medium for longer than in water. Furthermore, *S. aureus* was more resistant to the ultrasonic medium than *Pseudomonas aeruginosa*, also a significant cause of hospital-acquired infections. To prevent staphylococcal transmission by US equipment, they recommend disinfection of the probe and removal of the medium after each examination [19]. In the other study, aerobic cultures were obtained from each patient's periumbilical and suprapubic areas before the transabdominal scan and from the transducer head before and after wiping off the gel with a dry cloth. Of the abdominal skin cultures, 175 (92%) were positive; 35 (18%) were positive for serious organisms, and 140 (74%) were positive for organisms of low virulence. Sixty percent of the transducer head cultures from women with abdominal skin pathogens were positive before the gel was wiped off. None of the cultures from the transducer head were positive after removal of the gel. They concluded that many women carry potentially virulent pathogens on the abdominal skin and that transmission of these organisms to the transducer head commonly occurs [20]. In our study, the rate of bacterial contamination from probe heads was 59.1% after removal of the gel. In the US department decontamination of US transducers is an important issue because of the risks of cross infection from dirty probes. Also, coupling gels can potentially transmit pathogens. Muradali *et al*. [21] concluded that as the coupling gel can support bacterial growth, the inadequately wiped US probe could potentially become contaminated with bacteria and serve as a vector of nosocomial infection. Similarly, this finding is supported by a previous report of the growth of bacteria several days after the intentional inoculation of microorganisms into bottles of US coupling gel [14]. Another study has incriminated the US gel as a potential source of infection [10]. In our study, the growth of bacterial colony was seen in 2 of the gel examples taken from 10 gel folders.

The prevention of transmission of micro-organisms among patients is of great importance, particularly in

vulnerable patients who are susceptible to nosocomial infections, resulting in increased morbidity, mortality and costs [15]. The literature on US probe cleaning and minimising the risks of cross infection agrees that cleaning and sterilising is essential [22]. Aylirffe *et al*. [23] summarized the infection control guidelines in hospitals, which needs to be tailored in sonographical practice and there are no clear international guidelines regarding the cleaning methods of the US probes.

Several methods have been used for US probe disinfection, including single-paper and double-paper wiping and disinfection with alcohol, antiseptic solutions or ultraviolet C technology (UVC). Conflicting results have been obtained concerning the respective efficacy of these cleaning methods under routine conditions [21, 24, 26]. Some authors have considered that simple wiping of the probe with a paper towel is enough to avoid cross-contamination, whereas others found that bacteria were still present after dry-wiping and considered this method inadequate [21, 24, 25]. Muradali *et al*. [21] suggested that simply wiping the probe with a dry towel appears to be sufficient to remove the gel and to decontaminate the probe. The additional use of an antiseptic solution after each routine scanning procedure does not offer any additional benefit [21]. Tarzmani *et al*. [27] found that the probes that were cleaned by cloth soaked in alcohol, showed the growth of bacterial colony to be zero. In their study, in the probes cleaned by non-sterile cloth, the bacterial count was 48.38%, 22.6%, 9.7% for the *Staphylococcus epidermidis, Staphylococcus aureus* and *Pseudomas aeruginosa*, respectively. They concluded that cleaning the probe and US gel as a device of bacterial growth is time saving and cost effective. They recommend disinfection of probes using alcohol in patients prone to infection [27]. Similarly, in our study, no growth of bacterial colony has been detected at the examples taken before the start of examination from the probes that were cleaned with only alcohol after the end of scanning. On the other hand, routine alcohol wiping is not recommended because of possible degradation of the rubber seal and shortening of the working life of the probe [25, 28].

Recently, Kac *et al*. [26] shown that US probes may carry nosocomial pathogens unless properly cleaned after each patient. Treatment of carefully dry-wiped probes in a UVC-chamber significantly reduced bacterial load. UVC disinfection of US probes may reduce cross-transmission of pathogenic bacteria [26]. Bello *et al*. [13] concluded that single paper wipe is adequate for outpatients, but for inpatients, especially those with high risk of cross infection, double paper wipe is preferred with probe thoroughly wiped until visibly clean. The use of dry wipe is effective for abdominal scanning, whereas alcohol wipes are recommended for the axillar and the inguinal regions [25]. Mirza *et al*. [29] determined the effectiveness of three different methods of US probe cleaning for the prevention of nosocomial infections. Culture was sent before and after using three different techniques of cleaning US probe, which included sterilized paper towel, 0.9% saline and swipe over with standard bath soap applied on patients respectively. The overall reduction in pathogenic bacterial count after performing each cleaning method was 45%, 76% and 98% for paper cleaning, normal saline and soap cleaning method respectively. They concluded that, soap cleaning technique is the most effective method for reducing bacterial count acquired due to patients body contact with the US probes [29].

CONCLUSION

The US equipments may be a potential vector for nosocomial infection in staff and patients. In this study, the bacterial contamination was still present in 59.1% of probe heads after dry-wiping. In this context, we think that using nonsterile, dry, soft and absorbent paper towel after each procedure, could be inadequate for disinfection of probe head. Concerning probe handle; the rate of bacterial contamination after scanning was significantly higher than the rate obtained from the samples before the start of the examination ($p = 0.039$). Especially, good hand hygiene could decrease the rate of growth of bacterial colony at probe handle.

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] Ducell G, Fabry J, Nıcoll L. Prévention des infections nosocomiales, Guide pratique, 2nd ed., Organisation mondiale de la Santé. WHO. 2008.
[2] Brachman PS. Epidemiology infections. In: Bennett JV, Brachmann PS, eds. Hospital infections, 3rd ed. Boston: Little, Brown, 1993:3-20.
[3] Tikhomirov E. WHO Programme for the Control of Hospital Infections. Chemiotherapia 1987;3:148-51.
[4] Bures S, Fishbain JT, Uyehara CF, Parker JM, Berg BW. Computer keyboards and faucet handles as reservoirs of nosocomial pathogens in the intensive care unit. Am J Infect Control 2000;28:465-71.
[5] Spach DH, Silverstein FE, Stamm WE. Transmission of infection by gastrointestinal endoscopy and bronchoscopy. Ann Intern Med 1993;118:117-28.
[6] Steinberg PJ, de Hoop D. [The stethoscope as a vehicle of pathogenic microorganisms in the hospital]. Ned Tijdschr Geneeskd 1978;122:303-5. [Article in Dutch]
[7] Livornese LL Jr, Dias S, Samel C, Romanowski B, Taylor S, May P, et al. Hospital-acquired infection with vancomycin-resistant Enterococcus faecium transmitted by electronic thermometers. Ann Intern Med 1992;117:112-6.
[8] Gaillot O, Maruéjouls C, Abachin E, Lecuru F, Arlet G, Simonet M, et al. Nosocomial outbreak of Klebsiella pneumoniae producing SHV-5 extended-spectrum beta-lactamase, originating from a contaminated ultrasonography coupling gel. J Clin Microbiol 1998;36:1357-60.
[9] Weist K, Wendt C, Ptersen LR, Versmold H, Rüden H. An outbreak of pyodermas among neonates caused by ultrasound gel contaminated with methicillin-susceptible Staphylococcus aureus. Infect Control Hosp Epidemiol 2002;21:761-4.
[10] Hutchinson J, Runge W, Mulvey M, Norris G, Yetman M, Valkova N, et al. Burkholderia cepacia infections associated with intrinsically contaminated ultrasound gel: the role of microbial degradation of parabens. Infect Control Hosp Epidemiol 2004;25:291-6.
[11] Ohara T, Itoh Y, Itoh K. Contaminated ultrasound probes: a source of nosocomial infections. J Hosp Infect 1999;43:73.
[12] Kibria SM, Kerr KG, Dave J, Gough MJ, Homer-Vanniasinkam S, Mavor AI. Bacterial colonization of Doppler probes on vascular surgical wards. Eur J Vasc Endovasc Surg 2002;23:241-3.
[13] Bello TO, Taiwo SS, Oparinde DP, Hassan WO, Amure JO. Risk of nosocomial bacteria transmission: evaluation of cleaning methods of probes used for routine ultrasonography. West Afr J Med 2005;24:167-70.
[14] Spencer P, Spencer RC. Ultrasound scanning of post-operative wounds--the risks of cross-infection. Clin Radiol 1988;39:245-6.
[15] Burke J. Infection control: a problem for patient safety. N Engl J Med 2003;348:651-6.
[16] Marroni M, Fiorio M, Cao P, Parlani G, Morosi S, Stagni G. [Nosocomial infections in vascular surgery: 1-year surveillance]. Recenti Prog Med 2003;94:430-3. [Article in Italian]
[17] Valero LF, Sáenz MC. [The etiology of nosocomial infection in surgery: comparison of 2 years (1988 and 1996)]. Enferm Infecc Microbiol Clin 1998;16:79-82. [Article in Spanish]
[18] Sykes A, Appleby M, Perry J, Gould K. An investigation of the microbiological contamination of ultrasound equipment. J Infect Prevent 2006;7:16-20.
[19] Ohara T, Itoh Y, Itoh K. Ultrasound instruments as possible vectors of staphylococcal infection. J Hosp Infect 1998;40:73-7.
[20] Patterson SL, Monga M, Silva JB, Bishop KD, Blanco JD. Microbiologic assessment of the transabdominal ultrasound transducer head. South Med J 1996;89:503-4.
[21] Muradali D, Gold WL, Phillips A, Wilson S. Can ultrasound probes and coupling gel be a source of nosocomial infection in patients undergoing sonography? An in vivo and in vitro study. AJR Am J Roentgenol 1995;164:1521-4.
[22] Grouden MC, Keogh E, Colgan MP, Moore DJ, Shanik DG. Results of an infection control survey in ultrasound departments and recommended guidelines. BMUS Bulletin 1999;7:15-18.
[23] Aylirffe G, Babb J, Taylor L. Cleaning, disinfection or sterilization? Hospital acquired infection. 3rd ed. London: Arnold; 2001;1448.
[24] Tesch C, Froschle G. Sonography machines as a source of infection. Am J Roentgenol 1997;168:567-8.
[25] Karadeniz YM, Kiliç D, Kara Altan S, Altinok D, Güney S. Evaluation of the role of ultrasound machines as a source of nosocomial and cross-infection. Invest Radiol 2001;36:554-8.
[26] Kac G, Gueneret M, Rodi A, Abergel E, Grataloup C, Denaire N, et al. Evaluation of a new disinfection procedure for ultrasound probes using ultraviolet light. J Hosp Infect 2007;65:163-8.
[27] Tarzmani MK, Eshraghi N, Asghari PB, Estakhri R, Eshraghi A. Role of ultrasound probes in transmission of hospital infections. Casp J Intern Med 2010;1:134-6.
[28] Fowler C, McCracken D. US probes: risk of cross-infection and ways to reduce it-comparison of cleaning methods. Radiology 1999;213:299-300.
[29] Mirza WA, Imam SH, Kharal MS, Aslam M, Ali SA, Masroor I, et al. Cleaning methods for ultrasound probes. J Coll Phys Surg Pak 2008;18:286-9.

The European Research Journal 2019;5(4):588-593 ORIGINAL ARTICLE

Comparing the effect of two different exercise types, mini-trampoline and fast-walking to gastrocnemius/soleus muscle elasticity by sonoelastrography

Tuba Tülay Koca[1], Murat Baykara[2], Adnan Demirel[1], Ejder Berk[1]

[1]Department of Physical Medicine and Rehabilitation, Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey
[2]Department of Radiology, Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey

DOI: 10.18621/eurj.407527

ABSTRACT

Objectives: Sonoelastography is a newly introduced ultrasound technique that evaluates tissue elasticity and thus provides additional information to that offered by conventional ultrasound images. Here, we compared the effect of ballistic jumping on mini-trampolin with walk exercise to the elasticity of gastrocnemius/soleus muscles with quantitative measurements by sonoelastography.

Methods: Forty volunteer healty male cases between the ages of 20-22 years were included the study. Initially, both exercise groups were subjected to joint warm-up movements for 8 minutes. Twenty of the cases (40 legs) had mini-trampoline (balistic jumping) exercise for 15 minutes. Another 20 cases (40 legs) had 15 minutes fast-walk exercise. Measurements were made immediately before and after the procedure (within 5 minutes) with the sonoelastography.

Results: A statistically significant difference was observed in the gastrocnemius/soleus muscles after exercise in the trampoline group according to sonoelastography strain value (SESV) data separately ($p = 0.0001$ / $p = 0.0001$). According to this, when the SESV values evaluated after 15 minutes of jump with the trampoline, we obtained that the elasticity increases and stifness decreases in the calf muscles. In the walking group, no statistically difference was observed in the gastrocnemius/soleus muscles after exercise separately ($p = 0.7925$ / $p = 0.1879$).

Conclusions: According to the study, in the trampoline group in general, a decrease in strain values and an increase in elasticityin muscle groups were found; in the walking group, a decrease in muscle elasticity, an increase in stiffness and muscle strain were found eventually. We found that the 15-minutes exercise program on the mini-trampoline is more effective as a heating technique and has more positive effect on muscle elasticity than the 15-minutes walking exercise.

Keywords: sonoelastography, trampoline, walk, exercise, muscle, stifness, strain

Received: March 19, 2018; Accepted: July 5, 2018; Published Online: November 12, 2018

Sonoelastography (SE) is a newly introduced ultrasound technique that evaluates tissue elasticity and thus provides additional information to that offered by conventional ultrasound images [1]. It is a noninvasive method for measuring tissue elasticity whereby a quantitative estimate is obtained of the elasticity of various soft tissues, including muscles, tendons, salivary glands, and abdominal organs. The

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

imaging method is based on acoustic radiation force impulses through the tissue to obtain an elastic modulus. The result is a local measurement of the tissue elasticity at each point of interest of an organ. This imaging method is operator independent, reproducible, and quantitative [2-4].

It has been documented that exercises on a mini-trampoline involve a multi-component approach, including muscle coordination, strength and balance training, body stability, and joint flexibility training [5]. Muscle action and coordination in the lower extremities were continuously facilitated by maintaining body balance on an elastic surface. In general, the ability to maintain balance is based on three mechanisms, including increasing the base of support, counter-rotating segments around the center of mass, and applying an external force other than the ground reaction force. In performing the mini-trampoline exercise, the participants were challenged to stabilize their body while keeping the center of mass over the base of the support. They needed to exert muscle force and neuromuscular responses to stiffen their legs in order to overcome the unstable conditions [6].

The effect of different exercise types on muscle elasticity has not been studied sufficiently. To best of our knowledge, there is no study about mini-trampolin exercise's acute effect to gastroknemius/soleus muscle' elasticity, and the comparison of the results with fast-walk exercise by SE. Here, we compared the effect of mini-trampolin exercise with fast-walk exercise to the gastrocnemius/soleus muscles with quantitative measurements by SE.

METHODS

Study Population

Forty volunteer healty male cases between the ages of 20-22 years were included the study. Initially, both exercise groups were subjected to joint warm-up movements for 8 minutes. Twenty of the cases (40 legs) had mini-trampoline (balistic jumping) exercise for 15 mınutes. Another 20 cases (40 legs) had 15 minutes fast-walk exercise. Measurements were made immediately before and after the procedure (within 5 minutes) with the SE.

Sonoelastography

SE is an ultrasound-based technique that determines mechanical properties of the tissue quantitatively, visually, and qualitatively compared with the B-mode analysis (acoustic impedance) or the color Doppler ultrasound (vascular blood flow). The diagnostic difficulties can be overcome by using the SE method, which is increasingly used in the recent years. Strain elastography is the most commonly used measurement technique among several others, and the externally applied pressure causes more deformation in the soft tissues and less deformation in the hard tissues. This information is color-coded on a screen, and the quantitative data are obtained by measurements from the region of interest (ROI) [2-4].

A high-resolution ultrasonography system (Aplio ™ 400 Platinum, Toshiba Medical Systems Corporation, Tochigi, Japan) and a broad band linear probe (PLT-704SBT) were used. When the gastrocnemius / soleus muscles were visualized on a gray scale ultrasonography image of the area symmetrically, bilaterally and separately, elastography was inserted into the apparatus and pressure was applied. The SE strain value (SESV) of the subcutaneous fat tissue in the same image and SESV of the central segments of the muscles were detected using by measurements from ROI. The sonoelastography strain ratio (SESR) of the muscles was calculated by dividing the fat values by the muscle values. All procedures were performed by the same experienced radiologist who was kept uninformed about the clinical diagnosis.

Statistical Analysis

The approval for this study was granted by the Institutional Ethics Committee. Measurements and calculations derived from SE were expressed as mean ± standard deviation. Categorical data were presented as numbers and percentages. The Shapiro–Wilk test was used to examine the fitness of the variables for the normal distribution. Comparisons of the obtained strain rates were made by independent Student's t test. When P value was less than 0.05, the result was considered statistically significant.

RESULTS

Forty male cases (80 legs) between 20-22 years of

Table 1. Descriptive data of the groups

Group		Age (year)	Height (cm)	Weight (kg)
Trampoline	Mean ± SD	21 ± 1.02	174.5 ± 6.13	70 ± 9.19
Walking	Mean ± SD	20.56 ± 1.8	176.5 ± 4.4	68.38 ± 8.45
t		1.34	1.67	0.82
p value		0.18	0.09	0.41

SD = standard deviation

age were included the study. There was no significant difference in age, height and weight between trampoline and walking groups ($p = 0.182$ / $p = 0.097$ / $p = 0.414$). The descriptive data for the groups are summarized in Table 1.

A statistically significant difference was observed in the gastrocnemius / soleus muscles after exercise in the trampoline group according to SESV data ($p = 0.0001$ / $p = 0.0001$) (Table 2). According to this, when the SESV values evaluated after 15 minutes of jump with the trampoline, we obtained that the elasticity increases and stiffness decreases in the calf muscles.

In the walking group, no statistically significant difference was observed in the gastrocnemius/soleus muscles after exercise ($p = 0.7925$ / $p = 0.1879$) (Table 3). According to this, 15 minute fast-walking exercise

Table 2. Pre/post data of SESV values of gastrocnemius/soleus muscles in trampoline group

Trampoline	Mean ± SD	*p value*
Gastroknemius First	0.38 ± 0.23	**0.0001**
Gastroknemius Second	0.15 ± 0.08	
Soleus First	0.59 ± 0.32	**0.0001**
Soleus Second	0.22 ± 0.08	

SESV = sonoelastography strain value, SD = standard deviation

Table 3. Pre/post data of UESV values of gastrocnemius/soleus muscles in walking group

Walking	Mean ± SD	*p value*
Gastroknemius First	0.55 ± 0.38	0.7925
Gastrocnemius Second	0.52 ± 0.61	
Soleus First	0.72 ± 0.58	0.1879
Soleus Second	1.05 ± 1.46	

UESV = ultrasound elastography strain value, SD = standard deviation

Table 4. Changes in SESR values before/after exercise in the gastrocnemius/soleus muscles

Group		Gastrocnemius Percent (n = 40)	Soleus Percent (n = 40)
Trampoline	Mean ± SD	45.05 ± 26.79	46.60 ± 24.29
	Median	39.69	43.93
	Minimum	8.57	17.48
	Maximum	80.00	86.11
Walking	Mean ± SD	161.80 ± 251.74	188.90 ± 270.66
	Median	59.38	84.57
	Minimum	3.23	3.57
	Maximum	962.50	935.85
t		2.9167	3.3118
p value		**0.0046**	**0.0014**

SESR = sonoelastography strain ratio, SD = standard deviation

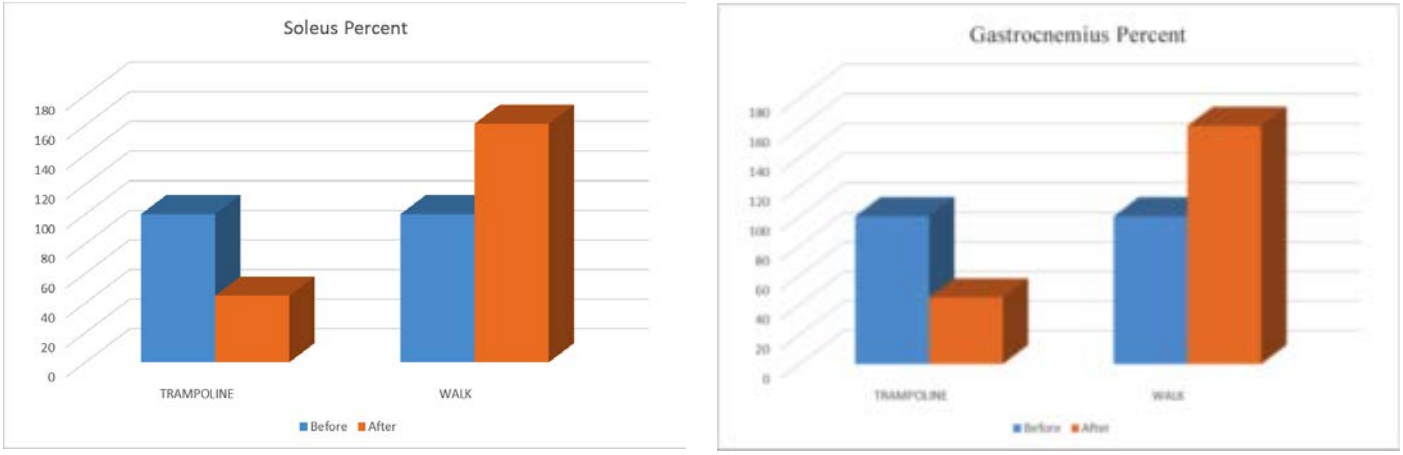


Figure 1. Graphical presentation of percent changes in SESRs in gastrocnemius/soleus muscles in trampoline and walk groups

did not cause any significant change in SESV valuesand did not affect muscle elasticity / stiffness positively.

When the percentages of SESR values before and after exercise were examined; the percent change in the both gastrocnemius/soleus muscle groups was significantly different at the trampoline group (p = 0.0046 / p = 0.0014) (Table 4). According to this, in the trampoline group in general, a decrease in strainvalues, an increase in elasticityatcalf muscles were found; in the walking group, a decrease in muscle elasticity, an increase in stiffness and muscle strain were found (Figure 1).

DISCUSSION

Fast-walking exercise was not found to have a positive effect on calf muscle elasticity. We found that the 15-minutes exercise program on the mini-trampoline is more effective as a heating technique and has more positive effect on muscle elasticity than the 15-minutes walking exercise.

Studies assessing the effect of exercise on muscle function and stiffness have used different measurement techniques and small cohorts, making it difficult to conclude on the overall efficacy of exercises types on these outcomes. Current data suggest that aerobic exercise training should be used as a primary treatment strategy for improving muscle function [5, 6].

Elasticity imaging is a relatively new ultrasound-based technique for investigating musculoskeletal injury. SE, the most commonly used technique, allows determination of the elastic properties of tissue by applying pressure, which provides a quantitative assessment of muscle tissue as a cheap, practical method [7-9]. Based on current of literature, SE seems to be at least as feasible as ultrasonografi (US) and magnetic rezonance imagination (MRI) for identify clinical muscle-tendon alterations [10].

Green *et al*. [11] used Magnetic Resonance Elastography (MRE), a noninvasive imaging technique, to assess the time-course of passive elasticity changes in the medial gastrocnemius/soleus muscles before and after a bout of eccentric exercise. Study findings by Crawford *et al*. [12] suggest that massage loading following eccentric exercise has a greater effect on reducing muscle stiffness.

Passive joint stiffness is an important quantitative measure of flexibility, but is affected by muscle volume and all of the anatomical structures located within and over the joint. Quantifying passive stretching responses of individual muscles by SE, helps the diagnosis of muscle disorders and aids the evaluation of surgical/rehabilitation treatments [13, 14]. The study by Hirata *et al* [15], showed the significant effectiveness of static stretching on the passive fasciclestiffness. Hirata *et al*. [16] also examined the muscle stiffness responses of the gastrocnemius/soleus during passive dorsiflexion before and after a static stretching by using US shear

wave elastography. They indicated that passive muscle stiffness differs among the triceps surae, and that the acute effect of a static stretching is observed only in the stiff muscle. Chino and Takahashi [17], determined muscle elasticity, measured independent of the confounding effects of muscle volume and the other nearby anatomical structures, is associated with passive joint stiffness in the joint position where the muscle is sufficiently lengthened. Chino and Takahashi [18] indicated that variations in the elasticity of other tissues, including medial gastroknemius aponeuroses or the ligaments and joint capsule of the ankle, would be associated with the variations in joint stiffness.

Similar to our study, Yanagisawa *et al*. [19] assessed the feasibility of SE for measuring exercise-induced changes in muscle stiffness and to compare the findings of it with those of a tissue stiffness for semi-quantitative assessment. They made participants to perform an arm-curl exercise. They found the strain ratio and the value obtained using the tissue stiffness significantly decreased, after exercise.

In our study, we observed a significant difference in elasticity and stiffness values in the calf muscle groups after 15 minutes on trampoline jumping exercise by SE. When we looked at the strain percentile changes, we also observed a significant decrease in total muscle strains in the trampoline group. We found jumping exercise with mini-trampoline as effective as a muscle heating technique. It has been observed in the literature that trampoline studies have resulted an increase in muscle strength, speed, jump, anerobic physical capacity, motor performance, balance and proprioception in long term [20-22]. We measured the positive effect of trampoline on muscle elasticity in the acute phase (in 5 minutes). At 15-minutes fast-walking group a decrease in muscle elasticity, an increase in stiffness and strain were found. Fast-walking exercise was found to be an ineffective heating method compared to trampoline.

SE has to be viewed as an experimental technique without sufficient supporting evidence to be used as a routine examination equivalent to US and MRI in musculoskeletal analysis. The usefulness of SE can be expected to increase rapidly in the musculoskeletal field, as soon as we learn to interpret elastographic artifacts as well as to take advantage of the new information provided by SE [23, 24].

Limitations

Small sample size and that ultrasound elastography standards have not been established yet in the literature are the limitations of the study.

CONCLUSION

Elasticity imaging is a relatively new ultrasound-based technique for investigating musculoskeletal injury. SE, the most commonly used technique, allows determination of the elastic properties of tissue by applying pressure, which provides a quantitative assessment of muscle tissue as a cheap, practical method. Heating with trampoline exercise is an effective, reliable method that generally increases elasticity and reduces stifness in calf muscles. The trampoline-jumping exercise was found to be superior to the fast-walking exercise in acute period.

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] Pedersen M, Fredberg U, Langberg H. Sonoelastography as a diagnostic tool in the assessment of musculoskeletal alterations: a systematic review. Ultraschall Med 2012;33:441-6.

[2] Demirel A, Baykara M, Koca TT, Berk E. Ultrasound elastography-based assessment of the elasticity of the supraspinatus muscle in impingement syndrome: does elastography has any diagnostic value? Clin Rheumatol 2018;37:1661-5.

[3] Xiang X, Yan F, Yang Y, Tang Y, Wang L, Zeng J, et al. Quantitative assessment of healthy skin elasticity: reliability and feasibility of shear wave elastography. Ultrasound Med Biol 2017;43:2:445-52.

[4] Hou SW, Merkle AN, Babb JS, McCabe R, Gyftopoulos S, Adler RS. Shear wave ultrasound elastographic evaluation of the rotator cuff tendon. J Ultrasound Med 2017;36:95-106.

[5] Miklitsch C, Krewer C, Freivogel S. Effects of a predefined mini-trampoline training programme on balance, mobility and activities of daily living after stroke: a randomized controlled pilot study. Clin Rehabil 2013;27:939-47.

[6] Giagazoglou P, Kokaridas D, Sidiropoulou M. Effects of a

trampoline exercise intervention on motor performance and balance ability of children with intellectual disabilities. Res Dev Disabil 2013;34:2701-7.
[7] Rosskopf AB, Ehrmann C, Buck FM, Gerber C, Flück M, Pfirrmann CW. Quantitative shear-wave US elastographyof the supraspinatus muscle: reliability of the method and relation to tendon integrity and muscle quality. Radiology 2016;278:465-74.
[8] Hoskins PR, Martin K, Thrush A. Diagnostic ultrasound : physics and equipment. 2nd ed. Cambridge medicine. Cambridge, UK; New York: Cambridge University Press. xi, 2010: p.263.
[9] Hasegawa H. Kanai H. Ultrasonic methods for measurement of small motion and deformation of biological tissues for assessment of viscoelasticity. Biomedical & Nanomedical Technologies. Momentum Press: New York, 2015: p.45.
[10] González Hidalgo M, Torres AM, Varona Gómez J. Deformation models : tracking, animation, and applications. Lecture notes in computational vision and biomechanics. Dordrecht; New York: Springer. xiv, 2013:p.297.
[11] Green MA, Sinkus R, Gandevia SC, Herbert RD, Bilston LE. Measuring changes in muscle stiffness after eccentric exercise using elastography. NMR Biomed 2012;25:852-8.
[12] Crawford SK, Haas C, Butterfield TA, Wang Q, Zhang X, Zhao Y, et al. Effects of immediate vs. delayed massage-like loading on skeletal muscle viscoelastic properties following eccentric exercise. Clin Biomech (Bristol, Avon) 2014;29:671-8.
[13] Koo TK, Guo JY, Cohen JH, Parker KJ. Quantifying the passive stretching response of human tibialis anterior muscle using shear wave elastography. Clin Biomech (Bristol, Avon) 2014;29:33-9.
[14] Terada S, Miaki H, Uchiyama K, Hayakawa S, Yamazaki T. Effects of isokinetic passive exercise and isometric muscle contraction on passive stiffness. J Phys Ther Sci 2013;25:1347-52.
[15] Hirata K, Kanehisa H, Miyamoto N. Acute effect of static stretching on passive stiffness of the human gastrocnemius fascicle measured by ultrasound shear wave elastography. Eur J Appl Physiol 2017;117:493-9.
[16] Hirata K, Miyamoto-Mikami E, Kanehisa H, Miyamoto N. Muscle-specific acute changes in passive stiffness of human triceps surae after stretching. Eur J Appl Physiol 2016;116:911-8.
[17] Chino K, Takahashi H. Measurement of gastrocnemius muscle elasticity by shear wave elastography: association with passive ankle joint stiffness and sex differences. Eur J Appl Physiol 2016;116:823-30.
[18] Chino K, Takahashi H. The association ofmuscleand tendon elasticity with passive joint stiffness: in vivo measurements using ultrasound shear wave elastography. Clin Biomech (Bristol, Avon) 2015;30:1230-5.
[19] Yanagisawa O, Niitsu M, Kurihara T, Fukubayashi T. Evaluation of human muscle hardness after dynamic exercise with ultrasound real-time tissue elastography: a feasibility study. Clin Radiol 2011;66:815-9.
[20] Aalizadeh B, Mohammadzadeh H, Khazani A, Dadras A. Effect of a trampoline exercise on the anthropometric measures and motor performance of adolescent students. Int J Prev Med 2016;7:91.
[21] Karakollukçu M, Aslan CS, Paoli A, Bianco A, Sahin FN. Effects of minitrampoline exerciseon male gymnasts' physiological parameters: a pilot study. J Sports Med Phys Fitness 2015;55:730-4.
[22] Giagazoglou P, Kokaridas D, Sidiropoulou M, Patsiaouras A, Karra C, Neofotistou K. Effects of a trampoline exercise intervention on motor performance and balance ability of children with intellectual disabilities. Res Dev Disabil 2013;34:2701-7.
[23] Melo X, Fernhall B, Santos DA, Pinto R, Pimenta NM, Sardinha LB, et al. The acute effect of maximal exercise on central and peripheral arterial stiffness indices and hemodynamics in children and adults. Appl Physiol Nutr Metab 2016;41:266-76.
[24] Klauser AS, Faschingbauer R, Jaschke WR. Is sonoelastography of value in assessing tendons? Semin Musculoskelet Radiol 2010;14:323-33.

The European Research Journal 2019;5(4):594-598 ORIGINAL ARTICLE

An assessment of vertigo patients presenting to the otorhinolaryngology and neurology outpatient clinics

Selman Sarıca[1], Yılmaz İnanç[2], Yusuf İnanç[3]

[1]Department of Ear, Nose and Throat, Kahramanmaraş Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey
[2]Department of Neurology, Kahramanmaraş Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey
[3]Department of Neurology, Gaziantep University School of Medicine, Gaziantep, Turkey

DOI: 10.18621/eurj.408135

ABSTRACT

Objective: Vertigo is a general term used for disorientation and is a frequent cause of admission to emergency services, otorhinolaryngology and neurology outpatient clinics. This study aims to evaluate the clinical findings, diagnostic laboratory tests, brain magnetic resonance imaging, and Doppler ultrasonography results of patients with complaints of vertigo.

Methods: Patients aged >18 years who admitted to the Otorhinolaryngology and Neurology Outpatient clinics of Kahramanmaraş Sütçü İmam University Training and Research Hospital with the main complaint of vertigo between January 2017 and August 2017 were retrospectively reviewed. The patients were evaluated in respect of anamnesis, examination findings, and diagnostic tests (pure tone audiometry, video nystagmography, brain magnetic resonance imaging, and carotid and vertebral artery Doppler ultrasonography).

Results: The study included a total of 101 patients with a mean age of 46.36 ± 16.1 years who presented with the complaint of vertigo. Of the patients, 16 had an ischemic gliotic region, 4 had a lacunar infarct, 2 had an arachnoid cyst, 2 had a cerebellar infarct, 1 had a meningioma, and 1 had a pineal gland cyst on the brain magnetic resonance imaging. Of the patients evaluated in the Otorhinolaryngology outpatient clinic, 87 (86.13%) were diagnosed with peripheral vertigo and 14 (13.6%) with central vertigo. A diagnosis of central vertigo was made in 23 (22.77%) patients evaluated in the Neurology outpatient clinic.

Conclusions: For patients presenting with the complaint of vertigo to the otorhinolaryngology and neurology outpatient clinics, a detailed anamnesis and a physical examination precede specific vestibular tests in the diagnosis. A coordinated communication of both clinics is important for a rapid diagnosis and prevention of unnecessary examinations.

Keywords: Vertigo, clinical evaluation, magnetic resonance imaging, Doppler ultrasonography, pure tone audiometry, video nystagmography

Received: March 20, 2018; Accepted: May 17, 2018; Published Online: September 3, 2018

Vertigo, which is the general term used for disorientation, is a frequent cause of admission to otorhinolaryngology and neurology outpatient clinics. Patients reporting vertigo have complaints such as the feeling of dizziness, sudden darkening of vision and imbalance [1-3]. The etiology of these symptoms is multifactorial and may include anemia, psychiatric disorders, hypoglycemia, drug effects, cardiovascular diseases and peripheral and central vestibular system disorders [4, 5]. Vertigo (real dizziness) is defined as

Address for correspondence: *Yılmaz İnanç, MD., Kahramanmaraş Sütçü İmam University School of Medicine, Department of Neurology, Kahramanmaraş, Turkey*
E-mail: drinancc@gmail.com

e-ISSN: 2149-3189

the illusion of movement which is not real, where the patient feels that they or the surroundings are turning [6]. Vertigo occurs with an asymmetrical involvement of any of the peripheral or central vestibular pathways of the vestibular system [7]. It should be focused on the vestibular system in every patient with a rotation anamnesis [6].

Vertigo is a symptom that should be attached importance because it affects a wide section of the population up to 20%-30%, causes loss of workforce, and can be a symptom of illnesses that may be life-threatening [3, 8, 9]. In studies conducted on emergency departments, it is reported that the rate of patients presented to emergency departments vary between 3% and 6.7% [2, 8, 10, 11]. In the evaluation of patients presenting with the complaint of vertigo, there is a need for various radiological and vestibular tests in addition to the anamnesis and physical examination. The main aim is to determine the etiology by differentiating whether the disease is of peripheral or central origin, to establish a diagnosis, and to apply a treatment [12, 13]. The physician should reach the correct diagnosis by correctly interpreting the anamnesis, and physical examination and test results and combining these with the symptoms of the patient. Despite all efforts of the clinician, difficulties may be experienced in the diagnosis and the determination of whether the disease is peripheral or central in some patients presenting with vertigo. In this period, patients tend to consult more than one physician for their diseases. This study aims to compare the clinical findings, diagnostic laboratory tests and imaging results of patients presenting to the Otorhinolaryngology and Neurology outpatient clinics with the complaint of vertigo.

METHODS

Patients aged >18 years who admitted to the Otorhinolaryngology and Neurology Outpatient clinics of Kahramanmaraş Sütçü İmam University Training and Research Hospital with the main complaint of vertigo between January 2017 and August 2017 were retrospectively reviewed. The approval for the study was granted by the Ethics Committee of Kahramanmaraş Sütçü İmam University School of Medicine in the meeting dated 06.12.2017 (session no:2017/04, decision no: 20). Patients with a neuropsychiatric disorder, systemic disease, history of chronic drug use or a diagnosis of malignancy were excluded from the study.

Detailed neurological and otorhinolaryngology examination findings were recorded and compared. Detailed diagnostic tests applied in respect of the etiology (pure tone audiometry, video nystagmography, brain magnetic resonance imaging (MRI), and carotid and vertebral artery Doppler ultrasonography) were reviewed. The patients were divided into groups according to the diagnosis as peripheral, central, and undefined on the basis of the clinical evaluations in the Otorhinolaryngology and Neurology outpatient clinics. Patients were treated according to the etiology.

The Dix-Hallpike maneuver was performed on patients applied to the Otorhinolaryngology outpatient clinic. The acetylsalicylic acid treatment was initiated in patients with stroke etiology in the Neurology outpatient clinic.

Statistical Analysis

The statistical analyses of the study data were made using the IBM SPSS for Windows Version 21.0 program. Numerical variables were reported as the mean ± standard deviation (SD) and the minimum and maximum values. Categorical variables were stated as number (n) and percentage (%). Before the comparison of the groups in terms of numerical variables, the parametric test assumptions were checked (conformity to normal distribution and homogeneity of variance). The diagnostic and symptom groups were compared in respect of age using the One-Way Variance Analysis. Paired comparisons were made with the Tukey's HSD test. Whether there is a difference between the groupsin respect of categorical variables or not was examined using the Chi-square test. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

A total of 101 patients admitted to the Otorhinolaryngology and Neurology Outpatient clinics with the complaint of vertigo. The patients comprised of 35 (31.65%) males and 66 (65.35%)

Table 1. Peripheral and central distribution of patients evaluated in otolaryngology and neurology outpatient clinics

	Peripheral vertigo n (%)	Central vertigo n (%)
ENT	87 (86.13%)	14 (13.6%)
Neurology	78 (78.23%)	23 (22.77%)

ENT = Otorhinolaryngology, n = the number of the patient

females with a mean age of 46.36 ± 16.1 years (range, 18-80 years). Of the patients evaluated in the Otorhinolaryngology outpatient clinic, 87 (86.13%) were diagnosed with peripheral vertigo and 14 (13.6%) with central vertigo. The Dix-Hallpike maneuver was applied to all the patients and a positive response was obtained in 72 (71.28%). Of the patients, 5 were diagnosed with Meniere's syndrome, 4 with vestibular neuritis, 5 with otosclerosis, and 1 with labyrinthitis. Grading in saccade that supports pathology, saccadic pursuit, optokinetic asymmetry, and vertical nystagmus that change direction with position were observed in 14 patients. Vertigo had begun suddenly in 89% and insidiously in 11% of the patients. A diagnosis of peripheral vertigo was made in 92% of the patients with sudden onset and in 50% of those with insidious onset. Chronic otitis was determined in 12 patients, and diplopia and dysarthria in 6 patients. Complaints of diplopia and paresthesia were present in 4 patients. In the hearing evaluation of the right ear, 73 patients were within the normal range at < 25 dB and a hearing loss was determined at a very mild level (26-40 dB) in 11 patients, mild (41-55 dB) in 1 patient, and at an advanced level (56-70 dB) in 2 patients (Table 1). In the evaluation of the left ear, 68 patients were normal and a hearing loss was determined at a very mild level in 14 patients, mild in 4 patients, and moderate in 4 patients. Of the12 patients with chronic otitis, 1 was diagnosed with labyrinthitis and 11 were diagnosed with benign paroxysmal positional vertigo (BPPV).

Table 2. Lesions detected in MRI

Detected lesion	n (%)
Ischemic gliotic region	16 (15.8)
Lacunar infarct	4 (3.9)
Arachnoid cyst	2 (1.9)
Cerebellar infarct	2 (1.9)
Meningioma	1 (0.9)
Pineal gland cyst	1 (0.9)

n = the number of the patient

Physical and neurological examinations were applied to all the patients evaluated in the neurology outpatient clinic. Central vertigo was diagnosed in 23 (22.77%) patients and peripheral vertigo in 78 (78.23%) (Table1). MRI was performed at an external center or in the Emergency Dept. Of the patients, 16 had an ischemic gliotic region, 4 had a lacunar infarct, 2 had an arachnoid cyst, 2 had a cerebellar infarct, 1 had a meningioma, and 1 had a pineal gland cyst on the brain magnetic resonance imaging (Table 2). The carotid vertebral Doppler USG tests were normal in these patients. Psychiatric causes, orthostatic hypotension and anemia were observed in 40%-45% of the patients presenting at both outpatient clinics.

DISCUSSION

Vertigo is most often caused by a dysfunction in the vestibular system from a peripheral or central lesion. Patients apply to many outpatient clinics such asemergency department, and otorhinolaryngology, neurology, and internal medicine outpatient clinics with the complaint of vertigo. As one of the most frequently seen complaints in the general population, vertigo has an extremely negative effect on the quality of life [3, 6, 14]. The frequencies of vertigo were 15% and 12%, respectively, in patients presenting to the otorhinolaryngology and neurology outpatient clinics. About 40%-45% of the patients had complaints such as psychiatric disorders, orthostatic hypotension, and anemia. The present study has similar data.In the literature, vertigo has been reported to be more frequent in females [13, 14]. In the present study group, vertigo was more commonly (66.35%) observed in the female gender. Central vertigo was more frequent (56.52%) in males, which can be explained by males having more risk factors for central etiologies [15]. In population-based studies on the etiology of vertigo, peripheral vestibular dysfunction has been reported in 40%, central causes in 10%, psychiatric causes in 15%, other reasons in 25%, and undetermined diagnosis in 10% of patients presenting at the emergency department and first stage outpatient clinics [16, 17]. In the present study, which

was more specific as it only included patients presenting to the Otorhinolaryngology and neurology outpatient clinics with the complaint of vertigo, peripheral causes were seen to be the primary cause, which was consistent with the literature. Patients with psychiatric causes were referred to the relevant departments in the neurology or otorhinolaryngology department at the first visit. Therefore, this study had no cases of vertigo due to psychiatric reasons. The central vertigo ratios in both departments were found to be 13.6% and 23%, respectively. The ratios in the neurology department were slightly higher than rates reported in the literature. The difference in the rate of peripheral and central vertigo in the same patient group presenting to the Otorhinolaryngology and neurology outpatient clinics was found to be a central rate of 13.6% in the otorhinolaryngology and 23% in neurology outpatient clinics and this could be attributed to a false negative on the diffusion-weighted MRI in patients with a cerebellar lesion or a brain stem lesion of small dimensions in the first few hours of ischemic stroke. In addition new clinic findings,this can be explained by the inclusion of the ischemic gliotic areas, developing in some regions of the brain conjunction with age and other risk factors, to the etiology group by the neurology outpatient clinic after making other differential diagnoses [18, 19]. In patients with a migraine, there are complaints of vertigo and imbalance at the rate of 70% either between or during the attacks. Vertigo alternately occurs with concomitant nausea. Just as it can follow the onset of a headache, it can also start during the recovery period [20]. The patients who presented with migrainous vertigo and peripheral vertigo were first evaluated in the present study. A diagnosis of migrainous vertigo was made in 4 patients with a history of a migraine in both the otorhinolaryngology and neurology outpatient clinics. Previous studies have reported migrainous vertigo betweenthe rates of 0.1% to 9% [21, 22]. Peripheral vertigo can be seen independently of a migraine in migraine patients. The peripheral vertigo was determined in 5 of the 9 patients in the present study with a history of a migraine. While the diagnosis of vestibular neuritis is easy with its typical clinical presentation, it is possible to confuse the pathologies at the level of eighth cranial nerve, vestibular nucleus or brain stem with the vestibular neuritis particularly during the Meniere's disease with recurrent vertigo episodes [23, 24]. In the diagnosis of Meniere's disease, detailed anamnesis (clinical findings such as dizziness, hearing loss, and fullness at the ear) and examination are important. Some of the patients in this study had findings that requiredimaging and other examinations. Diplopia and dysarthria were determined in 6 patients and 4 patients complained of diplopia and paresthesia.In both clinics, the treatments for patients presenting with vertigo were in three main categories as symptomatic, specific and rehabilitation treatments. For this purpose, vestibular suppressants such as meclizine, dimenhydrinate, promethazineand diazepam and anti-emetic drugs such as metoclopramide are used. For this purpose, anti-emetic drugs are used such as metoclopramide and vestibular suppressants such as meclizine, dimenhydrinate, promethazine and diazepam. Long-term use of drugs is not recommended and the formation of a normal compensation mechanism is preferred. Patients diagnosed with central vertigo in the otorhinolaryngology outpatient clinic are referred to theneurology department for the specific treatment. Although medical treatment for peripheral vertigo is given in the neurology outpatient clinic, patients are referred to the otorhinolaryngology outpatient clinic for rehabilitation. The Epley, Semont and Barbecue maneuvers are applied in patients with a specific diagnosis in the otorhinolaryngology outpatient clinic.

CONCLUSION

For patients presenting with the complaint of vertigo to the otorhinolaryngology and neurology outpatient clinics, a detailed anamnesis and a physical examination precede specific vestibular tests in the diagnosis. It was seen that the vast majority of patients that applied to both outpatient clinics had peripheral vertigo, especially BPPV. The use of maneuvers is promising in the BPPV treatment. A coordinated communication of both clinics is important for a rapid diagnosis and prevention of unnecessary examinations.

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] Zwergal A, Möhwald K, Dieterich M. [Vertigo and dizziness in the emergency room]. Nervenarzt 2017;88:587-96. [Article in German]
[2] Choi JY, Lee SH, Kim JS. Central vertigo. Curr Opin Neurol 2018;31:81-9.
[3] Strupp M, Dieterich M, Brandt T. The treatment and natural course of peripheral and central vertigo. Dtsch Arztebl Int 2013;110:505-15.
[4] Tarnutzer AA, Berkowitz AL, Robinson KA, Hsieh YH, Newman-Toker DE. Does my dizzy patient have a stroke? A systematic review of bedside diagnosis in acute vestibular syndrome. CMAJ 2011;183:E571-92.
[5] Chawla N, Olshaker JS. Diagnosis and management of dizziness and vertigo. Med Clin North Am 2006;90:291-304.
[6] Berisavac II, Pavlović AM, Trajković JJZ, Sternic NM, Bumbasirevic LG. Drug treatment of vertigo in neurological disorders. Neurol India 2015;63: 933-9.
[7] Tusa RJ. Bedside assessment of the dizzy patient. Neurol Clin 2005;23:655-73.
[8] Neuhauser HK. The epidemiology of dizziness and vertigo. Handb Clin Neurol 2016;137:67-82.
[9] Havia M, Kentala E, Pyykkö I. Prevalence of Menière's disease in general population of Southern Finland. Otolaryngol Head Neck Surg 2005;133:762-8.
[10] Kerber KA, Meurer WJ, West BT, Fendrick AM. Dizziness presentations in U.S. emergency departments, 1995-2004. Acad Emerg Med 2008;15:744-50.
[11] Reis LR, Lameiras R, Cavilhas P, Escada P. Epidemiology of vertigo on hospital emergency. Acta Medica Portuguesa 2016;29:326-331.
[12] Lee H, Sohn SI, Cho YW, Lee SR, Ahn BH, Park BR, et al. Cerebellar infarction presenting isolated vertigo: frequency and vascular topographical patterns. Neurology 2006;67:1178-83.
[13] Narita S, Kurose M, Kobayashi K, Himi T. [Study on 242 in patients reporting vertigo and dizziness]. Nihon Jibiinkoka Gakkai Kaiho 2003;106:21-7. [Article in Japanese]
[14] Uno A, Nagai M, Sakata Y, Moriwaki K, Kato T. [Statistical observation of vertigo and dizziness patients]. Nihon Jibiinkoka Gakkai Kaiho 2001;104:1119-25. [Article in Japanese]
[15] Giudice R, Izzo R, Manzi MV, Pagnano G, Santoro M, Rao MA, et al. Lifestyle-related risk factors, smoking status and cardiovascular disease. High Blood Press Cardiovasc Prev 2012;19:85-92.
[16] Neuhauser HK, Radtke A, von Brevern M, Lezius F, Feldmann M, Lempert T. Burden of dizziness and vertigo in the community. Arch Intern Med 2008;168:2118-24.
[17] Newman-Toker DE, Hsieh YH, Camargo CA, Pelletier AJ, Butchy GT, Edlow JA. Spectrum of dizziness visits to US emergency departments: cross-sectional analysis from a nationally representative sample. Mayo Clin Proc 2008;83:765-75.
[18] Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. Ann Neurol 1995;37:231-41.
[19] Fiebach JB, Schellinger PD, Jansen O, Meyer M, Wilde P, Bender J, et al. CT and diffusion-weighted MR imaging in randomized order: diffusion-weighted imaging results in higher accuracy and lower interrater variability in the diagnosis of hyperacute ischemic stroke. Stroke 2002;33:2206-10.
[20] Kattah JC, Talkad AV, Wang DZ, Hsieh YH, Newman-Toker DE. HINTS to diagnose stroke in the acute vestibular syndrome: three-step bedside oculomotor examination more sensitive than early MRI diffusion-weighted imaging. Stroke 2009;40:3504-10.
[21] Brantberg K, Trees N, Baloh RW. Migraine-associated vertigo. Acta Otolaryngol 2005;125:276-9.
[22] Karatas M. Central vertigo and dizziness: epidemiology, differential diagnosis, and common causes. Neurologist 2008;14:355-64.
[23] Neuhauser H, Leopold M, vonBrevern M, Arnold G, Lempert T. The inter relations of migraine, vertigo, and migrainous vertigo. Neurology 2001;56:436-41.
[24] Nelson JA, Viirre E. The clinical differentiation of cerebellar infarction from common vertigo syndromes. West J Emerg Med 2009;10:273-7.

The role of ultrasound imaging at detecting aortic aneurysm in emergency department

Suna Eraybar[1], Şule Akköse Aydın[2], Meral Leman Özkan[3], Serhat Atmaca[1], Yasemin Nennicioğlu[1]

[1]Department of Emergency Medicine, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey
[2]Department of Emergency Medicine, Uludağ University of School of Medicine, Bursa, Turkey
[3]Department of Emergency Medicine, Çekirge State Hospital, Bursa, Turkey

DOI: 10.18621/eurj.402076

ABSTRACT

Objective: Our study was carried out to investigate the effects of focused ultrasound imaging which is performed by emergency physicians in diagnosis and duration of treatment of abdominal aortic aneurysm.
Methods: The patients over 50 years; who applied to Uludağ University Emergency Department with the complaints of abdominal pain, side pain, chest pain, syncope, unexplained hypotension and under suspicion of the abdominal aortic aneurysm, were included in the study. Bedside ultrasound for abdominal aorta was done and diameter measurements of aorta recorded in order to determine the presence of an abdominal aortic aneurysm or to exclude the diagnosis.
Results: A total of 133 patients were included in the study. Eight patients were excluded from the study because of inadequate bedside US imaging. The aortic diameter was measured as ≥ 3 cm in the 54 (43.2%) patients. The aortic diameter was found more than 5 cm in 8 (6.4%) patients. After ultrasonographic investigations, aneurysm rupture (n = 5; 4%), aortic dissction (n = 13; 10.4%) and aortic aneurysm (n =36; 28.8%) were detected. The diagnosis was confirmed with computed tomography in all patients who had aortic pathology. Because of the continuance of clinic suspects in the patients whose aortic diameters were less than 3 cm, their computed tomography images were obtained and their aortic diameters were found within normal limits. Further imaging studies weren't performed at the remaining 48 (38.4%) patients because different prediagnosis was considered. Emergency ultrasound had a sensitivity of 100% (95% CI: 87-100), a specificity of 91% (95% CI: 90.8-99.8).
Conclusions: The diagnosis of abdominal aortic aneurysms is omitted 30% in emergency departments. It has a high morbidity and mortality if the diagnosis is skipped. In the presence of aortic aneurysm suspicion, evaluation of aortic diameter by bedside ultrasound is diagnostic. Bedside ultrasound evaluation by emergency physicians should become routine for using time and investigation numbers properly.

Keywords: emergency department, abdominal aortic aneurysms, bedside ultrasound

Received: March 5, 2018; Accepted: May 2, 2018; Published Online: August 29, 2018

Acute abdominal pain is a symptom which is presently less than a week, caused by non-traumatic reasons, developed in the progress of pathologies of abdominal or non-abdominal organs. Acute abdominal pain is the most important symptom of surgical or medical emergencies [1]. Abdominal pain

Address for correspondence: *Suna Eraybar, MD., University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Emergency Medicine, Mimar Sinan Mah., Emniyet Cad., Yıldırım, Bursa, Turkey*
E-mail: sunaeraybar@gmail.com

e-ISSN: 2149-3189

constitutes 5-10% of all emergency care applications [2]. Diagnosis and treatment of acute abdominal pain at emergency departments; is still one of the important clinical problems despite all the technological advancement. Especially at the situations when the patient is not stable, there are some problems at using imaging methods which origin from transporting difficulties.

Aortic aneurysms are at the 13th rank of most common death reasons in the USA [3]. Appraisal rate is 10/100.000 per year and it's estimated higher in elder groups. The frequency of acute aortic dissection is approximately 5.2 in a million [4] and detected as 1.5% at 60-80 age group in Turkey [5]. The frequency of aortic dissection is 2 to 5 times more in men than women. The diameter of an aneurysm is an important factor at detecting the rupture risk [6]. At many studies, it is shown that smoking affects the enlargement of an aneurysm [7-10]. It is detected that chronic obstructive lung disease increases the risk of aortic aneurysm rupture approximately 3.6 times [11].
Most of the patients who applied with acute aortic dissection describe a chest pain in a tearing character. The character of pain and radiating from chest to back and sometimes to waist is a very important clinical sign [10, 12]. If aortic dissections are left to their own natural course, they become substantially life threating. So, it must be diagnosed quickly and life-saving interventions must be started urgently. At this point, usage of diagnostic imaging methods at the emergency department has vital importance.

Ultrasound (US) is a conventional imaging method at differentiating between aneurysmatic and normal aorta. It has many important advantages like; no exposure to ionising radiation during imaging or any usage of contrast substances and it can be performed at the bedside [14]. The aim of the our study was investigate the effects of focused ultrasound imaging which is performed by emergency physicians in diagnosis and duration of treatment of abdominal aortic aneurysm (AAA) suspicion.

METHODS

Our study was performed prospectively for one year period at the Emergency Department of Uludağ University School of Medicine. Institutional ethics committee approval was taken for our study.

The patients over 50 years old; who admitted to the emergency department with the complaints of abdominal pain, side pain, chest pain, syncope, unexplained hypotension and who are under suspicion for an aortic aneurysm, were included to study. Diameter measurement and abdominal aorta imaging were performed by bedside ultrasound for detecting or excluding the abdominal aortic aneurysm in these patients.

Patients age, application clinics, vital signs, smoking history, co-morbidities, the presence of the abdominal aortic aneurysm in family history, known abdominal aortic aneurysm history, undergone aortic and other cardiac surgeries were recorded.

Informations like advanced age; hypertension history; severe abdominal, back and side pain in tearing character, syncope after abdominal pain, unexplained hypotension and also some physical examination signs like pulsatile mass at abdomen, tension arterial difference between right and left arm, difference at peripheral pulses, presence of focal neurologic deficit were noted as a value in suspicion of AAA.

Abdominal aortic diameter measurement was performed by bedside ultrasound imaging after stabilization of patients. Measurements were performed by emergency physicians who finished training course which is proper to US usage at emergency department protocol of American College of Emergency Physicians and that is arranged by Emergency Medicine Physicians Association of Turkey. US measurements were performed with Siemens Digital Color Doppler Ultrasound SIUI Apogee 3500 device, measurements were done at mode B with 3.5 MHz convex probe.

Abdominal aorta measurement was performed at the grey window, from diaphragmatic hiatus to aortic bifurcation on the transverse and longitudinal planes. Wall-to-wall diameter measurements from the widest area of aorta were recorded as < 3 cm, 3-5 cm, and > 5 cm. Measurements which are ≥ 3 cm were accepted as aneurysmatic dilatation. Aneurysm area was defined as suprarenal or infrarenal according to renal artery exit point. When the aneurysmatic segment was detected; its progress, presence of flap and intraaortic thrombus were recorded. Hepatorenal, splenorenal and pelvic regions were investigated ultrasonographically

for abdominal free fluid after the aortic measurement.

Contrast-enhanced thoracic and abdominopelvic computerized tomography (CT) imaging was performed for all of the patients whose measurements were ≥ 3cm. Information about patients' clinic was also given synchronously to the cardiovascular surgery clinic.

In the presence of ongoing clinical suspicion we applied further imaging methods despite aortic diameter has measured < 3 cm. For final diagnosis computed tomography were accepted as the golden standard for showing ultrasonography's sensitivity. CT was used at the situations where aortic diameter measurements couldn't be evaluated clearly or completely at the suprarenal or infrarenal levels. These patients were excluded from the study.

Statistical Analysis

All data belong to study were recorded via SPSS 13.0 for windows. Standard deviation (±) at continuous variables and n and % values at categorical variables, were used as descriptive statistics. Pearson chi-squared test, Fisher's exact chi-square test, and Mcnemar's test were used at comparing the categorical variables. $P < 0.05$ was accepted as statistically significant. Sensitivity and specificity values, positive and negative predictive values were calculated for evaluating the effectiveness of Computed Tomography and US at diagnosing.

RESULTS

Our study included 133 patients over the age of 50. Eight patients were excluded from the study because of inadequate bedside US imaging due to dense abdominal gas (n = 3), diffuse defence (n = 2), and obesity (n = 3). Computed tomography was used for excluding AAA in these patients. As a result, 125 patients who had bedside US imaging for the suspect of AAA at emergency room included to the study.

According to our study population 78 (62.4%) were male and remaining 47 (37.6%) were female. Mean age of patients was 67 yeras (min: 50 – max:90, std deviation 9.857). The most common complaint was an abdominal pain with 84 (67.2%) patients. Patients who had more than one complaint, symptoms were recorded separately. Most common complaints are summarized in Table 1. Smoking history was present in the 51.2% (n = 64) of the study population. Physical examination findings which support AAA; were evaluated as pulsatile mass at the abdomen, difference at peripheral pulses, tension arterial difference between right and left arm. There is a pulsatile mass in 18 (14.4%) patients, tension arterial difference between the arms in 24 (19.2%) patients, the difference at peripheral pulses in 21 (16.8%) patients.

After the bedside US evaluation, the aortic diameter was measured ≥3 cm in 54 (43.2%) patients. The aortic diameter was >5 cm in 8 (6.4%) patients. False lumen, flap, intraaortic thrombus and abdominal free fluid were investigated with US in all the patients who had a 3 cm aortic diameter. Flap in 14 (11.2%) patients, intraaortic thrombus in 27 (21,6%) patients, abdominal free fluid in 5 (4%) patients were detected. As a result of US investigations; AAA rupture in 5 (4%) patients, aortic dissection in 13 (10.4%) patients, and aortic aneurysm signs in 36 (28.8%) patients were detected. IV contrast-enhanced thoracic and abdominopelvic tomography imaging was planned for these patients. Clear results were acquired from 53 patients except for one patient, who was sent for computed tomography imaging after emergency evaluation and his situation was worsened during iv contrast enhancement. Aneurysmatic dilatation and flap presence with the false lumen at aorta was reported but dissection typology couldn't be performed due to unfinished sequencing and the report was interpreted inadequate evaluation.

Further imaging was performed due to the presence of ongoing clinical suspect by their physicians in 23 (18.4%) patients although their aortic

Table 1. The presenting symptoms of patients*

Symptom	Frequency (n)	Percent (%)
Abdominal pain	84	67.2
Back pain	61	48.8
Flank pain	34	27.2
Chest pain	15	12.0
Syncope	17	13.6
Hypotension	3	2.4
Neurological deficits	10	8
Cardiopulmonary arrest	1	0.8

*Some patients had more than one symptom.

diameters were measured as < 3 cm at US investigations. Aortic calibrations of these patients detected between normal range at CT and there were no signs of AAA or its complications. Thorax and abdominopelvic CT imaging were performed in total 77 patients.

Dissection typology of patients who got aortic dissection diagnosis by CT was performed by DeBakey classification. Types were recorded except one patient whose situation became worsen and CT imaging couldn't be finished. According to this, type 1 aortic dissection in 7 (53.8%) patients and type 3 aortic dissection in 5 (38.4%) patients were detected. At the remaining 48 (38.4%) patients despite other prediagnoses, aortic diameter measurement was performed with US for excluding AAA. The aortic diameter was measured as < 3 cm in these patients and further imaging wasn't performed. Additional imaging methods were used which belong their prediagnoses. Flowchart of diagnostic approaches of patients after bedside aortic US imaging, are shown at Figure 1.

In our study 29 (23.2%) patients have aortic aneurysm diagnosis whereas, fatal aortic pathologies which include aortic dissection and aneurysm rupture were detected in 18 (14.4%) patients. Nephrolithiasis was detected as the most common secondary diagnosis which clinically interferes with AAA at the patients whose aortic diameters were measured with US. Patients' final diagnoses are defined in Table 2.

Distribution of sex, co-morbidities, smoking history, physical examination signs of 29 patients who had AAA diagnosis and 18 patients who had aneurysm rupture or dissection, were evaluated retrospectively. Thirty-six (76.6%) of 47 patients were male and the remaining 11 (23.4%) were female. Thirty-nine (82.39%) patients were following for hypertension and there was additional medication usage. Male sex and hypertension effect at AAA diagnosis was determined as statistically significant ($p = 0.01$).

When the relation is calculated between the final diagnoses and smoking history, 70.2% (n = 33) of them has smoking history and smoking history was determined as an independent risk factor at AAA diagnosis ($p < 0.03$).

Aneurysm presence was considered in 54 patients after abdominal aortic evaluation with US at the emergency room but the aneurysmatic segment wasn't seen after CT imaging. In the light of these false positive ratios, the sensitivity of US at the diagnosis of AAA was calculated as 100% (95% CI: 87-100) and specificity of it calculated as 91%. Diagnosis is propounded by all the patients whose aortic diameters were measured >3 cm with US. At the patients, whose US investigations didn't show any an aneurysm but still got under CT imaging (7/125), any additional benefit of undergone imaging wasn't detected for aortic pathology. Positive predictive value of US is determined as 87%, and negative predictive value is detected as 100%. Sixty-one (48.8%) patients were hospitalized because of their diagnoses. Twenty-six

Table 2. The distribution of final diagnoses

Final diagnoses	Frequency (n)	Percent (%)
AAA	29	23.2
Aortic dissection	13	10.4
Aneurysm rupture	5	4.0
Other		
Nephrolithiasis	23	18.4
Acute coronary syndrome	14	11.2
Cholelithiasis	12	9.6
Acute pancreatitis	10	8.0
Activation of peptic ulcus	9	7.2
Arterial occlusion	4	3.2
Pulmonary embolism	2	1.6
Cerebrovascular event	2	1.6
Mesenteric iscemia	1	0.8
Renal infarction	1	0.8
Total	125	100

AAA = Abdominal aortic aneurysm

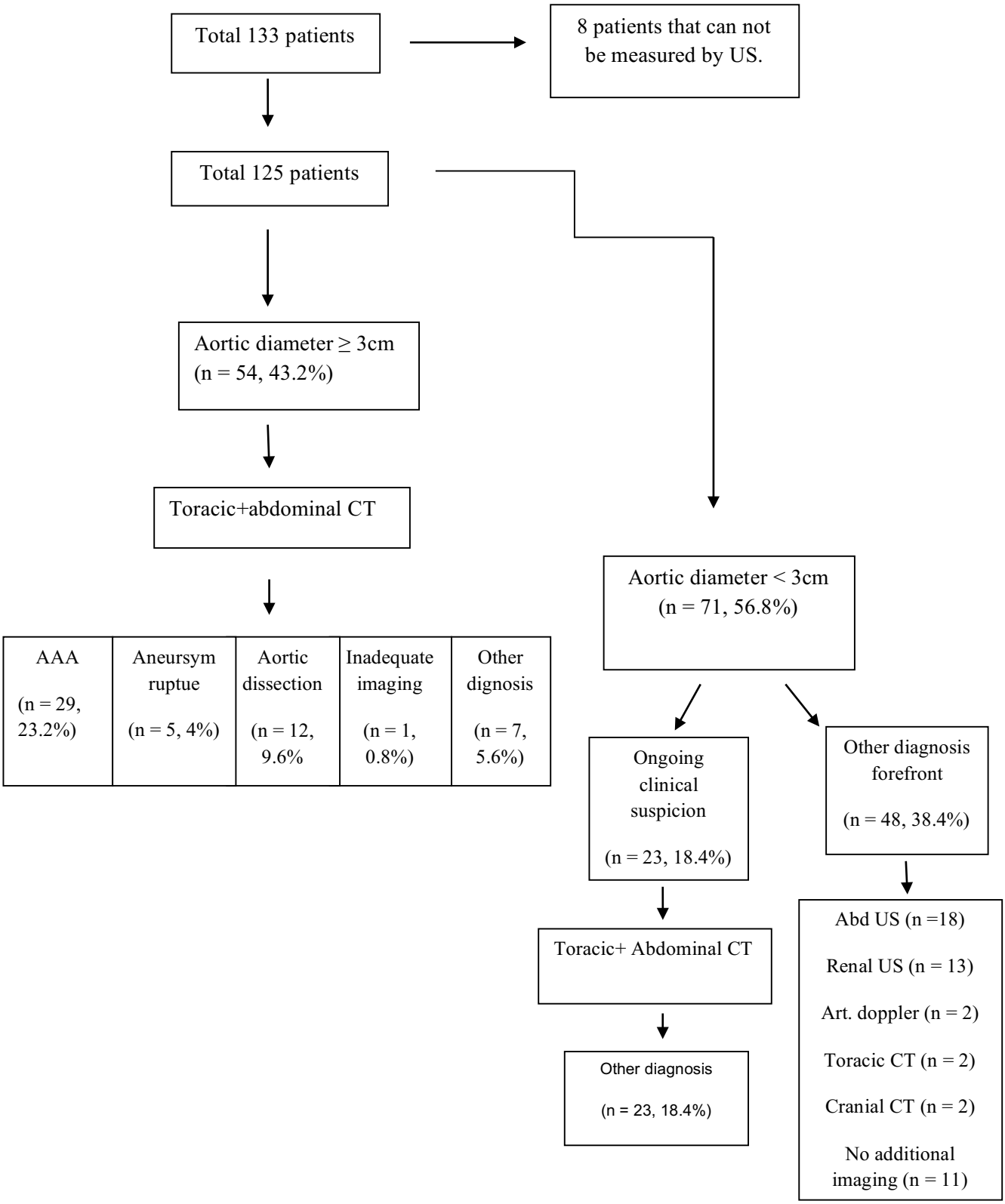


Figure 1: The distribution of additional imaging after emergency US. AAA =Abdominal Aortic Aneurysm, US = Ultrasound, CT = Computerized tomography, Abd = Abdominal.

(20.8%) patients were admitted to cardiovascular surgery intensive care unit and 14 (11.2%) patiens were admitted to coronary intensive care unit. One patient who got mesenteric ischemia diagnosis and total 7 (5.6%) patients who had acute cholecystitis and acute pancreatitis diagnoses were admitted to general surgery service.

One patient who admitted to emergency room with hypotension and abdominal pain, and bedside US aortic diameter measurement was >3 cm, also flap and intraaortic thrombus in US imaging detected were taken to CT imaging with the prediagnosis of aortic dissection but during imaging, arrest developed. There was another patient, who applied with the complaints of syncope and right leg pain and right leg femoral artery and distal couldn't be palpated; aortic diameter was measured as <3 cm but the clinical exclusion of diagnosis couldn't be done so CT imaging was performed. Thrombus was detected in the iliac artery. Both of these patients were resuscitated at the emergency room but they didn't respond and they're accepted as exitus.

Five (4%) patients left the emergency room during their follow up despite all of the risks and life threating character of their situation were told them. First of these patients were applied with back pain and syncope, the aortic diameter was measured between normal range and was followed by electrocardiogram and prediagnosis was the acute coronary syndrome. Three of the remaining 4 patients aortic dissection were detected by imaging (2 of them were DeBakey type 3, one of them was DeBakey type 1). The last patient had AAA diagnosis with intraaortic thrombus.

DISCUSSION

AAA is a true surgical emergency which is needed to diagnose urgently and has high mortality when it's missed, its morbidity and mortality can be reduced with early intervention [15]. In a cohort study, which includes 73,450 patients and evaluates prevalence and risk factors of AAA, smoking incidence was found as 75%. In our study smoking incidence was found as 70.2% at AAA patients and it is determined as an important factor. Hypertension is also evaluated as the independent risk factor for the rupture and dissection of AAAs [16]. Hypertension accompanied in the 82.9% of 47 AAA patients in our study. This ratio is similar with other studies. In Edinburg study which investigates peripheral artery diseases, hypertension accompanied to AAA in the 34 patients of 1,592 [17]. In our study, known peripheral artery disease was recorded at two patients and after investigations, AAA was detected at these patients. Another risk factor is positive family history for AAA [18]. There was no family history in patients who included our study.

US is an imaging method which is commonly preferred at AAA diagnosis. It is a non-invasive, low-cost and accessible method so it has application area for diagnosis at emergency departments. US's primary benefit is abdominal aortic aneurysm can be investigated correctly, quickly and sensitively at the bedside [13].

US sensitivity for detecting AAA is found as 100% in many studies [15, 18, 19]. In obese people and at the presence of severe abdominal gas, inadequate imaging can be performed and US is dependent to the person who performs it.

In the study of Kuhn *et al*. [15]; AAA detecting sensitivity and specificity of US at patients who had abdominal pain and are more than 50 years old were found as 100%, which is performed by emergency physicians who finished 3 days education program. In another study which was performed by Tayal *et al*. [20], US's positive predictive value was detected as 95% and the negative predictive value was detected as 100%. In our study, ultrasound was performed by three years emergency medicine residents and they finished one-day US education program. US sensitivity was detected as 100% and specificity was detected as 91% at AAA detecting in the emergency department in our study.

In suspected cases, the aneurysm can be excluded if aortic diameter is evaluated as normal with US [21, 22]. In our study, patients who had aneurysmatic dilatation diagnosis with bedside ultrasound could be followed up by cardiovascular surgery service. Detecting operation needs according to annual growth rate provided a base for viewing mortality rates at follow-ups.

Nephrolithiasis took the first place at misdiagnoses [23]. In our study after the clinical suspect, we performed CT imaging to some patients and 10% of them had nephrolithiasis. The similarity of pain characteristic and not the occurrence of co-

symptoms at the presence of risk factors cause the need of additional imaging methods for confirming the diagnosis. Co-diagnoses which were achieved by CT imaging which was performed for the suspect of AAA, was nephrolithiasis (13%), cholelithiasis (2.6%) and renal infarct (1.3%) respectively.

Usage of US as a screen test for AAA diagnosis was considering in a close future [13]. Early surgical consultation and intervention can be possible in the presence of rupture or dissection with abdominal aortic evaluation by US. At the presence of uncomplicated aneurysms, US can be used for follow up and detecting the time of elective surgery.

Bedside US can be done simultaneously with resuscitation or after the proper treatment because it is non-invasive and easily applicable.

As a result, the most important role of the emergency physician is detecting if there is a need for emergent surgical intervention or medical treatment. Etiology can be detected in many of the patients with detailed anamnesis which includes all of the pain's characteristics, proper physical examination, laboratory and radiologic investigations which are requested with correct indications. At this stage, patient's present clinical situation must be taught for deciding usage of imaging methods and if the patient is unstable could not be taken from the emergency room.

Limitations

This study has some limitations which have to be pointed out. First the small patient population do not allow us to draw any conclusion about the effectiveness of this technique. Furthermore, the follow-up was limited. Larger series are needed to confirm the effectiveness of the bedside ultrasound imaging in detecting aortic aneurysms. Second we have high aortic aneurysm and dissection rates according to the literatüre this may be due to narrow range of age and symptomatology of selected patients.

CONCLUSION

If there is AAA in the suspected diagnosis list, evaluation of an aortic aneurysm with bedside US is necessary and diagnostic. Aortic imaging in patients enables detecting of AAA, dissection diagnoses and rupture presence. Evaluating aorta as normal indicates the necessity of considering additional pathologies in the differential diagnosis. Thus, investigation and time can be used properly and adequate treatment steps can be chosen for patients. Bedside ultrasonographic imaging must be routinized by emergency medicine physicians for using time and investigation numbers properly.

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] Graff LG 4th, Robinson D. Abdominal pain and emergency department evaluation. Emerg Med Clin North Am 2001;19:123-36.

[2] Lameris W, Randen A, Dijkdraaf MG, Bossuyt PM, Stoker J, Boermeester MA. Optimization of diagnostic imaging use in patients with acute abdominal pain (OPTIMA): Design and rationale. BMC Emerg Med 2007;7:9.

[3] Majumper PP, St Jean PL, Ferrell RE, Webster MW, Steed DL. On the inheritance of abdominal aortic aneurysm. Am J Hum Genet 1991;48:164-70.

[4] Bickerstaff LK, Pailero PC, Hollier LH, Melton LJ, Van Peenen HJ, Cherry KJ, et al. Thoracic aortic aneurysms: a population based study. Surgery 1982;92:1103-8.

[5] Soysal M, Denizci U, Bayar R, Keşmer Y, Ulusoy M, Söylemez H, et al. Yaşlı popülasyonda abdominal aort anevrizmasısıklığının ve kardiyovasküler risk faktörleri ile ilişkisinin belirlenmesi. Klinik Gelişim 1996;9:4110-5.

[6] Coady A, Rizza JA, Hammond GL, Mandapati D, Darr U, Kopf GS, et al. What is appropriate size criterion for resection of thoracic aortic aneurysm? J Thorac Cardiovasc Surg 1997;113:476-91.

[7] Pasipoularides A, Murgo JP, Bird JJ, Craig WE. Fluid dynomics of aortic stenosis: mehanisms for the presence of subvalvular pressure gradients. Am J Physiol 1984;246(4 Pt 2):H542-50.

[8] Svensson LG Crawford ES (eds). Cardiovascular and vascular disease of the aorta. 1st edition. Philidelphia: WB Saunders Company; 1997.

[9] Strachan DP. Predictors of death from aortic aneurysm among middle-aged men: the White Hall Study. Br J Surg 1991;78:401-4.

[10] MacSeveney ST, Ellis M, Worrell PC, Greenhalgh RM, Powell JT. Smoking and growth rate of small abdominal aortic

aneurysms. Lancet 1994;344:651-2.
[11] Lobato AC, Puceh-Leao P. Predictive factors for rupture of thoracoabdominal aortic aneurysms. J Vasc Surg 1998;27:446-53.
[12] DeSanctis RW, Doroghazi RM, Austen WG, Buckley MJ. Aortic dissection. N Engl J Med 1987;317:1060-67.
[13] Barkin AZ, Rosen CL. Ultrasound detection of abdominal aortic aneurysm. Emerg Med Clin North Am 2004;22:675-8.
[14] American College of Emergency Physicians. Emergency ultrasonography imaging criteria compendum. ACEP Policy Statements. Ann Emerg Med 2009;53:550-70.
[15] Kuhn M, Bonnin RLL, Davey MJ, Rowland JL, Langlois SL. Emergency department ultrasound scanning for abdominal aortic aneurysm: accessible, accurate and advantageous. Ann Emerg Med 2000;36:219-23.
[16] Rodin MB, Daviglus ML, Wong GC, Liu K, Garside DB, Greenland P, et al. Middle age cardiovasculer risk faktors and abdominal aortic aneurysm in older age. Hypertension 2003;42:61-8.
[17] Fowkes FG, Housley E, Cawosa FH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburg Artery Study: prevelance of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 1991;20:384-92.
[18] Vowden P, Wilkinson D, Ausobsky JR, Kester RC. A comparison of three imaging techniques in the assessment of an abdominal aortic aneurysm. J Cardiovasc Surg (Torino) 1989;30:891-6.
[19] Ernst CB. Abdominal aortic aneurysm. N Engl J Med 1993;328:1167-72.
[20] Tayal VS, Graf CD, Gibbs MA. Prospective study of accuracy and outcome of emergency ultrasound for abdominal aortic aneurysm over two years. Acad Emerg Med 2003;10:867-71.
[21] Knaut AL, Kendall JL, Patten R, Ray C. Ultrasonographic measurement of aortic diameter by emergency physicians approximates results obtained by computed tomography. J Emerg Med 2005;28:119-26.
[22] Walker A, Brenchley J, Sloan JP, Lalanda M, Venables H. Ultrasound by emergency physicians to detect abdominal aortic aneurysms: a UK case series. Emerg Med J 2004;21:257-9.
[23] Rose WM III, Ernst CB. Abdominal aortic aneurysm. Comp Ther 1995;21:339-43.

The European Research Journal 2019;5(4):607-612 ORIGINAL ARTICLE

Relationship between students' performance on weekly task assessments and final practical exam at the preclinical restorative dentistry course

Muhammet Kerim Ayar

Department of Restorative Dentistry, Biruni University, Faculty of Dentistry, İstanbul, Turkey

DOI: 10.18621/eurj.400696

ABSTRACT

Objectives: The purpose of this study was to examine the relationships between dental students' performance on weekly practical task assessments, midterm practical exam and final practical exam in the preclinical restorative dentistry course.

Methods: Scores of final practical exam, midterm practical exam and weekly practical task assessments in the restorative dentistry preclinical course in the half year of the third year of the curriculum at Biruni University Faculty of Dentistry were compared. It was hypothesized that students that performed highly on weekly task assessments would perform highly on the midterm and final practical exams.

Results: The results showed that the weekly practical task assessment scores were correlated with the midterm practical exam and final practical exam scores and were a positive predictor. However, final practical exam scores were significantly lower than midterm practical exam and weekly practical task assessment scores.

Conclusions: The quality assessments of students' weekly tasks would be an effective predictor to assess student's preclinical performance. Thus, it would be recommended that integrating weekly task assessment into the preclinical restorative dentistry curriculum as an effective assessment tool.

Keywords: Preclinical examination, restorative dentistry, dental education

Received: March 2, 2018; Accepted: June 10, 2018; Published Online: June 23, 2018

The one of the important components of preclinical dental education is a restorative dentistry course. Preclinical restorative dentistry courses enable students acquire and develop their manual dexterity and gain knowledge about the clinical aspects of to restoring carious and/or defective teeth [1]. Manual dexterity is a fundamental component in restorative dentistry, as fine motor skills are necessary to carry
out complex treatments in small dimensions, with limited space and visibility in the oral cavity [2, 3]. Dental students learn these fundamental skills through simulated exercise in preclinical courses using either artificial teeth mounted in phantom head or extracted natural teeth, before delivering actual patient care in the clinic. Therefore, dental students should acquire of these psychomotor skills during the preclinical course of restorative dentistry to be prepared to deliver real patient care in the clinics [4].

The final practical examination has generally a greatest influence for assessing students' preclinical success in restorative dentistry courses. Students must

Address for correspondence: *Atilla Tekin, DDS, PhD., Biruni University, Faculty of Dentistry, Department of Restorative Dentistry, 10. Yıl Cad., No:45, 34010 İstanbul, Turkey, E-mail: kerimayar@biruni.edu.tr, Phone: +90 2124448276, Fax: +90 2124164646*

e-ISSN: 2149-3189

take at least 50 out of 100 points in the final exam to pass the restorative practical lesson in the faculty of dentistry at Biruni University. The score on the final exam on the year-end grade is 60%. The effect of the midterm exam was determined as 40% on the year-end grade. Weekly task assessments have not a direct numerical effect on the year-end score, but the completion of these tasks is a prerequisite for entering the final exam at the Biruni University. However, measuring student performance at a particular time, provide information about only single specific performance and not about psychomotor learning curve [3]. Therefore, validity of the final practical exam to assess whether student gained objective learning of restorative dentistry through the whole of preclinical course would be questionable.

The purpose of the present study was to determine if any correlations existed between dental students' final and midterm practical exam scores and their weekly task assessment scores in restorative dentistry preclinical course. It was hypothesized that students' performance in the preclinical restorative dentistry course would predict how successful they were in the clinic, using their weekly task assessment scores as a measure of performance instead of, or similar to final practical exam scores. It was claimed that students who did poorly work on weekly task assessments would receive low grades in the final exam in the present study. This correlation would recommend that weekly task assessment in a preclinical course is crucial in the improvement of manual dexterity and gaining dental knowledge needed for success in the clinic.

METHODS

Third-year students at dental school participate in a 16-week restorative dentistry preclinical course in the one semester during the Restorative Dentistry Practical Course at the Faculty of Dentistry of Biruni University in Istanbul, Turkey. A total of 84 dental students (50 females, 34 males) participated in the study. The participation of all students in the study was voluntary. Preclinical courses consisting of phantom head simulation sessions. The course curriculum through the semester was given in Table 1. The weekly task assessments were conducted each week after the course sessions. All of weekly assessment scores (nine in total) were averaged to calculate the mean weekly assessment scores. All weekly assessments were equally weighted. Additional to completion of all of weekly assessments, students have to pass midterm and final practical exams (a scale of 0 to 100). A midterm practical exam was conducted at the 7th week. The final practical exam was conducted in the last week of course. All assessments were performed by the same rater (M.K.A). Faculty and teaching assistants were available for additional feedback during preclinical course sessions. As usual, no feedback to students from the faculty stuff was given during mid and final practical exams.

Students were divided into three subgroups according to their weekly task assessment mean as following, lowest third, middle third and upper third to determine trends related to the midterm and final exams.

Statistical Analysis

Means and standard deviations were calculated for weekly task assessments, midterm exam and final exams. Comparison was made among averaged weekly task assessment scores, midterm exam and final exam scores, respectively. Paired t-tests were used for statistical analysis and the *p*-level was set at 0.05. Also, mean weekly task assessments of each student was correlated with his or her midterm and final exam scores, respectively to assess the strength of the relationship. Statistical analysis was carried out using SPSS version 18.0 for Windows statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

The means and standard deviations of weekly task assessment scores, midterm exam scores and final exam scores of the students on the preclinical restorative dentistry course throughout the 16-week study are shown in Table 2 and Figure 1. For the mean weekly task assessment, the mean score was 84.2 ± 8.7 with a range of 64.4 to 99.4. For the midterm exam, the mean score was 76.7 ± 13.7 with a range of 40 to 95. For the final exam, the mean score was 67.8 ± 13.7 with a range of 35 to 100. The coefficient of variation, a comparison measure of relative dispersion,

Table 1. Preclinical restorative dentistry curriculum for third year student at Biruni University (2017-2018)

Week #	Preclinical course topic	Activity
1	Introduction to the use of phantom head and working positions. Occlusal cavity preparation for amalgam at the phantom.	Teeth 46 and 47 O
2	Occlusal cavity and proximal cavity preparations on plastic teeth at the phantom.	Teeth 26 and 27 O, Teeth 24 and 25 DO.
3	Complex cavity preparations at the phantom.	Tooth 36 MOD, Teeth 37 MO, 34 and 35 DO.
4	Complex and cervical cavity preparations at the phantom	Teeth 14 MOD, 15 DO, and 17 DO, Tooth 16 occlusal and cervical.
5	Placement of glass ionomer base into the prepared cavities at the third and fourth lessons at the phantom.	
6	Cavity preparation and amalgam restoration at the phantom.	Teeth 24 MO, 25 DO, 26 O, 27 O
7	Midterm practical exam	Amalgam restoration of tooth 17 O, cavity preparation for amalgam of tooth 16 MO, placement of glass ionomer base into tooth 15 MO, placement of tofflemire matrice.
8	Re-preparation week. Students with unacceptable performance in the previous lessons redo their preparations in this week.	
9	Composite restoration at the phantom.	Teeth 47 O, 46 MO, 45 MO
10	Composite restoration at the phantom.	Teeth 27 DO, 26 MOD, 24 DO
11	Carious removal and composite restoration with extracted human teeth	
12	Proximal cavity preparation for anterior teeth at the phantom.	Teeth 13, 12, 11, 21, 22, 23
13	Composite restoration at the phantom.	Teeth 13, 12, 11, 21, 22, 23
14	Anterior tooth fracture preparation and restoration with resin composite	Teeth 11, 21
15	Tooth preparation for composite laminate veneer.	Teeth 11, 12, 21, 22
16	Final Exam	Tooth 46 DO amalgam cavity preparation with base placement, tooth 16 DO composite restoration, tooth 17 DO amalgam restoration, tooth 45 MOD cavity preparation for amalgam, placement of ivory matrice.

MO = Mesial + Occlusal, DO = Distal + Occlusal, MOD = Mesial + Distal + Occlusal

showed that the Mean Weekly Task Assessment varied in a narrow range (10.3%) while the midterm exam (17.9%) and final exam (30%) data were much more volatile.

Gradually increasing trends to the midterm exam and the final exam may be seen. The standard deviations were of similar value throughout the study period. Preparation of the complex and compound

Table 2. Descriptive statistical measures

Variable	Mean ± Standard Deviation	Coefficient of variation	Min - Max
Mean Weekly Task Assessment	84.2 ± 8.7[a]	10.3%	64.4 - 99.4
Midterm Exam	76.7 ±13.7[b]	17.9%	40 - 95
Final Exam	67.8 ± 13.7[c]	30%	30 - 100

Different superscripts indicate significant differences in the same column ($p < 0.05$)

cavity preparations showed gradual improvement from the second week to seventh week with reaching a plateau. The mean weekly task assessment is significantly higher than those of midterm exam ($p = 0.01$) and final exam ($p = 0.01$) respectively. Mean of the final exam is significantly lower the mean of midterm exam ($p = 0.01$).

Trends related to the midterm and final exams, among three subgroups including lowest third, middle third and upper third were shown in Figure 2. Students' performances were lowered at the midterm exam and final exam weeks, regardless their weekly task assessment means.

Correlation coefficients between the mean weekly task assessment and midterm exam score (r=0.623), between the mean weekly task assessment and final exam score (r=0.543), and between midterm exam score and final exam score (r=0.413), confirming relationship between practical measurement tools.

DISCUSSION

The results of the present study indicate correlations among assessment scores of student's weekly tasks and both of midterm and final practical exam scores, respectively. This confirms that student performs well at weekly task assessments likely will show better performance at the midterm and final practical exams. Therefore, we could accept that students' weekly performance scores would be a good predictor for final and midterm practical exam scores of the students, thus for clinical success. Additionally, these findings are consistent with Velayo *et al*. [5], who demonstrated a positive relationship between the preclinical and clinical performance of students.

The eventual aim of the preclinical restorative dentistry course is to get ready students to provide the best patient care in the clinic. It is estimated that students then continue to build on that base through

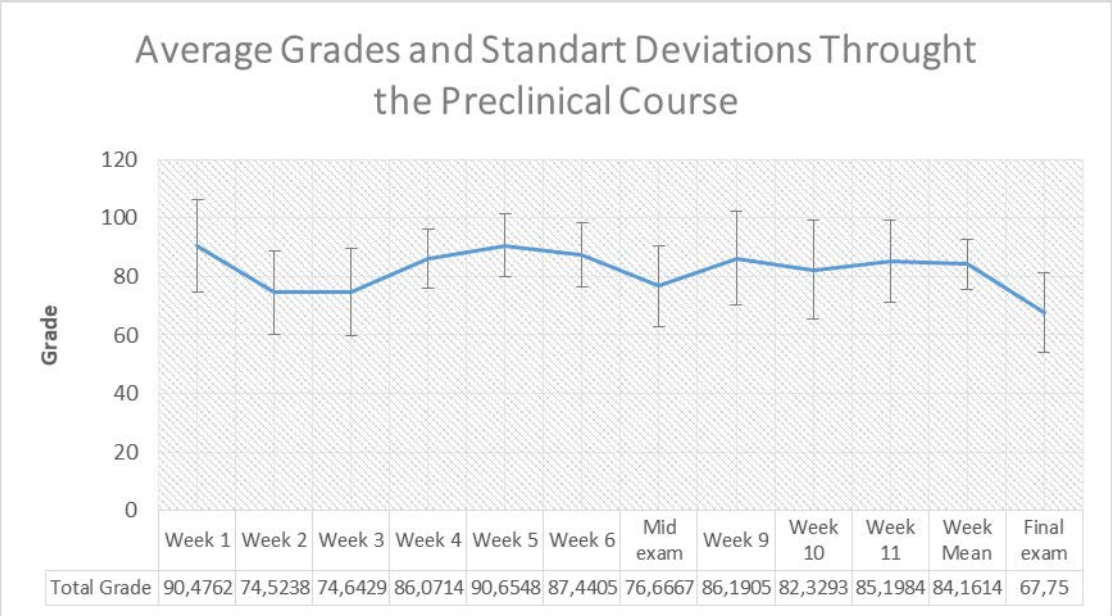


Figure 1. Average grades and standard deviation through the preclinical restorative dentistry course.

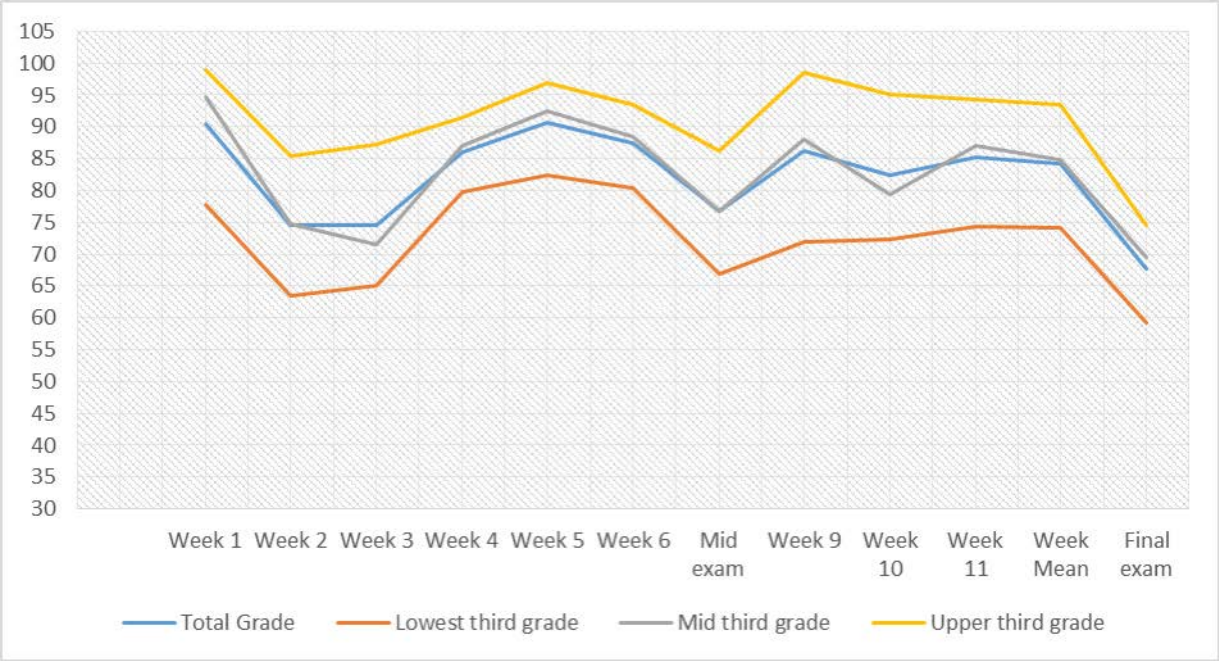


Figure 2. Grades of three subgroups of students (n = 27) according to weekly task assessment mean.

their clinical course and graduate to enter practice. This study indicates that the learning that takes place in the preclinical restorative dentistry course may persist in the clinic. The extra practice could be extremely effective since psychomotor skills improve with repetition [5, 6]. In addition, it would be logical that quality examination of each task performed by students during the weekly practical sessions by the faculty would encourage the students for increasing their work quality due to the fear of re-doing the task. This method would eventually further help to improve psychomotor skills along with the knowledge required to delivered patient care in the clinic.

One of the highlighting findings is that student's weekly task assessment scores are significantly higher than those of midterm and final practical exam scores, respectively. Also, this finding did not depend on student's weekly task assessment means. Students from lowest third of weekly assessment mean or students from upper third of weekly assessment mean generally showed better performance at weekly assessments than midterm and final exams. One possible explanation would be an immediate feedback, which occurs between student and instructor during preclinical session. The feedback enables student to recognize their errors and learn the way to correct them. However, similar interaction is not allowed during examination sessions, as usual. Therefore, students yield making more errors during midterm and final exams, lowering their scores.

Another reason why final exam scores are lower than midterm exam scores and the weekly task assessment score would be the stress of final exam that students live in the final exam. It can be suggested that the ultimate impact of final exam scores on end-year score of the student likely overwhelmingly stresses students, making probably them prone to make more errors during the final exam performance. The previous studies proposed that one of the major factors, which stress students during their education, is fear of failing course or year [7, 8]. The findings of the present study support this suggestion.

CONCLUSION

As a conclusion, weekly assessments of quality of student's tasks would be an effective predictor to assess student's preclinical performance as well as a final practical exam. However, it would fit better for student perspective as students live likely lower stress than that in the final exam. Therefore, it would be

recommended that integrating weekly task assessment into the preclinical restorative dentistry curriculum as an effective assessment tool.

Conflict of interest

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

Financing

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

REFERENCES

[1] Ayar MK. Dental students' perceptions on preclinical restorative dentistry course: Biruni University case. Eur Res J 2018;4:199-204.
[2] Luck O, Reitemeier B, Scheuch K. Testing of fine motor skills in dental students. Eur J Dent Educ 2000;4:10-4.
[3] Ben-Gal G, Katorza L, Weiss EI, Ziv A. Testing motor learning curves among dental students. J Dent Educ 2017;81:1171-8.
[4] Suksudaj N, Townsend G, Kaidonis J, Lekkas D, Winning T. Acquiring psychomotor skills in operative dentistry: do innate ability and motivation matter? Eur J Dent Educ 2012;16:e187-94.
[5] Velayo BC, Stark PC, Eisen SE, Kugel G. Using dental students' preclinical performance as an indicator of clinical success. J Dent Educ 2014;78:823-8.
[6] Chaiken SR, Kyllonen PC, Tirre WC. Organization and components of psychomotor ability. Cogn Psychol 2000;40:198-226.
[7] Polychronopoulou A, Divaris K. Perceived sources of stress among Greek dental students. J Dent Educ 2005;69:687-92.
[8] Abu-Ghazaleh SB, Sonbol HN, Rajab LD. A longitudinal study of psychological stress among undergraduate dental students at the University of Jordan. BMC Med Educ 2016;16:90.

The European Research Journal 2019;5(4):613-617 ORIGINAL ARTICLE

How accurate is the urine dipstick test for diagnosing urinary tract infection?

Esra Paydaş Hataysal[1], Beyza Saraçlıgil[2], Hatice Türk Dağı[3], Hüsamettin Vatansev[1]

[1]*Department of Biochemistry, Selçuk University School of Medicine, Konya, Turkey*
[2]*Department of Biochemistry, Karatay University School of Medicine, Konya, Turkey*
[3]*Department of Microbiology, Selçuk University School of Medicine, Konya, Turkey*

DOI: 10.18621/eurj.406215

ABSTRACT

Objectives: Urine dipstick is the first step laboratory test to diagnose a urinary tract infection (UTI) which is a common infectious disease diagnosed in the laboratories. Early treatment of UTI is very important in order to prevent long-term complications. The gold standard to diagnose UTI is urine culture so there are a number of unnecessary urine culture requests. However, urine culture results are not available earlier than 24-36 hours. Besides, urine culture is expensive and causes time-consuming of treatment. Our aim in this study was to compare urine leukocyte esterase test and nitrite test of urine dipstick with urine culture to determinate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Methods: Urine culture results and urine dipstick test results of patients who admitted to Selçuk University Hospital between May 2016 and May 2017 were collected retrospectively. The study included 11.169 patients and 3299 of them have positive urine cultures.

Results: In total, 3299 (29.5%) patients have positive urine culture. Out of these culture positive samples, positive dipstick results' ratios for leukocyte esterase and nitrite were 82.8% (n = 2733) and 22.4% (n = 774). Leukocyte esterase had 82.8% sensitivity and 68.1% specificity, with PPVs and NPVs of 52.1% and 90.5%, respectively.

Conclusions: The NPVs are found significantly higher than PPVs and it shows that urinary dipstick is more reliable to exclude disease than to diagnose the disease. Clinicians should not order urine culture from all patients without ant clinic signs.

Keywords: Urine culture, nitrite, leukocyte esterase, urine dipstick, urine analysis

Received: March 15, 2018; Accepted: June 22, 2018; Published Online: June 29, 2018

Urinary tract infection (UTI) is one of the most common infection diseases. Its' clinical symptoms vary from minimal dysuria to septic shock. UTI is the most common bacterial infection which diagnoses with the aid of clinical laboratories in young women and in the elderly [1].The second most common cause of bacteremia is UTI in hospitalized patients [2]. Many women experience UTI at least once in their whole lifetime [3].

The gold standard to diagnose UTI is urine culture so there are a number of unnecessary urine culture requests. However, urine culture results are not available earlier than 24 hours and this causes to delayed or inappropriate treatment [4]. Early treatment

Address for correspondence: *Esra Paydaş Hataysal, MD., Selçuk University School of Medicine, Department of Biochemistry, Konya, Turkey*
E-mail: dr.esrapaydas@hotmail.com

e-ISSN: 2149-3189

of UTI is important to prevent long-term complications. Additionally, urine culture test is expensive and causes delay of treatment [5]. Because of all these causes, a fast, easy, reliable, practicable and sensitive screening test is needed to begin treatment or rule out UTI as early as possible [3, 6].

Although the most common examination finding in patients with UTI is dysuria, dysuria is also the presenting complaint in another disease such as vaginitis. Patients with UTI sometimes show no typical symptoms and signs. Because of the fact that clinical symptoms or medical history are usually not enough to diagnose UTI, clinicians order lots of laboratory tests including urine culture, routine automated urinalysis even radiological tests to diagnose UTI. Nevertheless, suspected UTI is one of the most common indications for antimicrobial drugs use, with much prescribing of antimicrobials based on clinical symptoms and signs without confirmation by culture [7, 8].

Urine dipstick analysis is a quick, cheap and a useful test in predicting UTI. Because of the above mentioned limitations, urine analysis a preferred first-step investigation among clinicians.

The most frequently determined microorganism in urine culture is *Escherichia coli* in patients with UTI. Contamination is another frequently seen reason that causes positive culture results with a ratio of 29%-32% [3]. If the results of both nitrites and leukocyte esterase are negative, urine dipstick tests alone are useful in all populations to exclude the presence of infection rather than diagnose UTI in the presence of positive dipstick tests [9]. Several studies have examined the use of urinary dipstick tests to diagnose or rule out in UTI.

We aimed to compare urine leukocyte esterase test and nitrite test of urine dipstick with urine culture to determinate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

METHODS

Dates are obtained between May, 2016 and May, 2017 from laboratory information systems of Selçuk University School of Medicine which is a central hospital with 934 beds. The study was approved by Selçuk University Defense research ethics committee. Our electronic database (Enlil LIS) includes age, sex, main diagnosis, urine culture results and simultaneously automated urinalysis results. In the time period of our study, 15.487 requests of simultaneous urine cultures and urine dipstick tests. The dates of subjects who had simultaneously both urine dipstick test and urine culture test were evaluated in this study. All urine samples were completed within one hour after arrival to the laboratory in order to prevent contamination and overgrowth. If there is a patient with more than one request, only the first request evaluated.

For collection of the urine samples, sterile plastic urine sampling containers (Fırat MedPlastik, Ankara, Turkey) were used. After the spot mid-stream urine samples arrived to laboratory, every specimen was analyzed within 1 hour.

For the urine dipstick chemical analysis, Dirui H800 (Dirui Industrial Co, Ltd, Zhengzhou China) was used. LE and Nitrite was measured with Dirui H11-800 strips(Dirui Industrial Co, Ltd, Zhengzhou China).

Nitrite in the urine is diazotized to form a diazonium compound and the diazonium compound reacting with tetrahydro-benzo-quinolin-3-phenol causes the color change. Granulocyte leukocytes in urine contain catalyze that catalyze the hydrolysis of pyrrole amino change acid ester to 3-hydroxy-5-pheny pyrrole. This pyrrole reacting with diazonium forms a purple colour.

LE results were reported as negative,trace, 1 (+), 2 (+) and 3 (+). The nitrite results were reported as negative and positive. Cut-off values for a positive dipstick result was at least LE (+) or nitrite (+). Trace LE results were evaluated in a different category. For quality control, we made daily internal controls and 6 times in a year external quality control. (Randox Laboratories, Riqas, Ireland).

Urine cultures were performed in the Microbiology Laboratory of Selçuk University School of Medicine. Urine samples were inoculated in Columbia agar with 5% sheep blood and eosin methylene blue agar (bioMerieux, France) by calibrated sterile loops. The plates were aerobically incubated 24-48 hours at 35-37^{0}C. The colonies were then counted and 10^5cfu/ml was considered significant. Bacterial identification was performed with standard microbiological procedures and VITEK

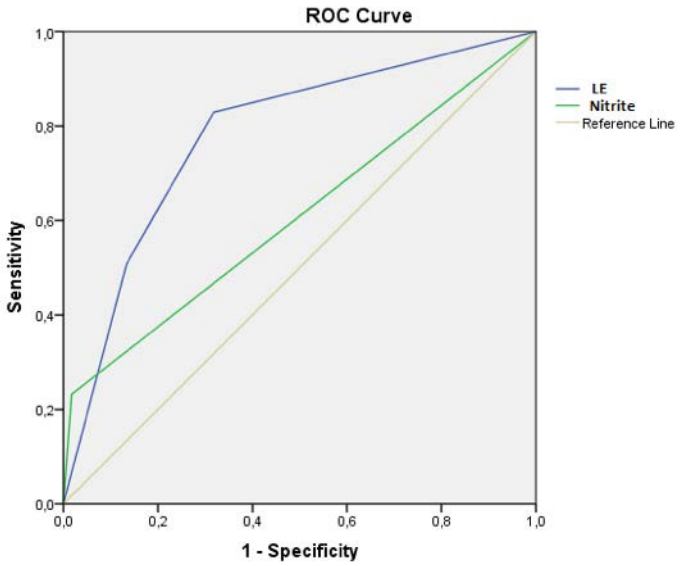


Figure 1. ROC curves for leukocyte esterase and nitrite. Area under curve (AUC) for Leukocyte Esterase 0.781 (95% CI = 0.771-0.790) and 0.607 (95% CI = 0.595-0.620) for Nitrite.

2 automated system (bioMerieux, France).

One thousand, four hundred and eighty-four subjects were excluded because of the fact that theirspecimens were accepted as contaminated. Two thousand, eight hundred and thirty-four subjects categorized differently because of trace LE results. In this retrospective and observational study, 11.169 individuals from 15.487 individuals remained.

Statistical Analysis

Statistical analysis performed by using SPSS version 15 (SPSS Inc, Chiacago, IL, USA). Calculation of sensitivity, specificity, positive and negative predictive values for LE and nitrite on dipstick was calculated as follows: Sensitivity = True positive/(True positive+False negative), Specificity = True negative/(True negative+False positive), Positive Predictive Value = True positive/(True positive + False positive) and Negative Predictive Value = True negative/(True negative + False negative) [5]. ROC analysis for LE and Nitrite on dipstick, Spearmen correlation between parameters were performed.

RESULTS

In our study, 11.169 subjects were evaluated [4,244 men (38%), 6,925 women (62%)] with the mean age of 25.9 years (ages ranges from 0 to 98). Three thousand, two hundred and ninety-nine subjects (29.5%) had positive urine cultures while 7870 specimens were negative. The predominant pathogen responsible for UTI was E. coli followed by *Klebsiella* spp. and *Enterococcus* spp. (Table 1).

In culture positive individuals, ratios of positive dipstick results for LE and nitrite were 82.8% (n = 2733) and 23.4% (n = 774). Leukocyte esterase had 82.8% sensitivity and 68.1% specificity, with PPVs and NPVs of 52.1% and 90.5%, respectively. Nitrite had 22.4% sensitivity and 99.3% specificity, with PPVs and NPVs of 84.3% and 75.1%, respectively. (Table 2). Nitrite had higher specificity and LE had higher sensitivity and NPV. Having trace LE subjects were evaluated, too. 82.4% of trace LE subjects were urine culture negative. The area under the curve (AUC) for LE was 0.781 (95% CI = 0.771-0.790) and

Table 1. Identification of microorganisms from culture plates

Organisms	n (%)
E. coli	1670 (50.6%)
Klebsiella spp.	405 (12.2%)
Enterococcus spp.	315 (9.5%)
Candida spp.	154 (4.6%)
Proteus spp.	132 (4%)
Pseudomonas spp.	120 (3.6%)

Table 2. *Performance characteristics of dipstick*

	LE	N	LE or N
Sensitivity	82.8%	22.4%	84.3%
Specificity	68.1%	99.3%	66.7%
PPV	52.1%	84.3%	51.4%
NPV	90.5%	75.1%	91%

LE = leukocyte esterase test, N = Nitrate test, PPV = Positive predictive value, NPV = Negative predictive value

for Nitrite AUC was 0.607 (95% CI = 0.595-0.620) in ROC analysis which is shown in Figure 1. Urine culture accepted as a reference method for ROC analysis.

DISCUSSION

In our study, we checked the reliability of urine dipstick LE and nitrite test for diagnosing UTI. Our findings demonstrated that there are many unnecessary urine culture requests. Only 29.5% of patients were culture positive. Definite diagnosis of UTI is course urine culture but ordering urine culture from all patients without UTI symptoms causes increased labor force, payment and delay of results. Kayalp et al. [3], Okado *et al*. [10], Christenson *et al*. [11] and Öztürk *et al*. [12] reported higher unnecessary culture requests then ours with a percentage of 97.7% ,80%, 82.1% and 88%, respectively. As expected, E. coli was the most common isolated bacteria in urine samples. Our specificity and sensitivity findings were similar as literature. The nitrate test is less sensitive because it is affected by many factors such as non-nitrate-reducing bacteria and lack of dietary nitrate [13]. Because of such reasons, sensitivity of nitrite test was low in our study. Therefore, a negative urinary nitrate test result cannot rule out UTI. In a different study, Ercan *et al*. [14] found the sensitivity and specificity for LE 85%, 61% and for Nitrite 43.1% and 99%, respectively. Öztürk *et al*. [12] found sensitivity and specificity for LE 76.4%, 64.2% and for Nitrite 40% and 99%, respectively. Najeeb *et al*. [15] reported for LE 58.8% sensitivity, 75% specificity and for nitrite 51.4% sensitivity, 94% specificity considering culture as gold standard. Contrary to our study, they reported lower sensitivity for LE [15]. Memişoğulları *et al*. [5] reported 65% sensitivity and 64% specificity for LE. They also suggested evaluation both of urinary microscopic examination and dipstick test because of increase of reliability of urine analysis. Trace LE levels showed that most of trace samples have negative urine culture results. If there is no clinical UTI symptom, it can be evaluated as negative.

The limitation of our study is that because of being a retrospective study, we couldn't classify patients according to their symptoms.

CONCLUSION

The NPVs are found significantly higher than PPVs and urinary dipstick is more reliable to exclude disease than to diagnose the disease. Urinalysis can rightly rule out UTI in the majority of patients. However, our findings support that only urine dipstick analysis is not enough to diagnose UTI. Clinicians should make decisions according to clinical examination of the patients and order urine culture if the urine analysis results don't match with the patient's clinic. When the clinician would like to start empirical treatment without waiting for culture results, routine urine dipstick analysis might be reliable in preliminary exclusion of UTI.

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] Patel HD, Livsey SA, Swann RA, Bukhari SS. Can urine dipstick testing for urinary tract infection at point of care reduce laboratory workload? J Clin Pathol 2005;58:951-4.

[2] Mambatta A, Jayarajan J, Rashme VL, Harini S, Menon S,

Kuppusamy J. Reliability of dipstick assay in predicting urinary tract infection. J Family Med Prim Care 2015;4:265-8.
[3] Kayalp D, Dogan K, Ceylan G, Senes M, Yucel D. Can routine automated urinalysis reduce culture requests? Clin Biochem 2013;46:1285-9.
[4] Williams GJ, Macaskill P, Chan SF, Turner RM, Hodson E, Craig JC. Absolute and relative accuracy of rapid urine tests for urinary tract infection in children: a metaanalysis. Lancet Infect Dis 2010;10:240-50.
[5] Memişoğulları R, Yüksel H, Ak Yıldırım H, Yavuz Ö. Performance characteristics of dipstick and microscopic urinalysis for diagnosis of urinary tract infection. Eur J Gen Med 2010;7:174-8.
[6] Whiting P, Westwood M, Watt I, Cooper J, Kleijnen J. Rapid tests and urine sampling techniques for the diagnosis of urinary tract infection (UTI) in children under five years: a systematic review. BMC Pediatr 2005;5:4.
[7] John AS, Boyd JC, Lowes AJ, Price CP. Clinical Chemistry/Use of dipstick testing to rule out UTI. Am J Clin Pathol 2006;126:428-36.
[8] Fahey T, Webb E, Montgomery AA, Heyderman RS. Clinical management of urinary tract infection in women: a prospective cohort study. Fam Pract 2003;20:1-6.
[9] Devillé W, Yzermans JC, van Duijn NP, Bezemer PD, wan der Windt D, Bouter LM. The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. BMC Urol 2004;4:4.
[10] Okada H, Sakai Y, Miyazaki S, Arakawa S, Hamaguchi Y, Kamidono S. Detection of significant bacteriuria by automatedurinalysis using flow cytometry. J Clin Microbiol 2000;38:2870-2.
[11] Christenson RH, Tucker JA, Allen E. Results of dipstick tests, visual inspection, microscopic examination of urine sediment, and microbiological cultures of urine compared for simplifying urinalysis. Clin Chem 1985;31:448-51.
[12] Öztürk A, Gınıs Z, Hancı T, Yıldız Z, Taşlıpınar MY, Uçar F, et al. Evaluation of diagnostic performance of routine automated urinalysis and association between urinary tract infection and leukocytosis. Acta Medica 2015;4: 42-7.
[13] Mambatta AK, Jayarajan J, Rashme VL, Harini S, Menon S, Kuppusamy J. Reliability of dipstick assay in predicting urinary tract infection. J Family Med Prim Care 2015;4:265-8.
[14] Ercan Ş, Yücel N, Özer RS, Kaptanağası Orçun A. [Evaluation of diagnostic performances of nitrite and leukocyte esterase with respect to age and gender]. Türk Klinik Biyokimya Derg 2014;12:91-8. [Article in Turkish]
[15] Najeeb S, Munir T, Rehman S, Hafiz A, Gilani M, Latif M. Comparison of urine dipstick test with conventional urine culture in diagnosis of urinary tract infection. J Coll Physicians Surg Pak 2015;25:108-10.

Effect of an adapted physical activity program on the morphological and physiological profile of hypertensive patients of University Clinics of Kinshasa

Teddy Bofosa, Betty Miangindula, Godefroid Kusuayi, Nicaise Kiana, Constant Nkiama

Department of Physical Medicine and Rehabilitation, University Clinics of Kinshasa, University of Kinshasa School of Medicine, Kinshasa, Democratic Republic of Congo

DOI: 10.18621/eurj.415593

ABSTRACT

Objectives: The treatment of arterial hypertension requires a comprehensive care because it is necessary not only to take the prescribed medication but also to apply certain rules of hygiene. The purpose of this study was to evaluate the effect of a program of physical activity adapted to the morphological and physiological state of the hypertensive patients.

Methods: An experimental study was conducted on a sample of 31 male hypertensive patients with an average age of 58.16 ± 3.7 years undergoing an aerobic and anaerobic physical activity program treadmill walking, cycling, ergonomics and aerobic exercise and muscle building exercises of moderate intensity, duration of forty-five minutes and a frequency of three times a week associated with low calorie nutrition education low in cholesterol and saturated fatty acids (bad fats) , low sodium rich in vegetables, fruits and vitamins for 4 months at the University Clinics of Kinshasa between January 2017and May 2017.

Results: After 4 months of intervention, we found statistically significant reductions in weight -7.2 kg, waist circumference -7.61 cm, body mass index -5.42 kg/m2, visceral fat percentage -1.4%, systolic blood pressure -6 mmHg, low-density lipoprotein -22 mg/dL, triglyceride -26.7 mg/dL with the exception of high-density lipoprotein and muscle that statistically increased +7.42 mg/dL and +15.3% while diastolic blood pressure -3.4 mmHg was not statistically modified.

Conclusion: The practice of adapted physical activities combined with nutritional education improves the morphological and physiological status of hypertensive patients.

Keywords: Adapted physical activity, morphological state, physiological

Received: April 16, 2018; Accepted: November 21, 2018; Published Online: December 3, 2018

It was stated that non-communicable diseases (cardiovascular diseases and related risk factors in 2020) would create problems in sub-Saharan African countries [1]. In addition, the prevalence of arterial hypertension in the Democratic Republic of the Congo has been reported to be high in both rural areas and urban areas of Kinshasa, while it has been reported to cause cerebrovascular disease and infarction. Three-step screening was performed in chronic diseases using the world health organization (WHO) STEPS [2-5]. As a result, the prevalence of hypertension was 11% in diabetic adults and 15.5% in diabetic patients

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

e-ISSN: 2149-3189

[6]. More than 20 million people in sub-Saharan Africa are said to have high blood pressure [7]. The WHO and all learned societies of cardiology or sports medicine recommend physical activity as a front-line intervention for treating hypertensive patients in combination with dietary measures. While being an inexpensive procedure with few adverse effects, physical activity is particularly interesting because of its favorable effects on other cardiovascular risk factor [8, 9]. However, the Congolese medicines rarely apply this prescription. We found that in the Democratic Republic of Congo, in the management of hypertensive patients, no study evaluated the effects of a physical activity program associated with nutrition education.

METHODS

Population

The population from which the sample was derived is made up of patients hypertendus from Medical fitness laboratory and functional exercises of the Department of Physical Medicine and Rehabilitation of University Clinics of Kinshasa whose average age is 58.16 ± 3.7 years. The total sample of 31 male hypertensive patients were submitted for 4 months to a physical activity program associated with nutrition education. All male hypertensive patients voluntarily participated in the program.

Measurements and Data Collection

The anthropometric, physiological and biological parameters collected were as follows: weight (kg) using a SECA brand weigh scale calibrated in kilograms (kg) to 100 grams near, size (cm) using of a mark of SECA mark, the waist circumference measurement using a tape measure of tailors, the percentage of visceral fat and muscle percentage using a brand Omeron BF-511 impedance meter, the tension arterial blood pressure (mmHg) using a mechanical tensiometer and HDL (mg/dL), LDL (mg/dL) were measured in the clinical biology laboratory of University Clinics of Kinshasa.

Protocol of the Intervention Program

The experimental program of aerobic physical exercises (treadmill exercise and ergocycle) and anaerobic (muscle strengthening exercises of the abdominals, upper and lower limbs). Participants exercised three times per week, with training progressing gradually in length and intensity. Heart rate monitors (Polar Electro) were used to adjust workloads to achieve target heart rate. Participants progressed from 15 to 20 min per session at 60% of maximum heart rate to 45 min per session at 75% of measured maximum heart rate.

The nutritional program consisted of a nutritional education which consisted on the basis of a list to feed hypertensive patients to eat at least 5 fruits and vegetables a day, reduce their total consumption of fats

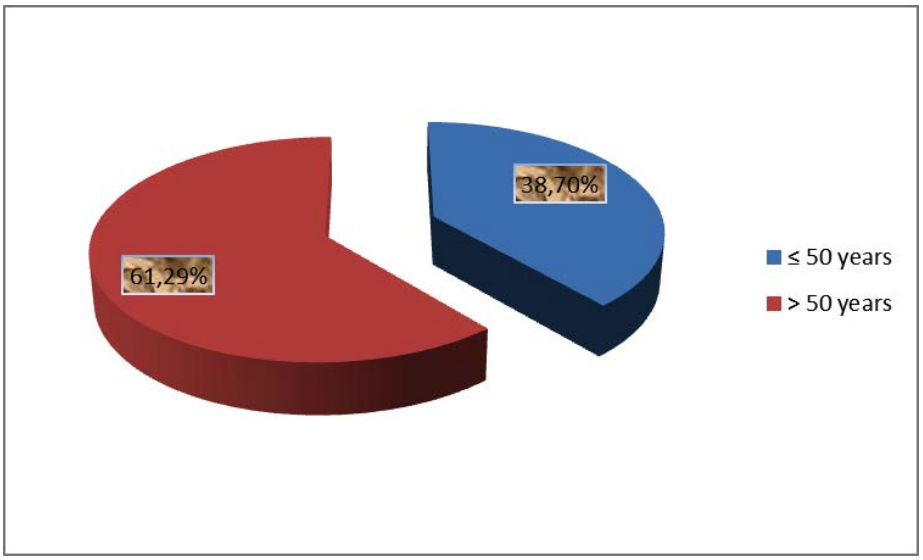


Figure 1. Distribution of subjects by age.

Table 1. Evolution of morphological parameters before and after the intervention

Variables	Before	After	*p* value
Weight (kg)	77.10 ± 3.2	69.9 ± 7.8	**0.0001**
WC (cm)	102.2 ± 11.09	94.59 ± 5.8	**0.0001**
BMI (kg/m^2)	31.6 ± 1.36	26.18 ± 1.3	**0.001**
%Visceral fat	10.1 ± 3.9	8.7 ± 2.2	**0.002**
%muscle	24.51 ± 1.6	39.21 ± 6.2	**0.0001**

WC = waist circumference, $p < 0.05$ = significant

(especially saturated) and incorporate but with moderation, healthy fats such as those found in olive oil, nuts and seeds.

Statistical Analysis

The data collected was entered using the Microsoft Excel 2013 software and imported into SPSS software version 21.0 (Statiscal Package For Social Sciences). The data were represented as mean ± standard deviation in the tables. The paired student parametric test t was used to compare the averages at the beginning and end of the intervention. The statistical test results used are interpreted at the significance level $p < 0.05$ for statistical decision making.

RESULTS

It is clear from this study that hypertensive subjects older than 50 years were more numerous with 61.29%, whereas subjects aged 50 or less accounted for only 38.70% (Figure 1).

Comparison of Means Before and After the Intervention Program

Table 1 shows that hypertensive patients significantly changed their morphological state after the intervention program.

The physiological parameters of hypertensive patients were significantly modified after the intervention program with the exception of diastolic blood pressure (Table 2).

DISCUSSION

This study found that high blood pressure was more prevalent in subjects aged 50 and over with 61.29% versus only 38.70% of subjects under 50 years of age. These results corroborate with those of the study conducted by Strokes [10] which emphasizes that the percentage of hypertensive treated varies by a factor of 10 according to the age groups, increasing in 2007 by 5% for the less from 45 to 59% for the over 75 years. In 2002, the figures at the same ages were 4.2% and 51.8%.

In analyzing the results of the morphological features, this study shows that hypertensive patients have significantly improved after-intervention program their weight (p <0.0001), waist circumference ($p < 0.0001$), body mass index (p <0.0001) and visceral fat (p <0.002), but their muscle increased (p <0.0001).

These results corroborate those of Zrnzević and Zrnzević [11], who showed in his study that weight, waist circumference, visceral fat, and muscle mass depend greatly on diet and practice physical activity.

Table 2. Evolution of physiological parameters before and after the intervention

Variables	Before	After	*p* value
SBP (mmHg)	145.9 ± 2.75	139.9 ± 3.4	0.0001
DBP (mmHg)	92.9 ± 2.19	89.5 ± 3.05	0.07
HDL Cholesterol (mg/dL)	64.21 ± 12,49	71.37 ± 9.39	0.0001
LDL Cholesterol (mg/dL)	193.33 ± 16.6	171.33 ± 18.94	0.0001
Triglycerides (mg/dL)	161.9 ± 27.8	135.2 ± 29.2	0.0001

SBP = systolic blood pressure, DBP = diastolic blood pressure

Regarding the physiological parameters, we noticed that after the intervention program the hypertensive subjects significantly improved their systolic blood pressure while their diastolic blood pressure was not statistically modified. Our results corroborate those of Sikiru and Okoye [12] who demonstrated that physical activity has a faster effect on systolic blood pressure than diastolic. A recent meta-analyses by Bangalore *et al*. [13], indicate that by training 3 to 5 times a week for 4 months at a rate of 20 to 60 minutes per training session, a decrease of -7.6 to 11.1 mmHg systolic pressure and - 6.7 to 7.6 mmHg diastolic pressure. These reductions compare favorably with what is achieved with some antihypertensive drugs [13]. A medline-type research conducted by Grassi *et al*. [14] using the arsenal anti hypertension key words and exercises, teaches us that more than 1,500 articles were written on the subject over the past 20 years. All of these articles confirm that regular exercise reduces blood pressure (BP) values by an average of 10/7.1. Or, we know that such an improvement in BP allows to expect a reduction incidence of stroke and myocardial infarction by 34% and 19% respectively, which is comparable to the effect of any antihypertensive drug used as monotherapy [14-17].

In regards to the biological parameters were statistically modified with a high density lipoprotein 64.21 ± 12.49 before 71.37 ± 9.39 mg/dL after (+ 7.42 mg/dL, $p < 0.0001$) and a lipoprotein of low density 193.33 ± 16.6 before 171.33 ± 18.94 mg/dL after (-22 mmg/dL, $p < 0.0001$).

In overweight individuals, exercise combined with low-calorie cholesterol and saturated fatty acids (bad fats) results in a greater increase in blood levels of good cholesterol (HDL) than in subjects diet. This is the conclusion of a study published in the New England Journal of Medicine that examined 264 men and women with moderate overweight [18, 19].

It has been shown that changes in HDL and triglyceride levels typically occur after a few months of moderate aerobic training, while there is often no change in LDL levels, even after about a year of training. However, a large volume of training at a high intensity can make LDL particles less damaging to health, even if their concentration in the blood does not change [20-22].

The literature shows that the HDL-cholesterol reacts quite well to physical activity. Indeed, improvements can be observed after 3 months of moderate aerobic training. Regular exercise can lead to an increase of about 10% in HDL levels. Although moderate intensity is usually sufficient to increase HDL, it appears that high intensity is even more effective. In addition, the increase in HDL is even more marked when training is accompanied by weight loss [23, 24].

CONCLUSION

It emerges from this study that the practice of physical activities adapted to a nutritional education makes it possible to significantly improve the anthropometric and physiological parameters of hypertensive subjects.

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] Akingkugbe O. [Hypertension research in Africa: past, present and future]. Trop Cardiol 1987;13(Suppl): S195-201. [Article in French]

[2] Bieleli EI, Moswa JL, Ditu M, Kandjingu Mulumba M, Mayangi M. [Prevalence of diabetes mellitus among the population of Kinshasa]. Congo Médical 2000;2:1055-61. [Article in French]

[3] Amaral SL, Zorn TM, Michelini LC. Exercise training normalizes wall-to-lumen ratio of the gracilis muscle arterioles and reduces pressure in spontaneously hypertensive rats. J Hypertens 2000;18:1563-72.

[4] Longo-Mbenza B, Tonduangu K, Muyeno K, Phanzu M, Kebolo Baku A, Muvova D, et al. Predictors of stroke-associated mortality in Africans. Rev Epidemiol Sante Publique 2000;48:31-9.

[5] WHO. Noncommunicable diseases: a strategy for the African Region. World Health Organisation, WHO Regional Office for Africa, Harare 2000.

[6] Blacher J, Halimi JM, Hanon O, Mourad JJ, Pathak A, Schnebert B, et al; Société française d'hypertension artérielle. [Management of arterial hypertension in adults: 2013 guidelines of the French Society of Arterial Hypertension]. Presse Med 2013;42:819-25. [Article in French]

[7] Collier SR, Kanaley JA, Carhart Jr R, Frechette V, Tobin MM, Hall AK, et al. Effect of 4 weeks of aerobic or resistance exercise training on arterial stiffness, blood flow and blood pressure in pre- and stage-1 hypertensives. J Hum Hypertens 2008;22:678-86.
[8] Godet-Thobie H, Vernay M, Noukpoape A, Salavane B, Malon A, Castetbon K, et al. [Mean blood pressure level and prevalence of hypertension in 18 to 74 year-old adults]. ENNS Survey 2006-2007]. BEH 2008;49-50:478-83. [Article in French]
[9] Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. Hypertension 2005;46:667-75.
[10] Strokes GS. Management of hypertension in the elderly patient. Clin Interv Aging 2009;4:379-89.
[11] Zrnzević N, Zrnzević JE. [Effects of teaching physical education on the functional abbilities of female students of younger school]. J Anthropol Soc Serbia 2015;50:1-9.
[12] Sikiru L, Okoye GC. Effect of interval training programme on pulse pressure in the management of hypertension : a randomized controlled trial. Afr Health Sci 2013;13:571-8.
[13] Bangalore S, Kumar S, Wetterslev J, Messerli FH. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. BMJ 2011;342:d2234.
[14] Grassi, G, Servalle, G, Calhoun, D, Bolla GB, Mancia G. Physical exercise in essential hypertension. Chest 1992;101(5 Suppl):312S-14S.
[15] Guimaraes GV, Ciolac EG, Carvalho VO, D'Avila VM, Bortolotto LA, Bocchi EA. Effects of continuous vs. interval exercise training on bloodpressure and arterial stiffness in treated hypertension. Hypertens 2010;33:627-32.
[16] 1999 World Health Organisation - International Society of Hypertension. Guidelines for the Management of Hypertension. Guidelines Subcommittee. J Hypertens 1999;17:151-83.
[17] Halliwill JR, Buck TM, Lacewell AN, Romero SA. Postexercise hypotension and sustained postexercise vasodilatation: what happens after we exercise? Exp Physiol 2013;98:7-18.
[18] Higashi Y, Yoshizumi M. Exercise and endothelial function: role of endothelium-derived nitric oxide and oxidative stress in healthy subjectsand hypertensive patients. Pharmacol Ther 2004;102:87-96.
[19] Kawano H, Tanaka H, Miyachi M. Resistance training and arterial compliance : Keeping the benefits while minimizing the stiffening. J Hypertens 2006;24:1753-9.
[20] Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34:2159-219.
[21] Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. Circulation 1998;97:596-601.
[22] Williams PT. Lower prevalence of hypertension, hypercholesterolemia, and diabetes in marathoners. Med Sci Sports Exerc 2009;41:523-9.
[23] Beck DT, Martin JS, Casey DP, Braith RW. Exercise training reduces peripheral arterial stiffness and myocardial oxygen demand in young pre-hypertensive subjects. Am J Hypertens 2013;26:1093-102.
[24] Yoshizawa S, Maeda S, Miyaki A, Misono M, Saito Y, Tanabe K, et al. Effect of 12 weeks of moderate-intensity resistance training on arterial stiffness : a randomised controlled trial in women aged 32-59 years. Br J Sports Med 2009;43:615-8.

The European Research Journal 2019;5(4):623-628 ORIGINAL ARTICLE

The correlation between red cell distribution width, autoimmunity and nail involvement in alopecia areata

Gülhan Gürel

Department of Dermatology, Bozok University School of Medicine, Yozgat, Turkey

DOI: 10.18621/eurj.408089

ABSTRACT

Objectives: Alopecia areata is a widespread autoimmune disease that targets hair follicles, and is characterized by nonscarring patches of hair loss. Red cell distribution width (RDW) is a routinely analyzed parameter during complete blood count, and indicates variations in diameters of red blood cells. Elevated RDW levels are associated with high level of inflammation and oxidative stress. In this study, we aimed to demonstrate the correlation between RDW levels, autoimmunity, and nail involvement in alopecia areata.

Methods: Medical records of 170 patients who were admitted to our dermatology clinic between May 2016 and May 2017 were retrospectively evaluated. A total of 170 patients with alopecia areata diagnosis were evaluated.

Results: The mean age of the patients was 24.61 ± 12.62 years (3-59 years). Sixty patients (35.3%) were female, and 110 patients (64.7%) were male. Twenty-seven patients (15.9%) had nail involvement, and 24 patients (14.1%) had a history of an autoimmune disease. RDW levels were significantly higher in patients with nail involvement and history of an autoimmune disease.

Conclusion: RDW can be used as a simple, cheap, and readily available marker of inflammation in patients with alopecia areata.

Keywords: Alopecia areata, red cell distribution width, autoimmunity

Received: March 20, 2018; Accepted: November 22, 2018; Published Online: November 23, 2018

Alopecia areata (AA) is a common autoimmune disease that targets hair follicles, and is characterized by nonscarring patches of hair loss [1]. AA affects only 0.1-0.2% of the general population, and can be seen in both genders and at all ages [2]. The exact cause of AA is not known; still, AA is considered as an autoimmune disease resulting from damage to hair follicles by T lymphocytes. The disease with localized hair loss is manifested by severe lymphocytic infiltration around the hair follicle [3, 4]. Genetic background, atopy, nonspecific immune reactions, organ-specific autoimmune reactions, emotional stress factors, infections, and neuropeptides are considered to play a role in disease etiology [5]. Red cell distribution width (RDW) is a routinely reported parameter in complete blood count, and represents the variation in diameters of red blood cells (RBCs) [6]. In addition to RDW, mean platelet volume (MPV) is also considered as a marker of inflammation, and indicates the average size of platelets in blood. Both parameters can be analyzed easily in a routine complete blood count [7]. RDW has been studied in several diseases, such

Address for correspondence: *Gülhan Gürel, MD., Bozok University School of Medicine, Department of Dermatology, Yozgat, Turkey*
E-mail: gulhanozturkgurel@hotmail.com, Tel: +90 354 2127060, Fax: +90 354 2177150

e-ISSN: 2149-3189

as heart failure, rheumatoid arthritis, inflammatory bowel disease, and psoriasis, and has been considered as a marker of inflammation [8, 9]. Elevated RDW levels have been linked to levels of inflammation and oxidative stress in the body [10]. Here, we aimed to demonstrate the correlation between RDW levels, autoimmunity, and nail involvement in alopecia areata.

METHODS

Medical records of 170 patients, who were admitted to our dermatology clinic between May 2016 and May 2017, and who were diagnosed with AA, were retrospectively evaluated.Patients' age, gender, area of involvement (scalp, beard, eyebrows, mixed, universal), nail involvement (pitting, leukonychia, trachonychia, longitudinal striation) and history of anautoimmunedisease (thyroid diseases, vitiligo, psoriasis, ankylosing spondilitis) were recorded from medical files.Patients with active inflammation and infection were excluded from the study.Laboratory parameters, including hemoglobin level, neutrophil count, lymphocyte count, RDW, MPV, glucose, vitamin B12, thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), thyroglobulin antibody (anti-TG), and thyroid peroxidase antibody (anti-TPO), were recorded retrospectively.

Statistical Analysis

SPSS v.18.0 software was used for statistical analysis. Descriptive statistics of continuous variables were expressed as median without normal distribution (minimum-maximum). Mann Whitney U test was used to identify the differences in continuous variables between the groups. Student's t-test was used for comparisons.For all tests, p values < 0.05 were considered as statistically significant.

RESULTS

A total of 170 patients with AA diagnosis were evaluated. The mean age of the patients was 24.61 ± 12.62 years (3-59 years). Sixty patients (35.3%) were female, and 110 patients (64.7%) were male. Scalp involvement was identified in 112 patients (65.9%), beard involvement was identified in 32 patients (18.8%), eyebrow involvement was identified in 4 patients (2.4%), mixed involvement was identified in 16 patients (9.4%), and universal involvement was identified in 6 patients (3.5%). Twenty-seven patients (15.9%) had nail involvement (pitting, leukonychia,

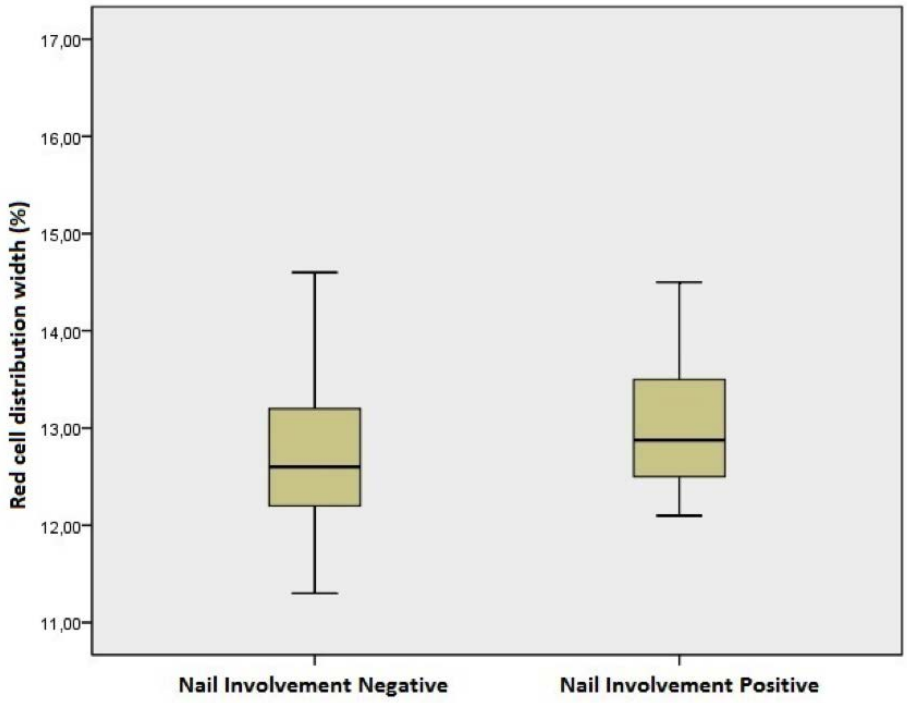


Figure 1. Relationship between RDW levels and nail involvement.

trachonychia, longitudinal striation). Twenty-four patients (14.1%) had a history of an autoimmune disease (most commonly thyroid diseases, vitiligo, psoriasis, and ankylosing spondylitis).

The mean age of patients without nail involvement was 25.84 ± 12.48 years, and the mean age of patients withnail involvementwas 18.11 ± 11.51 years ($p < 0.01$). There was no significant difference with respect to gender between patients with nail involvement and patients without nail involvement. No significant differences were found in lymphocyte count, hemoglobin, MPV, glucose, vitamin B12, TSH, sT3, anti-TG, and anti-TPO levels between patients with nail involvement and patients without nail involvement ($p > 0.05$). On the other hand, the mean neutrophil count was 4.20 ± 1.39 in patients without nail involvement, and 4.91 ± 2.16 in patients with nail involvement ($p = 0.02$). The mean RDW level was 12.77 ± 0.79 in patients without nail involvement, and 13.24 ± 1.13 in patients with nail involvement ($p = 0.041$) (Figure 1). The mean ST4 value was 1.00 ± 0.09 in patients without nail involvement, and 1.11 ± 0.18 in patients with nail involvement ($p < 0.01$). The correlation between nail involvementand laboratory findings is summarized in Table 1.

When we analyzed the correlation between having history of an autoimmune disease and gender, the mean age of patients with an history of autoimmune disease was 24.34 ± 12.29 years, while the mean age of patients without an autoimmune disease 26.25 ± 14.66 years. There was no significant difference with respect to age in both groups. Moreover, there was also no significant difference with respect to gender between patients with an history of autoimmune disease and patients without an history of an autoimmune disease. There were no significant differences in hemoglobin level, neutrophil count, leukocyte count, MPV, glucose, vitamin B12, TSH, and sT3 levels with respect to presence of an autoimmune disease ($p > 0.05$). A significant difference in the mean RDW level was found between patients without an autoimmune disease and patients with an autoimmune disease (12.75 ± 0.75 vs 13.37 ± 1.25; $p = 0.021$) (Figure 2). The mean ST4 level was 1.00 ± 0.09 in patients without an autoimmune disease, and 1.10 ± 0.19 in patients with an autoimmune disease ($p < 0.01$).The mean anti-TG level was 8.78 ± 64.58 in patients without an autoimmune disease, and 107.69 ± 259.52 in patients with an autoimmune disease ($p < 0.01$). The mean

Table 1. Comparison of nail involvement with demographic and laboratory parameters

Parameters	NI negative (n = 143)	NI positive (n = 27)	*p* value
Age (years)	25.84 ± 12.48	18.11 ± 11.51	< 0.01
Sex (Male/Female)	94/49	16/11	0.50
Hemoglobin(g/dL)	14.95 ± 1.51	14.54 ± 1.59	0.20
Neutrophil ($10^3/\mu L$)	4.20 ± 1.39	4.91 ± 2.16	0.02
Lymphocyte ($10^3/\mu L$)	2.84 ± 1.81	3.15 ± 2.48	0.93
Red cell distribution width (%)	12.77 ± 0.79	13.24 ± 1.13	0.041
Mean corpuscular volüme (fL)	10.32 ± 1.09	9.86 ± 1.32	0.057
Glucose (mg/dL)	92.10 ± 24.26	87.74 ± 9.84	0.16
Vitamin B12 (pg/mL)	338.80 ± 185.27	304.70 ± 124.49	0.88
Thyroid stimulating hormone (uIU/mL)	1.88 ± 1.04	2.25 ± 1.19	0.13
Freetriiodothyronine (pg/mL)	3.31 ± 0.55	3.41 ± 0.65	0.44
Freethyroxine (ng/dL)	1.00 ± 0.09	1.11 ± 0.18	< 0.01
Thyroglobulin antibody (IU/mL)	19.79 ± 111.96	38.43 ± 147.75	0.18
Thyroid peroxidase antibody (IU/mL)	18.38 ± 102.71	176.41 ± 355.17	0.23

Data are presented as mean ± standard deviation. NI = nail involvement

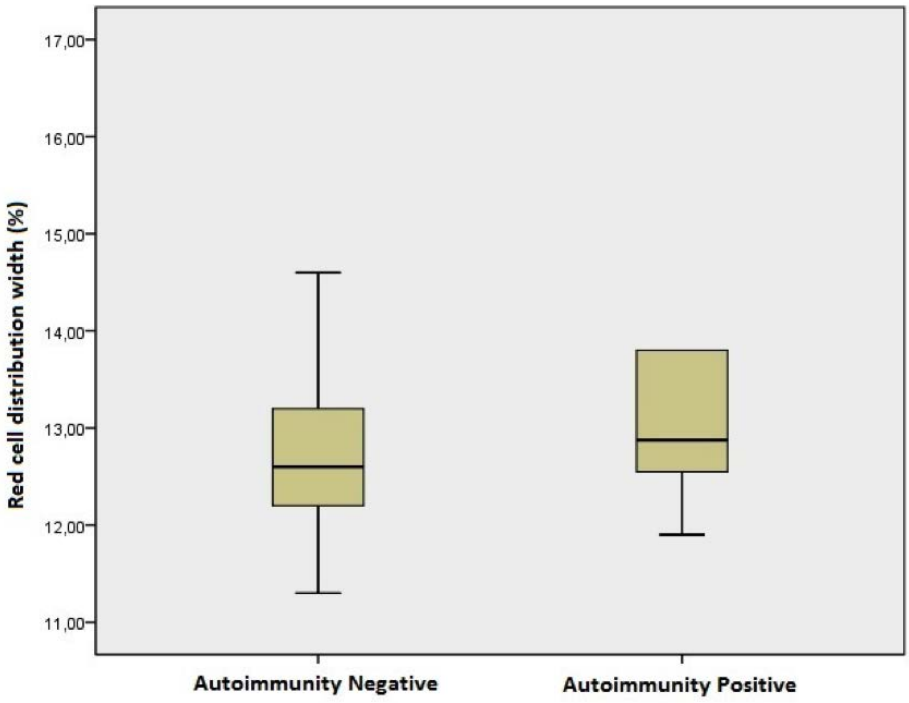


Figure 2. Relationship between RDW levels and autoimmunity.

anti-TPO value was 15.22 ± 88.19 in patients without an autoimmune disease, and 215.40 ± 383.98 in patients with an autoimmune disease ($p < 0.01$).The correlations between having a history of an autoimmune disease and laboratory findings is summarized in Table 2.

Overall, these results indicate that RDW levels are significantly higher in patients with nail involvement and a history of an autoimmune disease.

DISCUSSION

AA can be seen in both men and women. While some studies have reported an equal prevalence between women and men, others have reported that AA is more prevalent in women. Goh *et al*. [11] found the prevalence of AA in women and men to be 74.3% and 25.7%, respectively. The study by Kavak *et al*. [12] showed that the prevalence of AA in females and

Table 2. Comparison of autoimmunitywithdemographicandlaboratoryparameters

Parameters	Autoimmunity negative (n = 146)	Autoimmunity positive (n = 24)	*p* value
Age (years)	24.34 ± 12.29	26.25 ± 14.66	0.49
Sex (Male/Female)	94/52	16/8	0.83
Hemoglobin(g/dL)	14.90 ± 1.53	14.76 ± 1.48	0.67
Neutrophil ($10^3/\mu L$)	4.23 ± 1.42	4.81 ± 2.14	0.09
Lymphocyte ($10^3/\mu L$)	2.91 ± 1.93	2.77 ± 1.94	0.36
Red cell distribution width (%)	12.75 ± 0.75	13.37 ± 1.25	0.021
Mean corpuscular volüme (fL)	10.31 ± 1.02	9.89 ± 1.65	0.09
Glucose (mg/dL)	91.62 ± 24.03	90.13 ± 10.88	0.82
Vitamin B12 (pg/mL)	337.56 ± 182.04	307.95 ± 144.53	0.65
Thyroid stimulating hormone (uIU/mL)	1.89 ± 1.01	2.26 ± 1.35	0.11
Freetriiodothyronine (pg/mL)	3.35 ± 0.57	3.22 ± 0.59	0.36
Freethyroxine (ng/dL)	1.00 ± 0.09	1.10 ± 0.19	< 0.01
Thyroglobulinantibody (IU/mL)	8.78±64.58	107.69±259.52	< 0.01
Thyroidperoxidaseantibody (IU/mL)	15.22 ± 88.19	215.40 ± 383.98	< 0.01

Data are presented as mean±standard deviation.

males were 38.2% and 61.8%, respectively. The prevalence of AA in the current study also showed a similar pattern; 35.3% of the patients were female, and 67.7% of the patients were male. While AA can be seen at almost all ages, it is reported to be more common in patients younger than 40 years, usually occurring in the first 3 decades of life [13]. Seyrafi *et al*. [14] found the mean age of AA patients to be 24.05 ± 9.98years. In the present study, the mean age of the patients was 24.61 ± 12.62 years, and this finding was consistent with the literature.

While AA affects all, most commonly affected regions are scalp, beard, and other regions [15]. Consistent with the literature, we identified scalp involvement in 65.9% of the patients, beard involvement in 18.8% of the patients, eyebrow involvement in 2.4% of the patients, mixed involvement in 9.4% of the patients, and universal involvement in 3.5% of the patients.

Nail involvement in AA is seen in 7-66% of the cases, and it is reported that nail involvement is more common in cases of severe hair loss [16, 17]. Similarly, we identified nail involvement in 15.9% of the patients.

AA can be seen together with several organ-specific autoimmune diseases. Thyroid diseases and vitiligo are the most common diseases which are seen together with AA [3]. It is reported that 5-17.5% of the patients with AA also have other autoimmune diseases [18]. Similarly, 14.1% of the patients in the current study had a history of an autoimmune disease (most commonly thyroid diseases).

RDW and MPV have been defined as markers of inflammation, and are used to predict prognosis of various diseases, includingcardiac diseases, inflammatory bowel diseases, psoriasis, rheumatoid arthritis, Behçet's disease, brucellosis, and vasculitis [19].To best of our knowledge, the correlation between nail involvement, history of autoimmune disease, and RDW in AA has not been investigated previously. This study shows that RDW levels are significantly high in patients with nail involvementand history of anautoimmune disease.

Inflammation is considered to play an important role in elevated RDW levels. Inflammatory cytokines (such as interferon-ɣ, TNF-α, IL-1, IL-6, and IL-10) alters half-life of RBCs by causing changes in precursor cells and erythropoietin, thereby causing elevated RDW levels [20, 21].

Kim *et al*. [22] determined that patients with psoriasis have significantly higher RDW levels compared to healthy control subjects. At the same time, the authors revealed a correlation between RDW levels and disease severity; RDW levels were significantly higher in patients with moderate or severe psoriasis, compared to patients with mild psoriasis. Poor prognostic factors in AA include early disease onset, long disease duration, presence of alopecia totalis and alopecia universalis, nail involvement, comorbid atopical dermatitis, family history, and presence of other autoimmune disease [3]. Based on these studies, high RDW levels can be attributed to severe inflammation and poor prognosis in case of nail involvement and autoimmune disease in AA.

Another study by Kim *et al*. [8] showed that patients with systemic vasculitis have higher RDW levels, compared to patients with localized cutaneous vasculitis. In addition, the authors identified RDW as an independent predictor of cutaneous vasculitis progression to systemic vasculitis.

Farkas *et al*. [23] demonstrated that RDW is a valuable parameter for multiple pathological processes (vasculopathy, fibrosis, and inflammation) in systemic sclerosis. In another study, Lou *et al*. [24] measured RDW levels in patients infected with hepatitis B virus, and determined a correlation between RDW levels and mortality. Based on these findings, RDW may serve as a valuable parameter to predict prognosis of AA.

CONCLUSION

Taken together, this study shows that RDW values are significantly high in patients with nail involvement and history of an autoimmune disease. RDW may serve as a simple, cheap, and easily accessible marker to indicate inflammation in patients with AA. Considering that the current study is a retrospective, single-center study, multi-center, prospective studies involving healthy control groups are required to validate these findings in AA.

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] Alexis AF, Dudda-Subramanya R, Sinha AA. Alopecia areata: autoimmune basis of hair loss. Eur J Dermatol 2004;14:364-70.
[2] Kyriakis KP, Paltatzidou K, Kosma E, Sofouri E, Tadros A, Rachioti E. Alopecia areata prevalence by gender and age. J Eur Acad Dermatol Venereol 2009;23:572-3.
[3] Cotsarelis G, Botchkarev V. Biology of hair follicles. In:Wolff K, Katz SI, Goldsmith LA, Goldsmith L, Gilchrest B, Paller A, Leffell D, et al. Fitzpatrick's Dermatology in General Medicine. 7th ed. New York: Mc Graw Hill, 2007:pp. 39-9.
[4] Hordinsky MK. Alopecias. In:Horn, TD, Mascaro JM, Mancini AJ, et al. Dermatology. 1st ed. London: Mosby, 2003:pp. 1033-59.
[5] Wasserman D, Guzman-Sanchez DA, Scott K, McMichael A. Alopecia areata. Int J Dermatol 2007;46:121-31.
[6] Seçkin HY, Bütün I, Baş Y, Takcı Z, Kalkan G. Effects of colchicine treatment on mean platelet volume and the inflammatory markers in recurrent aphthous stomatitis. J Dermatolog Treat 2016;27:389-91.
[7] Schoorl M, Schoorl M, van Pelt J, Bartels PC. Application of innovative hemocytometric parameters and algorithms for improvement of microcytic anemia discrimination. Hematol Rep 2015;7:5843.
[8] Kim DS, Shin D, Kim TG, Kim SH, Kim DY, Kim SM, et al. Red blood cell distribution width as a useful indicator to predict systemic vasculitis in patients with cutaneous vasculitis. Rheumatol Int 2015;35:719-25.
[9] Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA, et al; CHARM Investigators. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. J Am Coll Cardiol 2007;50:40-7.
[10] Kurtul BE, Kabatas EU, Boybeyi SD, Caglar AA, Ozer PA. Increased red cell distribution width levels in children with seasonal allergic conjunctivitis. Int Ophthalmol 2018;38:1079-84.
[11] Goh C, Finkel M, Christos PJ, Sinha AA. Profile of 513 patients with alopecia areata: associations of disease subtypes with atopy, autoimmune disease and positive family history. J Eur Acad Dermatol Venereol 2006;20:1055-60.
[12] Kavak A, Yeşildal N, Parlak AH, Gökdemir G, Aydoğan I, Anul H, et al. Alopecia areata in Turkey: demographic and clinical features. J Eur Acad Dermatol Venereol 2008;22:977-81.
[13] Blaumeiser B, van der Goot I, Fimmers R, Hanneken S, Ritzmann S, Seymons K, et al. Familial aggregation of alopecia areata. J Am Acad Dermatol 2006;54:627-32.
[14] Seyrafi H, Akhiani M, Abbasi H, Mirpour S, Gholamrezanezhad A. Evaluation of the profile of alopecia areata and the prevalence of thyroid function test abnormalities and serum autoantibodies in Iranian patients. BMC Dermatol 2005;5:11.
[15] Berker DAR, Messenger AG, Sinclair RD. Disorders of hair. In: Rook's Textbook of Dermatology. Burns T, Breathnach S, Cox N, Griffiths C, eds. 7th ed. Oxford: Blackwell Science, 2004:pp. 1-63.
[16] Gandhi V, Baruah MC, Bhattacharaya SN. Nail changes in alopecia areata: incidence and pattern. Indian J Dermatol Venereol Leprol 2003;69:114-5.
[17] Kasumagic-Halilovic E, Prohic A. Nail changes in alopecia areata: frequency and clinical presentation. J Eur Acad Dermatol Venereol 2009;23:240-1.
[18] Sharma VK, Dawn G, Kumar B. Profile of alopecia areata in Northern India. Int J Dermatol 1996;35:22-7.
[19] Pancar GS, Eyupoglu O. Red cell distribution width and mean platelet volume in patients with pityriasis rosea. J Clin Med Res 2016;8:445-8.
[20] Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 2009;133:628-32.
[21] Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352:1011-23.
[22] Kim DS, Shin D, Jee H, Kim TG, Kim SH, Kim DY, et al. Red blood cell distribution width is increased in patients with psoriasis vulgaris: a retrospective study on 261 patients. J Dermatol 2015;42:567-71.
[23] Farkas N, Szabó A, Lóránd V, Sarlós DP, Minier T, Prohászka Z, et al. Clinical usefulness of measuring red blood cell distribution width in patients with systemic sclerosis. Rheumatology (Oxford) 2014;53:1439-45.
[24] Lou Y, Wang M, Mao W. Clinical usefulness of measuring red blood cell distribution width in patients with hepatitis B. PLoS One 2012;7:e37644.

The European Research Journal 2019;5(4):629-635 ORIGINAL ARTICLE

The role of inflammation markers in predicting the prognosis of Bell's palsy

Bülent Ulusoy[1], Kazım Bozdemir[2], Hayati Kale[3], Mehmet Hakan Korkmaz[2]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Selçuk University School of Medicine, Konya, Turkey
[2]Department of Otorhinolaryngology-Head and Neck Surgery, Yıldırım Beyazıt University School of Medicine, Ankara, Turkey
[3]Department of Otorhinolaryngology-Head and Neck Surgery, Dr. Sami Ulus Training and Research Hospital, Ankara, Turkey

DOI: 10.18621/eurj.404778

ABSTRACT

Objectives: This study aimed to investigate the relationship between the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) and Bell's palsy in addition to the usability of these markers to predict prognosis.

Methods: In this prospective study, the patient group included 24 patients that were diagnosed with Bell's palsy and 29 healthy volunteers that had similar characteristics to them regarding age and gender with patient group as the control group. The temporal gadolinium-enhanced magnetic resonance imaging (TGd-MRI) was performed to all patients. The complete blood count was also obtained from both the patient and the control groups, and these two groups were compared for NLR and PLR, mean platelet volume (MPV), platelet distribution width (PDW), and platelet count. The relationship between these markers and Bell's paralysis prognosis was also investigated.

Results: The patient and control groups were similar in age and gender ($p > 0.05$). NLR was significantly higher in the patient group compared with the control group ($p = 0.016$). There was no correlation between the NLR value and the prognosis of Bell's Palsy. The PDW and white blood cell count (WBC) were significantly higher in the patient group than the control group ($p = 0.023$ and $p = 0.012$, respectively). A comparison of the recovered and unrecovered patients revealed that the PDW value was significantly higher and the platelet count was lower in the recovered patients than the unrecovered patients ($p = 0.009$ and $p = 0.003$ respectively). The MPV value was higher in the recovered patients, though not statistically significant ($p = 0.063$). Based on the cut-off values determined in the receiver operator characteristic (ROC) curve analysis, a comparison of the recovered and unrecovered patients reveals that the likelihood of not healing was significantly higher in those that had normal PDW values ($p = 0.036$).

Conclusion: These results might support the theory of inflammation in patients with Bell's palsy.

Keywords: Bell palsy, inflammation, mean platelet volume, prognosis, platelet activation, ROC curve, neutrophil

Received: March 12, 2018; Accepted: August 15, 2018; Published Online: September 14, 2018

Bell's palsy is defined as an acute peripheral facial palsy, usually affecting one half of the face [1, 2]. The facial nerve provides the sense of a specific part of the auriculus, the sense of taste in two-thirds of the anterior tongue, and the autonomous innervation of the lacrimal and mandibular glands in addition to

Address for correspondence: *Bülent Ulusoy, MD., Assistant Professor, Selçuk University School of Medicine, Department of Otorhinolaryngology-Head and Neck Surgery, Konya, Turkey*
E-mail: ulusoybulent@hotmail.com, Tel: +90 332 2412181-43920, Fax: +90 332 2412184

e-ISSN: 2149-3189

the motor innervation of the facial muscles; thus, there are certain symptoms and findings (e.g., sudden-onset visual impairment on one side of the faces, dry eye, and incomplete eyes and mouth closure) emerging in relation to these functions [1]. Bell's palsy has an annual incidence of 15-30/100,000, which corresponds to 60-75% of all unilateral facial palsies [2]. Some patients reported being exposed to the air condition or an open window before the paralysis [1]. Although the etiology of facial paralysis is still unclear, viral infection, vascular ischemia, or autoimmunity are thought to be the causes of this disease [1, 2].

The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have recently been used frequently as a new marker of inflammation [3-5]. This study aimed to investigate the relationship between NLR and PLR values and Bell's palsy, and the usability of these markers to predict the prognosis.

METHODS

This study was conducted with 24 patients that were diagnosed with Bell's palsy between the years 2015 and 2016, and 29 healthy volunteers (the control group) with similar age and gender characteristics. The exclusion criteria included the following: patients with acute infection, diabetes mellitus, systemic hypertension, hyperlipidemia, acute or chronic renal failure, chronic liver disease, chronic obstructive pulmonary disease, coronary artery disease, connective tissue disease, inflammatory bowel disease, allergic rhinitis, smoking history, chronic otitis media and otosclerosis, and other otic diseases such as acoustic trauma, patients who are performed otological surgery before, and tumors or cochlear pathology detected on the temporal gadolinium-enhanced magnetic resonance imaging (TGd-MRI).

The stage of Bell's palsy was determined according to the House-Brackmann staging system [2] at the time of diagnosis and 1 month after the treatment. A complete ear-nose-throat and head and neck examinations were performed for all patients. Some tests, such as the complete blood count (CBC), pure tone audiometry, stapes reflex, routine blood biochemistry, and viral serological markers, were obtained from the patients diagnosed with unilateral peripheral facial paralysis before the treatment. Additionally, TGd-MRI was obtained from all patients at the onset of the treatment. In the control group was performed only CBC.

A systemic steroid (methylprednisolone) treatment at a dose of 1 mg/kg was started routinely for patients diagnosed with Bell's palsy, and the dose was reduced and terminated in 10 days. At the end of the treatment, the House-Brackmann grade 1-2 was regarded as a satisfactory recovery and grade 3-6 was regarded as unsatisfactory recovery [3]. Patients who did not change according to the pre-treatment stage were defined as unrecovered.

The patient and control groups were compared for NLR, PLR, mean platelet volume (MPV), and platelet distribution width (PDW). These markers were also evaluated for their usability in predicting the prognosis.

Hematological Analysis

NLR was calculated as a simple ratio between the absolute neutrophil and the absolute lymphocyte counts in the CBC. PLR was also calculated as a simple ratio between the absolute platelet count and the absolute lymphocyte count. Moreover, the MPV and PDW values were determined from the CBC. The NLR, PLR, MPV, and PDW values were calculated in the control group in a similar manner. An automated blood cell counter (Sysmex XE-2100; Kobe, Japan) was used for the analyses.

Approval of the Research Ethics Committee

The study was carried out with the permission (26379996/177) of the Clinical Research Ethics Committee.

Statistical Analysis

SPSS for Windows 11.5 package program (Chicago, Inc, USA) for statistical analysis was used. In the analyses, independent samples t test was used for the comparison of the variables in two groups as well as the variables with normal distribution. Mann-Whitney U Test was used for the variables that did not have a normal distribution.

The receiver operator characteristics (ROC) curve analysis was applied to determine the most appropriate cut-off values for the statistically significant variables among the groups. The chi-square and Fisher's exact tests were used to compare the cut-off values obtained

Table 1. Comparison between patient and control groups according to age and sex

	Control (n = 29)	Patient (n = 24)	*p value*
Sex Male/Female	13/16	13/11	0.498
Age (years) (Mean ± SD)	44.34 ± 9.97	45.12 ± 12.34	0.800

SD = standard deviation

as a result of these analyses. The statistical significance threshold was accepted as 0.05.

RESULTS

The mean age was 45.12 ± 12.34 years in the patient group and 44.34 ± 9.97 years in the control group with no statistically significant difference between these two groups ($p > 0.05$). The female/male ratio was 13/16 in the control group and 13/11 in the patient group, and when the groups compared according to gender were similar. ($p > 0.05$) (Table 1). Five patients who did not participate in the control examination after the treatment were excluded from the study. Satisfactory recovery was detected in 16 patients. Since the stage of the disease did not change before and after the treatment in three patients, they were classified under the unrecovered group.

The mean NLR was 2.86 ± 2.01 in the patient group and 1.68 ± 0.34 in the control group, and NLR was found to be significantly higher in the patient group compared with the control group ($p = 0.016$). The PDW value was 13.46 ± 2.40 fl in the patient group and 12.31 ± 1.02 fl in the control group. The white blood cell (WBC) count was 9.13 ± 3.33 ($\times 10^9$/l) in the patient group and 7.40 ± 1.22 ($\times 10^9$/l) in the control group. The PDW and WBC values were significantly higher in the patient group compared with the control group ($p = 0.023$ and $p = 0.012$, respectively). The PLR value was 121.90 ± 52.87 in the patient group and 99.98 ± 16.93 in the control

Table 2. Comparison of the patient and control groups in terms of variables

	Control (n = 29)	Patient (n = 24)	*p value*
PLR	99.98 ± 16.93	121.90 ± 52.87	0.133
NLR	1.68 ± 0.34	2.86 ± 2.01	**0.016**
MPV (fl)	10.46 ± 0.54	10.23 ± 1.25	0.378
Platelet count ($\times 10^9$ /l)	247.59 ± 43.20	245.58 ± 62.44	0.891
PDW (fl)	12.31 ± 1.02	13.46 ± 2.40	**0.023**
WBC ($\times 10^9$ /l)	7.40 ± 1.22	9.13 ± 3.33	**0.012**

Data are shown as mean ± standard deviation. MPV = mean platelet volume, NLR = neutrophil-to-lymphocyte ratio, PDW = platelet distribution width, PLR = platelet-to-lymphocyte ratio, WBC = white blood cell

Table 3. Comparison of the recovery results in the patient group

	Present (n = 16)	Absent (n = 3)	*p value*
PLR	132.16 ± 58.83	92.96 ± 30.89	0.211
NLR	2.89 ± 2.28	1.90 ± 0.68	0.793
MPV (fl)	10.30 ± 1.11	8.90 ± 1.15	**0.063**
Platelet counts ($\times 10^9$ /l)	240.63 ± 55.01	289.00 ± 2.00	**0.003**
PDW (fl)	13.91 ± 1.80	10.63 ± 1.69	**0.009**
WBC ($\times 10^9$ /l)	8.56 ± 3.62	10.12 ± 1.79	0.481

Data are shown as mean ± standard deviation. MPV = mean platelet volume, NLR = neutrophil-to-lymphocyte ratio, PDW = platelet distribution width, PLR = platelet-to-lymphocyte ratio, WBC = white blood cell

Table 4. ROC analysis results for NLR, PDW, and WBC.

	NLR	PDW	WBC
AUC	0.6936	0.670	0.671
SE	0.082	0.081	0.088
p value	**0.016**	**0.034**	**0.033**
Cut-off point	1.80	12.60	8.28

AUC = area under the ROC curve, ROC = receiver operator characteristics

group, but the difference was not statistically significant ($p > 0.05$). Similarly, no significant difference was found between the patient and control groups in terms of MPV and platelet count ($p > 0.05$) (Table 2).

The patient group was categorized into two subgroups: recovered and unrecovered. The PDW value was 13.91 ± 1.80 fl in the recovered group and 10.63 ± 1.69 fl in the unrecovered group ($p = 0.009$). On the contrary, the platelet count was 240.63 ± 55.1 ($\times 10^9$/l) in the recovered group and 289.00 ± 2.00 ($\times 10^9$/l) in the unrecovered group ($p = 0.003$). Interestingly, the study determined that the PDW value was significantly higher and the platelet count was lower ($p = 0.003$ and $p = 0.009$, respectively) in the recovered patients when the patient group was divided into two groups as recovered and unrecovered individuals. Additionally, the MPV value was higher in the recovered group but this result was not statistically significant ($p = 0.063$) (Table 3).

When the patient and control groups were taken into consideration, statistically significant cut-off values were determined for NLR, PDW, and WBC in the ROC analysis that was performed to determine the most appropriate cut-off values. The results were pathologically determined as NLR > 1.8, PDW > 12.6 fl, and WBC > 8.28 ($\times 10^9$/l) (Figure 1, Table 4). The pathological rates of NLR, PDW, and WBC were higher in the patient group (Table 5). No significant difference was obtained in the NLR and WBC values between recovered and unrecovered subgroups in the patient group; however, the possibility of not recovering was found to be significantly higher in the patients having normal PDW levels (Table 6).

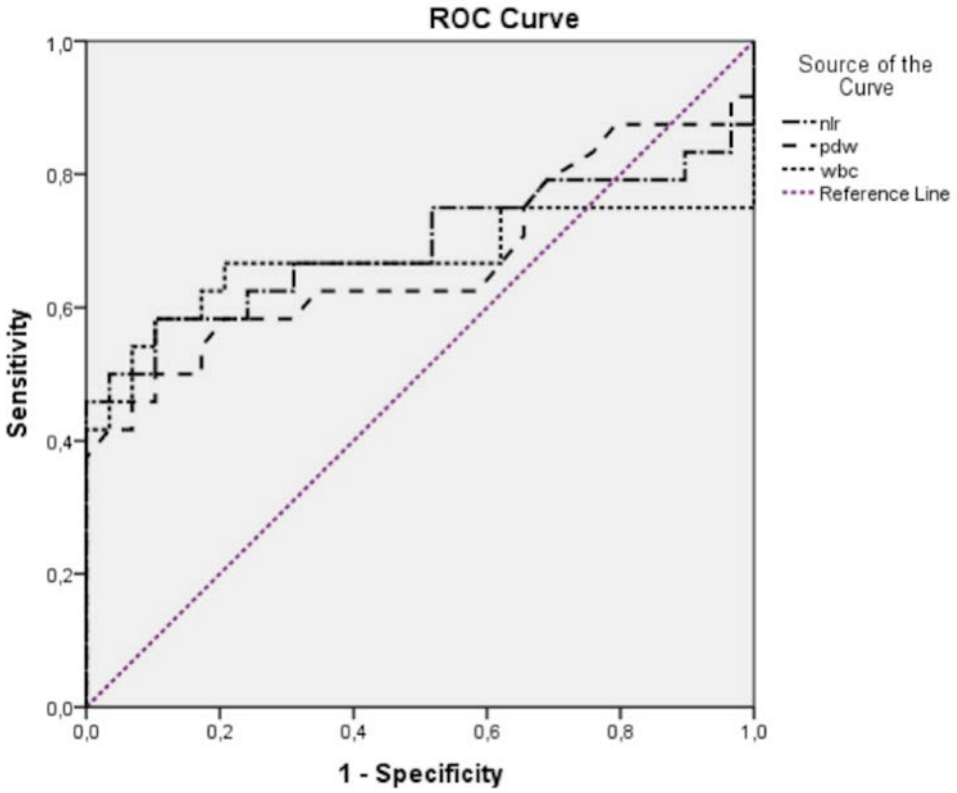


Figure 1. ROC analysis results for NLR, PDW, and WBC.

Table 5. Control and patient group comparison results according to the cut-off values for NLR, PDW, and WBC

	Control (n = 29)		Patient (n = 24)		*p value*
	n	%	n	%	
NLR					
Normal	20	69.0	8	33.3	**0.010**
Pathologic	9	31.0	16	66.7	
PDW					
Normal	19	65.5	9	37.5	**0.042**
Pathologic	10	34.5	15	62.5	
WBC					
Normal	23	79.3	8	33.3	**0.001**
Pathologic	6	20.7	16	66.7	

NLR = neutrophil-to-lymphocyte ratio, PDW = platelet distribution width, WBC = white blood cell

Table 6. Comparison of cut-off values for NLR, PDW, and WBC according to the recovery status in the patient group

	Present (n = 16)		Absent (n = 3)		*p value*
	n	%	n	%	
NLR					
Normal	6	85.7	1	14.3	0.704
Pathologic	10	83.3	2	16.7	
PDW					
Normal	4	57.1	3	42.9	**0.036**
Pathologic	12	100.0	0	0.0	
WBC					
Normal	7	100.0	0	0.0	0.227
Pathologic	9	75.0	3	25.0	

NLR = neutrophil-to-lymphocyte ratio, PDW = platelet distribution width, WBC = white blood cell

DISCUSSION

Bell's palsy is defined as a peripheral facial paralysis with a sudden onset, involving one half of the face. Its incidence has peaked in the last two to four decades. Although this occurs equally in males and females, a slight female predominance was seen in the previous studies [1, 2]. Although the etiology of facial paralysis has not been fully understood yet, infection, microcirculation, circulatory insufficiency, genetic, and immunological and inflammatory factors are thought to play a role in its occurrence [1, 2, 6]. Past studies reported that autoimmune mechanisms play an important role in the pathogenesis of Bell's palsy, and interleukin-1 (IL-1), IL-6, IL-8 and tumor necrosis factor-α (TNF-α) levels are higher in the patients with Bell's palsy compared with the control group [2, 7]. It was reported that there is increasing evidence about Bell's palsy occurring due to inflammation or autoimmune reaction in the facial nerve as a result of latent herpes virus reactivation [1, 2].

In terms of etiology, the TGd-MRI is usually necesseary, and the most common pathology is the contrast enhancement at the facial nerve distal intracanalicular portion and labyrinthine segment. A similar contrast enhancement can also be seen in the geniculate ganglion [2]. Kum *et al*. [4] conducted a retrospective study on patients with Bell's palsy and reported geniculate ganglion, distal intracranial segment, and labyrinthine segment enhancement. These contrast enhancements in the facial nerve were detected in only 3 out of 24 patients with Bell's paralysis in the present study. The contrast enhancement in the facial nerve was at the internal acoustic channel level in two of the patients and at the facial recess level in one of the patients.

NLR is frequently used as a new inflammation marker according to recent studies [3-5, 8]. NLR can be easily calculated with a CBC test. Bucak *et al*. [3] conducted a retrospective study in the patients with Bell's palsy and had showed that the neutrophil counts and the NLR value significantly increased in the patients with Bell's palsy compared to the control

group. They also reported that the NLR was higher in the group with an unsatisfactory recovery than in the group with a satisfactory recovery, and therefore the NLR marker could be used as a marker to predict the disease prognosis [3]. Similarly, Kum *et al*. [4] found that the NLR values were significantly higher in those with Bell's palsy than in the control group. Moreover, the TGd-MRI results showed that the NLR was higher in patients with facial nerve involvement than in those without involvements, and that a positively significant correlation existed between the NLR value and facial paralysis stage. On the contrary, no correlation was detected with the MPV value. That study also suggested that these results provided evidence to support inflammation theory rather than microvascular theory in the etiopathogenesis of Bell's palsy [4]. Özler *et al*. [9] showed that the NLR value was high in Bell's palsy, and that a positive correlation existed between the NLR value and the level of paralysis. Moreover, they reported that high NLR value was a marker of poor prognosis [9]. Tekgul *et al*. [6] had showed that both B-cells (CD19) and T helper (CD4) values decrease in Bell's palsy. Nevertheless, they had reported that there was no prognostic significance of lymphocyte subset analysis in peripheral blood to predict the outcome of patients with unsatisfactory recovery [6]. In a retrospective study conducted by Atan *et al*. [10], NLR and PLR values were higher in the group of patients with Bell's palsy, but they found no correlation between these values and the level of facial paralysis [10]. Sahin *et al*. [11] had showed that neutrophil counts and NLR value increase with in Bell palsy patients but there were no statistical significant changes of PLR, MPV and PDW values. Additionally, they had not detect of association between the NLR value and grade of Bell's palsy (HB grade) [11]. A study of pediatric patients showed that the neutrophil count and NLR was higher in the Bell's palsy group, but no correlation was found between NLR and the grade of facial paralysis [12]. Wasano *et al*. reported that neutrophil count and the NLR value were higher in unrecovered Bell's palsy while the lymphocyte count reduced. They had also reported a correlation between the changes in blood test values and the prognosis of facial paralysis as a consequence of viral infection's impact on the bone marrow [5]. In another study, Wasano *et al*. [13] had defined to prognosis prediction score system for Bell's palsy. This scoring system includes the age (≥ 65 years), gender (male) and NLR value (≥ 2.9) of the patients. They had reported that the palsy prognosis prediction scores are useful for predicting prognosis of Bell's palsy before beginning treatment [13]. In this study, the NLR value was significantly higher in the patient group, which is consistent with the previous studies. Additionally, PDW and WBC were found to be higher in the patient group. These results might support the inflammation theory in patients with Bell's palsy. Unlike previous studies, no correlation was found between the NLR value and theprognosis. This result might be due to the small number of unrecovered patients in this study.

MPV and PDW markers have been representing the platelet activation [14-16]. The MPV value shows the size of platelets while the PDWvalue is used to evaluate variations in platelet size. An increase in these markers suggests that bone marrow has released larger-volume platelets into blood circulation. Platelets with a large volume have been showed to be metabolically and enzymatically more active and more tendencies to aggregation compared with the small ones [15-17]. Özler *et al*. [18] had showed that the MPV and the PDW values in patients with Bell palsy were higher. Additionally, they had showed that there was positive correlation between PDW and MPV values with grade of facial paralysis. However, they had reported that there was no correlation between MPV and PDW values and prognosis of facial paralysis [18]. In contrast, Kum *et al*. [4] had reported no correlation with between the MPV value and grade of facial paralysis. In this study, the platelet count was significantly lower, the PDW value was higher, and the MPV value was higher (statistically not significant) in the recovered patients. When the recovered and unrecovered patients were compared according to the cut-off values in the ROC curve, no significant difference was found in the NLR and WBC values, but the possibility of not recovering was found to be significantly high in the patients with normal PDW values.The result might support the microcirculatory insufficiency theory in patients with Bell's palsy.

Limitations

The limitation of this study is the small number of patients because this is prospective and a single-center study.

CONCLUSION

Based on these results, this study showed that bone marrow functions may be affected in patients with Bell's palsy; however, there is need for prospective studies that more patients are included to confirm this possibility.

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 Assoc. Prof. Dr. Serdal Kenan Köse for the statistical analysis of the work.

This study was presented as E-poster at the 38th Turkish National Congress of Otorhinolaryngology-Head and Neck Surgery. 26-30 October 2016, Antalya, Turkey

REFERENCES

[1] Finsterer J. Management of peripheral facial nerve palsy. Eur Arch Otorhinolaryngol 2008; 265:743-52.
[2] Greco A, Gallo A, Fusconi M, Marinelli C, Macri GF, de Vincentiis M. Bell's palsy and autoimmunity. Autoimmun Rev 2012;12:323-8.
[3] Bucak A, Ulu S, Oruc S, Yucedag F, Tekin MS, Karakaya F, et al. Neutrophil-to-lymphocyte ratio as a novel-potential marker for predicting prognosis of Bell palsy. Laryngoscope 2014;124:1678-81.
[4] Kum RO, Yurtsever Kum N, Ozcan M, Yilmaz YF, Gungor V, Unal A, et al. Elevated neutrophil-to-lymphocyte ratio in Bell's palsy and its correlation with facial nerve enhancement on MRI. Otolaryngol Head Neck Surg 2015;152:130-5.
[5] Wasano K, Kawasaki T, Yamamoto S, Tomisato S, Shinden S, Ishikawa T, et al. Pretreatment hematologic findings as novel predictive markers for facial palsy prognosis. Otolaryngol Head Neck Surg 2016;155:581-7.
[6] Tekgul H, Polat M, Serdaroğlu G, Ikizoğlu T, Yalaz M, Kutukculer N, et al. Lymphocyte subsets in Bell's palsy: immune pathogenesis and outcome prediction. Pediatr Neurol 2004;31:258-60.
[7] Yilmaz M, Tarakcioglu M, Bayazit N, Bayazit YA, Namiduru M, Kanlikama M. Serum cytokine levels in Bell's palsy. J Neurol Sci 2002;15:69-72.
[8] Küçük E, Kocayiğit I, Günel C, Düzenli H. Neutrophil-to-lymphocyte ratio in occlusive vascular diseases: the literature review of the past 10 years. World J Emerg Med 2016;7:165-72.
[9] Özler GS, Günak G. Neutrophil-lymphocyte ratio: a new predictive and prognostic factor in patients with Bell palsy. J Craniofac Surg 2014;25:944-5.
[10] Atan D, Ikinciogullari A, Koseoglu S, Ozcan KM, Cetin MA, Ensari S, et al. New predictive parameters of Bell's palsy: neutrophil to lymphocyte ratio and platelet to lymphocyte ratio. Balkan Med J 2015;32:167-70.
[11] Sahin C, Varım C. Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume and red cell distribution width measures in Bells palsy. Open Access Maced J Med Sci 2017;15:14-8.
[12] Eryilmaz A, Basal Y, Tosun A, Kurt Omurlu I, Basak S. The neutrophil to lymphocyte ratios of our pediatric patients with Bell's palsy. Int J Pediatr Otorhinolaryngol 2015;79:2374-7.
[13] Wasano K, Ishikawa T, Kawasaki T, Yamamoto S, Tomisato S, Shinden S et al. Novel pre-therapeutic scoring system using patient and haematological data to predict facial palsy prognosis. Clin Otolaryngol 2017;42:1224-8.
[14] Chen Y, Xiao Y, Lin Z, Xiao X, He C, Bihl JC et al. The role of circulating platelets microparticles and platelet parameters in acute ischemic stroke patients. J Stroke Cerebrovasc Dis 2015;24:2313-20.
[15] Martin JF, Trowbridge EA, Salmon G, Plumb J. The biological significance of platelet volume: its relationship to bleeding time, platelet thromboxane B2 production and megakaryocyte nuclear DNA concentration. Thromb Res 1983;32:443-60.
[16] Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia 2010;14:28-32.
[17] Sevuk U, Bahadir MV, Altindag R, Baysal E, Yaylak B, Ay N, et al. Value of serial platelet indices measurements for the prediction of pulmonary embolism in patients with deep venous thrombosis. Ther Clin Risk Manag 2015;11:1243-9.
[18] Özler GS, Okuyucu S. Increased mean platelet volume in patients with Bell's palsy. Int Adv Otol 2014;10: 281-3.

The European Research Journal 2019;5(4):636-640 ORIGINAL ARTICLE

Does laparoscopic appendectomy increase the risk of intra-abdominal abscess in children who have perforated appendicitis?

Fatih Akbıyık[1], Günay Ekberli[1], Yusuf Hakan Çavuşoğlu[2]

[1]Department of Pediatric Surgery, Ankara Children's Hematology and Oncology Training and Research Hospital, Ankara, Turkey
[2]Department of Pediatric Surgery, Gazi University School of Medicine, Ankara, Turkey

DOI: 10.18621/eurj.412177

ABSTRACT

Objective: The aim of this study is to compare the rates of intraabdominal abscesses (IAAs), in laparoscopic appendectomy (LA) and open appendectomy (OA) for perforated appendicitis in children.

Methods: A retrospective database search of consecutive cases of children with a diagnosis of perforated appendicitis who underwent OA or LA by the first author or were operated under his supervision diagnosed with appendicitis between 2011 and 2014 and who underwent surgery as treatment was conducted.

Results: Seventy-eight patients were included in our study. Forty-two and 36 patients underwent LA and OA, respectively. One case was converted from LA to OA. There was no statistically significant difference at superficial incisional surgical-site infections and IAA between groups but drain placement ratio and length of hospital stay was higher in OA group.

Conclusions: The lack of difference in postoperative incidence of IAA supports the idea that LA does not increase the risk of IAA in perforated appendicitis. Although LA for perforated appendicitis in children has been intensely debated, our findings indicate that laparoscopic procedures performed by experienced pediatric surgeons will decrease the risk of complication and conversion to OA. Laparoscopy in children is a safe procedure for perforated, complicated appendicitis.

Keywords: appendicitis, abdominal abscess, laparoscopy, child

Received: April 3, 2018; Accepted: May 11, 2018; Published Online: August 13, 2018

Appendicitis is resulting from luminal obstruction and continuation of simple inflammation to perforation and subsequent abscess formation. Appendectomies are performed frequently in pediatric surgical practice. The use of laparoscopy by surgeons to manage appendicitis is increasing because laparoscopy offers the advantages of abdominal exploration associated with open procedures, along with decreased postoperative analgesic requirements, decreased length of hospital stay, and better cosmetic results, partly because of the technical advances in terms of refinements in instruments and increased technical experience of surgeons with the technique [1-3]. However, there is an intense debate regarding the occurrence of intraabdominal abscesses (IAAs) after laparoscopy, especially in cases of complicated appendicitis [4-6].

The aim of this study is to compare the rates

Address for correspondence: *Yusuf Hakan Çavuşoğlu, MD., Professor, Gazi University School of Medicine, Department of Pediatric Surgery, Ankara, Turkey*
E-mail: hakancavusoglu@hotmail.com

e-ISSN: 2149-3189

of IAA, i.e., surgical-site infections (SSIs), in laparoscopic appendectomy (LA) and open appendectomy (OA) for perforated appendicitis in children.

METHODS

Using the hospital information system at Ankara Children's Hematology Oncology Training and Research Hospital, Department of Pediatric Surgery, we conducted a retrospective database search of consecutive cases of children diagnosed with appendicitis between January 2011 and December 2014 and who underwent surgery as treatment.

Patients with a diagnosis of perforated appendicitis who underwent OA or LA by the first author (F.A.) or were operated under his supervision were included in this study. Ankara Children's Hematology Oncology Education and Research Hospital is a high-circulation training hospital that accepts patients not covered by health insurance as well. A total of five pediatric surgery specialists work at the pediatric surgery clinic.

The following patients were included in the study: those with a surgical diagnosis of perforated appendicitis in the operative records (intraoperative presence of appendiceal perforation and/or localized or generalized peritonitis or periappendiceal abscess); those without a surgical diagnosis but with a histopathological result of perforated appendicitis. We excluded cases of interval, non-perforated, and incidental appendectomy. There were no missing data. The patients' demographic and clinical data, operation type, LA to OA conversion status, length of hospital stay, histopathology reports, and postoperative complications were evaluated.

Operative Technique

Hospitalized children were allowed nothing by mouth and received intravenous hydration. Operations were performed when operating rooms were available. The patients underwent either LA or OA. OA was performed whenthe surgeon suspected severe intraabdominal adhesions or when a laparoscopy set was not available.

LA was performed with the "in" LA technique that uses three ports. An infraumbilical 10-mm camera port, two 5-mm working ports atthe suprapubic and left-lower quadrants, and a 30° 5-mm telescope were used. The mesoappendix was dissected using a bipolar vascular sealing device (Valleylab LigaSure, USA) or monopolar hook cautery, and the appendiceal stump was secured with polymer clips (Hem-o-lock®Weck, USA). The specimen was removed through the 10-mm port with or without a 5-mm laparoscopic bag, depending on the specimen size. The operative field was irrigated with 25-50 mL of physiological saline solution. Paracolic, pelvic, perihepatic, and splenic regions were checked and all existing purulent material was aspirated. In the presence of intensive purulent material, a ¼" Penrose drain catheter was placed through the 5-mm suprapubic port.

OA was performed through aright-lower quadrant transverse or paramedian incision. After the appendix, has been removed, all purulent material in the abdominal cavity was aspirated. The operative field and the fields with purulent material were wiped with saline-soaked gauze, performed. A ¼" Penrose drain catheter was placed through a separate incision when copious purulent material was present.

Postoperative Care

All patients who underwent appendectomy received a triple-antibiotic regimen (ampicillin/penicillin + amikacin + ornidazole, in appropriate therapeutic dosages) intravenously before the skin incision. The regimen was continued until discharge. Nasogastric decompression was used only when required. All wounds underwent primary closure. Drains were removed before discharge. Antibiotics were continued after dischargeonly if the patients had SSIs.

The infectious complications were diagnosed according to criteria for defining a SSI in the Guidelines for Prevention of Surgical Site Infections, 1999 [7]. IAA was treated conservatively by wide spectrum parenteral antibiotics.

Statistical analysis

Statistical analyses were made with SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was evaluated using the one-sample Kolmogorov–Smirnov test. Mean ± standard deviations were used for presenting normally distributed data, whereas median and ranges were used for presenting non-normally distributed data. Two averages for constant variables were compared using

the t-test for normally distributed data and the Mann–Whitney U-test for non-normally distributed data.Categorical variables were analyzed using the chi-square test and Fisher's exact test when required. A p value of < 0.05 was considered significant.

RESULTS

A total of 1793 patients underwent surgery between 2011 and 2014. Of these, 215 were diagnosed with perforated appendicitis. The first author performed or supervised surgery on 78 of these patients, and these were included in our study. Forty-two and 36 patients underwent LA and OA, respectively. One case was converted from LA to OA. Patients had a mean age of 9.5 ± 4.2 (range; 2-18 years) and 10.0 ± 3.8 (range; 2-18 years) years in the LA and OA groups, respectively. The age difference between groups was not statistically significant (p = 0.530). Demographic data and patient characteristics are presented in Table 1.

One case was converted from LA to OA because of difficult dissection. There were no intraoperative complications or deaths in either group.

There was no statistically significant difference in the rates of superficial incisional SSI and IAA between groups but drain placement ratio and length of hospital stay was higher in the OA group (Table 1). There was a urinary tract infection at LA group as postoperative complication other than SSI. There were no other pathologies except appendicitis at histopathology reports. The mean follow-up period was 3.6 ± 1.7 months.

DISCUSSION

LA has the following advantages: less postoperative pain, decreased length of hospital stay, and better cosmetic results. In addition, it allows the surgeon to perform a whole-abdomen examination and pelvic examination in girls [1, 2]. These advantages increased the frequency at which laparoscopic surgeries have been performed for the treatment of appendicitis in children. Cheong *et al*. [3] reported increased LA rates from 28.8% to 66.4% between 2004 and 2010 in Canada. Although Lin *et al*. [4] noted that althoughthe LA rates for perforated appendicitis have increased from 9.9% in 1999 to 46.6% in 2007 in the United States, there is still debate about performing laparoscopy in complicated appendicitis.

The subject discussed most frequently by investigators who object to LA for perforated appendicitis is IAA. Gupta *et al*. [5] argued that using too much irrigation fluid and aggressive manipulation of the infected appendix increased the incidence of

Table 1. Characteristics of patients who underwent laparoscopic versus open appendectomy

	Laparoscopic Appendectomy (n = 42)	Open Appendectomy (n = 36)	*p*
Age (range), years	9.5 ± 4.2 (2-18)	10.0 ± 3.8 (2-18)	0.530*
Male/Female	24/18	26/10	0.166**
Operative time (min)	39.3 ± 12.6	41.5 ± 9.6	0.381*
Drain placement	3 (7.1%)	10 (27.8%)	**0.015****
Removing time of drain (days)	2.7 ± 1.5	3.6 ± 2.6	0.577*
Superficial Incisional SSI	2 (4.8%)	4 (11.1%)	0.267***
IAA	2 (4.8%)	1 (2.8%)	0.558***
Length of stay (range), days	3.2 ± 1.3 (2-8)	4.4 ± 2.6 (3-15)	**0.018***

IAA = Intra-abdominal abscess, SSI = Surgical site infection, *t-test, **chi-square, ***Fisher's exact test

IAA. Memon *et al*. [6] argues that pneumoperitoneum created by carbondioxide increased bacterial translocation. Moore *et al*. [8] reported in a study recently done that IAA rates increased if irrigation was done in LA. Another study found that irrigation did not change the ratio of abscess, but it prolonged operation time [9]. The authors of the current study tended to avoid intense irrigation, and they used irrigation only for hemostasis in the operative field. The purulent material is aspirated in LA and OA, and the abdominal cavity is wiped with wet sponge gauze in OA. Some authors such as Pokala *et al*. [10] argued that IAAs, which have never been observed in OA, occurred in 14% of LA cases. Moreover, Paik *et al*. [11] argued that LA was inconvenient in complicated appendicitis. Recently, Ferranti *et al*. [12] compared the LA and OA techniques for perforated appendicitis in a study on adults, and observed that IAA was found in 16.6% and 5% of LA and OA cases, respectively, difference between the groups was not statistically significant and he suggested that laparoscopic approach is a safe procedure for the treatment of uncomplicated appendicitis, but LA should be used with caution, or even avoided, in the cases of perforated appendicitis. Esposito *et al*. [13] reported that there was no difference in terms of formation of abscess between both techniques in a meta-analysis of 26 studies in children, which included over 1,00,000 cases. According to an analysis of results from more than one hundred thousand cases, Markar *et al*. [14] reported that although LA decreased the overall morbidity, it increased the risk of IAA. Chang *et al*. [15] found in a study done on children that the rates of IAA is 3% in LA and 2% in OA. In our study, the difference in IAA rates were not significant as in this analysis.

Li *et al*. [16] mentioned that as the surgeons became more experienced, they did more complicated operations laparoscopically, which might have increased complications and conversion rates[16]. Akkoyun *et al*. [17] and Narci *et al*. [18] have concluded that irrigation and drainage were not necessary. The authors of the current study did not use drainage cathetersin cases of perforated appendicitis. In this study, drainage catheters were used in three patients (3/42) in LA and 10 patients (10/36) in OA. The lack of difference in postoperative incidence of IAA supports the idea that laparoscopy provides better aspiration of purulent material.

CONCLUSION

Although LA for perforated appendicitis in children has been intensely debated, our findings indicate that laparoscopic proceduresperformed by experienced pediatric surgeons will decrease the risk of complication and conversion to OA. Laparoscopy in children is a safe procedure for perforated, complicated appendicitis.

Authors' Contributions

F.A: Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision; G.E: Acquisition of data, analysis and interpretation of data, drafting of manuscript; Y.H.Ç: Study conception and design, analysis and interpretation of data, drafting of manuscript, critical revision.

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] Guller U, Anstrom KJ, Holman WL, Allman RM, Sansom M, Peterson ED. Outcomes of early extubation after bypass surgery in the elderly. Ann Thorac Surg 2004;77:781-8.
[2] Croce E, Olmi S, Bertolini A, Magnone S. Laparoscopic surgery of pancreatic cancer: state of the art. Hepatogastroenterology 2005;52:1889-94.
[3] Cheong LH, Emil S. Pediatric laparoscopic appendectomy: a population-based study of trends, associations, and outcomes. J Pediatr Surg 2014;49:1714-8.
[4] Lin HF, Lai HS, Lai IR. Laparoscopic treatment of perforated appendicitis. World J Gastroenterol 2014;20:14338-47.
[5] Gupta R, Sample C, Bamehriz F, Birch DW. Infectious complications following laparoscopic appendectomy. Can J Surg 2006;49:397-400.
[6] Memon MA, Fitztgibbons RJ, Jr. The role of minimal access surgery in the acute abdomen. Surg Clin North Am 1997;77:1333-53.
[7] Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR.

Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250-78; quiz 79-80.
[8] Denning DW, Park S, Lass-Florl C, Fraczek MG, Kirwan M, Gore R, et al. High-frequency triazole resistance found In nonculturable Aspergillus fumigatus from lungs of patients with chronic fungal disease. Clin Infect Dis 2011;52:1123-9.
[9] Adibe OO, St Peter SD. Equipoise, ethics, and the necessity of randomized trials in surgery. Arch Surg 2012;147:899-900.
[10] Pokala N, Sadhasivam S, Kiran RP, Parithivel V. Complicated appendicitis--is the laparoscopic approach appropriate? A comparative study with the open approach: outcome in a community hospital setting. Am Surg 2007;73:737-41; discussion 41-2.
[11] Paik PS, Towson JA, Anthone GJ, Ortega AE, Simons AJ, Beart RW, Jr. Intra-abdominal abscesses following laparoscopic and open appendectomies. J Gastrointest Surg 1997;1:188-92; discussion 92-3.
[12] Siani LM, Ferranti F, De Carlo A, Quintiliani A. Completely laparoscopic versus open total gastrectomy in stage I-III/C gastric cancer: safety, efficacy and five-year oncologic outcome. Minerva Chir 2012;67:319-26.
[13] Caputo I, Secondo A, Lepretti M, Paolella G, Auricchio S, Barone MV, et al. Gliadin peptides induce tissue transglutaminase activation and ER-stress through Ca2+ mobilization in Caco-2 cells. PLoS One 2012;7:e45209.
[14] Markar SR, Koehler R, Low DE, Ross A. Novel multimodality endoscopic closure of postoperative esophageal fistula. Int J Surg Case Rep 2012;3:577-9.
[15] Chang HK, Han SJ, Choi SH, Oh JT. Feasibility of a laparoscopic approach for generalized peritonitis from perforated appendicitis in children. Yonsei Med J 2013;54:1478-83.
[16] Li X, Zhang J, Sang L, Zhang W, Chu Z, Li X, et al. Laparoscopic versus conventional appendectomy--a meta-analysis of randomized controlled trials. BMC Gastroenterol 2010;10:129.
[17] Akkoyun I, Tuna AT. Advantages of abandoning abdominal cavity irrigation and drainage in operations performed on children with perforated appendicitis. J Pediatr Surg 2012;47:1886-90.
[18] Narci A, Karaman I, Karaman A, Erdogan D, Cavusoglu YH, Aslan MK, et al. Is peritoneal drainage necessary in childhood perforated appendicitis?--a comparative study. J Pediatr Surg 2007;42:1864-8.

Investigation of effects of neurotrophic factors on painful diabetic neuropathy: an experimental study

Faruk Kılınç[1], Ramis Çolak[2], Mete Özcan[3], Ahmet Ayar[4]

[1]*Department of Endocrinology, Fırat University School of Medicine, Elazığ, Turkey*
[2]*Department of Endocrinology, Ondokuz Mayıs University School of Medicine, Samsun, Turkey*
[3]*Department of Physiology, Fırat University School of Medicine, Elazığ, Turkey*
[4]*Department of Physiology, Karadeniz Technical University School of Medicine, Trabzon, Turkey*

DOI: 10.18621/eurj.414105

ABSTRACT

Objective: We have studied the effects of neurotrophin-4 (NT-4) different doses on the pain levels of streptozocin-induced diabetic rats.

Methods: Thirty-five 3-week-old male rats were used. After induction of diabetes in rats with streptozocin (nearly 4 weeks); diabetic animals were divided into 4 groups. The first group; healthy control group (n = 15), the second group; diabetic control group (n = 10), the third group; low dose (0.3 mg/ kg) recombinant human NT-4 was applied (n = 4) and the fourth group; high dose recombinant human NT-4 was applied (n = 6).

Results: In the low-dose NT-4 group, the pain threshold values did not differ from the diabetic control and healthy control groups. In the high dose NT-4 group, a rise was observed in the pain threshold values of hot plate in comparison with the healthy control group, diabetic control group and low dose applied group and this rise reached at the level of statistical significance ($p < 0.05$).

Conclusion: Neurotrophic factors (neurotrophin-4) have been shown to be effective on painful diabetic neuropathy in streptozocin-induced diabetic rats. However, there is a need for larger-scale and longer-term studies for clinical use.

Keywords: Diabetic neuropathy, hot plate, neurotrophin-4, streptozocin

Received: April 10, 2018; Accepted: June 11, 2018; Published Online: August 7, 2018

Diabetes mellitus (DM) is a chronic metabolicdisorder characterized by hyperglycemia that caused by a defect in insulin secretion, insulin action, or both; this results in carbohydrate, lipid, and protein metabolism disorders; accelerated atherosclerosis; and microvascular and macrovascular complications [1].

Diabetic neuropathy is a clinically or subclinically detectable disorder of the somatic or autonomous parts of the peripheral nervous system occurring in the presence of DM [2].

Diabetic neuropathy is the most frequent cause of neuropathy in developed countries, and it accounts for 50-75% of non-traumatic amputations. It is the most important cause in the etiology of diabetic foot problems [2].

Neurotrophic factors are small proteins supporting the survival and growth of neurons [3]. These factors constitute the neurotrophin (NT) group of pro-

Address for correspondence: *Faruk Kılınç, MD., Assistant Professor, Fırat University School of Medicine, Department of Endocrinology, 23100, Elazığ, Turkey*
E-mail: drfarukkilinc@hotmail.com, Tel: +90 424 2333555 (2453) Fax: +90 424 233 3558

e-ISSN: 2149-3189

teins involving nerve growth factor (NGF), NT-3, brain-derived neurotrophic factor (BDNF), and NT-4/5. These molecules ensure the development, differentiation, and maintenance of the nervous system. Recent studies have demonstrated impaired NT support in DM and have suggested that this contributes to diabetic neuropathy pathogenesis [4, 5].

The demonstration of the neuroprotective roles of neurotrophic factors against damage to sensory neurons has necessitated testing the effectiveness of these agents for treating neuropathic pain. Among these agents, glial cell line-derived neurotrophic factor has been demonstrated to exert analgesic effects by suppressing ectopic afferent activity and has been used for treating experimentally induced neuropathy [4-7]. Glial cell line-derived neurotrophic factor has been effectively used in the treatment of an experimental mice model of diabetic neuropathy; however, the efficacy of the recently discovered agents has not been tested [8].

In the present study, the effects of different doses of NT-4 on hot plate pain threshold values were investigated to examine the effects of neurotrophic factors on painful diabetic neuropathy in streptozotocin (STZ)-induced diabetic mice.

METHODS

This study was conducted at Fırat University Experimental Research Center in collaboration with the Department of Physiology at Fırat University Faculty of Medicine, and approval was obtained from Fırat University Animal Studies Ethics Committee (Project no: 1667).

Laboratory Animals

Male BALB-C mice used in the experiments were supplied from Fırat University Experimental Research Center.

Diabetes Induction

Totally, 180 mg/kg of STZ (Pharmacia, France) was dissolved in 0.4 ml (0.1 M) sodiumcitrate buffer (pH: 4.5) and intraperitoneally administered as a single injection usinga 26-gauge insulin injector to induce diabetes in 35 mice [9]. By sampling blood from the tail area after one week, mice with postprandial blood glucose levels of >400 mg/dL measured using a glucose meter were considered diabetic.

Groups

A total of 35 mice were used. Our study consisted of 4 groups in total. Group 1 was designated as the healthy control group, whereas groups 2, 3, and 4 were designated as the experimental groups. Four groups were created as follows:

Group 1 (n = 15): Healthy control group.
Group 2 (n = 10): Diabetic control group
Group 3 (n = 4): Low-dose group: Group treated with low dose-recombinant human NT-4
Group 4 (n = 6): High-dose group: Group treated with high-dose recombinant human NT-4.

Approximately 90% of mice in the control group and the experimental groups completed the study.hree mice with a blood glucose level exceeding 500 mg/dL were excluded. Symptoms of hyperglycemia such as drinking excessive water, frequently urinating, and consuming more food were observed in STZ-treated mice. Approximately 90% of mice in the control group and the experimental groups completed the study. Three mice with a blood glucose level exceeding 500 mg/dL were excluded. Symptoms of hyperglycemia such as drinking excessive water, frequently urinating, and consuming more food were observed in STZ-treated mice. Initially, the pre-injection pain threshold values of mice were measured. Following these procedures, the animals in the control group received an intraperitoneal injection of normal saline; low dose recombinant human NT-4 (0.3 mg/kg), high dose recombinant human NT-4 (3 mg/kg), respectively. The time of injection was set at 0 min, and pain thresholds in all groups were measured with 1-h intervals. This procedure was followed in all groups for 24 h. The pain threshold values were measured every 24 h for 6 days to monitor the induction of chronic neuropathic pain and evaluate the response of chronic diabetic neuropathy to neurotrophic factors in mice within the diabetic control group and low- and high-dose groups.

Hot Plate Test

The hot plate test is an indirect indicator of acute thermal hyperalgesia. It is a thermal acute pain model

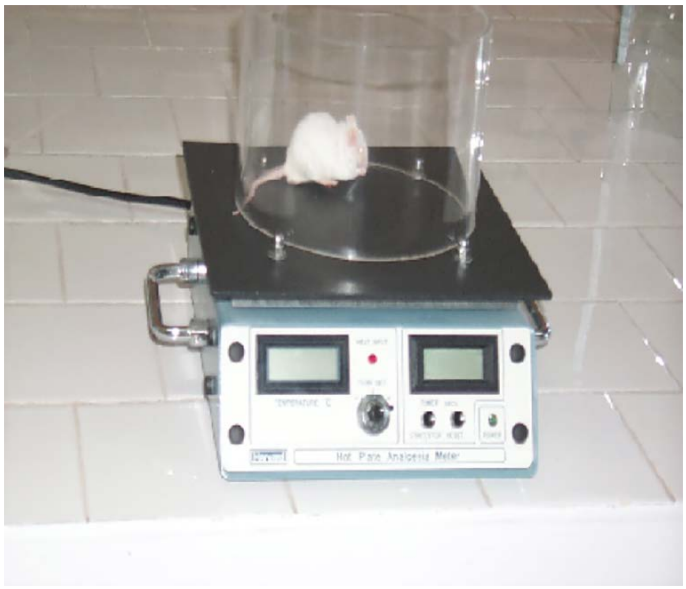


Figure 1. A harvard hot plate analgesia meter (Edenbridge, England) [10].

that examines the pain threshold by measuring the latency of an animal placed on a hot surface to heat stimulus. The appropriate size hot plate analgesia meter (Harvard, Edenbridge, UK) was used to provide easy mobility for the rats in the study (Figure 1). The test was performed by placing the mice on the platepreset to 50 ± 0.5°C and surrounded with a transparent plastic barrier confining the animal to the test area. The latency time to behavioral responses to the heat stimulus after placing the mice on the hot surface was measured. In this study, behavioral responses tothe heat stimulus indicating the pain threshold were defined as forepaw licking, forepaw lifting, or jumping.

Statistical Analysis

Statistical analyses were performed using SPSS 12.0, and charts were constructed using Microsoft Office 2003 Excel. One-way analysis of variance was used along with Student's t-test and Fisher's PLSD post hoc test for the statistical analysis ofstudy data. Descriptive statistics were expressed in the form of cross tabulations for categorical variables, and in mean, median, standard deviation (SD), minimum, and maximum for numeric variables. The Bonferroni test was performed following one-way analysis of variance to compare the diabetic control group with the low- and high-dose groups. Independent Student's t-test was performed between the control group and the diabetic control group. Variances within same group at different time points were evaluated usingStudent's t-test for paired groups. In all analyses, a *p* value of less than 0.05 was considered statistically significant.

RESULTS

Weekly blood glucose levels in blood samples obtained from the tail vein inthe experimental groups are shown in Table 1. During the experiment, blood glucose levels were notlower than 300 mg/dL in the weekly measurements inthe three experimental groups. Three mice with a blood glucose level exceeding 500 mg/dL were excluded.

Measurements were complete in one week. A significant difference was not observed in pain threshold values between days 1 and 7. The mean pain

Table 1. Weekly mean blood glucose levels in the experimental groups

Weeks	Mean Blood Glucose Levels (mg/dL)		
	Diabetic control group	Low-dose group	High-dose group
Week 1	414.57	417.25	363.2
Week 2	389.44	401.45	415.52
Week 3	412.36	394.24	386.52
Week 4	371.27	425.54	415.32
Week 5	428.56	412.68	406.55
Week 6	438.74	429.27	411.54
Week 7	446.27	432.36	438.71

Table 2. Pain threshold values in the control group and diabetic control group. Effects of normal saline and neurotrophin-4 (NT-4) administration in mice.

Time	Pain Threshold Values			
	Healthy control group	Diabetic control group	Low-dose group	High-dose group
0 h	20.23 ± 0.72	20.46 ± 1.63	23.15 ± 2.16	18.65 ± 1.45
1 h	19.87 ± 0.43	19.45 ± 1.33	29.98 ± 2.49 **(0.002)[a] (0.009)[b]**	19.30 ± 1.86
3 h	19.68 ± 0.39	22.65 ± 2.13	23.92 ± 2.59	19.98 ± 0.53
6 h	18.57 ± 0.58	20.12 ± 1.28	26.60 ± 3.18	19.63 ± 0.44
24 h	19.22 ± 0.32	18.79 ± 1.49	24.78 ± 1.19 **(0.026)[a]**	20.35 ± 1.23
Day 2		18.62 ± 1.62	25.02 ± 1.14 **(0.021)[a]**	19.98 ± 0.61
Day 3		18.24 ± 1.24	22.83 ± 1.19 **(0.045)[a]**	19.45 ± 0.50
Day 4		18.46 ± 1.27	23.65 ± 0.65 **(0.02)[a]**	20.68 ± 1.64
Day 5		18.07 ± 1.46	26.23 ± 2.25 (0.008)[a]	20.55 ± 0.38
Day 6		19.47 ± 1.11	25.57 ± 1.05 **(0.005)[a] (0.041)[b]**	19.90 ± 1.57
Day 7		18.89 ± 0.99	25.52 ± 1.35 **(0.001)[a] (0.049)[b]**	20.45 ± 0.49

Data are shown mean ± standard deviation.
[a] Significant difference compared to the diabetic control group ($p < 0.05$)
[b] Significant difference compared to the low-dose group ($p < 0.05$)

threshold values were 24.78 ± 1.19 at 24 h and 25.52 ± 1.35 at day 7 in the high-dose group and 20.35 ± 1.23 at 24 h and 20.45 ± 0.49 at day 7 in the low-dose group ($p = 0.001$) ($p < 0.05$; Table 2, Figure 2).

The mean pain threshold values in the healthy control group were 20.23 ± 0.72 s, 19.87 ± 0.43 s, 19.68 ± 0.39 s, 18.57 ± 0.58 s, and 19.22 ± 0.32 s, respectively; the corresponding mean pain threshold values in the diabetic control group were 20.46 ± 1.63 s, 19.45 ± 1.33 s, 22.65 ± 2.13 s, 20.12 ± 1.28 s, and 18.79 ± 1.49 s (Table 2).

The mean pain threshold values following the administration of low-dose NT-4 were 18.65 ± 1.45 s, 19.30 ± 1.86 s, 19.98 ± 0.53 s, 19.63 ± 0.44 s, 20.35 ± 1.23 s, 19.98 ± 0.61 s, 19.45 ± 0.50 s, 20.68 ± 1.64 s, 20.55 ± 0.38 s, 19.90 ± 1.57 s, and 20.45 ± 0.49 s, respectively; the corresponding mean pain threshold values following the administration of high-dose NT-4 were 23.15 ± 2.16 s, 29.98 ± 2.49 s ($p = 0.002$), 23.92 ± 2.59 s, 26.60 ± 3.18 s, 24.78 ± 1.19 s ($p = 0.026$), 25.02 ± 1.14 s ($p = 0.021$), 22.83 ± 1.19 s ($p = 0.045$), 23.65 ± 0.65 s ($p = 0.02$), 26.23 ± 2.25 s ($p = 0.008$), 25.57 ± 1.05 s ($p = 0.005$), and 25.52 ± 1.35 s ($p = 0.001$) (Table 2). Compared to the low-dose group, the high-dose group showed maximum response at 1 h (pain threshold value: 29.98 ± 2.49) and although a decrease in pain threshold values was observed in the following hours, the mean values were maintained at the same level with a significant difference (day 7: 25.52 ± 1.35, $p = 0.001$) ($p < 0.05$; Table 2, Figure 3).

The averages of time-dependent responses to heat (pain threshold values) were compared between the mice in the healthy control groups and healthy diabetic groups (Figure 2) and then between those in the low- and high-dose groups (Figure 3).

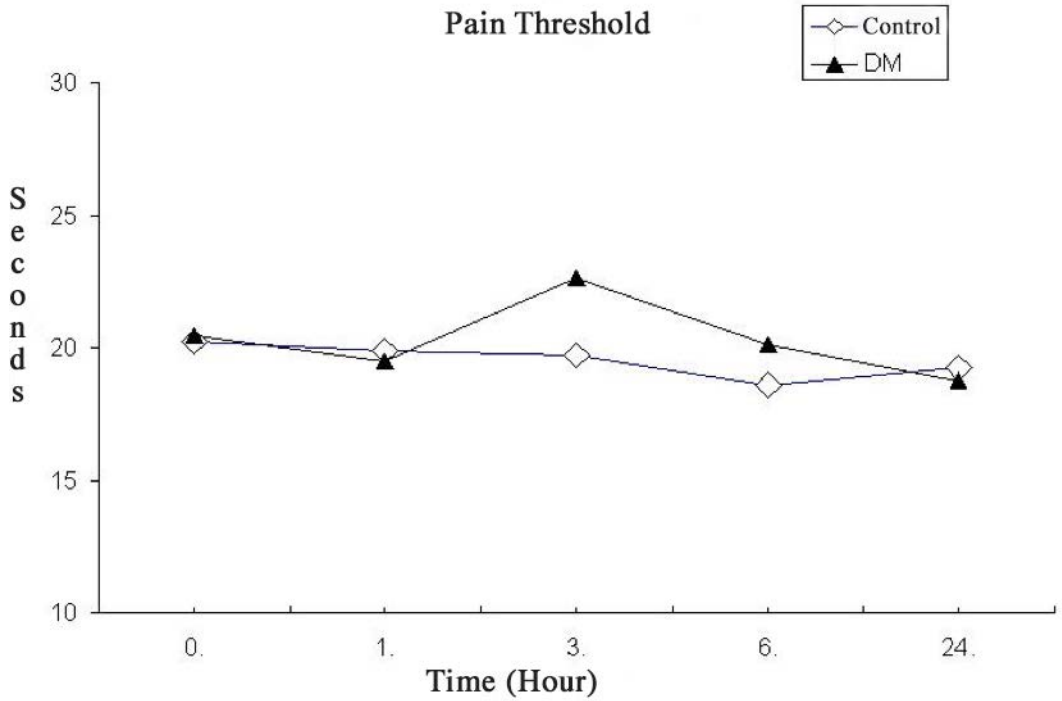


Figure 2. The comparison of mean pain threshold values between the healthy control group and diabetic control group ($p < 0.05$). DM = Diabetes mellitus group

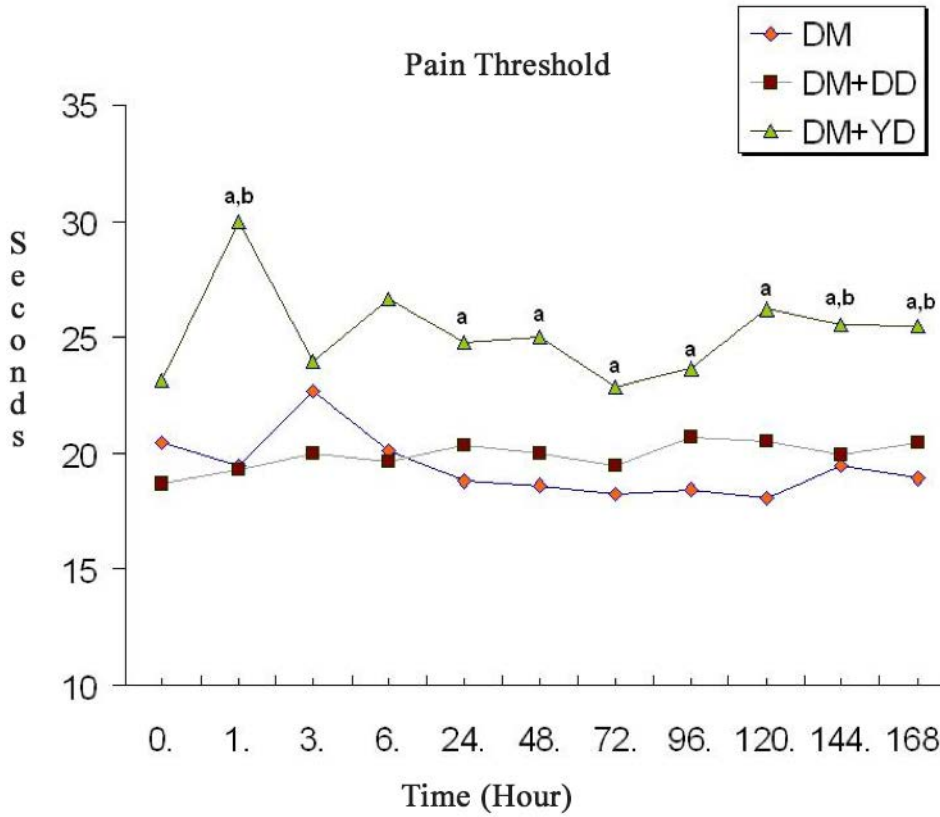


Figure 3. Comparison of the mean pain threshold values between the DM, DM + LD, and DM + HD groups ($p < 0.05$). DM = Diabetes mellitus group, DM+LD =: Diabetes mellitus + low-dose neutrophin-4 group, DM+HD = Diabetes mellitus+ high-dose neutrophin-4 group. The pain threshold values in the low-dose group did not vary across the DM and healthy control groups. aSignificant difference compared to the DM group ($p < 0.05$), bSignificant difference compared to the DM+LD group ($p < 0.05$)

DISCUSSION

Diabetic neuropathy is a chronic complication that seriously affects the quality of life of diabetic people; it occurs in 60-70% of patients with symptoms including spontaneous pain, hyperalgesia, and diminished sensation [11, 12]. Currently, the only effective therapy to prevent or retard the development of diabetic neuropathy and alleviate its symptoms is glucose control and pain management [13]. Recently, some new antiepileptic agents have been reported to be good for neuropathic pain. However, an optimal treatment has not been developed yet.

STZ administration to mice and rats is widely performed to induce diabetic neuropathy [14, 15]. In STZ-induced diabetic mice, hyperalgesia begins to develop at day 8 after STZ injection and lasts for at least four weeks [16]. STZ impairs pain threshold responses in diabetic mice by increasing the action potential of C fibers [17]. In our study, we induced diabetes and hyperalgesia at a dose and within the period stated in the literature using 180 mg/kg STZ.

Studies on pain threshold in diabetic mice have yielded controversial results. Among mechanical hyperalgesia studies, one large series demonstrated a 30-40% decrease in nociceptive threshold values [18]. Increased hypersensitivity responses have been observed in experimental models created with formalin injection [19, 20]. Changes in thermal nociceptive threshold values observed in hyperalgesia considerably varied across studied models [21, 22].

In experimental animal models, among nociceptive test models, the hot plate and tail-flick tests are used to evaluate thermal acute pain responses. The tail-flick test is performed by touching a 16.5-V heat source to a rat's tail. The baseline value is 20 s in the hot plate test and 12 s in the tail-flick test. The mechanical pain test is another nociceptive test performed by applying pressure to a rat's hind paws [23]. The hot plate test is an indirect in vivo method; results are quantitatively evaluated. It has been reported that pain threshold responses help obtain indirect information on diabetic neuropathic pain [18]. In our study, we used the hot plate test.

As the neuroprotective roles of neurotrophic factors against damage to sensory neurons have been revealed, this has necessitated determining whether these agents are effective for treating neuropathic pain. Glial cell line-derived neuropathic factor is one of these agents showing analgesic effects in the treatment of experimental neuropathy by suppressing the afferent ectopic activity [4-7].

Most neurotrophic factors have been discovered because of their effects on specific neural populations in the peripheral nervous system. It has been proved that some of these factors are beneficial in the treatment of diabetic peripheral neuropathy. Most members of the neuropathic gene family (NGF, BDNF, NT-3 and NT-4/5, insulin-like growth factor [IGF]-1, IGF-II, and glial cell line-derived neurotrophic factor) have been extensively studied in animal models of diabetic neuropathy and have shown encouraging results. Recombinant human nerve growth factor was tested in phase II clinical experiments in the treatment of diabetic patients [24].

NT-4 is primarily effective on peripheral sensory neurons as well as many other neurons such as cortical, hippocampal, and basal forebrain cholinergic neurons. NT-4 is synthesized in the form of a 30 kDa precursor protein and is transformed to a 13-kDa mature form [25]. In our study, we used the newly discovered NT-4 belonging to a family of neurotrophic factors that has rarely been studied in the literature.
Studies in diabetic animal models have yielded similar evidence to that obtained from diabetic human subjects with regard to the contribution of neurotrophic factors in the pathogenesis of diabetic peripheral neuropathy. In both in vivo and animal models of neuropathy conducted using NT-4, NGF, NT-3, IGF-1 and IGF-II, it has been demonstrated that these factors improve nerve degeneration [26].

Christianson *et al*. [8] evaluated behavioral responses to different harmful stimuli in the treatment of STZ-induced diabetic mice. The differences in responses to harmful heat (radiant heat), cold (acetone), and harmful mechanical stimuli applied to the hind paws of nondiabetic and diabetic mice were evaluated. NGF and glial cell line-derived neurotrophic factor) were administered intrathecally to three-week-old mice to determine whether the NT therapy normalizes neuropathic deficits. The mice receiving NT therapy were also compared with diabetic mice receiving insulin for three weeks. It was determined that both NGF and insulin therapy improved the mechanical and chromegenic behaviors of mice. Therefore, the sensitivity caused by

mechanical and chemical stimuli was decreased in diabetes-induced mice and the dorsal root ganglion nerves of diabetic mice gave response to NGF or glial cell line-derived neurotrophic factor therapy [8]. In our study, the treatment was not administered to STZ-induced diabetic mice. The animals with a blood glucose level between 200 and 500 mg/dL were included in the study. It was reported that the pain threshold significantly increased particularly in mice receiving high dose NT-4.

Akkina *et al*. [27] administered nonpeptidergic unmyelinated primary afferents rescue therapy of glial cell line-derived neurotrophic factor in STZ-induced diabetic mice. Within a four-week period following diabetes induction, a decrease was detected in isolectin thiamine monophosphate (TMP) activity in lamina II of the lumbar dorsal horn, particularly on distal sciatic afferents in the medial area. It was found that TMP healed spinal deficits in central afferents and that that both glial cell line-derived neurotrophic factor and NGF/NT-4 may repair spinal deficits on nonpeptidergic afferents in STZ-induced diabetic mice receiving glial cell line-derived neurotrophic factor or NT-4/NGF for two weeks. The results demonstrated that the administration of both glial cell line-derived neurotrophic factor and NGF/NT-4 selectively improved diabetes-related deficits in the TMP subpopulation of sensitive diabetics with nonpeptidergic unmyelinated sensory neurons [27].

Apfel *et al*. [28] conducted a study on the effects of neurotrophic factors in peripheral neuropathy and demonstrated that these factors contribute to the pathophysiology and treatment of various types of neuropathy, particularly of diabetic neuropathy; they suggested the efficacy of NT-3 in fibril neuropathy, of NT-4/5 IGF-1, CNTF and BDNF in motor neuron disease, and of NGF in small fibril sensory neuropathy [28].

In a randomized placebo controlled study conducted by Wellmer *et al*. [29], the subcutaneous administration of recombinant BDNF for three months improved the threshold values for cold sensation; this suggests that BDNF has some neuroprotective effects on neurons sensitive to thermal stimuli [29]. Siuciak *et al*. [30] found that NT-3 has an effect on spinal interneurons through a naloxone-sensitive mechanism. NT-3 triggered long-term analgesia in pathways involving serotonergic and opioid mechanisms when it was injected at the midbrain level [30].

As there are a very limited number of studies investigating the role of NT-4 on the development of spinal pain, we cited studies conducted using NT-4 and other members of the NT gene family having effects and structures similar to NT-4 (NGF, BDNF, CNTF, glial cell line-derived neurotrophic factor, NT-3, NT-5) in the discussion section. In our study, we referred to papers using BDNF and NGF along with NT-4 as NGF structurally resembles NT-4 and BDNF shows an effect over tyrosine kinase B receptor as NT-4. Most studies have been conducted using NGF, which was the first neurotrophic factor to be discovered; studies on the recently discovered NT-3and NT 4/5 are still continuing, and we suggest that there is a need for determining the efficacy of these recently discovered neurotrophic factors in experimental and clinical studies using different pain models and different doses.

In line with the literature, the present study found that recombinant human NT-4 at a dose of 3 mg/kg (high dose) significantly increased pain threshold values in the hot plate test, which measures pain threshold values for acute thermal stimuli; however, these effects did not occur at low doses (0.3 mg/kg). The hot plate test was performed with the aim of investigating the effects of neurotrophic factors on painful diabetic neuropathy in STZ-induced diabetic mice and the following are the important findings of the present study: Hyperglycemia was induced to an extent that would lead to diabetic neuropathy. The period of time required to develop diabetic neuropathy was completed. The pain threshold values in the low-dose group were not different than from those in the diabetic control and healthy control groups (Table 2, Figure 2). An increase was observed in the hot plate pain threshold values in the high-dose group compared to that in the healthy control group, diabetic control group, and low dose group; this difference reached statistical significance ($p < 0.05$, Table 2, Figure 3).

CONCLUSION

In conclusion, neurotrophic factors (neurotrophin-4) have been shown to be effective on painful diabetic

neuropathy in streptozocin-induced diabetic rats. However, there is a need for larger-scale and longer-term studies for clinical use.

Conflict of interest

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

Funding Statement

This work was partially supported by grants from Fırat University School of Medicine.

REFERENCES

[1] Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum. Indian J Endocrinol Metab 2016;20:546-51.
[2] Davon A. M, Chronic pain. A primary Care Guide to Practical Management, second ed., Human Pres: Totawa, NJ. 2005;114-5.
[3] Price RD, Milne SA, Sharkey J, Matsuoka N, Advances in small molecules promoting neurotrophic function. Pharmacol Ther 2007;115:292-306.
[4] Bennett DL. Neurotrophic factors important regulators of nociceptive function. Neuroscientist 2001;7:13-7.
[5] Skaper SD. The neurotrophin family of neurotrophic factors: an overview. Methods Mol Biol 2012;846:1-12.
[6] Kerr BJ, Bradbury EJ, Bennett DL, Trivedi PM, Dassan P, French J, et al. Brain-derived neurotrophic factor modulates nociceptive sensory inputs and NMDA-evoked responses in the rat spinal cord. J Neurosci 1999;19:5138-48.
[7] Chen SQ, Cai Q, Shen YY, Cai XY, Lei HY. Combined use of NGF/BDNF/bFGF promotes proliferation and differentiation of neural stem cells in vitro. Int J Dev Neurosci 2014;38:74-8.
[8] Christianson JA, Ryals JM, McCarson KE, Wright DE. Beneficial actions of neurotrophin therapy on diabetes-induced hypoalgesia in mice. J Pain 2003;4:493-504.
[9] Christianson JA, Ryals JM, Johnson MS , Dobrowsky RT, Wright DE. Neurotrophic modulation of myelinated cutaneous innervation and mechanical sensory loss in diabetic mice. Neuroscience 2007;145:303-13.
[10] Handwerker HO, Kobal G. Psychophysiology of experimentally induced pain. Physiol Rev 1993;73:639-71.
[11] Deli G, Bosecyak E, Pusch G, Komoly S, Feher G. Diabetic neuropathies: diagnosis and management. Neuroendocrinology 2013;98:267-80.
[12] Vinik AI, Park TS, Stansberry K B, Pittenger GL. Diabetic neuropathies. Diabetologia 2000;43;957-73.
[13] Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol 2002;11:521-34.
[14] Rees DA, Alcolado JC. Animal models of diabetes mellitus. Diabet Med 2005;22:359-70.
[15] Malik RA. Current and future strategies for the management of diabetic neuropathy. Treat Endocrinol 2003;2:389-400.
[16] Ahlgren SC, Levine JD. Mechanical hyperlgesia in streptozocin diabetic rat is not sympathetically maintained. Brain Res 1993;616:171-5.
[17] Ahlgren SC, White DM, Levine JD. Increased responsiveness of sensory neurons in the saphenous nerve of the streptozotocin-diabetic rat. J Neurophysiol 1992;68:2077-85.
[18] Piercy V, Banner SE, Bhattacharyya A, Parsons AA, Sanger GJ, Smith SA, et al. Thermal but not mechanical, nociceptive behavior is altered in the Zucker Diabetic Fatty rat and is independent of glycemic status. J Diabetes Complications 1999;13:163-9.
[19] Zhuang HX, Secyder CK, Pu SF, Ishii DN. Insulin-like growth factors reverse or arrest diabetic neuropathy: effects on hyperalgesia and impaired nerve regeneration in rats. Exp Neurol 1996;140:198-205.
[20] Calcutt NA, Jorge MC, Yaksh TL, Chaplan SR. Tactile allodynia and formalin hyperalgesia in streptozotocin-diabetic rats: effects of insulin, aldose reductase inhibition and lidocaine. Pain 1996;68 293-9.
[21] Fox A, Eastwood C, Gentry C, Manning D, Urban L. Critical evaluation of the streptozotocin model in the rat. Pain 1999;81:307-16.
[22] Raz I, Hasdai D, Seltzer M, Melmed RN. Effect of hyperglycemia on pain perception and on efficacy of morphine analgesia in rats. Diabetes 1988;37:1253-9.
[23] Klitgaard H, Matagne A, Gobert J, Wülfert E. Evidence for a unique profile of levetiracetam in rodent models of seizures and epilepsy. Eur J Pharmacol 1998;353:191-206.
[24] Apfel SC. Neurotrophic factors in the therapy of diabetic neuropathy. Am J Med 2000;107:34-42.
[25] Schuman EM. Neurotropin regulation of synaptic transmission. Curr Opin Neurobiol 1999;9:105-9.
[26] Apfel SC. Neurotrophic factors and diabetic peripheral neuropathy. Eur Neurol 1999;41:27-34.
[27] Akkina SK, Patterson CL, Wright DE. GDNF rescues nonpeptidergic unmyelinated primary afferents in streptozotocin-treated diabetic mice. Exp Neurol 2001;167:173-82.
[28] Apfel SC, Kessler JA. Neurotrophic factors in the therapy of peripheral neuropathy, Baillieres Clin Neurol 1995;4:593-606.
[29] Wellmer A, Misra VP, Sharief MK, Kopelman PG, Anand P. A double-blind placebo-controlled clinical trial of recombinant human brain-derived neurotrophic factor (rhBDNF) in diabetic polyneuropathy. J Peripher Nerv Syst 2001;6:204-10.
[30] Siuciak JA, Wong V, Pearsall D, Wiegand SJ, Lindsay RM. BDNF produces analgesia in the formalin test and modifies neuropeptide levels in rat brain and spinal cord areas associated with nociception. Eur J Neurosci 1995;7663-70.

Cardioprotective effect of vitamin D and melatonin on doxorubicin-induced cardiotoxicity in rat model: an electrocardiographic, scintigraphic and biochemical study

Serdar Savaş Gül[1], Hatice Aygün[2]

[1]*Department of Nuclear Medicine, Gaziosmanpaşa University School of Medicine, Tokat, Turkey*
[2]*Department of Physiology, Gaziosmanpaşa University School of Medicine, Tokat, Turkey*

DOI: 10.18621/eurj.410029

ABSTRACT

Objectives: Doxorubicin (DOX) is an antineoplastic drug that is widely used in chemotherapy but its cardiotoxicity is the most important side effect that limits the clinical use of this drug. We investigated DOX treatment and the effects of vitamin D and melatonin on heart by electrocardiography, scintigraphic and biochemical methods.

Methods: In this study, forty-nine adult male Wistar albino rats (220 ± 15 g) were randomly divided into seven groups (n = 7 each), namely control (CON, n = 7), doxorubicin (DOX, n = 7), melatonin (MEL, n = 7), vitamin D (Vit D, n = 7), doxorubicin plus melatonin (DOX+MEL, n = 7), doxorubicin plus vitamin D (DOX+Vit D, n = 7), and doxorubicin plus melatonin and vitamin D (DOX+MEL+Vit D, n = 7) groups. Cardiotoxicity was induced by intraperitoneal injection (i.p.) of DOX (18 mg/kg, i.p.) on the 15th, 16th and 17th days. Rats receiving vitamin D and melatonin treatment in the DOX-induced cardiotoxicity group received vitamin D (60,000 IU/kg, i.p.) were administered in a single dose and melatonin (40 mg/kg/day, i.p.) for 17 days and were injected with (18 mg/kg, i.p.) on doxorubicin 15th, 16th, and 17th days. On the 18th day electrocardiography (ECG), ^{99m}Technetium pyrophosphate scintigraphy and biochemical parameters were assessed.

Results: DOX caused changes in the ECG pattern, a significant decrease in heartbeat ($p < 0.01$), P wave ($p < 0.001$) and QRS complex durations ($p < 0.001$), R wave amplitude ($p < 0.001$); elevation in ST-segment ($p < 0.001$) and decrease in QT interval ($p < 0,001$), and R-R interval durations ($p < 0.001$); increase in the serum levels of cardiac injury markers (CK, BUN, cardiac troponin T), ($p < 0.01$), and increased ^{99m}Technetium pyrophosphate uptake ($p < 0.001$) as compared to the CON group. MEL, Vit D and MEL+Vit D administration showed a same protective effect against DOX-induced altered ECG pattern. Pre-treatment with MEL, Vit D and MEL+Vit D significantly protected the heart from the toxic effect of DOX, by decreasing the levels of of cardiac injury markers (CK, BUN, cardiac troponin T) ($p < 0.001$) and decreased the elevated level of ^{99m}Technetium pyrophosphate uptake ($p < 0.001$).

Conclusion: Vitamin D and melatonin treatment prevented all the parameters of DOX-induced cardiotoxicity in rats.

Keywords: doxorubicin-induced cardiotoxicty, vitamin D, melatonin, ^{99m}Technetium pyrophosphate

Received: March 27, 2018; Accepted: July 23, 2018; Published Online: September 12, 2018

Address for correspondence: *Serdar Savaş Gül, MD., Gaziosmanpaşa University School of Medicine, Department of Nuclear Medicine, Tokat, Turkey*
E-mail: opnukleertip@gmail.com

e-ISSN: 2149-3189

Doxorubicin (DOX) is an anthracycline derivative antibiotic commonly used for the treatment of leukemias, malignant lymphoma and various solid tumors. However, its clinical use is limited because of dose-dependent cardiotoxicity [1]. DOX causes various toxic effects, the most common of which is cardiotoxicity that can be divided into acute effects (electrocardiogram changes), late effect of DOX administration is cardiomyopathy and congestive heart failure [2].

The pathogenesis of DOX-induced cardiotoxicity is acted by different mechanisms; thought that oxidative stres induced cell injury, lipid peroxidation, mitochondrial damage, inflammation, and apoptosis play a role. However, the most popular hypothesis is that it should be noted that DOX increased free radical production and oxidative stress, play a major role in DOX-induced cardiotoxicity [3]. Oxidative stress is characterized as an imbalance between antioxidant defense systems and reactive oxygen species. DOX-induced oxidative stress has been shown to be inhibited by the administration of certain antioxidants to experimental animals [2, 4, 5].

Melatonin as an important natural antioxidant, may reduce DOX-induced oxidative stress [6]. The protective effect of melatonin on cardiotoxicity induced by DOX has been demonstrated [2]. Ahmed *et al*. [7] demonstrated that treatment with melatonin could reduce DOX-induced cardiotoxicity by reduced oxidative stress and increased activity of the antioxidative enzymes.

Vitamin D (Vit D) plays regulatory activity in body function including the cardiovascular system. It is known that the pleiotropic effects of Vit D regulatory activation are responsible for the distribution of Vit D regulatory activity every where in the human body nervous system, intestine, kidney, bone, parathyroid gland, cardiovascular systemand myocardium [8-10]. A lot of study has shown that Vit D deficiency is significantly associated with cardiovascular disease [11, 12]. Vit D deficiency leads to increase in serum parathyroid hormone (PTH) [13]. Increased PTH levels were reported to be associated with left ventricular hypertrophy and increased risk of heart failure [14]. In addition, treatment with Vit D decreased blood pressure in patients with hypertension and modified the heart failure, decrease in cardiovascular mortality [15-17].

Although many previous studies have examined the role of Vit D in cardiovascular disease, accorfing to our knowledge none have studied with examined the effects of Vit D on DOX-induced cardiotoxicity. This study was conducted to investigate the potential protective effects of melatonin plus Vit D on DOX-induced cardiotoxicity manifested by changes in the ECG pattern, changes in biochemical parameters such as serum creatine kinase (CK), blood urea nitrogen (BUN), and cardiac troponin T (cTnT) and changes in ^{99m}Technetium pyrophosphate (^{99m}Tc PYP) scintigraphy. ^{99m}Tc PYP radiopharmaceuticals are involved in the necrotic tissue by binding to the calcium complex. It is routinely used in necrosis imaging in the nuclear medicine department. Additionally, our recent study has shown that combined melatonin plus Vit D treatment was superior to either one alone for protecting DOX-induced cardiotoxicity.

METHODS

Study Design

This is a randomized controlled experimental study.

Animal Selection

Forty-nine adult male Wistar albino rats (220 ± 15 g) were kept seven per cage, under standardized conditions of equal periods of light and dark in a room with lighting control (12-hour light/dark cycle, 24 ± 2ºC) and had free access to food and water. All the experimental procedures were approved by the Animal Ethics Committee of Gaziosmanpaşa University.

Experimental Procedures

The animals were randomly divided into 7 groups of 7 rats in each:

Group 1: Rats received standard laboratory diet and drinking water ad libitum, and received normal saline 5 ml/kg body weight intraperitoneal (i.p.) and served as normal control (CON) groups.

Group 2: Rats were injected with a DOX at a cumulative dose of 18 mg/kg, i.p. at an interval of 24 h on the 15th, 16th and 17th days and served as the doxorubicin (DOX) group.

Group 3: Rats were injected melatoninat a dose of 40 mg/kg/day, i.p., (sigma, soluble in pure water) for 17

days and served as the melatonin (MEL) group.

Group 4: The first day of the experiment, rats were administered in a single dose of vitamin D (60.000 IU mg/kg, i.p.) and served as the vitamin D (Vit D) group.
Group 5: Rats received melatonin treatment (40 mg/kg/day, i.p., sigma, soluble in pure water) for 17 days and were injected with doxorubicin (cumulative dose: 18 mg/kg, i.p.) on the 15th, 16th and 17th days and and served as the doxorubicin plus melatonin (DOX+MEL) group.
Group 6: The first day of the experiment, rats received a single dose of Vit D (60.000 IU mg/kg, i.p.) and were injected with doxorubicin (cumulative dose: 18 mg/kg, i.p.) on the 15th, 16th and 17th days and served as the doxorubicin plus vitamin D (DOX+Vit D) group.
Group 7: Rats received melatonin treatment (40 mg/kg/day, i.p., sigma, soluble in pure water) for 17 days and the first day of the experiment, rats received a single dose of vitamin D (60.000 IU mg/kg/i.p) and were injected with DOX (cumulative dose: 18 mg/kg, i.p.) on the 15th, 16th and 17th days and served as the doxorubicin plus melatonin and vitamin D (DOX+MEL+Vit D) group.

Electrocardiography

Anesthesia was assessed clinically by pedal reflex. Then, needle electrodes were inserted under the skin of the rats in lead II position. Electrocardiography (ECG) recordings were taken for 1 minutes using the acknowledge software (version 3.8) and the MP-150 multi-channel physiological analysis system (BioPac Systems Inc., USA). Changes in ECG pattern (amplitude of ST segment, R-amplitude, duration of P wave, QRS complex, QT interval, and R-R interval) were considered.

Biochemical Assays

At the end of the experimental period, all the rats were anesthetized under light anesthesia and blood was collected from the heart into Vacutainer serum-separated tubes. After 30 min, the tubes were centrifuged at 1500 × g for 10 min. Then, the clear serum was used for all following biochemical assays. CK, BUN, cTnT were estimated by kinetic determination using the commercial kits of Bechman by Bechman Coulter LX-2000 (Brea, CA, USA).

Scintigraphic Images

When experimental model 18th days, 1 mCi ^{99m}Tc PYP radiopharmaceutical was administered through i.p. in anesthetized rats. One hour after ^{99m}Tc PYP radiopharmaceutical administration, static imaging with dual head gamma camera (E-CAM, Siemens, Germany) was performed in anterior and posterior positions with 2.55 zoom factor. The radionuclide uptake heart area was measured by drawing equal rectangular regions of interest (ROI) and ^{99m}Tc PYP uptake was calculated by semi-quantitative method to the all study groups.

Statistical Analysis

Statistical analyses on each parameter were performed using SPSS 20.0 program. Comparison of the groups was made by one-way analysis of variance (ANOVA), followed by the post hoc Tukey test. Pearson correlation analysis revealed a significant correlation between the ^{99m}Tc PYP uptake ratio and serum levels of cardiac injury markers. The results are expressed as the means ± standard error of mean (SEM). For all statistical tests, $p < 0.05$ was considered statistically significant.

Table 1. Electrocardiographic parameters of the groups

Groups	Heart beat (bpm)	P wave duration (s)	QRS complex duration (s)	QT interval duration (s)	R-R interval (s)	R wave amplitude (mV)	ST segment amplitude (mV)
CON	280 ± 4	0.034 ± 0.01	0.060 ± 0.0	0.064 ± 0.01	0.145 ± 0.01	0.91 ± 0.2	0.054 ± 0.05
DOX	220 ± 3[c]	0.022 ± 0.02[c]	0.035 ± 0.0[c]	0.086 ± 0.02[c]	0.242 ± 0.01[c]	0.52 ± 0.2c	0.174 ± 0.06[c]
MEL	279 ± 4	0.033 ± 0.02	0.057 ± 0.01	0.065 ± 0.02	0.154 ± 0.03	0.93 ± 0.2	0.055 ± 0.01
ViTD	274 ± 2	0.035 ± 0.01	0.058 ± 0.01	0.064 ± 0.02	0.140 ± 0.01	0.92 ± 0.2	0.050 ± 0.02
DOX+MEL	251 ± 4[b, e]	0.031 ± 0.01[f]	0.057 ± 0.02[f]	0.069 ± 0.03[f]	0.158 ± 0.02[f]	0.69 ± 0.2[c, f]	0.059 ± 0.01[f]
DOX+ViTD	253 ± 5[a, f]	0.035 ± 0.01[f]	0.061 ± 0.01[f]	0.071 ± 0.01[e]	0.166 ± 0.01[f]	0.73 ± 0.2[c, f]	0.063 ± 0.01[f]
DOX+VitD+MEL	250 ± 8[b, e]	0.033 ± 0.0[f]	0.060 ± 0.01[f]	0.068 ± 0.01[f]	0.142 ± 0.01[f]	0.70 ± 0.2[c, f]	0.057 ± 0.06[f]

CON = control, DOX = doxorubicin, MEL = melatonin, Vit D = vitamin D, DOX+MEL = doxorubicin plus melatonin, DOX+Vit D = doxorubicin plus vitamin D, DOX+MEL+Vit D = doxorubicin plus melatonin and vitamin D
[a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$ all groups as compared to CON groups
[d]$p < 0.05$, [e]$p < 0.01$, [f]$p < 0.001$ DOX+MEL, DOX+ViT D, DOX+Vit D+MELgroups as compared to DOX groups

RESULTS

Electrocardiography

The study show significant alteration of electrocardiographic patterns (duration of both P wave and QRS complex, QT interval, R-R interval, and heart rate, amplitude of ST-segment, R-wave amplitude) in DOX-administered rats as compared to normal control rats. CON group showed a normal pattern on ECG, whereas the DOX-treated group showed an decreased heart beat ($p < 0.01$), P wave ($p < 0.001$) and QRS complex durations ($p < 0.001$), R wave amplitude ($p < 0.001$); elevation in ST-segment ($p < 0.001$) and decrease in QT interval ($p < 0.001$), and R-R interval durations ($p < 0.001$) as compared to the CON group.

MEL pre-co-treatment in the DOX-treated group showed a decreased heart beat ($p < 0.01$) and R wave amplitude ($p < 0.001$), but did not show significant changes the other ECG parameters compared with the CON group. MEL pre-co-treatment in the DOX-treated group showed a icreased heart beat ($p < 0.01$), P wave ($p < 0.001$), QRS complex durations ($p < 0.001$) and R wave amplitude ($p < 0.001$), decreased QT interval ($p < 0.001$), and R-R interval durations (p < 0.001), ST-segment-amplitude ($p < 0.001$) was significant when compared to the DOX alone-treated group.

Vit D pre-co-treatment in the DOX-treated group showed a decreased heart beat ($p < 0.05$) and R wave amplitude ($p < 0.001$), but did not show significant changes the other ECG parameters compared with the

Table 2. The statistical analysis of the cardiac marker enzyme levels

Groups	BUN	CK	cTnT
CON	17.11 ± 0.59	0.48 ± 0.1	3499 ± 244
DOX	183.77 ± 2.99c	3.87 ± 0.13[c]	10306 ± 366c
MEL	16.31 ± 0.46	0.41 ± 0.01	2175 ± 34
ViTD	22.5 ± 0.98	0.40 ± 0.01	2376 ± 68
DOX+MEL	84.75 ± 14.41[c, f]	1.64 ± 0.31[c, f]	5673 ± 689[c, f]
DOX+ViTD	126.56 ± 2.25[c, f]	2.18 ± 0.41[c, f]	7336 ± 641[c, f]
DOX+VitD+MEL	86.44 ± 18.84[c, f]	2.11 ± 0.45[c, f]	6089 ± 681[c, f]

CON = control, DOX = doxorubicin, MEL = melatonin, Vit D = vitamin D, DOX+MEL = doxorubicin plus melatonin, DOX+Vit D = doxorubicin plus vitamin D, DOX+MEL+Vit D = doxorubicin plus melatonin and vitamin D, BUN = blood urea nitrogen, CK = creatine kinase, cTnT = cardiac troponin T
[a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$ all groups as compared to CON groups
[d]$p < 0.05$, [e]$p < 0.01$, [f]$p < 0.001$ DOX+MEL, DOX+ViT D, DOX+Vit D+MELgroups as compared to DOX groups

Table 3. The statistical analysis of the scintigraphic data for the groups

Groups	Tc-99m PYP Uptake (cpm)
CON	52140 ± 559
DOX	279266 ± 684[c]
MEL	53946 ± 987
ViTD	54646 ± 660
DOX+MEL	185793 ± 7073[c, f]
DOX+ViTD	212600 ± 7550[c, f]
DOX+VitD+MEL	150431 ± 13843[c, f]

CON = control, DOX = doxorubicin, MEL = melatonin, Vit D = vitamin D, DOX+MEL = doxorubicin plus melatonin, DOX+Vit D = doxorubicin plus vitamin D, DOX+MEL+Vit D = doxorubicin plus melatonin and vitamin D
[a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$ all groups as compared to CON groups
[d]$p < 0.05$, [e]$p < 0.01$, [f]$p < 0.001$ DOX+MEL, DOX+ViT D, DOX+Vit D+MELgroups as compared to DOX groups

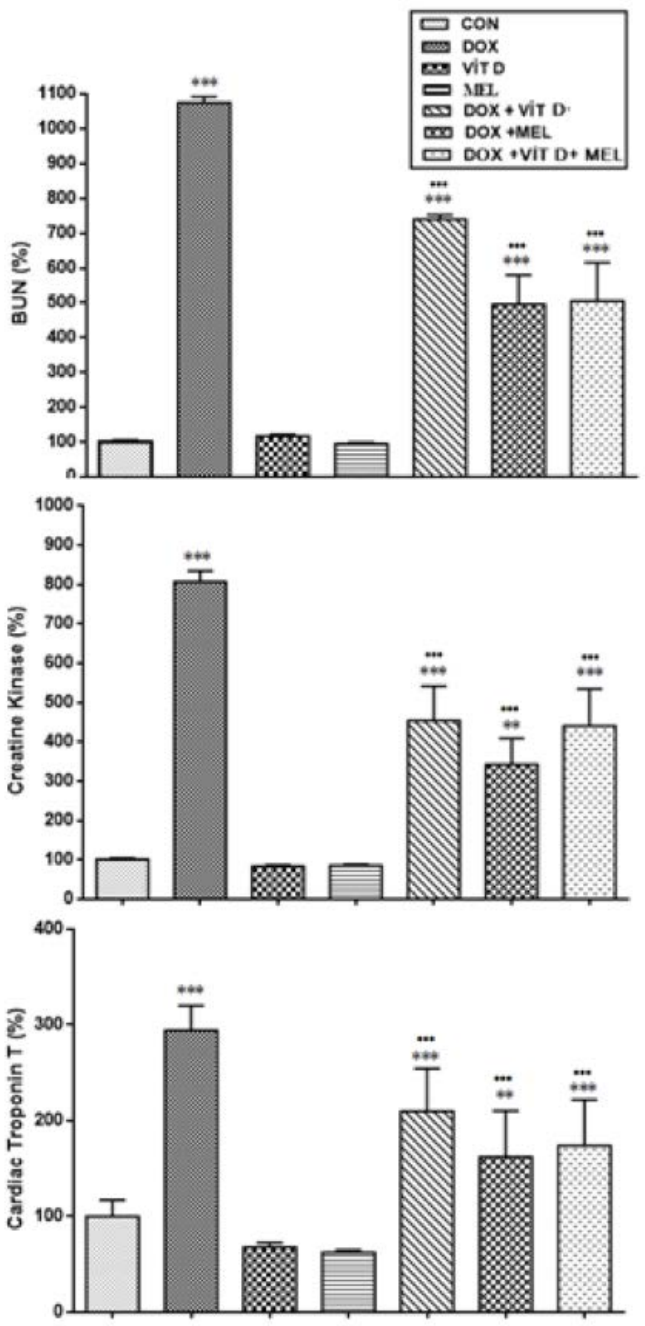


Figure 1. The effect of control (CON), doxorubicin (DOX), melatonin (MEL), vitamin D (Vit D), doxorubicin plus melatonin (DOX+MEL), doxorubicin plus vitamin D (DOX+Vit D), and doxorubicin plus melatonin and vitamin D (DOX+MEL+Vit D) groups pre-treatment on the effect of cardiac marker enzymes, blood urea nitrogen (BUN), creatine kinase and cardiac troponin T. The DOX, DOX+MEL, DOX+ViT D and DOX+Vit D+MEL groups significantly increased the BUN, creatine kinase, cardiac troponin compared to control group (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). Pre-treatment groups of DOX+MEL,DOX+ViT D and DOX+Vit D+MEL significantly decreased the BUN, creatine kinase, cardiac troponin compared to DOX group ($p < 0.05$, ($p < 0.01$), ($p < 0.001$).

control group. Vit D pre-co-treatment in the DOX-treated group showed a icreased heart beat ($p < 0.01$), P wave ($p < 0.001$), QRS complex durations ($p < 0.001$) and R wave amplitude ($p < 0.001$), decreased QT interval ($p < 0.01$), and R-R interval durations ($p < 0.001$), ST-segment-amplitude ($p < 0.001$) was significant when compared to the DOX alone-treated group.

MEL+Vit D+DOX pre-co-treatment in the DOX-treated group showed a decreased heart beat ($p < 0.01$) and R wave amplitude ($p < 0.001$), but did not show significant changes the other ECG parameters compared with the CON group. MEL+Vit D+DOX pre-co-treatment in the DOX-treated group showed an increased heart beat ($p < 0.01$), P wave ($p < 0.001$), QRS complex durations ($p < 0.001$) and R wave amplitude ($p < 0.001$), decreased QT interval ($p < 0.01$) and R-R interval durations ($p < 0.001$), ST-segment-amplitude ($p < 0.001$) was significant when compared to the DOX alone-treated group (Table 1).

Biochemical Assays

DOX-treated group showed an increased BUN ($p < 0.001$), CK ($p < 0.001$, cTnT ($p < 0.001$) as compared to the CON group. MEL, Vit D, MEL+Vit D+DOX pre-co-treatment in the DOX-treated groups showed an increased BUN ($p < 0.001$), CK ($p < 0.001$, cTnT ($p < 0.001$) as compared to the CON group. MEL, Vit D, MEL+Vit D+DOX pre-co-treatment in the DOX-treated groups showed an decreased BUN ($p < 0.001$), CK ($p < 0.001$, cTnT ($p < 0.001$) were significant when compared to the DOX alone-treated group (Figure 1, Table 2).

Scintigraphic Images

^{99m}Tc PYP scintigraphy images of the all study groups are shoen in Figure 2. DOX-treated group showed an increased ^{99m}Tc PYP uptakeas compared to the CON group. MEL, Vit D, and DOX+MEL+Vit D pre-co-treatment in the DOX-treated groups showed an increased ^{99m}Tc PYP radiopharmaceutical uptake ($p < 0.001$) as compared to the CON group. MEL, Vit D, and DOX+MEL+Vit D pre-co-treatment in the DOX-treated groups showed an decreased ^{99m}Tc PYP uptake ($p < 0.001$) were significant when compared to the DOX alone-treated group (Figure 3, Table 3).

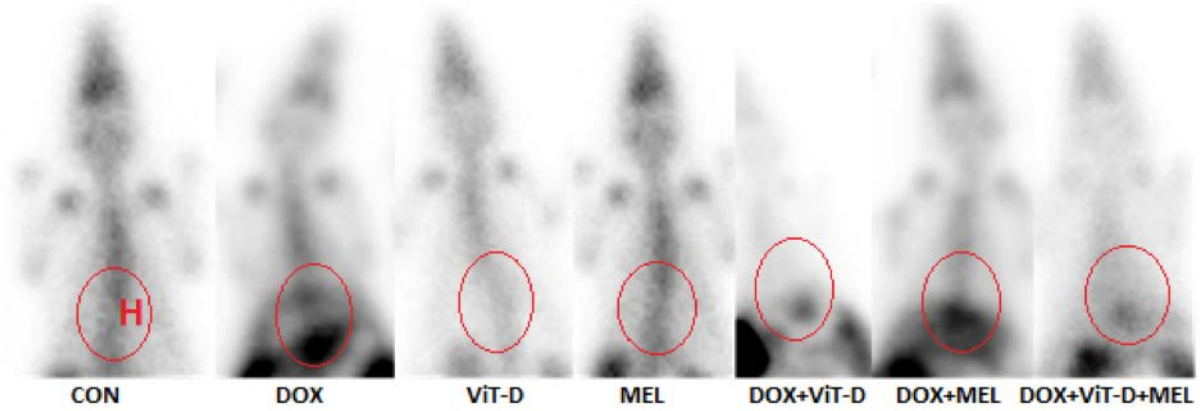


Figure 2. It is present that the ^{99m}Tc PYP scintigraphic images of the all control (CON), doxorubicin (DOX), melatonin (MEL), vitamin D (Vit D), doxorubicin plus melatonin (DOX+MEL), doxorubicin plus vitamin D (DOX+Vit D), and doxorubicin plus melatonin and vitamin D (DOX+MEL+Vit D) groups. The radiopharmaceutical uptake was calculated for each rat by drawing equal rectangular ROI at heart area (H).

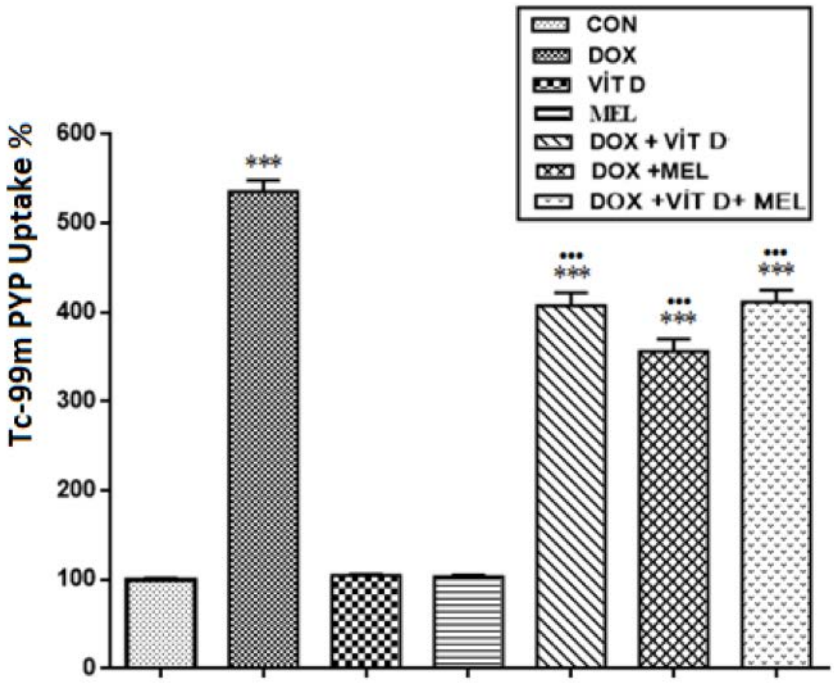


Figure 3. The effect of control (CON), doxorubicin (DOX), melatonin (MEL), vitamin D (Vit D), doxorubicin plus melatonin (DOX+MEL), doxorubicin plus vitamin D (DOX+Vit D), and doxorubicin plus melatonin and vitamin D (DOX+MEL+Vit D) groups on the effect of ^{99m}Tc PYP radiopharmaceutical uptake. The DOX, DOX+MEL, DOX+ViT D andDOX+Vit D+MEL groups significantly increased the the ^{99m}Tc PYP radiopharmaceutical uptake compared to control group (*$p < 0.05$ **$p < 0.01$, ***$p < 0.001$). Pre-treatment groups of DOX+MEL,DOX+ViT D and DOX+Vit D+MEL significantly decreased the the ^{99m}Tc PYP radiopharmaceutical uptake compared to DOX group ($p < 0.05$, ($p < 0.01$), ($p < 0.001$).

DISCUSSION

Previous studies demostrated that DOX treatment-induced ECG abnormalities, which consist of non-specific P wave changes, sinus tachycardia, QRS complex, RR interval and R amplitude are frequently transient and cannot be said to be specific to anthracyclines. Prolonged QTc interval and elevation ST segment amplitude have been reported to be relatively characteristic ECG findings in receiving anthracyclines. The consecutive loss of cellular membrane damage due to oxidative stress might be

characterized by ST elevation and prolonged QTc interval [18-21].

Our results confirmed that a cumulative dose of DOX (18 mg/kg) induces cardiotoxicity in rats as evidenced by ECG changes, ^{99m}Tc PYP scintigraphic images and increased levels of cardiac biomarker enzymes. In the present study MEL and Vit D treated rats demonstrates several major findings regarding the effects of DOX-induced cardiotoxicity. First, we found that all of the ECG parameters changed significantly in the DOX-treated group as compared to the CON group, but MEL and Vit D restored the changes in ECG parameters in the DOX group to the pattern of the CON group. Second, cardiac marker enzymes (BUN, CK, cTnT) of the DOX-treated group increased significantly when compared with the CON group, whereas MEL and Vit D treatment could be attributed in part to the suppression of DOX-induced elevation in the levels of these cardiac marker enzymes. Third, ^{99m}Tc PYP scintigraphic images of the DOX-treated group was significantly changed as compared to the CON group, but MEL and Vit D treatment restored the changes in ^{99m}Tc PYP scintigraphic images of the DOX group to the compared of the CON group.

In this study, ECG after DOX administration showed significant changes. DOX treatment induces a decrease P wave, QRS complex, in the amplitude of R wave, an increase in QT interval, R-R interval and ST segment which may link to its degenerative effect on cell membrane [22, 23]. Treatment with MEL, Vit D and combination MEL and Vit D groups caused increased in P-wave, QRS complex, R amplitude and decreased QT interval, R-R interval, ST segment was also near to normal. These changes in the electrocardiogram pattern induced by MEL and Vitamin D may be due to its membrane stabilizing action.

One of the major toxic effects of DOX is inducing lipid peroxidation. Its activation leads to acute membrane damage and releasing of cellular enzymes which decreased supply of oxygen to the myocardial cell leading to hypoxia [24-26]. The degree of DOX-induced cardiotoxicity can be estimated in serum and used as biomarkers to check the damage caused to the myocardium [27]. Several investigators reported that DOX causes elevation in the levels of CK-MB, BUN and cTnT serum biomarker activities after DOX administration [28, 29]. In comparison to the CON group, the DOX-treated group showed significant elevation in the levels of cardiac marker enzymes in the serum. Treatment with MEL and Vit D caused a significant decrease in the levels of troponin T, BUN and CK-MB enzymes. This effect shows that MEL and Vit D can be prevent damage to the rat myocardium and stabilized the membrane.

As phosphorous compounds have high affinity for hydroxyapatite crystals, ^{99m}Tc PYP scintigraphy has been widely used in the detection of bone tumors and metabolic bone diseases. ^{99m}Tc PYP radiopharmaceutical accumulates predominantly as apatite-like crystals in mitochondria and cytoplasm of infarcted myocardial cells. Therefore, it has been considered beneficial in the diagnosis of acute phase myocardial infarction and quantification of the infarct size in the clinical setting [30-33]. Previous studies have also suggested that the degree of radiopharmaceutical accumulation such as ^{99m}Tc-labeled phosphonates, and ^{99m}Tc PYP is a good index of the severity of tissue damage [34-38]. In the present study, we observed increased ^{99m}Tc PYP radiopharmaceutical uptake on heart area in the DOX-induced cardiotoxicity rat model.

Limitations

This study was conducted to investigate the potential protective effects of melatonin plus Vit D on DOX-induced cardiotoxicity manifested by changes in the ECG pattern, changes in biochemical parameters and changes in ^{99m}Tc PYP scintigraphy. Histopathological examination was not performed in this study.

CONCLUSION

The results of the present study revealed that subchronic and systemic administration of Vit D doses showed a considerable cardioprotective effect similar to MEL on DOX-induced cardiotoxicityin rat model. MEL is an antioxidant agent that prevents apoptosis in in experimental toxic animal models. Cardiotoxicity induced by DOX ECG findings are very variable and chemical biomarkers alone are not sufficient, therefore additional diagnostic methods are needed. As a result of the study, it was thought that MEL and Vit D administration may be effective in preventing DOX-

induced cardiotoxicity and that ^{99m}Tc PYP scintigraphy could be used in the follow-up of chemotherapy patients using DOX.

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] Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 1973;32:302-14.
[2] Bilginoğlu A, Aydın D, Ozsoy S, Aygün H. Protective effect of melatonin on adriamycin-induced cardiotoxicity in rats. Turk Kardiyol Dern Ars 2014;42:265-73.
[3] Swamy AH, Wangikar U, Koti BC, Thippeswamy AH, Ronad PM, Manjula DV. Cardioprotective effect of ascorbic acid on doxorubicin-induced myocardial toxicity in rats. Indian J Pharmacol 2011;43:507-11.
[4] Anjos Ferreira AL, Russell RM, Rocha N, Placido Ladeira MS, Favero Salvadori DM, Oliveira Nascimento MC, et al. Effect of lycopene on doxorubicin-induced cardiotoxicity: an echocardiographic, histological and morphometrical assessment. Basic Clin Pharmacol Toxicol 2007;101:16-24.
[5] Xin Y, Zhang S, Gu L, Liu S, Gao H, You Z, et al. Electrocardiographic and biochemical evidence for the cardioprotective effect of antioxidants in acute doxorubicin-induced cardiotoxicity in the beagle dogs. Biol Pharm Bull 2011;34:1523-6.
[6] Othman AI, El-Missiry MA, Amer MA, Arafa M. Melatonin controls oxidative stress and modulates iron, ferritin, and transferrin levels in adriamycin treated rats. Life Sci 2008;83:563-8.
[7] Ahmed HH, Mannaa F, Elmegeed GA, Doss SH. Cardioprotective activity of melatonin and its novel synthesized derivates on doxorubicin-induced cardiotoxicity. Bioorg Med Chem 2005;13:1847-57.
[8] Prufer K, Veenstra TD, Jirikowski GF, Kumar R. Distribution of 1,25- dihydroxyvitamin D3 receptor immunoreactivity in the rat brain and spinal cord. J Chem Immunol 1999;16:135-45.
[9] Langub MC, Herman JP, Malluche HH, Koszewski NJ. Evidence of functional vitamin D receptors in rat hippocampus. Neuroscience 2001;104:49-56.
[10] Walbert T, Jirikowski GF, Prufer K. Distribution of 1,25-dihydroxyvitamin D3 receptor immunoreactivity in the limbic system. Horm Metab Res 2001;33:525-31.
[11] Kunadian V, Ford GA, Bawamia B, Qiu W, Manson JE. Vitamin D deficiency and coronary artery disease: a review of the evidence. Am Heart J 2014;167:283-91.
[12] Majumdar V, Prabhakar P, Kulkarni GB, Christopher R. Vitamin D status, hypertension and ischemic stroke: a clinical perspective. J Hum Hypertens 2015;29: 669-74.
[13] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. J Clin Endocrinol Metab 2012;97:1153-8.
[14] Bansal N, Zelnick L, Robinson-Cohen C, Hoofnagle AN, Ix JH, Lima JA, et al. Serum parathyroid hormone and 25-hydroxyvitamin D concentrations and risk of incident heart failure: the Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc 2014;3:e001278.
[15] Park CW, Oh YS, Shin YS, Kim CM, Kim YS, Kim SY, et al. Intravenous calcitriol regresses myocardial hypertrophy in hemodialysis patients with secondary hyperparathyroidism. Am J Kidney Dis 1999;33:73-81.
[16] Shoji T, Shinohara K, Kimoto E, Emoto M, Tahara H, Koyama H, et al. Lower risk forcardiovascular mortality in oral 1-alpha-hydroxy vitamin D3 users in a haemodialysis population. Nephrol Dial Transplant 2004;19:179-84.
[17] Nemerovski CW, Dorsch MP, Simpson RU, Bone HG, Aaronson KD, Bleske BE. Vitamin D and cardiovascular disease. Pharmacotherapy 2009;29:691-708.
[18] Suzuki J, Yanagisawa A, Shigeyama T, Tsubota J, Yasumura T, Shimoyama K, et al. Early detection of anthracycline-induced cardiotoxicity by radionuclide angiocardiography. Angiology1999;50:37-45.
[19] Kelishomi RB, Ejtemaeemehr S, Tavangar SM, Rahimian R, Mobarakeh JI, Dehpour AR. Morphine is protective against doxorubicin-induced cardiotoxicity in rat. Toxicology 2008;243;96-104.
[20] Koti BC, Nagathan S, Vishwanathswamy A, Gadad PC, Thippeswamy A. Cardioprotective effect of Vedic Guard against doxorubicin-induced cardiotoxicity in rats: A biochemical, electrocardiographic, and histopathological study. Pharmacogn Mag 2013;9:176-81.
[21] Bhatt L, Joshi V. Mangifera indica L. leaf extract alleviates doxorubicin induced cardiac stress. J Intercult Ethnopharmacol 2017;6:284-9.
[22] Rossi F, Filippelli W, Russo S, Filippelli A, Berrino L. Cardiotoxicity of doxorubicin: Effects of drugs inhibiting the release of vasoactive substances. Pharmacol Toxicol 1994;75:99-107.
[23] Holland RP, Brooks H. TQ-ST segment mapping: Critical review and analysis of current concepts. Am J Cardiol 1977;40:110-29.
[24] Villani F, Monti E, Piccinini F, Favalli L, Lanza E, Rozza

Dionigi A, et al. Relationship between doxorubicin-induced ECG changes and myocardial alterations in rats. Tumori 1986;72:323-9.
[25] Fujita T. Formation and removal of reactive oxygen species, lipid peroxides and free radicals, and their biological effects. Yakugaku Zasshi 2002;122:203-18.
[26] Zhang YW, Shi J, Li YJ, Wei L. Cardiomyocyte death in doxorubicin-induced cardiotoxicity. Arch Immunol Ther Exp (Warsz) 2009;57:435-45.
[27] Christenson ES, James T, Agrawal V, Park BH. Use of biomarkers for the assessment of chemotherapy-induced cardiac toxicity. Clin Biochem 2015;48:223-35.
[28] Ozdoğan K, Taşkın E, Dursun N. Protective effect of carnosine on adriamycin-induced oxidative heart damage in rats. Anadolu Kardiyol Derg 2011;11:3-10.
[29] Momin F, Shikalgar T, Naikwade N, Kalai B. Cardioprotective effect of methanolic extract of Ixora coccinea Linn. leaves on doxorubicin-induced cardiac toxicity in rats. Indian J Pharmacol 2012;44:178-83.
[30] Okuda K, Nohara R, Fujita M, Tamaki N, Konishi J, Sasayama S. Technetium-99m-pyrophosphate uptake as an indicator of myocardial injury without infarct. J Nucl Med 1994;35:1366-70.
[31] Okuda K, Nohara R, Ogino M, Tamaki N, Konishi J, Fujita M, et al. Limitation of infarct size with preconditioning and calcium antagonist (diltiazem): difference in 99mTc-PYP uptake in the myocardium. Ann Nucl Med 1996;10:201-9.
[32] Kawano M, Taki J, Kinuya S, Higuchi T, Nakajima K, Miyazaki Y, et al. Improvement of 99mTc-pyrophosphate scintigraphy in detection of acute myocardial infarction: combined with 99mTc-tetrofosmin. Kaku Igaku 2001;38:707-13.
[33] Mochizuki T, Murase K, Higashino H, Miyagawa M, Sugawara Y, Kikuchi T, et al. Ischemic "memory image" in acute myocardial infarction of 123I-BMIPP after reperfusion therapy: a comparison with 99mTc-pyrophosphate and 201Tl dual-isotope SPECT. Ann Nucl Med 2002;16:563-8.
[34] Affleck DG, Edelman L, Morris SE, Saffle JR. Assessment of tissue viability in complex extremity injuries: utility of the pyrophosphate nuclear scan. J Trauma 2001;50:263-9.
[35] Chang HR, Kao CH, Lian JD, Shu KH, Cheng CH, Wu MJ, et al. Evaluation of the severity of traumatic rhabdomyolysis using technetium-99m pyrophosphate scintigraphy. Am J Nephrol 2001;21:208-14.
[36] Matthews KL, Aarsvold JN, Mintzer RA, Chen CT, Lee RC. Tc-99m pyrophosphate imaging of poloxamer-treated electroporated skeletal muscle in an in vivo rat model. Burns 2006;32:755-64.
[37] Walker UA, Garve K, Brink I, Miehle N, Peter HH, Kelly T. 99mTechnetium pyrophosphate scintigraphy in the detection of skeletal muscle disease. Clin Rheumatol 2007;26:1119-22.
[38] Çiftçi ÖD, Gül SS, Açıksarı K, Maman A, Çavuşoğlu T, Bademci R, et al. The diagnostic utility of scintigraphy in esophageal burn: a rat model. J Surg Res 2016;200:495-500.

The European Research Journal 2019;5(4):658-662 ORIGINAL ARTICLE

Clinical and functional outcomes of extracorporeal shock wave therapy in isolated medial epicondylitis

Yalçın Turhan, Mehmet Arıcan, Zekeriya Okan Karaduman

Department of Orthopedics and Traumatology, Düzce University School of Medicine, Düzce, Turkey

DOI: 10.18621/eurj.448849

ABSTRACT

Objective: To evaluate the effectiveness of extracorporeal shock wave therapy (ESWT) for the patients with isolated medial epicondylitis refractory to other conservative methods.

Methods: A retrospective analysis of 57 patients with the diagnosis of isolated medial epicondylitis refractory to conservative measures was done. 36 of them who met our eligibility criteria were included. Patients were subjected to three sessions of extracorporeal shock wave therapy with 2000 pulses per a session in a dose of 0.06-0.12 mJ/mm2. Pain and clinical/functional scores were measured by visual analogue scale (VAS) and Quick-Disabilities of the Arm, Shoulder and Hand (Q-DASH) respectively before the treatment and at 1st week and 12th week of the last session.

Results: Mean age of the patients was 47.3 (25-67) years and there was a higher female presentation (24 female and 12 male patients). The VAS scores were improved from a mean of 7.8 before the treatment to 5.3 at 1st week ($p < 0.001$) and to 2.9 at 12th week ($p < 0.001$). Also the results of the Q-DASH showed a mean improvement from 50.4 before the treatment to 27.1 at 1st week ($p < 0.001$) and 9.6 at 12th week ($p < 0.001$). There were no significant differences in the improvements of VAS and Q-DASH scores by the time between the male and female patients.

Conclusion: According to the results of this study which will be one of the limited studies about isolated medial epicondylitis; ESWT is a good conservative treatment option for medial epicondylitis in refractory cases like in lateral epicondylitis.

Keywords: Medial epicondylitis, extracorporeal shock wave therapy, visual analogue scale, quick-disabilities of the arm shoulder and hand

Received: July 29, 2018; Accepted: August 19, 2018; Published Online: January 8, 2019

Medial epicondylitis with the other popular name "golfer's elbow" is common orthopedic problem. The prevalence is about 1% in population [1, 2]. With the result of repetitive micro-trauma over years to the common flexor origin of the humeral medial epicondyle, it typically occurs in the 4th-6th decades of life [3]. There are some treatment modalities for this condition including resting, physical therapy, non-steroidal anti-inflammatory drug (NSAID) usage, steroid injection, exercise therapy and orthosis. Although there are a lot of treatment options, the optimal treatment modality remains unclear [4, 5].

While initial conservative therapy and if failed open surgical management are the most popular treat-

Address for correspondence: *Yalçın Turhan, MD., Assistant Professor, Düzce University School of Medicine, Department of Orthopedics and Traumatology, Düzce, Turkey*
E-mail: yturhan_2000@yahoo.com

e-ISSN: 2149-3189

ment modalities; some of non-traditional methods like extracorporeal shock wave therapy (ESWT) have been used widely in orthopedic field. ESWT had been commonly used in the treatment of urolithiasis and choledocholithiasis. After the 1990's, it has been using for the common musculoskeletal disorders like plantar fasciitis and epicondylitis [6, 7]. Most of the previous studies were conducted to patients who failed to respond to conservative treatment modalities after the acute phase. Also the effectiveness of ESWT in the newly diagnosed lateral epicondylitis or medial epicondylitis was investigated in 2012 [8]. There are little studies showing the effectiveness of ESWT only in the management of medial epicondylitis.

This study aimed to evaluate the outcomes of ESWT in the treatment of isolated medial epicondylitis and to show its clinical and functional outcomes.

METHODS

The present study was designed as a retrospective observational study and was approved by ethics committee of our university with a number of 2018/64. A total of 57 patients were admitted to our outpatient clinics with the diagnosis of medial epicondylitis and treated with ESWT in the period between January 2010 and September 2017. The data of all of the patients were analyzed and the 36 patients who meet our criteria (patients with; unilateral and isolated medial epicondylitis, ESWT treatment was applied once in a week for three times and between the ages of 18-70) were included in our study. The exclusion criteria of the study were; presence of pregnancy, active infection or fracture around elbow joint, cervical radiculopathy, coagulopathy, upper extremity nerve entrapment syndrome, ipsilateral lateral epicondylitis or patients who were treated with local steroid injections, platelet rich plasma (PRP) etc. in 6 weeks of first ESWT application.

In all cases medial epicondylitis diagnosis were verified before the treatment by clinical tests, i.e. a painful local palpation at humeral medial epicondyle and positive "golfer's elbow test". Indications for ESWT involved persistence of pain and function impairment refractory to rest, ice, sling, pharmacological therapies (systemic and /or local non-steroidal anti-inflammatory drugs) or local steroid injections. All patients provided informed consent regarding that their medical records would be used in scientific studies.

Treatment

Treatments were performed using Swiss Dolorclast Master® ESWT machine (EMS Electro Medical Systems, Nyon, Switzerland), which produces radial shockwaves. Three sessions of radial ESWT (2000 pulses per a session in a dose of 0.06-0.12 mJ/mm^2) were administered weekly for three weeks in every patient.

Clinical Evaluation

Pain intensity and clinical/functional scores were measured by Visual Analogue Scale (VAS) and Quick-Disabilities of the Arm, Shoulder and Hand (Q-DASH) scoring systems respectively. The scoring records were subsequently obtained just before the treatment, at 1st week and at 12th week of the last session. VAS is a scale and is useful for measuring pain that is believed to range across a continuum of values and cannot easily be directly measured. The simplest VAS is a straight horizontal line of fixed length, usually 100 mm. The Q-DASH is an abbreviated version of the original DASH outcome measure. In comparison to the original 30 item DASH outcome measure, the Q-DASH only contains 11 items. It is a questionnaire that measures an individual's ability to complete tasks, absorb forces, and severity of symptoms. The Q-DASH tool uses a 5-point scale from which the patient can select an appropriate number corresponding to his/her severity and function level. Like the original version, the Q-DASH score ranges from 0 (no disability) to 100 (severest disability) [9, 10].

Statistical Analysis

One-way repeated measure of variance analysis was used in the analysis of the change of the time-dependent measurements. Two-way repeated measures of variance analysis was used to examine the variation of time-dependent measures relative to groups All analyses were performed with the Statistical Package for Social Sciences (SPSS) software ver. 22 (SPSS, Chicago, IL, USA). The *p*-values < 0.05 were considered statistically significant.

RESULTS

A total of 36 patients who met our eligibility criteria were included. There was a higher female presentation (24 females and 12 males). Mean age of the cohort was 47.3 (25-67) years. The affected extremity was right in 22 and left in 14 patients and the dominant arm was involved in 28 patients (77.7 %).

The VAS score was measured before the treatment, at 1st week and at 12th week of the last session of ESWT. A score from 0 to 10 was recorded. The VAS scores were improved from a mean of 7.8 (5-10) before the treatment to 5.3 (3-8) at 1st week ($p < 0.001$) and to 2.9 (1-7) at 12th week ($p < 0.001$). The changes of VAS score from 1st week to 12th week was also statistically significant ($p < 0.001$).

The Q-DASH score (0-100 points; 0 representing the best and 100 worst result) was also measured before the treatment, at 1st and at 12th weeks of the last session. The results showed a mean improvement from 50.4 (31.75-79.5) before the treatment to 27.1 (9-45.25) at 1st week ($p < 0.001$) and 9.6 (0-20.25) at 12th week ($p < 0.001$). There was also a statistically significant improvement of Q-DASH score values from 1st to 12th week ($p < 0.001$).

There were no statistically significant differences in the improvements of VAS and Q-DASH scores by the time between the male and female patients ($p = 0.682$ and $p = 0.693$ respectively).

There was a statistically significant proportional relationship between VAS and Q-DASH scores at before the treatment, 1st and 12th weeks (Table 1).

DISCUSSION

Medial epicondylitis is a painful, chronic and frequent clinical condition and there are a lot of treatment modalities but no one is the gold standard [11]. It involves degeneration of the flexor-pronator muscle groups of the forearm. Most of the patients having medial epicondylitis are not professional athletes but it has been associated with golfers, throwing athletes and workers requiring repetitive wrist flexion [12, 13]. There are less studies showing evidence for the treatment of medial epicondylitis and most of the knowledge comes from studies on lateral epicondylitis, this should be because of the reduced incidence of medial epicondylitis compared to lateral epicondylitis [14]. Conservative management is the basis of initial treatment for most of the cases as for other tendinopathies and consists of stopping activities causing symptoms, topically or oral NSAIDs and ice application. Injection therapies (steroid etc.) should be considered if these simple measures fail [1, 13, 15]. When the initial conservative treatment modalities and injection therapies fail to manage the problem, other conservative measures like ESWT should be considered. The positive effects of repeated application of shockwave therapy for the treatment of various musculoskeletal conditions like tendinitis,

Table1. The relationship between VAS Q-DASH scores BT, at 1st and 12th weeks

		Q-DASH-BT	Q-DASH-1st week	Q-DASH-12th week
VAS-BT	Pearson Correlation	.804	.484	.223
	Sig. (2-tailed)	**< 0.001**	**0.003**	0.191
	N	36	36	36
VAS-1st week	Pearson Correlation	.650	.585	.488
	Sig. (2-tailed)	**< 0.001**	**< 0.001**	**0.003**
	N	36	36	36
VAS-12th week	Pearson Correlation	.467	.410	.442
	Sig. (2-tailed)	**0.004**	**0.013**	**0.007**
	N	36	36	36

BT = before the treatment, N = number of the patients, Q-DASH = Quick-Disabilities of the Arm, Shoulder and Hand, VAS = visual analogue scale

fasciitis or calcified lesions had been reported [16]. ESWT converts electrical currents into shockwaves and delivers them onto target structures and has been using for the common musculoskeletal disorders like plantar fasciitis and epicondylitis since 1990's [7, 17]. We used low energy shock wave in this study according to the definition of energy dose established by Speed [7] in 2004; here, 0.12 mJ/mm^2 is a cut of value and above doses was defined as high energy shock wave and below doses was as low energy shock wave. Rompe *et al*. [18] and Oh *et al*. [19] reported that responses of tendon to shockwaves are dependent on energy dose and high energy shock wave therapy is more effective in treatment. However local anesthesia might be required when a high energy delivered because of severe pain and also higher energy doses above 0.60 mJ/mm^2 could cause necrosis of tendon [18]. Pettrone and McCall [20] in 2005 reported satisfactory clinical results from the delivery of 2000 low energy shock waves with a one week interval for three times totally in patients with chronic lateral epicondylitis and this therapy regimen was also used for newly diagnosed medial epicondylitis and lateral epicondylitis in a study by Lee *et al*. [8] in 2012. In this present study three sessions of radial ESWT (2000 pulses per a session in a dose of 0.06-0.12 mJ/mm^2) were administered weekly for three weeks in every patient and local anesthesia is never used.

Some minor complications have been discussed in the literature with limited reports associated with ESWT treatment like subdermal hematoma,local reddening and ecchymosis and they are considered as negligible [21, 22]. There is only one study reporting a case having ulnar neuropathy after ESWT application for medial epicondylitis in which the patient was operated for ulnar neuropath and his symptoms did not resolved totally [23]. We did not encounter any complications in our patients in this present study.

There are various reports on the use of ESWT in epicondylitis management with inconclusive results and most of them are about lateral epicondylitis [6, 24-27].

Limitations

This study is a non-controlled retrospective study on a limited patient group and patients' demographic features are variable. However despite of the fact, our study is a single center work on a series of patients with homogenous diagnosis, treated with a standard protocol and evaluated with a considerable follow-up time. The patients' mean VAS score results were 7.8 at just before the treatment protocol and reduced to 2.9 at the last control. Likewise the Q-DASH scores were 50.4 at the beginning of treatment and reduced to 9.6 at the lost follow-up. This shows nearly all of the patients are satisfied with this therapy regimen.

CONCLUSION

This work is one of the limited studies in the literature discussing about isolated medial epicondylitis and showed good clinical and functional outcomes. Like in lateral epicondylitis, ESWT is a good conservative treatment option for medial epicondylitis in refractory cases.

Authors Contributions

YT = Study design, Acquisition of data, Analysis and interpretation of data, and Drafting of manuscript. MA = Study design, Acquisition of data, and Critical revision. ZOK = Critical revision, Analysis and interpretation of data.

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] Shiri R, Viikari-Juntura E, Varonen H, Heliövaara M. Prevalence and determinants of lateral and medial epicondylitis: a population study. Am J Epidemiol 2006;164:1065-74.
[2] Descatha A, Leclerc A, Chastang JF, Roquelaure Y. Medial epicondylitis in occupational settings: prevalence, incidence and associated risk factors. J Occup Environ Med 2003;45:993-1001.
[3] Wolf JM, Mountcastle S, Burks R, Sturdivant RX, Owens BD. Epidemiology of lateral and medial epicondylitis in a military population. Mil Med 2010;175:336-9.
[4] Boyd HB, Mcleod JR AC. Tennis elbow. J Bone Joint Surg Am 1973;55:1183-7.

[5] Friedlander HL, Reid RL, Cape RF. Tennis elbow. Clin Orthop Relat Res 1967;51:109-16.
[6] Furia JP. Safety efficacy of extracorporeal shock wave therapy for chronic lateral epicondylitis. Am J Orthop (Belle Mead, NJ) 2005;34:13-9.
[7] Speed CA. Extracorporeal shock-wave therapy in the management of chronic soft-tissue conditions. J Bone Joint Surg Br 2004;86:165-71.
[8] Lee SS, Kang S, Park NK, Lee CW, Song HS, Sohn MK, et al. Effectiveness of initial extracorporeal shock wave therapy on the newly diagnosed lateral or medial epicondylitis. Ann Rehabil Med 2012;36:681-7.
[9] Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med 1996;29:602-8.
[10] Beaton DE, Wright JG, Katz JN; Upper Extremity Collaborative Group. Development of the QuickDASH: comparison of three item- reduction approaches. J Bone Joint Surg Am 2005;87:1038-46.
[11] Hamilton PG. The prevalence of humeral epicondylitis: a survey in general practice. J R Coll Gen Pract 1986;36:464-5.
[12] Amin NH, Kumar NS, Schickendantz MS. Medial epicondylitis: evaluation and management. J Am Acad Orthop Surg 2015;23:348-55.
[13] Ciccotti MC, Schwartz MA, Ciccotti MG. Diagnosis and treatment of medial epicondylitis of the elbow. Clin Sports Med 2004;23:693-705.
[14] Donaldson O, Vannet N, Gosens T, Kulkarni R. Tendinopathies around the elbow part 2: medial elbow, distal biceps and triceps tendinopathies. Shoulder Elbow 2014;6:47-56.
[15] Stahl S, Kaufman T. The efficacy of an injection of steroids for medial epicondylitis. A prospective study of sixty elbows. J Bone Joint SurgAm 1997;79:1648-52.
[16] Speed C. A systematic review of shockwave therapies in soft tissue conditions: Focusing on the evidence. Br J Sports Med 2014;48:1538-42.
[17] Wang CJ. Extracorporeal shockwave therapy in musculoskeletal disorders. J Orthop Surg Res 2012;7:11.
[18] Rompe JD, Kirkpatrick CJ, Kullmer K, Schwitalle M, Krischek O. Dose-related effects of shock waves on rabbit tendon Achillis: A sonographic and histological study. J Bone Joint Surg Br 1998;80:546-52.
[19] Oh JH, Yoon JP, C Oh HH, Jo KH, Gong HS. Dose related effect of extracorporeal shock wave therapy for lateral epicondylitis. J Korean Shoulder Elbow Soc 2009;12:21-6.
[20] Pettrone FA, McCall BR. Extracorporeal shock wave therapy without local anesthesia for chronic lateral epicondylitis. J Bone Joint Surg Am 2005;87:1297-304.
[21] Daecke W, Loew M, Schuknecht B, Kusnierzcak D. DerEinfluss der Applikationsdosis auf die Wirksamkeit der ESWA bei der Tendinosiscalcarea der Schulter. Orthop Praxis 1997;33:119-23.
[22] Rompe JD, Rumler F, Hopf C, Nafe J. Extracorporeal shock wave therapy for calcifying tendinitis of the shoulder. Clin Orthop 1995;321:196-201.
[23] Shim JS, Chung SG, Bang H, Lee HJ, Kim K. Ulnar neuropathy after extracorporeal shockwave therapy: a case report. PMR 2015;7:667-70.
[24] Hume PA, Reid D, Edwards T. Epicondylar injury in sport. Epidemiology, type, mechanisms, assessment, management and prevention. Sports Med 2006;36:151-70.
[25] Speed CA, Nichols D, Richards C, Humphreys H, Wies JT, Burnet S, et al. Extracorporeal shock wave therapy for lateral epicondylitis – a double blind randomised controlled trial. J Orthop Res 2002;20:895-8.
[26] Chung B, Wiley JP, Rose MS. Long-term effectiveness of extracorporeal shockwave therapy in previously untreated lateral epicondylitis. Clin J Sport Med 2005;15:305-12.
[27] Lebrun CM. Low-dose extracorporeal shock wave therapy for previously untreated lateral epicondylitis. Clin J Sport Med 2005;15:401-2.

The European Research Journal 2019;5(4):663-666 ORIGINAL ARTICLE

Mesenteric panniculitis - a rare disorder: radiological features

Ghanshyam Dev[1], Anshita Gupta[1], Mohd Ilyas[2]

[1]*Department of Radiodiagnosis, Govt. Medical College, Jammu, India*
[2]*Department of Radiodiagnosis, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India*

DOI: 10.18621/eurj.411289

ABSTRACT

Objectives: The main objective of this study was to assess the key computed tomographic features of various types of mesenteric panniculitis and to assess their etiology.

Methods: In this retrospective study, the radiological scans of seven patients were evaluated, the computed tomographic features and etiology were assessed. The Coulier's criteria were used for the radiological inclusion of a patient as a case of mesenteric panniculitis.

Results: Four of the patients had a history of some procedure or surgery performed 6 weeks to six months before presenting with panniculitis. Two of the seven cases were idiopathic while the seventh case presented after an episode of pyonephrosis. Mesentric panniculitis is one of the broad range of disorders that may result in imaging finding of misty mesentry on computed tomography. The key computed tomography finding seen in all these cases was regional increase in mesenteric fat density that was seen at abdominopelvic computed tomography.

Conclusion: Computed tomography has a particular picture in the cases of mesenteric panniculitis and forms one of the most sensitive non-invasive modality of investigation in the diagnosis of mesenteric panniculitis.

Keywords: Mesenteric panniculitis, computed tomography, fibrosis

Received: March 30, 2018; Accepted: October 6, 2018; Published Online: November 19, 2018

Mesenteric panniculitis is an acute benign fibrosing and inflammatory condition that involves the adipose tissue of the mesentery. It can be categorized according to three pathological changes: chronic nonspecific inflammation, fat necrosis and fibrosis [1]. If inflammation and fat necrosis predominate over fibrosis, the condition is known as mesenteric panniculitis, and when fibrosis and retraction predominate, the result is retractile mesenteritis. Mesentric panniculitis is one of the broad range of disorders that may result in imaging finding of misty mesentry on computed tomography (CT). The term 'misty mesentry' refers to regional increase in mesenteric fat density that is seen frequently at abdominopelvic CT. The main aim of this study is to describe the key CT findings associated with mesenteric panniculitis and to assess their etiology.

METHODS

The present study included seven patients who were diagnosed with mesenteric panniculitis on CT and were retrospectively studied. The patients presented with symptoms of pain abdomen with a vague mass / lump in abdomen. Mean age of presentation was 35 years. Four of the cases were male and three females. X ray and ultrasound examinations

Address for correspondence: *Ghanshyam Dev, MD., Professor and Head, Govt. Medical College, Department of Radiodiagnosis, Jammu, 180001 India*
E-mail: drghanshyamdev@gmail.com

e-ISSN: 2149-3189

were done and was followed by CT of the abdomen using reconstructed slice thickness of 5 mm after oral and intravenous contrast administration. The CT features of all these cases were noted and compared to each other and based on that analysis, they were classified.

The Coulier CT criteria were used for radiologic inclusion. Mesenteric panniculitis was considered confirmed if three out of five criteria were present: (A) Fatty mass lesion in the small intestinal mesentery, (B) hyper attenuation of the fat, (C) lymph nodes in the fatty mass (D) halo surrounding lymph nodes or vessels and (E) pseudo capsule. The images were graded using a scoring system based on the five diagnostic criteria (A-E). Scores 0-3 were given for each criterion. Zero corresponded to no pathological findings and 3 to extensive findings. A total score of 3-4 represented mild, 5-10 moderate and 11-20 extensive radiological changes.

RESULTS

The contrast enhanced computed tomography examination of the abdomen revealed the presence of masslike region of heterogeneously increased fat attenuation but without displacing surrounding mesenteric vascular structures; consistent with mesenteric panniculitis. Four of the patients had history of some procedure or surgery performed 6weeks to six months before presenting with panniculitis - one following a caesarian delivery about 2months back, 6 weeks after cholecystectomy, 3months post-appendicectomy while the fourth one followed percutaneous nephrolithotomy. Two of the seven cases were idiopathic in whom no obvious cause was found while the seventh case presented after an episode of pyonephrosis. Mean age of presentation was 35 years. Four of the cases were male and three females. X-ray and ultrasound revealed no significant abnormality in five patients while two of them presented with an ill-defined mass.

CT revealed the diagnosis of mesenteric panniculitis in all patients (Figures 1-5).

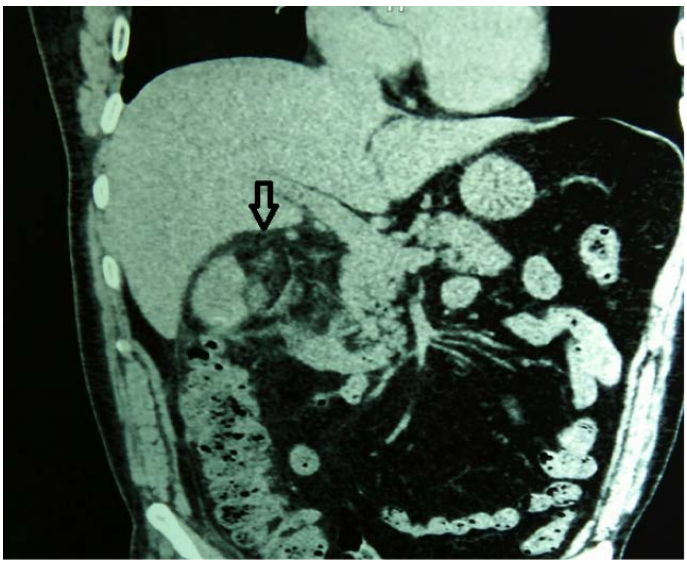


Figure 1. CT image of a case with previous caesarian delivery with stranding in the supra-umbilical and right hypochondriac region, which was most probably inflammatory in origin and suggestive of mesenteric panniculitis (arrow).

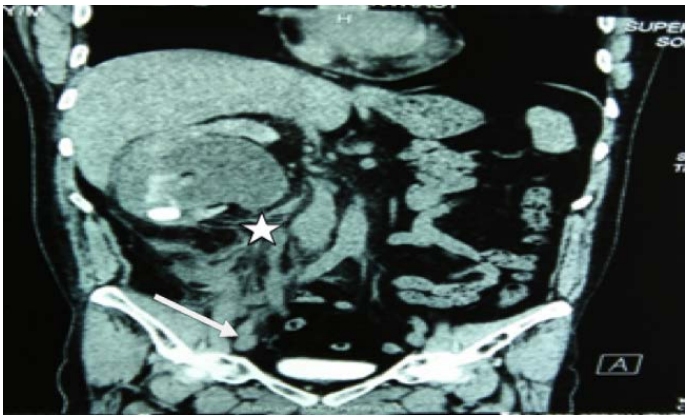


Figure 2. CT examination revealed right sided pyonephrosis (star) with inflamed mesentery in right lumbar region with intervening linear soft tissue bands consistent with mesenteric panniculitis.(arrow).

DISCUSSION

Mesenteric panniculitis is a rare, nonspecific, benign and chronic fibrosing inflammatory disease that affects the adipose tissue of the mesentery of the small intestine and colon [2, 3]. Most of the cases are idiopathic. Autoimmune response to unknown sources and ischemia of the mesentery have been proposed as pathogenetic mechanisms. Recent surgery especially cholecystectomy and appendicectomy apparently predispose to its development [2]. The diagnosis is suggested by computed tomography and is usually

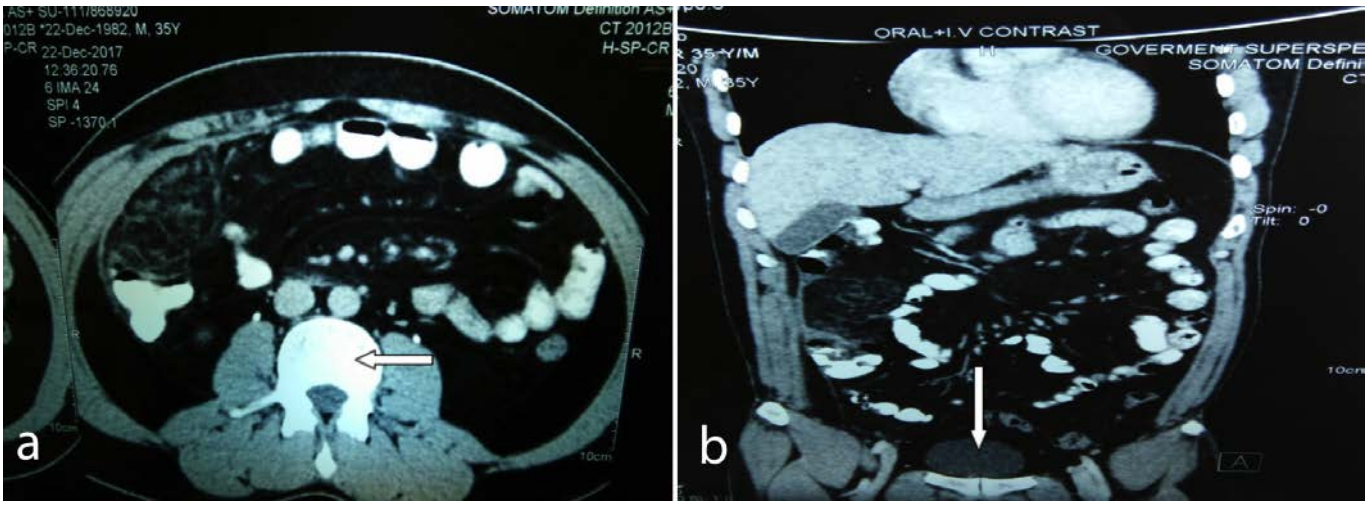


Figure 3a&3b. CT revealed an inflammatory mass of mesentery in the right mesocolic region with vessels passing through it as thin cords with the halo ring sign specific for mesenteric panniculitis (arrow).

confirmed by surgical biopsies. The cause of the disease is unclear. Whether mesenteric panniculitis occurs independently or in association with other disorders has been a subject of discussion. The disease has been related to a variety of conditions such as vasculitis, granulomatous disease, rheumatic disease, malignancies, and pancreatitis [3].

The disease is more common in men. The condition is mostly described in middle or late adulthood with a slight male predominance and several reports have indicated it to be more common in Caucasian men. Incidence increases with age, and pediatric cases are exceptional, probably because children have less mesenteric fat when compared to adults [4].

Patients had a history of abdominal trauma or surgery. Furthermore, the disease is related to other factors, such as mesenteric thrombosis, mesenteric arteriopathy, drugs, thermal or chemical injuries, vasculitis, avitaminosis, autoimmune disease, retained suture material, pancreatitis, bile or urine leakage, hypersensitivity reactions, and even bacterial infection [4, 5]. Other factors, such as gallstones, coronary disease, cirrhosis, abdominal aortic aneurysm, peptic ulcer, or chylous ascites, have also been linked to this disease [6].

The mean clinical progression is usually 6 months, ranging from 2 weeks to 16 years. The disease is often asymptomatic. When present, clinical symptoms vary greatly, and may include anorexia, abdominal pain,

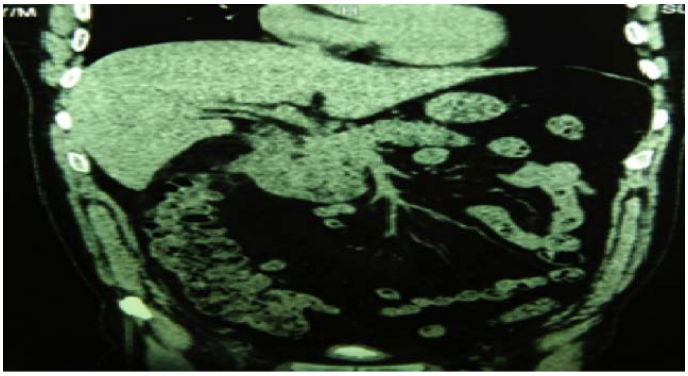


Figure 4. Mesenteric panniculitis presenting in a patient after laproscopic cholecystectomy.

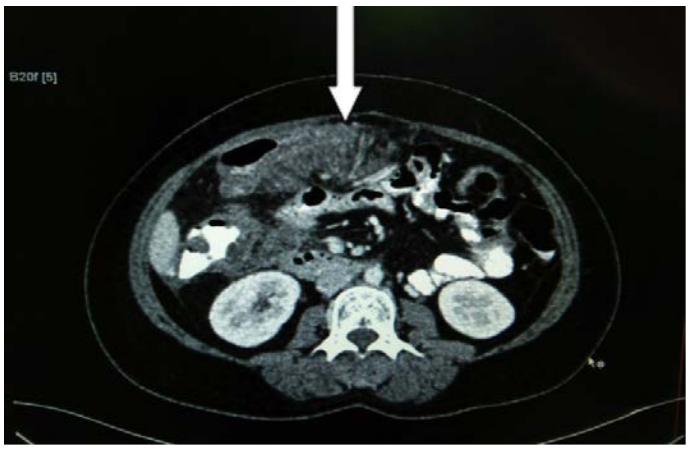


Figure 5. Case of mesenteric panniculitis showing increased CT density of mesentery forming an ill-defined mass (arrow).

abdominal fullness, nausea, pyrexia, and weight loss [7]. On occasions, the disease may also present with merely a single or multiple palpable mass. Symptoms may be progressive, intermittent, or absent. Laboratory findings, including elevation in erythrocyte sedimentation rate and anemia, are absent or nonspecific. CT or magnetic resonance imaging, distinguishing mesenteric panniculitis from other mesenteric diseases with similar imaging features such as carcinomatosis, carcinoid tumor, lymphoma, desmoid tumor, and mesenteric edema seems possible and feasible. The imaging appearance of mesenteric panniculitis varies depending on the predominant tissue component (fat necrosis, inflammation, or fibrosis) [8]. It is visualized usually as a heterogeneous mass with a large fat component and interposed linear bands with soft tissue density in cases of mesenteric panniculitis, or as a homogeneous mass of soft tissue density in cases of retractile mesenteritis [9, 10].

Mesentric panniculitis results in a masslike area of heterogeneously increased fat attenuation on CT that may displace local bowel loops but typically does not displace the surrounding mesenteric vascular structures [11]. Mesentric lymph nodes areoften seen within the region of segmental mesenteric stranding and nodes may be enlarged to greater than 1cm in a small percentage of cases [12]. Approximately 90% of cases involve the small bowel mesentry [13] and changes are more commonly centered to the left of the midline corresponding with the jejunal mesentry.

Mesenteric panniculitis resolves spontaneously in most cases; however, palpable masses may often be found between 2 and 11 years after diagnosis, especially in patients with associated comorbidity [4].

CONCLUSION

Mesenteric panniculitis is a very rare disorder usually occurring post-operative with various radiological appearances. The computed tomography forms the most sensitive modality available for the diagnosis.

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] Emory TS, Monihan JM, Carr NJ, Sobin LH. Sclerosing mesenteritis, mesenteric panniculitis and mesenteric lipodystrophy: a single entity? Am J Surg Pathol 1997;21:392-8.
[2] Hartz R, Stryker S, Sparberg M, Poticha SM. Mesenteric tumefactions. Am Surg 1980;46:525-9.
[3] Ogden WW, Bradburn DM, Rives JD. Mesenteric panniculitis: review of 27 cases. Ann Surg 1965;161:864-73.
[4] Delgado Plasencia L, Rodríguez Ballester L, López-Tomassetti EM, Hernández Morales A, Carrillo Pallarés A, Hernández Siverio N. [Mesenteric panniculitis: experience in our center]. Rev Esp Enferm Dig 2007;99:291-7. [Article in Spanish]
[5] Daskalogiannaki M, Voloudaki A, Prassopoulos P, Magkanas E, Stefanaki K, Apostolaki E, et al. CT evaluation of mesenteric panniculitis: prevalence and associated diseases. AJR Am J Roentgenol 2000;174:427-31.
[6] Patel N, Saleeb SF, Teplick SK. General case of the day. Mesenteric panniculitis with extensive inflammatory involvement of the peritoneum and intraperitoneal structures. Radiographics 1999;19:1083-5.
[7] Shah AN, You CH. Mesenteric lipodystrophy presenting as an acute abdomen. South Med J 1982;75:1025-6.
[8] Horton KM, Lawler LP, Fishman EK. CT findings in sclerosing mesenteritis (panniculitis): spectrum of disease. Radiographics 2003;23:1561-7.
[9] Kram S, Pardi DS, Schaffner JA, Smyrk TC. Sclerosing mesenteritis: clinical features, treatment, and outcome in ninety-two patients. Clin Gastroenterol Hepatol 2007;5:589-96; quiz 523-4.
[10] Coulier B. Mesenteric panniculitis. Part 1: MDCT--pictorial review. JBR-BTR 2011;94:229-40.
[11] Filippone A, Cianci R, Di Fabio F, Storto ML. Misty mesentry: a pictorial review of multidetector - row CT findings. Radiol Med 2011;116:351-65.
[12] Sabate J, Torrubia S, Maideu J. Sclerosing mesentritis: imaging findings in 17 patients. AJR 1999;172:625-9.
[13] Akram S, Pardi DS, Schaffner JA, Smyrk TC. Sclerosing mesentritis: clinical features, treatment and outcome in ninety-two patients. Clin Gastroenterol Hepatol 2007;5:589-96.

The European Research Journal 2019;5(4):667-672 ORIGINAL ARTICLE

Investigation of the comorbidity of dissociative disorders in patients with bipolar disorder

Atilla Tekin[1], Esra Özdil Demiryürek[2], Mehmet Diyaddin Güleken[3], Bahadır Bakım[4], Ömer Akil Özer[5], Oğuz Karamustafalıoğlu[5]

[1]Department of Psychology, Haliç University, Faculty of Arts and Sciences, İstanbul, Turkey
[2]Department of Psychiatry, Sakarya Training and Research Hospital, Sakarya, Turkey
[3]Department of Psychiatry, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey
[4]Department of Psychiatry, Yeni Yüzyıl University School of Medicine, İstanbul, Turkey
[5]Department of Psychiatry, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Turkey

DOI: 10.18621/eurj.412272

ABSTRACT

Objectives: The aim of this study was to investigate the comorbidity of dissociative disorders in patients with bipolar disorder.

Methods: Fifty-one patients who are diagnosed with bipolar disorder in euthymic state and forty-nine healty controls were included in the study. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D), Dissociative Experiences Scale (DES) and Childhood Trauma Questionnaire (CTQ-28) were administered to all participants with a sociodemographic form.

Results: Mean DES and CTQ-28 total scores were statistically higher in patients group than control group ($p < 0.001$ and $p < 0.001$, respectively). Emotional abuse, emotional neglect, physical abuse, physical neglect and sexual abuse subscale scores of CTQ-28 were higher in patients group than healthy controls group ($p = 0.002$, $p < 0.001$, $p = 0.005$, $p < 0.001$ and $p < 0.021$, respectively). The rate of any dissociative disorder comorbidity was 35.4% in patients with bipolar disorder. The most frequent dissociative disorder in patient with bipolar disorder was depersonalization disorder (17.6%). There was a positive correlation between DES score and number of suicidal attempts (r = 0.284). Negative correlations were found between DES score and age of disease onset, and CTQ-28 total score and age of disease onset (r = -0.332 and r = -0.291).

Conclusion: Our results have shown that dissociative disorders may be frequently accompanied in patients with bipolar disorder. Dissociation and childhood traumatic events can be related with clinical features in patients with bipolar disorder.

Keywords: childhood trauma, dissociation, bipolar disorder

Received: April 3, 2018; Accepted: May 2, 2018; Published Online: June 22, 2018

Traumatic experiences during childhood are frequently emphasized in the aetiology of bipolar disorder as well as many other psychiatric disorders. In bipolar patients with a history of childhood trauma, studies have shown that the age of disease onset age is earlier, the number of affective episodes is higher, the rate of rapid cycling is increased and psychotic symptoms as well as suicide attempts are more

Address for correspondence: *Atilla Tekin, MD., Assist. Prof., Haliç University, Faculty of Arts and Sciences, Department of Psychology, İstanbul, Turkey, E-mail: md.atillatekin@gmail.com, Phone: +90 212 9242444, Fax: +90 212 999787852*

e-ISSN: 2149-3189

common [1-8].

Dissociation, which is characterized with changes in or deterioration of the normal integrative functions of memory, identity and consciousness, manifests in many psychiatric disorders. Some studies have demonstrated dissociative symptoms to be present in psychotic disorders such as schizophrenia, anxiety disorders and in borderline personality disorders and that there is a relationship between childhood traumatic experiences and dissociative symptoms. It seems that the comorbidity of dissociative disorder is related with poor prognostic features in other psychiatric disorders [9, 10]. However, it is notable that the dissociative disorders in bipolar disorders have been less evaluated in literature [11, 12].

We hypothesized that dissociative disorders may be accompanied in patients with bipolar disorders frequently, and comorbidity of dissociative disorders is related with poor clinical features in patients with bipolar disorder. The primary aim of this study was to investigate the comorbidity rate of dissociative disorders in patients with bipolar disorder. The second aim of the study was to investigate the relationship between dissociation and childhood traumas, and clinical features in patients with bipolar disorder.

METHODS

This study included 51 bipolar patients in a euthymic state, who had previously been diagnosed according to the DSM-IV-TR diagnostic criteria, who were being followed at Şişli Hamidiye Etfal Training and Research Hospital Psychiatry Outpatient Clinic, and 49 healthy volunteers with no psychiatric diagnosis. The research protocol was approved by the Şişli Hamidiye Etfal Education and Research Hospital Ethics Committee. Each study participant signed an informed consent form that was approved by the ethics committee. The research was carried out in accordance with the World Medical Association Code of Ethics for Medical Research Involving Human Subjects Declaration of Helsinki Good Clinical Practice Guidelines.

Patients

The patient group of this study were volunteer euthymic individuals between the ages 18-65, at least primary school graduates, had no severe neurologic and internal diseases, had no current other Axis-I diagnosis, did not have coexisting schizophrenia or any other psychotic disorder, had no alcohol or substance addiction or abuse and had been diagnosed as bipolar according to the DSM-IV diagnostic criteria. Excluding criteria for the patient group included those younger than 18 years and older than 65 years of age, illiterate individuals, those with severe neurologic or internal disease and those with alcohol or substance abuse or addiction.

Clinical evaluation

Each participant who volunteered to participate in this study was asked to fill out a sociodemographics data form, a Childhood Traumatic Questionnaire (CTQ) and a Dissociative Experiences Scale (DES). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D) was applied by the interviewer to each participant.

SCID-I is a clinical interview structured by First *et al*. [13] for DSM-IV Axis I disorders. The adaptation and reliability studies of SCID-I for Turkey were performed by Çorapçıoğlu *et al*. [14]. SCID-D is a structured clinical interview chart for DSM-IV dissociative disorders developed by Steinberg [15]. It can be used to evaluate the dissociative symptoms and disorders of the subject in various psychiatric diseases. The reliability and validity studies for Turkey have been conducted by Kundakçı *et al*. [16].

DES is a scale consisting of 28 items developed by Bernstein and Putnam [17]. For each item of the scale, subjects give points between 0-100 and the result is obtained by calculating the average of the total scores. Total scores that are higher than 30, are indicative of a dissociative disorder. The reliability and validity studies for Turkey were performed by Yargıç *et al*. [18]. CTQ was developed by Bernstein *et al*. [19]. It is a self- reported quintet Likert type scale. It includes questions for evaluating childhood emotional, physical and sexual abuse and physical and emotional neglect. The reliability and validity studies for Turkey were performed by Şar *et al*. [20].

Statistical Analysis

Statistical analyses of the present study were performed with the SPSS 16.0 program. Descriptive

Table 1. Comparison of the sociodemographic features of the patients and control groups

Variable		Patient Group (n = 51)	Control Group (n = 49)	*p* value
Age (years)		35.1 ± 10.19	37.1 ± 9.1	0.363[1]
Gender	Female	26 (51)	29 (59.2)	0.410[2]
	Male	25 (49)	20 (40.8)	
Education	Primary-Secondary	16 (31.4)	16 (32.7)	0.721[2]
	High	23 (45.1)	18 (36.7)	
	University	12 (23.5)	15 (30.6)	
Maritalstatus	Married	26 (51)	32 (65.3)	0.310[2]
	Single	25 (49)	17 (34.7)	
Smoking	(Have)	22 (43.1)	23 (46.9)	0.702[2]
Alcohol consumption	(Have)	7 (13.7)	14 (28.6)	0.068[2]

Data are shown as mean±standard deviation or number (%). [1]independentsample t test, [2]Chi-square test

statistics were given as frequency, percentage, mean, standard deviation, and minimum-maximum. values. Differences between categorical variables in the groups were analyzed with the Chi-square test. Normality assessment of the continuous variables was performed with Shapiro-Wilk test. Comparisons of the variables that fitted normal distribution were evaluated with the Student's t-test. The correlation between the variables of the patient group was evaluated with the Spearman nonparametric test. Results were evaluated at a $p < 0.05$ level of significance.

RESULTS

There is no difference on age between the patients and controls groups (35.1 ± 10.19 years and 37.1 ± 9.1 years, respectively) ($p = 0.363$). There was no statistically significant difference between the patient and control groups of the study in terms of socio-demographic data (Table 1). The mean age of the disease onset in patients with bipolar disorder was 24.41 ± 4.37 years. The mean number of hospitalization of the patients was 3.39 ± 1.03. The mean number of suicide attempts of the patients was 1.71 ± 0.44.

CTQ-28 total, emotional abuse, emotional neglect, physical abuse, physical neglect and sexual abuse subscale scores were higher in patients group than healthy control group ($p < 0.001$, $p = 0.002$, $p < 0.001$, $p = 0.005$, $p < 0.001$ and $p < 0.021$; respectively). Mean DES score of the patients group was higher than the healthy controls (Table 2).

The most prevalent dissociative disorder was

Table 2. Comparison of DES and CTQ-28 scales scores betwee the patients and controls group.

Scale	Patient Group (n = 51)	Control Group (n = 49)	*p* value
CTQ-Emotional abuse	7.90 ± 3.36	6.20 ± 1.47	0.002
CTQ-Emotional neglect	10.16 ± 4.17	7.10 ± 2.19	**< 0.001**
CTQ-Physicalabuse	6.67 ± 2.98	5.39 ± 0.95	0.005
CTQ-Physical neglect	7.61 ± 2.85	5.47 ± 0.84	**< 0.001**
CTQ-Sexual abuse	6.59 ± 3.70	5.33 ± 0.85	0.021
CTQ-total	38.92 ± 12.45	29.57 ± 5.07	**< 0.001**
DES	20.73 ± 15.09	7.13 ± 4.54	**< 0.001**

Data are shown as mean±standard deviation. CTQ = Childhood Traumatic Questionnaire, DES = Dissociative Experiences Scale

Table 3. Comorbid dissociative disorders in patients with bipolar disorder (by using SCID-D)

Dissociative Disorders	Data n (%)
Dissociative amnesia	4 (7.8%)
Dissociative fugue	1 (1.9%)
Dissociative idendity disorder	2 (3.9%)
Depersonalization disorder	9 (17.6%)
Dissociative disorder not otherwise specified	8 (15.6%)

depersonalization disorder in patients with bipolar disorder (17.6%). Other comorbid dissociative disorders in patients with bipolar were shown at the Table 3.

There was a positive correlation between DES score and number of suicidal attempt (r = 0.284). A negative relationship was found between DES score and age of the disease (r = -0.332). Emotional neglect score was correlate with number of suicide attempt and age of the disease onset (r = 0.328 and r = -0.333). CTQ-total score was negatively correlate with age of the disease onset (r = -0.291) (Table 4).

DISCUSSION

The primary aim of the present study was to investigate the comorbidity of dissociative disorders in patients with bipolar disorder. The second aim of the study was to investigate the relationship between dissociation and childhood traumatic events, and clinical features of the patients.

Many studies have emphasized the relationship between bipolar disorder and childhood trauma [21-24]. In a study conducted by Garno *et al*. [24], it has been reported that there are at least one type of childhood trauma in almost half of bipolar patients and two or more types in about one third of them. In a study conducted by Leboyer *et al*. [22], bipolar patients and healthy individuals were compared for childhood traumatic experiences. According to their results, while the incidence of at least one type of childhood trauma in bipolar patients was 54.4%, this incidence was found to be 31.9% in healthy individuals [22]. The results of our study are similar to those of other studies in literature. Indeed, according to the results of our study, each CTQ subscale score (emotional abuse, physical abuse, physical neglect, emotional neglect and sexual abuse) was significantly higher in patients with bipolar disorder than in the healthy volunteers. The fact that childhood traumas are seen more frequently in bipolar patients brings to mind the question of how these childhood traumas affect the clinical course. Many studies have shown that there is a relationship between childhood trauma and the early age of disease onset, more suicidal attempts, more psychotic symptoms, higher rates of rapid cycling and more substance abuse in patients with bipolar disorder [6, 23-26]. Leverich *et al*. [26] have indicated that there is a relationship between physical and sexual abuse with early age of disease onset, rapid cycling and increased suicidal attempts in patients with bipolar disorder. Garno *et al*. [24] have found that in bipolar patients with childhood trauma, the age of disease onset was earlier and that patients with a history of sexual abuse were found to have more suicidal attempts. In a study conducted by Brown *et al*. [6], it has been found that the number of hospitalizations is higher in bipolar patients with childhood trauma and alcohol abuse was more in those with a history of sexual and physical abuse. Romero *et al*. [27] have found that there is more suicidal attempts and substance abuse in bipolar patients with

Table4. Correations of DES and CTQ-28 scale scores with clinical features in patients with bipolar disorder

	DES	Emotional Abuse	Emotional Neglect	Physical Abuse	Physical Neglect	Sexual Abuse	CTQ-28 Total
Number of Hospitalization	r=0.148	r=0.139	r=0.106	r=0.002	r=0.048	r=0.155	r=0.097
Number of SuicideAttempt	**r=0.284***	r=0.106	**r=0.328***	r=0.092	r=0.046	r=0.205	r=0.219
Age of Onset	**r=-0.332***	r=-0.264	**r=-0.333***	r=-0.174	r=-0.029	r=-0.240	**r=-0.291***

DES = Dissociative Experiences Scale, CTQ = Childhood Traumatic Questionnaire, *$p < 0.05$

childhood trauma. According to the results of the present study, CTQ-28 total and emotional neglect subscale scores are correlated with early onset of the disease. Additionally, we have found that emotional neglect score was positively correlate with number of suicidal attempt in patients with bipolar disorder. The negative effects of childhood trauma on the clinical course of bipolar disease may be associated with various neurobiological impairments. Indeed, it has been demonstrated that childhood traumas leads to disruptions in the sensitivity of the neuroendocrine stress response and activity of the hypothalamic-pituitary-adrenal axis and damages in the cortical areas such as the hippocampus and amygdala that have an important role in cognitive and emotional functions [4, 28, 29].

There are less studies in literature that investigate the relationship between bipolar disorder and dissociation. In a study conducted by Latalova *et al*. [11], bipolar patients and healthy individuals were compared for level of dissociation. Latalova *et al*. [11] have found that DES score was higher in patients with bipolar disorder than healthy controls. Coryell [30] reported in a case report that multiple personality may occur as an epiphenomenon of the affective disorder or of other illnesses. Steingard and Frankel [31] reported a patient with a diagnosis of bipolar disorder, rapid cycling type, who in fact was experiencing dissociative episodes manifested as psychotic states. We have found that the mean DES score of the patients with bipolar disorder was higher than healthy controls. The most important result of the present study is that dissociative disorders are frequently accompanying to bipolar disorder. According to our results, the most prevalent dissociative disorders that accompanied to bipolar disorder are depersonalization disorder and dissociative disorder not otherwise specified (17.6% and 15.6%, respectively).

According to the results of the previous studies, it can be said that higher levels of dissociation has negatively affect the clinical course of bipolar disorder. Latalova *et al*. [11] have found that there is a relationship between higher levels of dissociation and earlier onset of the disease in patients with bipolar disorder. Spitzer *et al*. [32] have demonstrated lower treatment responses in bipolar patients with high dissociation scores. Bakım *et al*. [33] have found the relationship between higher DES scores and duration hospital stay in patients with bipolar disorder. In our study, we found the age of disorder onset to be earlier and number of suicide attempts to be higher in bipolar patients with high dissociation scores. Consequently, it can be said that the results of the present study have supported the results of previous studies.

Limitations

The present study has some limitations. Firstly, sample size of the present study was relatively smaller. Second limitation of the present study is that the correlation coefficients between our variables were smaller than 0.4. Namely, our results need to confirm with larger sample.

CONCLUSION

In conclusion, dissociative disorders are frequently observed in bipolar patients. In bipolar disorder patients with childhood trauma or high dissociation scores, the onset of the disease may be earlier and the number of suicide attempts may be greater.

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] Fisher HL, Hosang GM. Childhood maltreatment and bipolar disorder: a critical review of the evidence. Mind Brain 2010;1:750-85.
[2] Larsson S, Aas M, Klungsøyr O, Agartz I, Mork E, Steen NE, et al. Patterns of childhood adverse events are associated with clinical characteristics of bipolar disorder. BMC Psychiatry 2013;13:97.
[3] Daruy-Filho L, Brietzke E, Lafer B, Grassi-Oliveira R. Childhood maltreatment and clinical outcomes of bipolar disorder. Acta Psychiatr Scand 2011;124:427-34.

[4] Etain B, Mathieu F, Henry C, Raust A, Roy I, Germain A, et al. Preferential association between childhood emotional abuse and bipolar disorder. J Trauma Stress 2010;23:376-83.
[5] Janssen I, Krabbendam L, Bak M, Hanssen M, Vollebergh W, De GR, et al. Childhood abuse as a risk factor for psychotic experiences. Acta Psychiatr Scand 2004;109:38-45.
[6] Brown GR, McBride L, Bauer MS, Williford WO; Cooperative Studies Program 430 Study Team. Impact of childhood abuse on the course of bipolar disorder: a replication study in U.S. veterans. J Affect Disord 2005;89:57-67.
[7] Alvarez MJ, Roura P, Oses A, Foguet Q, Sola J, Arrufat FX. Prevalence and clinical impact of childhood trauma in patients with severe mental disorders. J Nerv Ment Dis 2011;199:156-61.
[8] Holowka DV, King S, Sahep D, Pukal M, Brunet A. Childhood abuse and dissociative symptoms in adult schizophrenia. Schizophr Res 2003; 60:87-90.
[9] Zanarini MC, Ruser T, Frankenburg FR, Hennen J. The dissociative experiences of borderline patients. Compr Psychiatry 2000;41:223-7.
[10] Sar V, Taycan O, Bolat N, Ozmen M, Duran A, Ozturk E, et al. Childhood trauma and dissociation in schizophrenia. Psychopathology 2010;43:33-40.
[11] Latalova K, Prasko J, Pastucha P, Grambal A, Kamaradova D, Diveky T, et al. Bipolar affective disorder and dissociation - comparison with healthy controls. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2010;155:181-6.
[12] Hariri AG, Yazıcı-Güleç M, Cengiz-Örengül FF, Aydın-Sümbül A, Yeni-Elbay R, Güleç H. Dissociation in bipolar disorder: relationships between clinical variables and childhood trauma. J Affect Disord 2015;184:104-10.
[13] First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinical Version. Washington: American Psychiatric Press, 1997.
[14] Çorapçıoğlu A, Aydemir O, Yıldız M, Danacı AE, Köroğlu E. DSM-IV Eksen-I Bozuklukları için Yapılandırılmış Klinik Görüşme. Ankara: HYB, 1999.
[15] Steinberg M, Cicchetti DV, Buchanan J, Hall PE, Rounsaville B. Clinical assessment of dissociative symptoms and disorders. The Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D). Dissociation 1993;6:3-15.
[16] Kundakci T, Şar V, Kiziltan E, Yargic LI, Tutkun H. The reliability and validity of the Turkish Version of the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D): A preliminary study. J Trauma Dissociation 2014;15:24-34.
[17] Bernstein EM, Putnam PW. Development, reliability and validity of a dissociation scale. J Nerv Ment Dis 1986;174:727-35.
[18] Yargıç LI, Tutkun H, Şar V. The reliability and validity of the Turkish version of the dissociative experiences scale. Dissociation 1995;8:10-3.
[19] Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J Psychiatry 1994;151:1132-6.
[20] Şar V, Öztürk E, İkikardeş E. Çocukluk Çağı Ruhsal Travma Ölçeğinin Türkçe uyarlamasının geçerlilik ve güvenilirliği. Turkiye Klinikleri J Med Sci 2012;32:1054-63.
[21] Hyun M, Friedman SD, Dunner DL. Relationship of childhood physical and sexual abuse to adult bipolar disorder. Bipolar Disord 2000;2:131-5.
[22] Leboyer M, Etain B, Mathieu F, Henry C, Jamain S, Bellivier F. Childhood affective trauma in bipolar affective disorder. Bipolar Disord 2007; 9(Suppl 1):9.
[23] Leverich GS, Post RM. Course of bipolar illness after history of childhood trauma. Lancet 2006;367:1040-2.
[24] Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. Impact of childhood abuse on the clinical course of bipolar disorder. Br J Psychiatry 2005;186:121-5.
[25] Hammersley P, Dias A, Todd G, Bowen-Jones K, Reilly B, Bentall RP. Childhood trauma and hallucinations in bipolar affective disorder: preliminary investigation. Br J Psychiatry 2003;182:543-7.
[26] Leverich GS, Mcelroy SL, Suppes T, Keck PE, Denicoff KD, Nolen WA, et al. Early physical and sexual abuse associated with an adverse course of bipolar illness. Biol Psychiatry 2002;51:288-297.
[27] Romero S, Birmaher B, Axelson D, Goldstein T, Goldstein BI, Gill MK, et al. Prevalence and correlates of physical and sexual abuse in children and adolescents with bipolar disorder. J Affect Disord 2009;112:144-50.
[28] Heim C, Mletzko T, Purselle D, Muselman DL, Nemeroff CB. The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. Biol Psychiatry 2008;63:398-405.
[29] Teicher MH, Anderson CM, Polcari A. Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. Proc Natl Acad Sci U S A 2012;109:E563-72.
[30] Coryell W. Single case study. Multiple personality and primary affective disorder. J Nerv Ment Dis 1983;171:388-390.
[31] Steingard S, Frankel FH. Dissociation and psychotic symptoms. Am J Psychiatry 1985;142:953-5.
[32] Spitzer C, Barnow S, Freyberger HJ, Grabe HJ. Dissociation predicts symptom-related treatment outcome in short-term inpatient psychotherapy. Aust N Z J Psychiatry 2007;41:682-7.
[33] Bakım B, Baran E, Güleken MD, Tankaya O, Yayla S, Akpınar A, et al. Comparison of the patient groups with and without dissociative disorder comorbidity among the inpatients with bipolar disorder. Fam Pract Palliat Care 2016;1:35-42.

The European Research Journal 2019;5(4):673-677 ORIGINAL ARTICLE

Examination of surgical and conservative treatment effects on depression of patients with moderate carpal tunnel syndrome

Kenan Güvenç[1], Mustafa Kemal İlik[2], Faik İlik[3], Murat Gönen[4], Fatih Kayhan[5]

[1]*Department of Orthopedics, Mersin University School of Medicine, Mersin, Turkey*
[2]*Department of Neurosurgery, Farabi Hospital, Konya, Turkey*
[3]*Department of Neurology, Konya Medicana Hospital, Konya, Turkey*
[4]*Department of Neurology, Fırat University School of Medicine, Elazığ, Turkey*
[5]*Consultant Psychiatrist, Soul Psychiatry Private Practice, Konya, Turkey*

DOI: 10.18621/eurj.414363

ABSTRACT

Objective: The aim of this study is to examine the outcomes of conservative and surgical treatments of patients with carpal tunnel syndrome as well as the effects of these two treatment options on depressive symptoms of these patients.

Methods: A case-control study carried out from June 2015 to February 2016 and 111 moderate moderate carpal tunnel syndrome patients were included in the study whose diagnosis was confirmed by electroneuromyography (ENMG). The 78 of the patients had surgical treatment and 33 of them, who did not accept the surgery, received steroids via injection and splinting technique was performed for 8 weeks. Boston Carpal Tunnel Questionnaire, quick disabilities of the arm, shoulder and hand score and Beck Depression Invertory scales were applied six months before and after treatments.

Results: It was detected that pain functional assessment scores and Beck depression scores significantly recovered the disease in patients who had surgical treatment compared to ones who had the conservative treatment.

Conclusions: It can be concluded that surgical treatment plays a more active role in the recovery of depressive symptoms in patients with moderate carpal tunnel syndrome.

Keywords: Carpal tunnel syndrome, surgical, conservative, depression

Received: April 11, 2018; Accepted: July 9, 2018; Published Online: September 27, 2018

Carpal tunnel syndrome (CTS) occurs due to the compression of the median nerve in the wrist alignment [1, 2]. Its prevalence is 2.7% [2, 3]. It can lead to paresthesia, pain, weakness and sometimes thenar atrophy in the median nerve innervation area [4]. The physiological basis of CTS depends on the median nerve ischemia as a result of the increased pressure in the carpal tunnel due to the transverse carpal ligament compression or circulatory disorders [5]. Besides, tenosynovitis of the tendons nearby nerve is the other hypothesis that tries to explain the CTS. Collagen vascular diseases, metabolic diseases, pregnancy and wrist fractures or dislocations can lead to CTS [6]. However, it is substantially idiopathic. It can be diagnosed with the help of anamnesis, physical examination and electrophysiological tests [7]. Decompressive surgery and local corticosteroid injections are the recommended treatment options. According to pre-

Address for correspondence: *Kenan Güvenç, MD., Mersin University School of Medicine, Department of Orthopedics, Mersin, Turkey*
E-mail: guvenckenan@hotmail.com, Fax: +90 324 361 00 73

e-ISSN: 2149-3189

vious studies, neurophysiological parameters improved in patients who had the surgical treatment [8]. It was been observed that neuropathic pain lead to depression in CTS patients [9]. In CTS, the relation between depressive symptoms and the outcome of surgery is of particular interest because depression and CTS are both highly prevalent conditions, specifically among women [10, 11]. There is no published evidence about the optimal treatment method for mild disease [12]. Some studies have reported no effect of depression on the outcome of treatment of CTS, others stated that depression affects scar pain or patient satisfaction and perceived disability [13-15]. The aim of this study is to compare the effects of surgical and conservative treatments on the depression levels of patients with moderate CTS.

METHODS

A case-control study carried out from June 2015 to February 2016 and 111 moderate CTS patients were included in the study whose diagnosis was confirmed by electroneuromyography (ENMG). The CTS classification was performed by nerve conduction studies. The findings were assessed according to the Padua criteria and CTS classification was performed. The electrophysiological classification criteria of Padua are:

1) Most severe: It is the 'most severe' when motor and sensory action potential cannot be obtained.

2) Severe: It is 'severe' when there is no sensory response and there is an abnormal motor distal response.

3) Moderate: It is 'moderate' when there are sensory conduction and motor abnormalities together in the finger wrist segment.

4) Mild: It is 'mild' when there are abnormalities in the sensory conduction speed in the finger wrist segment and when the distal motor latency is normal.

5) Light: It is 'light' when there are abnormalities in the finger wrist segment according to the comparative assessment.

6) Normal

The 3rd group of Padua (moderate CTS patients) was included in our study since there is no consensus on the treatment of moderate carpal tunnel syndrome in the literature. Out of 111 patients, 78 of them had the surgical treatment and 33 of them, who did not accept the surgery, had the conservative treatment. Surgical treatment was performed by using standard mini-open incision technique. All operations were conducted under the local anesthesia. Transverse carpal ligament was reached with the help of one mini incision (approximately 2-3 cm) on the third long web axis. An attempt was made to protect median and ulnar nerves in the palmar cutaneous branch during the dissection. Carpal tunnel was loosened from antebrachial fascia till transverse carpal ligament along the ulnar edge. Steroid injection and 8 weeks splinting treatments were performed in the conservative conservative treatment. Boston Carpal Tunnel Syndrome Questionnaire BCTSQ, Beck Depression Inventory (BDI), and Quick Disability of the Arm, Shoulder, and Hand (qDASH) surveys were performed before and 6 months after the treatment. BCTSQ is a disease specific survey. It is composed of the two scales which evaluate the severity of symptoms and the functional capacity. There is a Turkish validity and reliability study of the scale and some studies suggest that it is useful to use it in the effectiveness of the treatment [16, 17]. There are five different responses which can be scored between 1 and 5. The mean score is obtained by dividing the total score to the total number of questions and it changes between 1 and 5. High score indicates that the functional capacity decreases. The mean score is calculated separately for the symptom severity and functional capacity. Symptom score is composed of 11 and function score is composed of 8 questions.

Out of 11 titles, at least 10 titles should be answered in order to calculate qDASH score. Each title contains five answers and the score of the scale is calculated by using title scores (0: no disability, 100: most severe disability) [18, 19]. BDI test was used in order to determine the presence of the depressive signs and severity of these symptoms. BDI is a scale which is composed of 21 questions for the evaluation of the depression signs classified into three areas such as physical, emotional, cognitive. The maximum score can be 63. According to BDI scores, scores between 10 and 16 represent mild, scores between 17 and 29 represent moderate and scores between 30 and 63 represent severe depressive symptoms. The cut-off point of the scale is 17 and score higher than 17 represents significant clinical depressive signs [20].

Table1. Demographic features of the patients

	Surgical group	Conservative group	*p* value
Age, mean (range) (years)	53.5 (21-77)	51 (20-81)	0.14
Sex			0.07
Male (n)	7	6	
Female (n)	71	27	

Patients' ages and hand dominance were recorded. The exclusion criteria of the study were; being in the period of pregnancy or lactation, having an anamnesis of wrist fracture or dislocation, being diagnosed with polyneuropathy and previously diagnosed with a psychiatric disease.

Statistical analysis

Results were statistically compared to each other by using SPSS program. Kolmogrov Smirnov test was used to assess whether or not the variables were normally distributed. Chi-square or Fischer exact tests (when needed) were used in order to compare the categorical variables. Mann Whitney U test was used to analyze the numerical variables.

RESULTS

The 111 moderate CTS patients were included in the study. The 97 of the patients were female and 14 of the patients were male. The dominant hand was the right hand in 104 of the patients whereas the dominant hand was left hand in 9 of the patients. The mean age of the patients was 52.7 years. The surgical treatment was applied to 78 patients and conservative treatment was applied to 33 patients. There was no difference between these two groups in terms of their demographic characteristics (Table 1).

There was a statistically significant recovery in patients who were treated with surgical intervention compared to ones who received conservative treatment according to their BCTSQ, qDASH and BDI scores (Table 2).

DISCUSSION

Even though CTS is the most frequently observed peripheral nerve entrapment syndrome, there are problems in its diagnosis and treatment [1, 2, 21]. Although the endoscopic technique has been commonly used, the gold standard in CTS surgery is the open carpal tunnel release. Steroid injections, splinting, exercise, low level laser therapy, ultrasound therapy and paraffin bath can be applied in the conservative treatment of CTS [22, 23]. It has been already shown in previous studies that there is an association between the pain intensity and the depression [9]. It has also been specified that neuropathic pain can lead to depression and anxiety with the effect of nociceptive responses in animal

Table 2. Outcomes of rating scales

Rating scale	Surgical group		Conservative group	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
BCTQ				
FS	4.08 ± 0.15	1.20 ± 0.11*	4.09 ± 0.15	2.28 ± 0.35*
SS	3.77 ± 0.15	1.89 ± 1.96*	3.78 ± 0.13	2.43 ± 0.30*
BDS	24.07 ± 2.51	6.21 ± 2.76*	24.81 ± 2.51	17.87 ± 2.64*
qDASH score	35.95 ± 8.14	4.72 ± 2.97*	36.08 ± 8.34	25.96 ± 3.53*

Data are given as mean ± standard deviation. BCTQ = Boston carpal tunnel questionnaire, FS = functional status, SS = symptoms severity, BDS = Beck depression scale, qDASH = quick disabilities of the arm, shoulder and hand score, * $p < 0.01$

models [24]. It has been thought that chronic pain leads to depression since the peripheral inflammation reaches the central nervous system. It has also been considered in animal models that tumor necrosis factor-α (TNF-α) can be the key mediator which explains the association of depression and the neuropathic pain [25].

In a previous study, patients who were operated had better results compared to the ones who had the steroid injections in terms of symptomatic and neurophysiological outcomes [26]. When these two treatment methods were compared to each other, it was shown in another study that the results of patients who had surgical treatment were better in the end of the two years compared to others [27]. Similar to other studies, it was shown in our study that surgically treated patients had prominent recovery according to the patients who were treated conservatively. In our study, another important finding was that the depression frequency and the severity of patients who were treated with the surgical method were lower compared to the other patients treated with conservative methods. In a previous study, it was shown that the emotional status of CTS patients was evaluated and it was shown that depression was correlated with the diminished sensation of hand, hand weakness, thenar atrophy and pain [28, 29]. It was considered that the recovery in the depressive signs of patients who received surgical treatment was due to the prominent decrease in the pain and functional healing.

CONCLUSION

Conclusively, surgical treatment is superior to the conservative treatment in the moderate CTS according to pain and function hand scorings. As a result of these findings, surgical treatment should be prioritized in moderate CTS 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] Andreu JL, Ly-Pen D, Millán I, de Blas G, Sánchez-Olaso A. Local injection versus surgery in carpal tunnel syndrome: neurophysiologic outcomes of a randomized clinical trial. Clin Neurophysiol 2014;125:1479-84.
[2] Bakhtiary AH, Rashidy-Pour A. Ultrasound and laser therapy in the treatment of carpal tunnel syndrome. Aust J Physiother 2004;50:147-51.
[3] Baptista-de-Souza D, Nunciato AC, Pereira BC, Fachinni G, Zaniboni CR, Canto-de-Souza A. Mice undergoing neuropathic pain induce anxiogenic-like effects and hypernociception in cagemates. Behav Pharmacol 2015;26:664-72.
[4] Baysal O, Altay Z, Ozcan C, Ertem K, Yologlu S, Kayhan A. Comparison of three conservative treatment protocols in carpal tunnel syndrome. Int J Clin Pract 2006;60:820-8.
[5] Beaton DE, Wright JG, Katz JN. Development of the QuickDASH: comparison of three item-reduction approaches. J Bone Joint Surg Am 2005;87:1038-46.
[6] Bonfiglioli R, Mattioli S, Fiorentini C, Graziosi F, Curti S, Violante FS. Relationship between repetitive work and the prevalence of carpal tunnel syndrome in part-time and full-time female supermarket cashiers: a quasi-experimental study. Int Arch Occup Environ Health 2007;80:248-53.
[7] Burt S, Crombie K, Jin Y, Wurzelbacher S, Ramsey J, Deddens J. Workplace and individual risk factors for carpal tunnel syndrome. Occup Environ Med 2011;68:928-33.
[8] Cobb TK, Amadio PC, Leatherwood DF, Schleck CD, Ilstrup DM. Outcome of reoperation for carpal tunnel syndrome. J Hand Surg Am 1996;21:347-56.
[9] de Krom MC, de Krom CJ, Spaans F. [Carpal tunnel syndrome: diagnosis, treatment, prevention and its relevance to dentistry]. Ned Tijdschr Tandheelkd 2009;116:97-101. [Article in Dutch]
[10] Datema M, Tannemaat MR, Hoitsma E, van Zwet EW, Smits F, van Dijk JG, et al. Outcome of carpal tunnel release and the relation with depression. J Hand Surg Am 2018;43:16-23.
[11] Shin YH, Yoon JO, Kim YK, Kim JK. Psychological status is associated with symptom severity in patients with carpal tunnel syndrome. J Hand Surg Am. 2018;43: 484.e1-484.e8.
[12] Ebrahimzadeh MH, Mashhadinejad H, Moradi A, Kachooei AR. Carpal tunnel release in diabetic and non-diabetic patients. Arch Bone Jt Surg 2013;1:23-7.
[13] Hobby JL, Venkatesh R, Motkur P. The effect of psychological disturbance on symptoms, self-reported disability and surgical outcome in carpal tunnel syndrome. J Bone Joint Surg Br 2005;87:196-200.
[14] Becker SJ, Makanji HS, Ring D. Expected and actual improvement of symptoms with carpal tunnel release. J Hand Surg Am 2012;37:1324-9.e1-5.
[15] Kim JK, Kim YK. Predictors of scar pain after open carpal tunnel release. J Hand Surg Am 2011;36:1042-6.
[16] Fernández-de-las-Peñas C, Fernández-Muñoz JJ, Palacios-Ceña M, Navarro-Pardo E, Ambite-Quesada S, Salom-Moreno J. Direct and indirect effects of function in associated variables such as depression and severity on pain intensity in women with carpal tunnel syndrome. Pain Med 2015;16:2405-11.

[17] Heybeli N, Ozerdemoglu RA, Aksoy OG, Mumcu EF. [Functional and symptomatic scoring used for the assessment of outcome in carpal tunnel release]. Acta Orthop Traumatol Turc 2001; 35:147-51. [Article in Turkish]
[18] Hisli N. A study about validity of Beck depression inventory. J Psychol 1988;6:118-22.
[19] Hui AC, Wong S, Leung CH, Tong P, Mok V, Poon D, et al. A randomized controlled trial of surgery vs steroid injection for carpal tunnel syndrome. Neurology 2005;64:2074-8.
[20] Koldas Dogan S, Ay S, Evcik D, Baser O. Adaptation of Turkish version of the questionnaire Quick Disability of the Arm, Shoulder, and Hand (Quick DASH) in patients with carpal tunnel syndrome. Clin Rheumatol 2011;30:185-91.
[21] Ly-Pen D, Andréu JL, Millán I, de Blas G, Sánchez-Olaso A. Comparison of surgical decompression and local steroid injection in the treatment of carpal tunnel syndrome: 2-year clinical results from a randomized trial. Rheumatology (Oxford) 2012;51:1447-54.
[22] Papanicolaou GD, McCabe SJ, Firrell J. The prevalence and characteristics of nerve compression symptoms in the general population. J Hand Surg Am 2001;26:460-6.
[23] Pogorzelski R, Kułakowska A, Halicka D, Drozdowski W. [Neurological and emotional profile of carpal tunnel syndrome patients]. Przegl Lek. 2011;68:269-73. [Article in Polish]
[24] Robert A, Werner R, Andray M. Electrodiagnostic evaluation of carpal tunnel syndrome. Muscle Nerve 2011;44:597-607.
[25] Salaffi F, De Angelis R, Grassi W; MArche Pain Prevalence; Investigation Group (MAPPING) study. Prevalence of Musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study. Clin Exp Rheumatol 2005;23:819-28.
[26] Sen D, Chhaya S, Morris VH. Carpal tunnel syndrome. Hosp Med 2002;63:392-5.
]27] Verdugo RJ, Salinas RS, Castillo J, Cea JG. Surgical versus non-surgical treatment for carpal tunnel syndrome. Cochrane Database Syst Rev. 2003;(3):CD001552. Review. Update in: Cochrane Database Syst Rev 2008;(4):CD001552.
[28] Yücel H, Seyithanoğlu H. Choosing the most efficacious scoring method for carpal tunnel syndrome. Acta Orthop Traumatol Turc 2015;49:23-9.
[29] Lozano Calderon SA, Paiva A, Ring D. Patient satisfaction after open carpal tunnel release correlates with depression. J Hand Surg Am 2008;33:303-7.

The European Research Journal 2019;5(4):678-685 ORIGINAL ARTICLE

The relationship between atherogenic index of plasma and major risk factors of cardiovascular disease in obese and non-obese individuals

Seher Sayın, Ruhuşen Kutlu, Ahmet Koçak

Department of Family Medicine, Necmettin Erbakan University Meram School of Medicine, Konya, Turkey

DOI: 10.18621/eurj.414561

ABSTRACT

Objectives: Obesity is a health problem with gradually increasing prevalence and directly contribute to the development of cardiovascular disease (CVD). We aimed to investigate the relationship between atherogenic index of plasma (AIP) and major risk factors of CVD in obese and non-obese individuals.

Methods: This analytical case-control study was carried out on 501 individuals. Obese patients were included in the case group and normal-overweight individuals were included in the control group. The groups were similar in terms of ages and gender. Detailed medical background of the participants was recorded and antropometric parameters were measured. High-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, total cholesterol, triglyceride, fasting blood glucose (FBG) and insulin were measured. AIP risk categories were created according to published epidemiological data: AIP < 0.1 is associated with low risk, 0.1-0.24 with moderate risk, and > 0.24 with high risk.

Results: There was a statistically significant relationship between obesity, male gender, older age, smoking, insulin resistance, high waist circumference, elevation of the blood pressure, FBG and high CVD risk ($p < 0.005$). CVD risk in males were 6.254 times more than in females [OR = 6.254, 95% CI; (2.287-17.107)], CVD risk in obese was 3.436 times more than in none-obese and CVD risk in individuals with insulin resistance was 5.560-fold increase than individuals without insulin resistance [OR = 5.560, 95% CI; (3.069-10.070)] ($p < 0.001$).

Conclusions: Our findings showed that increasing in AIP is associated with obesity and other cardiovascular risk factors. Therefore, AIP can be used as a simple, economic and non invasive marker to identify for CVD risk.

Keywords: Obesity, cardiovascular disease, atherogenic index of plasma, insulin resistance

Received: April 11, 2018; Accepted: September 21, 2018; Published Online: November 6, 2018

Cardiovascular diseases (CVD) are the leading causes of morbidity and mortality worldwide [1]. According to the recent Turkish Statistical Institute recording system in our country, cardiovascular diseases ranked first in all causes of death with 40.4 % in 2014 [2]. The main risk factors for the development of CVD are: modifiable (hypertension, smoking, obesity, elevated total cholesterol or low-density lipoprotein-cholesterol (LDL-C) concentrations, reduced levels of high-density lipoprotein-cholesterol (HDL-

Address for correspondence: *Seher Sayın, MD., Necmettin Erbakan University Meram School of Medicine, Department of Family Medicine, Konya, Turkey*
E-mail: sehercidem@hotmail.com, Tel: +09 0332 223 6867

e-ISSN: 2149-3189

C), type 2 diabetes) and nonmodifiable (age, sex, genetic predisposition) [3]. The American Heart Association (AHA) has classified obesity as a major, modifiable risk factor for CVD in 1988 (4). The risk of CVD is significantly increased in obese patients, regardless of other risk factors. In particular, abdominal obesity is recognized as an independent risk factor of obesity-related diseases and death [5].

Atherogenic dyslipidemia that often accompany obesity is also associated cardiovascular diseases. Atherogenic dyslipidemia is characterized by low levels of HDL-C, high levels of triglycerides and LDL-C [6]. Although the concentrations of LDL-C continue to hold a principal role in the association of lipids to CVD, the atherogenic potential of a high TG: HDL-C molar ratio is now recognized by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III [7]. Atherogenic index of plasma (AIP), a new marker of atherogenicity, has been shown to significantly increase with cardiovascular risk. It has been suggested that AIP < 0.1 is associated with low risk, 0.1-0.24 with moderate risk, and > 0.24 with high risk (8).

As AIP is a strong marker to predict the risk of atherosclerosis and CVD, we aimed to investigate the relationship between AIP and major risk factors of CVD in obese and non-obese individuals.

METHODS

Study Design, Setting and Population

This analytical case-control study was constituted of 501 individuals aged 18 and older between 25.04.2017 and 01.08.2017. The study population was chosen randomly from the patients who applied with any problem to Family Medicine Outpatient Clinic. At first, the female and male subjects were matched according to their ages and gender. After calculating their body mass indexes (BMIs), the participants were categorized as nonobese and obese. Obese patients were included in the case group and normal-overweight individuals were included in the control group. In the previous studies, obesity prevalence in our country was found to be 35% [9]. In our study, the number of the subjects that had to be included in the study was calculated by using $n = t^2.p.q/d^2$ formula because the number of the individuals in the universe was not known. According to this calculation, 501 individuals aged 18 and older were included in our study.

Exclusion Criteria

Those with CVD, hypertension, diabetes mellitus, liver and kidney failure; patients who have been diagnosed with hyperlipidemia previously and who use antihyperlipidemic drugs; those who were pregnant, lactating women, and those who did not agree to participate in the study were not included in the research.

Ethical Considerations

The study protocol was approved by the Ethics Committee of Medical Faculty (Number: 2017/896) before participation in this study. All of the participants were volunteers. The participants were duly informed and written, and oral consent was obtained from volunteers according to the Principles of the Helsinki Declaration.

Collection of Data

The questionnaire prepared by the researcher was filled in with face to face interview technique. The question form was prepared to determine demographic features (age, gender, marital status, occupation, education, smoking status etc.). Of all the patients, systolic (SBP) and diastolic blood pressures (DBP) were measured by a sphygmomanometer in the supine position after at least 5 min of resting.

Major Risk Factors of CVD

The cardiovascular risk factors of the patients were determined in the direction of the 2018 guideline of the European Society of Cardiology.

Risk Factors

- Male sex
- Smoking
- Waist circumference (female) > 88 cm
- Waist circumference (male) > 102 cm
- BMI ≥ 30 kg/m2
- HOMA-IR ≥ 2.5
- Systolic blood pressure ≥ 140 mmHg
- Diastolic blood pressure ≥ 90mmHg
- Fasting blood glucose ≥ 100mg/dl

Antropometric Measurements

Anthropometric parameters including height, weight, and waist circumference (WC) were measured. Weight was measured while subjects wore only light clothing; height was assessed without shoes, back squared against the wall tape, eyes looking straight ahead using a stadiometer. WC (at the smallest point between lower costal and 10th rib border) was determined using a nonelastic fiberglass measuring tape. All of these measurements were done by the same researcher. BMI was calculated by dividing body weight in kilograms to square of body height in meters and expressed in units of (kg/m2). They were classifed as normal weight if BMI value was between 18.50-24.99 kg/m2, overweight if BMI value was between 25.0-29.99 kg/m2 and obese if it was higher than 30.0 kg/m2. According to WHO obesity criteria, waist circumference cut off value was accepted to be 88 cm in women and 102 cm in men [10]. Waist circumference was measured using a non-flexible tape, in the standing position and in midway between the lowest rib and the superior border of iliac crest.

Laboratory Analyses

In all subjects, a fasting blood sample was collected in the morning after fasting at least 10-12 h for analysis of the following biochemical parameters using standard techniques: Total cholesterol (TC), TG, LDL-C, HDL-C, FBG and insulin.

Atherogenic Index of Plasma (AIP)

AIP was calculated as the logarithmically transformed ratio of TG to HDL-C [log (TG/HDL-C)] measured in mmol/L. AIP risk categories were created according to published epidemiological data: AIP < 0.1 is associated with low risk, 0.1-0.24 with moderate risk, and > 0.24 with high risk [8].

Insulin Resistance

Homeostasis model assessment as an index of insulin resistance (HOMA-IR) test which was developed by Matthews *et al*. [11] is a simple test to show insulin resistance. For insulin resistance, HOMA-IR was calculated with the formula below by using fasting plasma glucose and insulin levels. Cut-off value of HOMA-IR was taken as 2.5. HOMA-IR = Serum glucose (mg/dL) × plasma insulin (μU/mL) / 405.

Statistical Aanalysis

While evaluating the results obtained in the study, SPSS 20.0 packet program was used for statistical analyses. Descriptive statistics for continuous variables were given in terms of average and standard deviation; and descriptive statistics for categorical data were given in terms of frequency and percentage. To compare quantitative data in doublet groups; student-t test was used if they corresponded normal distribution hypothesis and Mann-Whitney U test was used if they did not correspond normal distribution hypothesis and if they showed a skew distribution. Chi square test was used to compare categorical data. Results were evaluated at 95% confidence interval and significance was evaluated in $p < 0.05$ level.

RESULTS

Of all the participants, 372 (74.3%) were female, 129 (25.7%) were male, the mean age was 35.47 ± 10.91 years (34.16 ± 10.75 years in female, 39.26 ± 10.48 years in male), 389 (77.6%) were married, 164 (32.7%) primary school graduate, 192 (38.3%) university graduate, 203 (40.5%) were housewives. The frequency of smoking was 16.6% (n = 83). Of the participants, 127 (25.3%) were normal weight, 150 (29.9%) were overweight and 224 (44.7%) were obese.

When sociodemographic characteristics were compared with obesity; the prevalence of obesity was significantly higher in individuals aged 35 years and older ($p = 0.005$). The prevalence of obesity in individuals who were married, had low education and who were non-working were higher. This difference was statistically significant ($p < 0.001$). There was not a significant relationship between obesity and smoking ($p > 0.05$) (Table 1).

When investigating the relationship between BMI and insulin resistance; insulin resistance in obese group was significantly higher than normal weight group. This difference was statistically significant ($p < 0.001$). Systolic ($p < 0.001$) and diastolic ($p = 0.007$) blood pressures in obese group were significantly higher than non obese group. In the obese group, the risk of CVD was significantly higher than in the non-obese group ($p <0.001$) (Table 1).

When we compared with FBG, serum lipids and BMI

in our study; while the levels of FBG ($p < 0.001$), total cholesterol ($p = 0.026$), LDL-C ($p = 0.004$) and triglyceride ($p < 0.001$) were significantly higher, the level of HDL-C ($p < 0.001$) was significantly lower in the obese group (Table 2).

The CVD risk was significantly higher in individuals aged 35 years and older ($p = 0.003$), in smokers ($p = 0.002$), in male gender ($p < 0.001$) and

Table 1. Comparison of sociodemographic characteristics and BMI

Sociodemographic characteristics	Non-obese group (n = 277)		Obese group (n = 224)		χ^2	*p* value
	n	%	n	%		
Age						
< 35 years	157	61.3	99	38.7	7.722	**0.005**
≥ 35 years	120	49.0	125	51.0		
Gender						
Female	214	57.5	158	42.5	2.926	0.087
Male	63	48.8	66	51.2		
Marital status						
Married	193	49.6	196	50.4	22.670	**< 0.001**
Single	84	75.0	28	25.0		
Education level						
≤ Secondaryeducation	74	33.9	114	66.1	71.126	**< 0.001**
≥ High schooleducation	203	71.7	80	28.3		
Working status						
Working	193	68.9	87	31.1	47.767	**< 0.001**
Non-working	84	38.0	137	62.0		
Smoking						
Yes	52	62.7	31	37.3	2.181	0.140
No	225	53.8	193	46.2		
HOMA-IR						
<2.5	250	64.8	136	35.2	61.102	**< 0.001**
≥2.5	27	23.5	88	76.5		
Systolic blood pressure						
<140 mmHg	251	60.3	165	39.7	25.267	**< 0.001**
≥140 mmHg	26	30.6	59	69.4		
Diastolic blood pressure						
< 90 mmHg	263	57.0	198	43.0	7.239	**0.007**
≥ 90 mmHg	14	35.0	26	65.0		
AIP						
<0.1 low CVD risk	75	80.6	18	19.4		
0.1-0.24 moderate CVD risk	59	66.3	30	33.7	42.669	**< 0.001**
>0.24 high CVD risk	143	44.8	176	55.2		

AIP = atherogenic index of plasma, CVD = cardiovascular disease, BMI = body mass index, HOMA-IR = homeostasis model assessment as an index of insulin resistance

Table 2. Comparison of FBG and serum lipids in obese and non-obese groups

Parameters	Non-obese group (n = 277)	Obese group (n = 224)		
	Mean ± SD	Mean ± SD	t	*p value*
FBG (mg/dL)	91.11 ± 9.00	94.85 ± 9.03	-4.624	**< 0.001**
Total cholesterol (mg/dL)	185.42 ± 41.14	193.53 ± 39.57	-2.231	**0.026**
LDL-C (mg/dL)	114.12 ± 36.53	123.13 ± 33.25	-2.854	**0.004**
HDL-C (mg/dL)	49.40 ± 12.17	43.62 ± 9.26	5.862	**< 0.001**
Triglyceride (mg/dL)	105.72 ± 59.76	135.57 ± 67.80	-5.233	**< 0.001**

FBG = fasting blood glucose, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol

Table 3. Comparison of sociodemographic characteristics and CVD risk

Sociodemographic characteristics	Low/moderate CVD risk AIP ≤ 0.24 (n = 182)		High CVD risk AIP > 0.24 (n = 319)		χ^2	*p value*
	n	%	n	%		
Age						
< 35 years	109	42.6	147	57.4	8.843	**0.003**
≥ 35 years	73	29.8	172	70.2		
Gender						
Female	164	44.1	208	55.9	37.599	**< 0.001**
Male	18	14.0	111	86.0		
Smoking						
Yes	18	21.7	65	78.3	9.219	**0.002**
No	164	39.2	254	60.8		
WC (female)						
≤ 88 cm	102	60.0	68	40.0	32.164	**< 0.001**
> 88 cm	62	30.7	140	69.3		
WC (male)						
≤ 102 cm	14	25.0	42	75.0	10.057	**0.002**
> 102 cm	4	5.5	69	94.5		
Obesity						
BMI < 30 kg/m^2	134	48.4	143	51.6	38.879	**< 0.001**
BMI ≥ 30 kg/m^2	48	21.4	176	78.6		
HOMA-IR						
<2.5	168	43.5	218	56.5	37.646	**< 0.001**
≥2.5	14	12.2	101	87.8		
SBP						
< 140 mmHg	169	39.4	260	60.6	12.136	**< 0.001**
≥ 140 mmHg	13	18.1	59	81.9		
DBP						
< 90 mmHg	170	36.8	292	63.2	0.565	0.452
≥ 90 mmHg	12	30.8	27	69.2		
FBG						
< 100 mg/dl	158	40.0	237	60.0	10.887	**< 0.001**
≥ 100mg/dl	24	22.6	82	77.4		

BMI = body mass index, CVD = cardiovascular disease, FBG = fasting blood glucose, DBP = diastolic blood pressure, HOMA-IR = homeostasis model assessment as an index of insulin resistance, SBP = systolic blood pressure, WC = waist circumference

Table 4. Comparison of some parameters and CVD risks (AIP > 0.24).

Parameters		OR	%95 CI		*p value*
			Lower	Upper	
Gender	Female	1	2.838	8.331	**< 0.001**
	Male	4.862			
WC (female)	≤ 88 cm	1	2.207	5.199	**< 0.001**
	> 88 cm	3.387			
WC (male)	≤ 102 cm	1	1.775	18.629	**0.002**
	> 102 cm	5.570			
Obesity	BMI < 30 kg/m^2	1	2.311	5.109	**< 0.001**
	BMI ≥ 30 kg/m^2	3.436			
HOMA-IR	< 2.5	1	3.069	10.070	**< 0.001**
	≥ 2.5	5.560			

AIP = atherogenic index of plasma, BMI = body mass index, CVD = cardiovascular disease, HOMA-IR = homeostasis model assessment as an index of insulin resistance, WC = waist circumference

Table 5. Correlations of some parameters in obese and non-obese groups

PARAMETERS		1	2	3	4	5	6
1. AIP	r	1					
	p						
2. Age (year)	r	0.190	1				
	p	**< 0.001**					
3. BMI (kg/m²)	r	0.354	0.165	1			
	p	**< 0.001**	**< 0.001**				
4. WC (cm)	r	0.456	0.293	0.819	1		
	p	**< 0.001**	**< 0.001**	**< 0.001**			
5. Insulin	r	0.266	-0.102	0.311	0.275	1	
	p	**< 0.001**	**0.024**	**< 0.001**	**< 0.001**		
6. HOMA-IR	r	0.261	-0.070	0.299	0.258	0.983	1
	p	**< 0.001**	0.112	**< 0.001**	**< 0.001**	**< 0.001**	

AIP = atherogenic index of plasma, BMI = body mass index, HOMA-IR = homeostasis model assessment as an index of insulin resistance, WC = waist circumference

in individuals with insulin resistance ($p < 0.001$) (Table 3).

CVD risk in males were 6.254 times more than in females [OR = 6.254, 95% CI; (2.287-17.107)], and this difference was found to be statistically significant ($p < 0.001$). CVD risk in individuals with insulin resistance was 5.560-fold increase than individuals without insulin resistance [OR = 5.560, 95% CI; (3.069-10.070)] and this difference was found to be highly statistically significant ($p < 0.001$). The odds ratios of the other parameters were shown in Table 4.

When the correlation between AIP and waist circumference is examined; AIP was correlated with waist circumference (r = 0.456, $p < 0.001$) (Table 5). When linear regression analysis is performed; 20.8% of the increase in AIP is attributed to the increase in waist circumference ($R^2 = 0.208$, $p < 0.001$) (Figure 1).

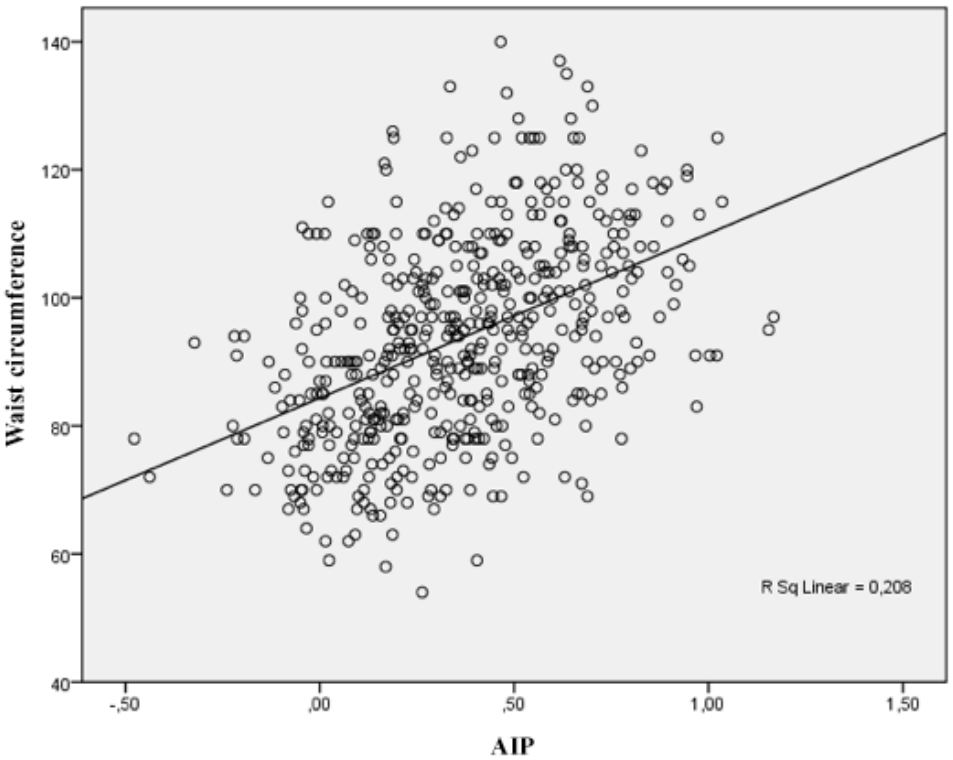


Figure 1. Linear regression analysis between waist circumference and AIP. R^2= Regression determinant coefficient (R2=0.208, $p < 0.001$)

DISCUSSION

Before mentioning the conclusions, the limitations of the study should be considered. Although the overall sample was relatively large, we reached a small group. In addition, although a quite close match, this study group is not entirely representative of the Turkish population. The study includes only the citizens of Konya. The most important limitation of our study is that the physical activity and nutritional status have not been assessed.

Obesity is a complicated and multifactorial disease which provides a basis for many diseases, reduces life quality and longevity of individuals and it causes deaths. Overweight and obesity directly contribute to the development of cardiovascular diseases and type 2 diabetes mellitus. For this reason, it has become an important public health concern on a global scale [12]. In this study, we assessed the correlation between AIP and the major risk factors of CVD in obese and non-obese individuals.

When we looked at the relation between obesity and cardiovascular risks in our study, it was seen that as BMI increased, cardiovascular risk increased as well. Cardiovascular risk in obese individuals was 3.436 times more than in none-obese individuals. Chhezom *et al*. [12] found out in their study that obese individuals had significantly higher cardiovascular risk. It was discovered in many studies that waist circumference as a marker of abdominal obesity is a better marker to reveal cardiovascular risk than BMI [13]. In our study, there was a significant relation between WC and cardiovascular risks. Shen *et al*. [14] showed that there was a positive relationship between waist circumference and AIP in their studies. Ying Lee *et al*. [15] stated in their meta-analysis study that preventing abdominal obesity is especially more important to reduce cardiovascular risk.

The strongest independent risk factor for CVD development is age. It was discovered in our study that cardiovascular risk in individuals above 35 years of age is 4.862 times more than in ones under 35 years of age. In women in premenopausal period, CVD is seen 10 years later compared to men. The reason of this delay is attributed to protective effect of estrogen [16]. The risk increases in women during premenopausal period but this risk is lower than in men when making an evaluation between age groups. In the study performed by Yıldız *et al*. [16] in our country, it was shown that cardiovascular risk increases significantly in postmenopausal women compared to premenopausal women. The studies indicate that cardiovascular risk in men is significantly higher than in women in all groups of age [17, 18]. We also determined that cardiovascular risk is 5.570 times more in men than in women.

In our study, cardiovascular risk in smokers was significantly higher than in non-smokers. Smoking increases CVD risk 2-3 times and causes the risk to increase more by interacting with other risk factors. Smoking stimulates sympathetic nervous system, increases blood pressure and reduces oxygen delivery in myocardium. Besides, it has also effects on atherosclerosis. A decrease is observed in events related to CVD when smoking is given up [19].

It has long been known that hypertension plays an important role in pathogenesis of coronary artery disease and other cardiovascular diseases. Hypertension is responsible for 35% of all atherosclerotic cardiovascular events [20]. In our study, CVD risk is significantly higher in individuals whose systolic blood pressure was higher. Onat [21], stated in their study that high blood pressure increases cardiovascular risk significantly.

In our study, we determined that cardiovascular risk was 5.560 times more in individuals with high insulin resistance. Insulin resistance makes a significant contribution to atherosclerosis even before the occurrence of overt diabetes. In meta-analysis studies, it was seen that increased insulin and fasting blood glucose in non-diabetic patients increase CVD risk significantly [22, 23]. It was found out in our study that CVD risk was significantly higher in individuals with high FBG. Similiar to our study, Oluyombo *et al*. [24] showed that as FBG level increases, cardiovascular risk increases in individuals as well. The studies indicate that mortality risk related to cardiovascular events in diabetic patients was 2-6 times more than in non-diabetic patients [25].

CONCLUSION

FBG, insulin resistance, high waist circumference, elevation of the blood pressure, LDL-C, total cholesterol, triglyceride in obese group were

significantly higher than non obese group. Only, the level of HDL-C was significantly lower in the obese group. AIP, a new marker of atherogenicity, has been shown to significantly increase with cardiovascular risks. AIP could be a convenient and practical approach for assessment of CVD risks in public health settings and primary health centers. In this study, there was a statistically significant relationship between obesity, male gender, older age, smoking, insulin resistance, high waist circumference, elevation of the blood pressure, FBG and AIP > 0.24 (high CVD 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.

REFERENCES

[1] WHO. World health statistics 2015. Geneva: World Health Organization; 2015e.
[2] Statistics of causes of death, 2015. [Internet] Available from: www.turkstat.gov.tr Accessed: 26.5.2017.
[3] Després JP, Arsenault BJ, Côté M, Cartier A, Lemieux I. Abdominal obesity: the cholesterol of the 21st century? Can J Cardiol 2008;24:7-12.
[4] Eckel RH, Krauss RM. American Heart Association call to action: obesity as a major risk factor for coronary heart disease. AHA Nutrition Committee. Circulation 1998;97:2099-100.
[5] Pi-Sunyer X. The medical risks of obesity. Postgrad Med 2009;121:21-33.
[6] Manjunath CN, Rawal JR, Irani PM, Madhu K. Atherogenic dyslipidemia. Indian J Endocrinol Metab 2013;17:969-76.
[7] Executive Summary of The 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). JAMA 2001;285:2486-97.
[8] Dobiasova M. Atherogenic index of plasma as a significant predictor of cardiovascular risk: from research to practice. Vnitr Lek 2006;52:64-71.
[9] Bahceci M. Obesity. In: TEMD Obesity, Dyslipidemia. Hypertension Study Group eds. Turkish Association of Endocrinology and Metabolism. Hypertension, Obesity and Lipid Metabolism Diagnosis and Treatment Guide 2011;50-80.
[10] WHO. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 894. Geneva: World Health Organization, 2011.
[11] 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.
[12] Chhezom K, Arslan MI, Hoque MM, Biswas SK. Biomarkers of cardiovascular and metabolic diseases in otherwise healthy overweight subjects in Bangladesh. Diabetes Metab Syndr 2017;11 Suppl 1;S381-4.
[13] Guasch-Ferré M, Bulló M, Martínez-González MÁ, Corella D, Estruch R, Covas MI, et al. Waist-to-height ratio and cardiovascular risk factors in elderly individuals at high cardiovascular risk. PLoS One 2012;7:e43275.
[14] Shen SW, Lu Y, Li F, Yang CJ, Feng YB, Li HW, et al. Atherogenic index of plasma is an effective index for estimating abdominal obesity. Lipids Health Dis 2018;17:11.
[15] Ying Lee CM, Huxley RR, Wildman RP, Woodward M. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. J Clin Epidemiol 2008;61:646-53.
[16] Yıldız C, Yıldız A, Tekiner F. Comparison of serum lipid profile and plasma atherogenic index between premenopausal and postmenopausal women. Dicle Medical Journal 2015;42:36-40.
[17] Niroumand S, Khajedaluee M, Khadem-Rezaiyan M, Abrishami M, Juya M, Khodaee G, et al. Atherogenic Index of Plasma (AIP): A marker of cardiovascular disease. Med J Islam Repub Iran 2015;29:240.
[18] Andreeva-Gateva PA, Konsulova P, Orbetzova M, Georgieva-Nikolova R, Tafradjiiska-Hadjiolova R, Angelova V, et al. Differentiation of obese patients at moderate or higher Findrisc score based on their atherogenic index. Postgrad Med 2016;128:790-6.
[19] Buğan B, Çelik T. Risk factors for coronary artery disease. J Clin Anal Med 2014;5:159-63.
[20] Abacı A. The current status of cardiovascular risk factors in Turkey. Arch Turk Soc Cardiol 2011;39:1-5.
[21] Onat A. Dynamics in cardiometabolic risk among Turkish adults: similarities to that in Iranians? Int J Prev Med 2011;2:56-63.
[22] Gast KB, Tjeerdema N, Stijnen T, Smit JW, Dekkers OM. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. PLoS One 2012;7:e52036.
[23] Young EE, Okafor CN, Iroezindu MO, Agbalu IS. Insulin resistance, metabolic syndrome, and lipids in African women. Niger J Clin Pract 2016;19:793-8.
[24] Oluyombo R, Akinwusi PO, Olamoyegun MO, Ayodele OE, Fawale MB, Okunola OO, et al. Clustering of cardiovascular risk factors in semi-urban communities in south-western Nigeria. Cardiovasc J Afr 2016;27:322-7.
[25] Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular

The European Research Journal 2019;5(4):686-690 ORIGINAL ARTICLE

The alteration of first trimester screening markers in fresh and frozen-thawed blastocyst transfers

Nur Dokuzeylül Güngör[1], Tuğba Gürbüz[2], Ayşe Filiz Gökmen Karasu[3], Aynur Erşahin[1]

[1]Department of In Vitro Fertilization Center, Bahçeşehir University, Medical Park Göztepe Hospital, İstanbul, Turkey
[2]Department of Gynecology and Obstetrics, Bahçeşehir University, Medical Park Göztepe Hospital, İstanbul, Turkey
[3]Department of Gynecology and Obstetrics, Bezmialem University School of Medicine, İstanbul, Turkey

DOI: 10.18621/eurj.400462

ABSTRACT

Objectives: The aim of this study was to investigate whether first trimester combined screening for major fetal trisomies is influenced by assisted reproduction techniques (ART) from blastocyst transfer, with or without cryopreservation.

Methods: This study is a retrospective analysis involving 115 singleton pregnancies with euploid fetuses recruited between January 2017 and December 2017. Sixty-five women conceived with fresh blastocysts from *in vitro* fertilization (IVF) cycles (fresh-blasto), 50 with frozen-thawed blastocysts. All cases underwent ultrasound assessment at 11+0 - 13+6 weeks with measurements of crown rump length, nuchal translucency (NT) , free beta-human chorionic gonadotrophin (free β-hCG) and pregnancy-associated plasma protein A (PAPP-A) concentrations.

Results: Baseline characteristics and pregnancy outcomes did not differ substantially among the study groups. The NT was not significantly different in the frozen-thawed -blasto compared to the fresh-blasto group (p = 0.741). The free β-hCG levels was not significantly different in frozen-thawed-blasto group compared to fresh-blasto group (p = 0.495). The two groups showed no significant difference in the PAPP-A levels (p = 0,139). The median delta crown rump length was also not significantly different among the two groups (p = 0.758).

Conclusions: In ART pregnancies from blastocyst transfer, with or without cryopreservation, the NT measurement, free β-hCG concentration and PAPP-A levels did not show any significant difference. These features are apparently unrelated to the outcome of pregnancy and may be due to alterations or delays in embryogenesis or placentation with potential relevance for the screening test performance.

Keywords: Assisted reproductive technique, blastocyst, first trimester screening, frozen-thawed embryo transfer, fresh embryo transfer

Received: March 2, 2018; Accepted: March 21, 2018; Published Online: June 19, 2018

Women with pregnancies achieved by assisted reproduction techniques (ART) are older than average and are therefore at higher risk for Down syndrome and other aneuploidies [1]. An effective screening test with a low false-positive rate (FPR) should be applied to these patients. Combined first trimester screening, utilizing maternal age, nuchal translucency (NT) measurement and maternal biochemistry (free beta-human chorionic gonadotrophin [free β-hCG] and pregnancy-associated

Address for correspondence: *Tuğba Gürbüz, MD., Bahçeşehir University, Medical Park Göztepe Hospital, Department of Gynecology and Obstetrics, 23 Nisan Cad., No: 17, Merdivenköy /Kadıköy, İstanbul, Turkey*
E-mail: drtgurbuz@hotmail.com

e-ISSN: 2149-3189

plasma protein A [PAPP-A]), has been shown to detect 85-90% of cases with trisomy 21 and other major aneuploidies at a screen positive rate of 5-6% [2-5].

In pregnancies affected by Down syndrome, maternal serum levels of PAPP-A are reduced [6] while free β-hCG subunits are elevated [7] in the first trimester. When combined with ultrasound measurement of NT, these two markers provide an effective means for screening for Down syndrome [8-11]. Maternal serum levels of PAPP-A and free β-hCG are affected by variables such as maternal cigarette smoking, parity, maternal weight and fetal gender [12, 13]. Studies also suggest a reduction in PAPP-A level in *in vitro* fertilization (IVF) pregnancies [14-17]. In IVF pregnancies, the currently largest explored group, an increase in free β-HCG and/or decrease in PAPP-A values have been reported [14, 15, 18-20].

In some studies, a relationship between unexplained elevations and reductions in maternal serum markers and obstetric complications has been reported [21, 22] . Therefore, altered first trimester serum concentrations in assisted-conception pregnancies could be an indicator of abnormal trophoblast invasion.

In the present study, we investigated the effects of fresh or frozen thawed embryo transfer on first trimester serum PAPP-A and free β-hCG levels.

METHODS

This retrospective study was approved by the Ethics Committee of Göztepe Medicalpark Hospital, Istanbul, Turkey (No: 2018/16). One hundred fifteen singleton pregnancies conceived by ART, who received combined first-trimester Down syndrome screening from January 2017 to December 2017 in IVF center.

Women who conceived with fresh or frozen-thawed embryos from conventional IVF were referred to IVF center for counselling on the risk of fetal chromosomal disorders. Preimplantation genetic screening tests didn't performed in cases. All cases underwent ultrasound assessment at 11+0 - 13+6 weeks with measurements of crown rump length (CRL), NT, free β-hCG and PAPP-A concentrations. Exclusion criteria were pregnancies with structural fetal malformations or aneuploidy, pregnancies resulting in miscarriage and stillbirth, singleton pregnancies following embryo reduction or spontaneous reduction of earlier multiple implantation. Those pregnancies with more than one gestational sacseen on ultrasound examination 5-6 weeks after theassisted reproduction procedure were excluded from thisstudy.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) software package version 17.0 for Windows. The Shapiro-Wilk test was used to determine the normality of data distribution. Significance of differences between the groups was determined by the non-parametric Mann-Whitney U-test. Differences in serum values and fetal NT were evaluated with the Kruskal-Wallis test. Significance was assumed at p value of < 0.05.

RESULTS

Table 1 summarizes the maternal age, maternal weight and gestational age at blood sampling of the

Table 1. Maternal characteristics and gestational age at sampling of the cases

Parameters	Fresh embryos n = 65	Frozen embryos n = 50	*p value**
Maternal age (years)	32.48 ± 4.184	31.86 ± 4.83	0.461
Maternal weight at sampling (kg)	65.67 ± 1.56	63.36 ± 1.71	0.231
Gestational age at sampling (week)	12.38 ± 0.64	12.17 ± 0.68	0.091
Nuchal translucency	1.44 ± 0.51	1.47 ± 0.04	0.741
Crown rump length	58.9 ± 0.97	58.6 ± 1.17	0.758

Data are shown as mean±standard deviation. *The Shapiro-Wilk test was used to determine p value.

Table 2. PAPP-A and free β-hCG levels of the cases

Parameters	Fresh embryos n = 65	Frozen embryos n = 50	*p value**
Free β-hCG levels (IU/L)	36.39 ± 4.29	35.87 ± 4.71	0.495
PAPP-A levels (IU/L)	3.24 ± 0.40	2.74 ± 0.32	0.139

Data are shown as median±standard deviation. β-hCG = beta-human chorionic gonadotrophin, PAPP-A = pregnancy – associated plasma protein A, *The Mann-Whitney U test was used to determine p value

cases and controls. Baseline characteristics maternal age (p = 0.461), maternal weight at sampling (p = 0.231) and gestational age at sampling (p = 0.091) did not differ significantly among the study groups. The NT was not significantly different in the frozen-thawed -blasto compared to the fresh-blasto group (p = 0.741). The free β-hCG levels (IU/L) was not significantly different in frozen-thawed -blasto group compared to fresh-blasto group (p = 0.495). The two groups showed no significant differences in the PAPP-A levels (IU/L) (p = 0.139). The median delta CRL was also not significantly different among the two groups (p = 0.758). Table 2 shows the PAPP-A multiple of the median (MoM) and free β-hCG MoM of the cases.

DISCUSSION

Biochemical markers (biomarkers) are serum proteins synthesized by placenta (PAPP-A, free β-hCG, hCG and unconjugated estriol [uE3]) and by the fetus (alpha fetoprotein [AFP]). Whereas a reduced maternal serum level of AFP in second trimester is caused by defective differentiation of the fetal liver in Down's syndrome fetuses [23] the changes in the levels of placenta-derived proteins have not been explained.

IVF is normally performed after controlled ovarian hyperstimulation, which results in marked endocrine changes related to maturation of multiple follicles and later development of multiple corpora lutea. These endocrine changes may have a negative effect on implantation and early pregnancy, including changes in the level of biomarkers for genetic diagnostic testing. In contrast to fresh IVF cycles, frozen-thawed blastocysts (FET) is usually performed in natural or mildly stimulated cycles, which may affect the level of first trimester serum markers differently.

This study examined the different effects of transfer type (fresh vs frozen-thawed) of embryos on PAPP-A and free β-hCG levels between 11+0 to 13+6 weeks. We found no significant reduction of PAPP-A concentration in pregnancies conceived either with fresh or FET.

In the first trimester, PAPP-A is the most effective serum marker for fetal Down syndrome, both in combined and integrated screening [24]. In ART pregnancies, the reduced PAPP-A concentration is likely to result in a high FPR during screening.

Mode of fertilization, culture media and culture conditions are some aspects of the fertility treatment which may affect the embryo, implantation and early pregnancy [25]. Lower PAPP-A has been reported regardless of whether the cause of infertility was due to the male, female, or both. The pathophysiological basis for this reduction in PAPP-A levels after ART pregnancies when compared with natural pregnancies is still not known. A placental problem is the most likely explanation for the observed biochemical changes. PAPP-A and β-hCG are both produced in the placenta. A delayed placental maturation induced by the infertility itself [26] the drugs used for ovarian stimulation, laboratory manipulation, or all of these factors seem to be suitable explanations for these changes.Infertility itself or its severity can be directly related to these findings. In fact, Ranta *et al*. [26] found that PAPP-A values were significantly reduced in pregnancies conceived naturally after a time to pregnancy greater than 2 years compared with those conceived after a shorter time. This shows that infertility itself could be responsible for these biochemical changes. NT is unaffected by the mode

of conception. Singleton pregnancies achieved by IVF and intracytoplasmic sperm injection (ICSI) with non-donor oocytes have reduced maternal serum PAPP-A and increased FPR, which are significant only in ICSI cycles. Pregnancies from frozen embryos with hormone therapy also show decreased PAPP-A, but without affecting the FPR. Elevated maternal serum free β-hCG levels in oocyte donation do not influence the FPR [27].

In ART pregnancies from blastocyst transfer, with or without cryopreservation, both the NT measurement and free β-hCG concentration are higher as compared to spontaneous conceptions, whereas PAPP-A does not show any significant difference. These features are apparently unrelated to the outcome of pregnancy and may be due to alterations or delays in embryogenesis or placentation with potential relevance for the screening test performance [28].

CONCLUSION

Today, the data on the effect of ART for the components of first trimester combined screening for chromosomal analysis are still controversial. In ART pregnancies from blastocyst transfer, with or without cryopreservation, NT measurement, free β-hCG concentration and PAPP-A levels did not show any significant difference. These features are apparently unrelated to the outcome of pregnancy and may be due to alterations or delays in embryogenesis or placentation with potential relevance for the screening test performance. While appropriate adjustment is necessary in applying this marker in the screening program for ART pregnancies, further studies are warranted to find out the cause for the lower PAPP-A level in pregnancies following ART.

Ethics Committee Approval

This retrospective study was approved by the Ethics Committee of Göztepe Medicalpark Hospital, Istanbul, Turkey.

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] Anckaert E, Schiettecatte J, Sleurs E, Devroey P, Smitz J. First trimester screening for Down's syndrome after assisted reproductive technology: non-male factor infertility is associated with elevated free beta-human chorionic gonadotropin levels at 10-14 weeks of gestation. Fertil Steril 2008;90:1206-10.
[2] Krantz DA, Hallahan TW, Orlandi F, Buchanan P, Larsen JW, Macri JN. First-trimester Down syndrome screening using dried blood biochemistry and nuchal translucency. Obstet Gynecol 2000;96:207-13.
[3] Spencer K, Nicolaides KH. Screening for trisomy 21 in twins using first trimester ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years experience. Br J Obstet Gynecol 2003;110:276-80.
[4] Spencer K, Souter V, Tul N, Snijders R, Nicolaides KH. A screening program for trisomy 21 at 10-14 weeks using fetal nuchal translucency, maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 1999;13:231-7.
[5] Spencer K, Spencer CE, Power M, Dawson C, Nicolaides KH. Screening for chromosomal abnormalities in the first trimester using ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years prospective experience. Br J Obstet Gynecol 2003;110:281-6.
[6] Brambati B, Macintosh MC, Teisner B. Low maternal serum levels of pregnancy associated plasma protein A (PAPP-A) in the first trimester in association with abnormal fetal karyotype. Br J Obstet Gynaecol 1993;100:324-6.
[7] Brambati B, Tului L, Bonacchi I, Shrimanker K, Suzuki Y, Grudzinskas JG. Serum PAPP-A and free beta-hCG are firsttrimester screening markers for Down syndrome. Prenat Diagn 1994;14:1043-7.
[8] Wald NJ, George L, Smith D, Densem JW, Petterson K. Serum screening for Down's syndrome between 8 and 14 weeks ofpregnancy. International prenatal screening research group. Br J Obstet Gynaecol 1996;103:407-12.
[9] Haddow JE, Palomaki GE, Knight GJ, Williams J, Miller WA, Johnson A. Screening of maternal serum for fetal Down'ssyndrome in the first trimester. N Engl J Med 1998;338:955-61.
[10] Spencer K. The influence of smoking on maternal serum PAPPA and free beta-hCG levels in the first trimester of pregnancy. Prenat Diagn 1999;19:1065-6.
[11] Bindra R, Heath V, Liao A, Spencer K, Nicolaides KH. One stop clinic for assessment of risk for trisomy 21 at 11-14 weeks: a prospective study of 15 030 pregnancies. Ultrasound Obstet Gynecol 2002;20:219-25.
[12] De Graaf IM, Cuckle HS, Pajkrt E, Leschot NJ, Bleker OP, van Lith JM. Co-variables in first trimester maternal serum screening. Prenat Diagn 2000;20:186-9.
[13] Niemimaa M, Heinonen S, Seppala M, Ryynanen M. The influence of smoking on the pregnancy-associated plasma protein A, free beta human chorionic gonadotrophin and nuchal translucency. BJOG 2003;110:664-7.

[14] Liao AW, Heath V, Kametas N, Spencer K, Nicolaides KH. First-trimester screening for trisomy 21 in singleton pregnancies achieved by assisted reproduction. Hum Reprod 2001;16:1501-4.
[15] Maymon R, Shulman A. Serial first- and second-trimester Down's syndrome screening tests among IVF-versus naturally conceived singletons. Hum Reprod 2002;17:1081-5.
[16] Orlandi F, Rossi C, Allegra A. First trimester screening with free beta-hCG, PAPP-A and nuchal translucency in pregnancies conceived with assisted reproduction. Prenat Diagn 2002;22:718-21.
[17] Bersinger NA, Wunder D, Vanderlick F. Maternal serum levels of placental proteins after in vitro fertilisation and their implications for prenatal screening. Prenat Diagn 2004;24:471-7.
[18] Niemimaa M, Heinonen S, Seppala M, Hippelainen M, Martikainen H, Ryynanen M. First-trimester screening for Down's syndrome in in-vitro fertilization pregnancies. Fertil Steril 2001;76:1282-83.
[19] Maymon R, Shulman A. Integrated first- and second-trimester Down syndrome screening test among unaffected IVF pregnancies. Prenat Diagn 2004;24:125-9.
[20] Ghisoni L, Ferrazzi E, Castagna C, Levi Setti PE, Masini AC, PigniA. Prenatal diagnosis after ART success: the role of early combined screening tests in counselling pregnant patients. Placenta 2003;24:99-103.
[21] Ong CY, Liao AW, Spencer K, Munim S, Nicolaides KH. First trimester maternal serum free beta human chorionic gonadotrophin and pregnancy associated plasma protein A as predictors of pregnancy complications. Br J Obstet Gynecol 2000;107:1265-70.
[22] Phil K, Larsen T, Krebs L, Christiansen M. First trimester maternal serum PAPP-A, β-hCG and ADAM12 in prediction of small-for-gestational-age fetuses. Prenat Diagn 2008;28:1131-5.
[23] Chen H, Egan JO, Ohlu JF. Regulation and activities of alpha-fetoprotein. Crit Rev Eukaryot Gene Expr 1997;7:11-41.
[24] Gardner DK, Balaban B. Choosing between day 3 and day 5 embryo transfers. Clin Obstet Gynecol 2006;49:85-92.
[25] Dumoulin JC, Land JA, Van Montfoort AP, Nelissen EC, Coonen E, Derhaag JG, et al. Effect of in vitro culture of human embryos on birthweight of newborns, Hum Reprod 2010;25:605-12.
[26] Ranta JK, Raatikainen K, Romppanen J, Pulkki K, Heinonen S. Increased time-to-pregnancy and first trimester Down's syndrome screening. Hum Reprod 2010;25:412-7.
[27] Bellver J, Casanova C, Garrido N, Lara C, Remohí J, Pellicer A, et al. Additive effect of factors related to assisted conception on the reduction of maternal serum PAPP-A concentrations and the increasedfalse-positive rates in first-trimester Down syndrome screening. Fertil Steril 2013;100:1314-20.
[28] Cavoretto P, Dallagiovanna C, Vigano P, Somigliana E, Persico N, Papaleo E, et al. First trimester combined screening test in pregnancies derived from blastocyst transfer. Eur J Obstet Gynecol Reprod Biol 2016;198:50-5.

The European Research Journal 2019;5(4):691-696 ORIGINAL ARTICLE

Increased P wave duration and dispersion is associated with catheter-related atrial fibrillation during electrophysiological study

Yahya Kemal İçen[1], Hilmi Erdem Sümbül[2], Mevlüt Koç[1]

[1]*Department of Cardiology, University of Health Sciences, Adana City Training and Research Hospital, Adana, Turkey*
[2]*Department of Internal Medicine, University of Health Sciences, Adana City Training and Research Hospital, Adana, Turkey*

DOI: 10.18621/eurj.412058

ABSTRACT

Objectives: Catheter-related atrial fibrillation (AF) is a common cause during electrophysiological study (EPS) and prolongs the duration of the procedure. In our study, we compared P wave duration and dispersion in patients with and without catheter-related atrial fibrillation during EPS.

Methods: One hundred forty five patients who had normal EPS findings and who were found to have catheter related atrial fibrillation were included in our study. Electrocardiogram was performed in all patients and the pulse rate, the longest P wave duration (Pmax), the shortest P wave duration (Pmin) and the difference between of those (P wave dispersion: Pdisp) were recorded. EPS was performed in all patients. The patients were divided into two groups as the group 1 (without catheter-related AF) and group 2 (with catheter-related AF).

Results: In group 2, EPS time was significantly longer, Pmax and Pdisp were found to be significantly higher, Pmin was found to be significantly lower. Binominal logistic regression analysis revealed that, Pmax (OR: 1.077, 95% CI: 1.043-1.112, $p < 0.001$), Pmin (OR: 0.889, 95% CI: 0.853-926, $p < 0.001$) and Pdisp (OR: 1.125, 95% CI: 1.080-1.173, $p < 0.001$) were all independent predictors for catheter-related AF. In ROC analyses, Pmax cut-off value of 120 ms determined the catheter-related AF with 61% sensitivity and 67% specificity, Pdisp cut-off value of 35 ms determined the catheter-related AF with 80% sensitivity and 71% specificity.

Conclusion: Patients with longer Pdisp and Pmax and shorter Pmin may develop catheter-related AF during EPS.

Keywords: Atrial fibrillation, P wave dispersion, electrophysiological study

Received: April 2, 2018; Accepted: July 21, 2018; Published Online: September 10, 2018

Electrophysiological study (EPS) is a common invasive method that is used for diagnosis and treatment of arrhythmic patients which was recommended by guidelines [1]. If ablation is not performed, the diagnostic EPS can be done in a short time. In some patients, arrhythmias including dual pathway, accessory pathway or atrial tachycardia are not found and only catheter-related atrial fibrillation (AF) episodes may develop. This episodes may lead to prolongation of the EPS time and more radiation exposure.

P wave dispersion (Pdisp) is calculated as the difference between the longest P wave duration and the shortest P wave duration on 12 lead surface elec-

Address for correspondence: *Yahya Kemal İçen, MD., Assistant Professor, University of Health Sciences, Adana City Training and Research Hospital, Department of Cardiology, Adana, Turkey*
E-mail: dryahyakemalicen@gmail.com

e-ISSN: 2149-3189

trocardiogram (ECG) [2]. Pdisp demonstrates electrical heterogeneity in the atriums so have been identified as indicator in patients with AF [2-6]. It is inevitable that the EPS catheter is in contact with the atrium wall during EPS. So, catheter-related irregular atrial arrhythmias may develop including AF and EPS time may delay.

If we can predict which patients will develop AF, we can be more careful while placing catheter and reduce the probability of catheter related AF. In the literature, there is no clear association between catheter-related AF and P wave duration-Pdisp. In this study, we aim to investigate whether there is a relationship between catheterrelated AF and P wave duration-Pdisp.

METHODS

Patient Population

A total of 145 patients who preformed EPS due to palpiation were included retrospectively between 2011 and 2015 in this study. Inclusion criteria were accepted as being in sinus rhythm before and after EPS. The patients with coronary artery disease were excluded due to their possible possibility to develop AF. Also, structural heart disease and another chronic disease as well as another arrhythmia in association with AF (Such as atrioventricular nodal reentran tachycardia, atrioventricular reciprocal tachycardia, Wolf-Parkinson-White syndrome) were excluded from the study. Demographic findings were recorded in all patients. The study protocol was approved by the local ethics committee.

Electrocardiographic and Echocardiographic Assessment

Twelve-lead surface ECGs of all patients were recorded by the Nihon Kohden Cardiofax V model ECG-1550K device before the EPS procedure. ECGs with a speed of 25 mm/s and standard calibration of 1 mv/10 mm were used. These ECGs were assessed by two cardiologists independently. The longest P wave duration on sufrace ECG was accepted Pmax, the shortest P wave duration was accepted as Pmin. The difference between these parameters was accepted to be P wave dispersion (Pdisp). Mean values were recorded. Echocardiographic examinations were performed by using an Epiq 7 (Philips Healthcare, DA Best, Netherlands) echocardiography system. Ejection fraction (EF) by Simpson's method, left atrial volüme (LAV), left atrial diameter, E wave velocity and A wave velocity were measured with transthoracic echocardiography.

Electrophysiological Study Data Assessment

All antiarrhythmic drugs were discontinued for at least five half-lives before initiation of the EPS. The patients were subsequently transferred into EPS laboratory. EP Tracer device was used for the procedure (Medtronic Inc., USA). A four pole diagnostic catheter (6F, 110 cm, Mariner® SC Series, Medtronic, Minneapolis, MN, USA) was placed in the right atrial appendix. A four pole radiofrequency ablation catheter (7F, 110 cm, RF Mariner® MC, Medtronic, USA) was placed in the region where sensory recording was made in the right ventricle. Tachycardia was attempted to be induced with programmed atrial and ventricular beats in all patients. Irregular and chaotic atrial rhythm in intra cardiac record was accepted catheter-related AF (Figure 1A and 1B). Patients without catheter-related AF were accepted group 1 and with catheter-related AF were accepted group 2. The EPS time was recorded in both groups.

Statistical analysis

The variables were divided into two groups as continuous and categorical variables. Kolmogorov-Smirnov test was used to determine whether continuous variables had normal distribution or not. Continuous variables were expressed as a mean ± standard deviation and were analyzed with independent samples t-test. Not normal distributed variableswere expressed as a median value (maximum and minimum value) and were analyzed with the Mann-Whitney U-test. A value of $p < 0.05$ was considered to be significant. Correlation analyses was performed with continuous variables. Binominal logistic regression analysis was performed with the significant values in univariate analyses. Independent predictors were determined for AF. ROC analyses were done.

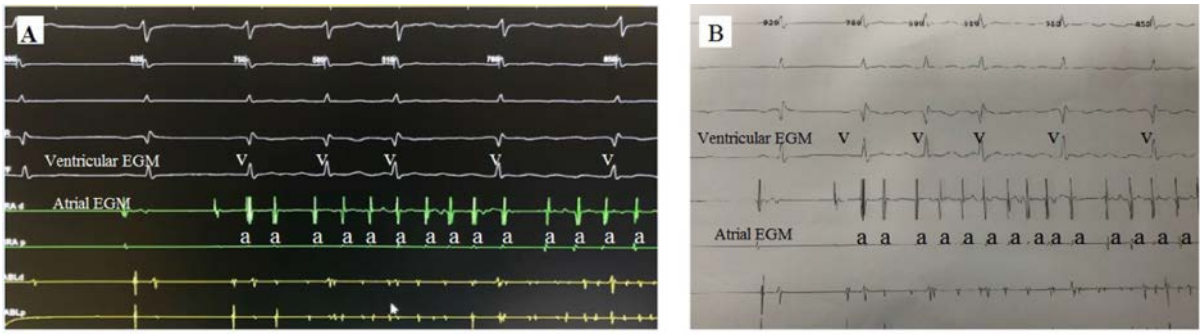


Figure 1A and 1B. Showing of catheter-related atrial fibrillation with intracardiac EGM. a = irregular and caotic electrical signal of the atrium, v = irregular ventricular signal.

RESULTS

Sixty-eight patients were in the group 1 (median age: 48 years, range: 18-70 years) and 77 patients were in the group 2 (median age: 43 years, range:18-70 years). Mean catheter-related AF duration was 145 ± 35 ms (13 of these patients duration < 30 ms). Demographic findings and medications were similar in both groups (Table 1 and 2). The procedure time was significantly longer in the group 2 [median value: 20 min (11-35) vs. 14 min (9-17)]. Pmax [median time: 120 ms (70-160) vs. 110 ms (80-160), $p < 0.001$] and Pdisp [median time: 45 ms (10-80) vs. 25 ms (10-80), $p < 0.001$] were found to be significantly higher in group 2, Pmin [median time: 75 ms (40-95) vs. 80 ms (45-120), $p < 0.001$] was found to be significantly higher in group 1. Echocardiographic parameters were similar in both groups (Table 3). In correlation analyses, there was positive correlation between Pmax and Pmin, Pmax and Pdisp. There was negative correlation Pmin and Pdisp (Table 4). In the multiple logistic regression analysis, it was found that Pmax (OR:1.077, 95% CI: 1.043-1.112, $p < 0.001$), Pmin (OR: 0.889, 95% CI: 0.853-926, $p < 0.001$) and Pdisp (OR:1.125, 95% CI: 1.080-1.173, $p < 0.001$) were all independent predictors for AF (Table 5). In ROC

Table 1. Comparison of demographic findings

	Goup 1 (n = 68)	Group 2 (n = 77)	*p* value
Age, years	48 (18-80)	43 (17-80)	0.283
Male gender, n (%)	28 (41.2)	30 (39.0)	0.786
Pulse, n (beat/minute)	75 (115-55)	75 (45-150)	0.820
BMI, n (kg/m^2)	23 (34-21)	24 (33-22)	0.202
DM, n (%)	8 (11.8)	6 (7.8)	0.419
HT, n (%)	16 (23.5)	10 (13.0)	0.099
HPL, n (%)	2 (2.9)	4 (5.2)	0.401
Smoking, n (%)	9 (13.2)	5 (6.5)	0.17

BMI = body mass index, DM = diabetes mellitus, HT = hypertension, HPL = hyperlipidemia

Table 2. Comparison of patients medications

	Goup 1 (n = 68)	Group 2 (n = 77)	*p* value
ACE, n (%)	8 (11.8)	12 (15.6)	0.506
ARB, n (%)	5 (7.4)	3 (3.9)	0.293
B blocker, n (%)	17 (25)	19 (24.7)	0.558
Statin, n (%)	2 (2.9)	5 (6.5)	0.275

ACE = angiotensin converting enzym, ARB = angiotensin receptor blocker

Table 3. Comparison of echocardiographic and electrocardiographic findings

	Goup 1 (n = 68)	Group 2 (n = 77)	*p* value
Pmax (ms)	110 (80-160)	120 (70-160)	0.002
Pmin(ms)	80 (45-120)	75 (40-95)	<0.001
Pdisp(ms)	25 (10-80)	45 (10-80)	<0.001
EPS time (minute)	14 (9-17)	20 (11-35)	<0.001
EF (%)	60 (53-65)	60 (55-65)	0.606
LAD (mm)	35 (30-41)	35 (30-39)	0.325
LAV (ml)	48 (45-54)	48 (38-54)	0.481
E velocity (m/s)	0.83 ± 0.11	0.84 ± 0.12	0.576
A velocity (m/s)	0.28 ± 0.06	0.28 ± 0.05	0.592

EPS = electrophysiology, LAD = left atrial diameter, LAV = left atrial volume, EF = ejection fraction, Pmax = the longest P wave duration, Pmin = the shortest P wave duration, Pdisp = P wave dispersion

Table 4. Correlation analyses between continious parameters

		EF	LAD	LAV	Pmax	Pmin	Pdisp	E velocity	A velocity
EF	r	1	0.012	-0.154	0.083	-0.072	0.113	0.111	-0.144
	p	.	0.889	0.065	0.320	0.392	0.174	0.201	0.095
LAD	r	0.012	1	0.117	0.013	-0.067	0.045	0.007	0.001
	p	0.889	.	0.163	0.874	0.423	0.593	0.939	0.994
LAV	r	0.154	0.117	1	0.021	-0.018	0.030	-0.003	-0.048
	p	0.065	0.163	.	0.802	0.828	0.724	0.969	0.580
P max	r	0.083	0.013	0.021	1	0.276**	0.712**	-0.074	-0.167
	p	0.320	0.874	0.802	.	0.001	0.000	0.391	0.052
P min	r	0.072	-0.067	-0.018	0.276**	1	-0.426**	0.026	-0.025
	p	0.392	0.423	0.828	0.001	.	0.000	0.766	0.777
Pdisp	r	0.113	0.045	0.030	0.712**	-0.426**	1	-0.068	-0.115
	p	0.174	0.593	0.724	0.000	0.000	.	0.430	0.183
E velocity	r	0.111	0.007	-0.003	-0.074	0.026	-0.068	1	0.002
	p	0.201	0.939	0.969	0.391	0.766	0.430	.	0.979
A velocity	r	0.144	0.001	-0.048	-0.167	-0.025	-0.115	0.002	1
	p	0.095	0.994	0.580	0.052	0.777	0.183	0.979	.

LAD = left atrial diameter, LAV = left atrial volume, EF = ejection fraction, Pmax = the longest P wave duration, Pmin = the shortest P wave duration, Pdisp = P wave dispersion

analyses, Pmax cut-off value of 120 ms determined the catheter-related AF with 61% sensitivity and 67% specificity [AUC: 0.652 (0.562-0.741), $p = 0.002$], Pdisp cut-off value of 35 msec determined the catheter-related AF with 80% sensitivity and 71% specificity [AUC: 0.818 (0.748-0.888), $p < 0.001$] (Figure 2).

Table 5. Independent predictors for AF

	Odds ratio	95% CI	*p* value
Pmax	1.077	1.043-1.112	**< 0.001**
Pmin	0.889	0.853-926	**< 0.001**
Pdisp	1.125	1.080-1.173	**< 0.001**

AF = atrial fibrillation, CI = confidence interval, Pmax = the longest P wave duration, Pmin: the shortest P wave duration, Pdisp = P wave dispersion

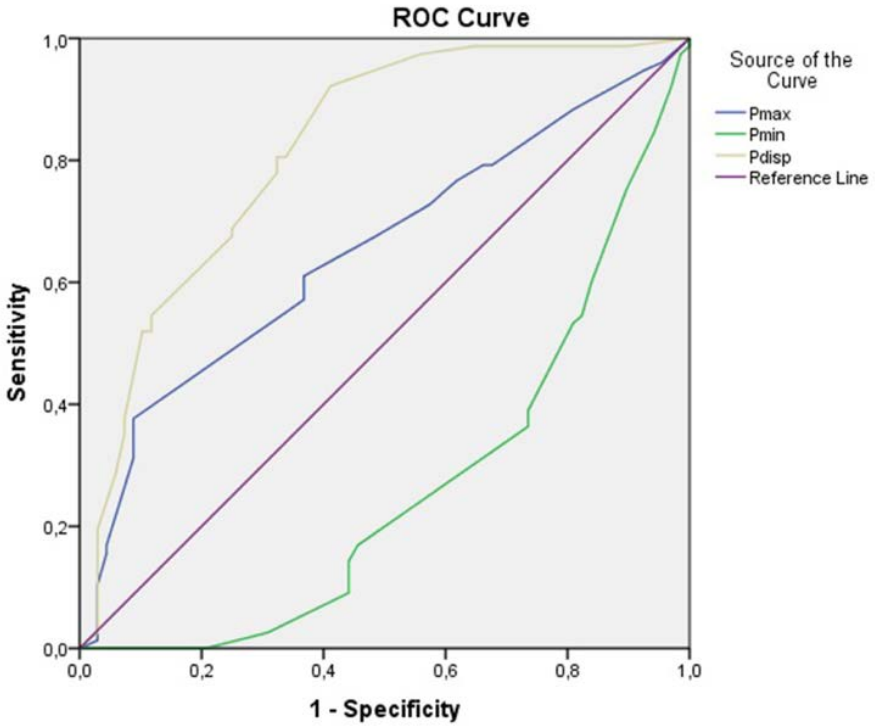


Figure 2. ROC analyses to determine predictive value of Pmax, Pmin and Pdisp for catheter-related atrial fibrillation.

DISCUSSION

We found some important findings in our study. Increased Pmax and Pdisp are closely associated with catheter-related AF. Also, EPS time is significantly prolonged in patients with catheter related AF.

P wave duration on 12 surface ECG shows interatrial conduction time [7]. Atrial dyssynchrony is defined as the difference in P wave durations between leads on superficial ECG [2]. Atrial dyssynchrony is the substrate for many atrial arrhythmias, especially atrial fibrillation [8]. In an update related with Pdisp, it was reported that the probability of atrial tachycardia increased above a value of 40 ms [9]. In a study, it was determined that when taken Pdisp > 40 ms, AF determined to high sensitivity and specificity [2]. In another study, when cut-off value taken 36 ms, AF predicted with a sensitivity of 77% [6]. In a recent meta-analysis, increased Pdisp, especially in obese patients, has said to be predictor of AF [8]. In our study, Pdisp was significantly increased in the patient with catheter-related AF. We thoughtthat these patients had increased interatrial heterogeneous electrical condution. When we contact the catheter directly with the right atrium wall, we think that AF may be started. In addition, a cut-off value of 35 ms of Pdisp detected patients with AF in an overlapping manner with previous studies.

In the literature, it was reported that Pdisp especially in the D2 and V1 derivations was an independent marker in development of Afib in an observational study conducted with a high number of patients [9]. In another study, the persistent AF group was compared with the control group and Pdisp was found to be shorter in the control group [7]. In a study conducted with patients with lone AF, Pdisp was found to be longer and Pmin was found to be shorter compared to the control group [11]. In another study, Pdisp and Pmax were found to be longer in patients with paroxysmal AF [12]. In a study conducted with relapsing AF, it was reported that Pdisp was not an independent predictor of relapse and only prolonged P wave was an independent predictor of relapse [13]. In another relapse study, it was reported that prolonged Pdisp was a predictor for relapse in patients with atrioventricular nodal reentrant tachycardia who were treated with radiofrequency [14]. Besides, Pdisp was shown to be significantly correlated with epicardial adipose tissue, prolonged in cryptogenic stroke and an independent predictor of AF in hypertensive patients

in some studies [15-17]. Our study showed no significant correlation between P wave and other parameters.

Limitations

The duration of AF in our 13 patients is less than 30 sec. In these patients, there is no definition in the guidelines [1]. The radiation dose received by the patients whose EPS lasted longer was not recorded. The patients who developed AF during the procedure were not followed up later. The CHA_2DS_2-VASc score was not calculated after the procedure in the patients with AF. No anticoagulant treatment was initiated. Because our study was retrospective, we did not know if they became symptomatic after the procedure? and if they had a complication due to AF?

CONCLUSION

Patients with longer Pdisp and Pmax and shorter Pmin may develop AF more frequently during EPS and their procedure times may delay. Physician should be careful when placing catheter in these 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] Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: Executive summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm 2016;13:e92-135.
[2] Dilaveris PE, Gialafos JE. P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol 2001;6:159-65.
[3] Yoshizawa T, Niwano S, Niwano H, Igarashi T, Fujiishi T, Ishizue N, et al. Prediction of new onset atrial fibrillation through P wave analysis in 12 lead ECG. Int Heart J 2014;55:422-7.
[4] Nussinovitch U. Meta-analysis of p-wave dispersion values in healthy individuals: the influence of clinical characteristics. Ann Noninvasive Electrocardiol 2012;17:28-35.
[5] Perez MV, Dewey FE, Marcus R, Ashley EA, Al-Ahmad AA, Wang PJ, et al. Electrocardiographic predictors of atrial fibrillation. Am Heart J 2009;158:622-8.
[6] Aytemir K, Ozer N, Atalar E, Sade E, Aksöyek S, Ovünç K, et al. P wave dispersion on 12-lead electrocardiography in patients with paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 2000;23:1109-12.
[7] Censi F, Corazza I, Reggiani E, Calcagnini G, Mattei E, Triventi M, et al. P-wave variability and atrial fibrillation. Sci Rep 2016;6:26799.
[8] Aizawa Y, Watanabe H, Okumura K. Electrocardiogram (ECG) for the prediction of incident atrial fibrillation: an overview. J Atr Fibrillation 2017;10:1724.
[9] Perez-Riera AR, de Abreu LC, Barbosa-Barros R, Grindler J, Fernandes-Cardoso A, Baranchuk A. P-wave dispersion: an update. Indian Pacing Electrophysiol J 2016;16:126-33.
[10] Yoshizawa T, Niwano S, Niwano H, Igarashi T, Fujiishi T, Ishizue N, et al. Prediction of new onset atrial fibrillation through P wave analysis in 12 lead ECG. Int Heart J 2014;55:422-7.
[11] Chang IC, Austin E, Krishnan B, Benditt DG, Quay CN, Ling LH, Chen LY. Shorter minimum p-wave duration is associated with paroxysmal lone atrial fibrillation. Electrocardiol 2014;47:106-12.
[12] Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J 1998;135(5 Pt 1):733-8.
[13] Dilaveris PE, Gialafos EJ, Andrikopoulos GK, Richter DJ, Papanikolaou V, Poralis K, et al. Clinical and electrocardiographic predictors of recurrent atrial fibrillation. Pacing Clin Electrophysiol 2000;23:352-8.
[14] Amasyali B, Kose S, Aytemir K, Kilic A, Turhan H, Celik T, et al. P wave dispersion predicts recurrence of paroxysmal atrial fibrillation in patients with atrioventricular nodal reentrant tachycardia treated with radiofrequency catheter ablation. Ann Noninvasive Electrocardiol 2006;11:263-70.
[15] Çiçek Y, Doğan S, Durakoğlugil ME, Balcıoğlu AS, Erdoğan T, Şatıroğlu Ö, et al. The relationship between epicardial adipose tissue and P wave and QT dispersions. Turk Kardiyol Dern Ars 2015;43:621-9.
[16] Vural MG, Cetin S, Yilmaz M, Akdemir R, Gunduz H. Relation between left atrial remodeling in young patients with cryptogenic stroke and normal inter-atrial anatomy. J Stroke 2015;17:312-9.
[17] Tsioufis C, Syrseloudis D, Hatziyianni A, Tzamou V, Andrikou I, Tolis P, et al. Relationships of CRP and P wave dispersion with atrial fibrillation in hypertensive subjects. Am J Hypertens 2010;23:202-7.

The European Research Journal 2019;5(4):697-706 ORIGINAL ARTICLE

Effectiveness of balance training with kinesthetic ability trainer (KAT 2000) in patients with peripheral neuropathic pain: a randomised controlled study

Duygu Kerim, Aslıhan Uzunkulaoğlu, Saime Ay

Department of Physical Medicine and Rehabilitation, Ufuk University School of Medicine, Ankara, Turkey

DOI: 10.18621/eurj.408381

ABSTRACT

Objectives: The aim of this study isto determine the effectiveness of balance training with Kinesthetic Ability Trainer (KAT 2000) in patients with peripheral neuropathic pain related balance disorder.

Methods: Sixty patients were included into this controlled prospective study and randomized into either balance exercises group (Group 1) or KAT 2000 exercises group (Group 2). Balance exercises were given to all patients.Also, KAT 2000 balance exercises were given all patients in Group 2 (n = 30). All patients received 45-min individualized training session for three times a week for 4 weeks. Douleur Neuropathique 4 (DN4) questionnaire for neuropathic pain; visual analogue scale (VAS) for pain severity; KAT 2000 for static and dynamic balance; Nottingham Health Profile (NHP) for Quality of Life (QoL) was used. Dynamic balance and mobility also was assessed using the Berg Balance Scale (BBS) and Time Up and Go (TUG) test. Patients were evaluated at baseline and the end of the 4-week exercise program.

Results: At the end of the treatment; VAS, BBS, KAT 2000, TUG, NHP, physical activity, NHP pain, NHP social isolation and NHP emotional reactions scores improved significantly in both groups ($p < 0.05$) except NHP sleep and NHP energy level scores in balance exercises group ($p > 0.05$). Statistical differences in VAS pain on movement, global assessment of patient, global assessment of doctor, NHP energy level scores were found between the groups ($p < 0.05$); but there were no statistical difference in VAS at rest, VAS at night, BBS, KAT 2000, TUG, NHP physical activity, NHP pain, NHP sleep, NHP social isolation and NHP emotional reactions scores between the groups ($p > 0.05$).

Conclusion: When combined with the KAT 2000 device, positive effects of balance-coordination exercises on pain on movement and energy level are more evident in patients with peripheral neuropathic pain.

Keywords: Neuropathic pain, balance, KAT 2000, quality of life

Received: March 21, 2018; Accepted: July 14, 2018; Published Online: November 23, 2018

Neuropathic pain is a chronic pain disorder caused by a lesion or disease of the somatosensory system [1]. Neuropathic pain syndromes can be divided into two general categories as consequences of a peripheral or central lesion or peripheral or central disease [2]. Neuropathic pain affects millions of people all over the world. Patients experience one of many symptoms, such as pain, paresthesia, dysesthesia, hyperalgesia, and allodynia [3].

Balance disorders are more common as people get

Address for correspondence: *Aslıhan Uzunkulaoğlu, MD., Assistant Professor, Ufuk University School of Medicine, Department of Physical Medicine and Rehabilitation, Dr. Rıdvan Ege Hastanesi, 06520 Balgat, Ankara, Turkey*
E-mail: aslihanseyrek@gmail.com, Tel: +90 312 2044358, Fax:+90 312 2872390

e-ISSN: 2149-3189

older. It can reduce mobility and independence in the elderly and can cause substantial morbidity and mortality [4, 5]. The fact that an increased incidence of nerve conduction abnormalities has been found in elderly with a history of balance impairment also suggests that peripheral nerve dysfunction can contribute to balance impairments [6]. It is known that distal sensory peripheral neuropathy and motor impairments may cause postural instability in elderly [7]. The association between peripheral neuropathy and balance impairments has been noted by many authors. It is known that subjects with peripheral neuropathy balanced less reliably on one foot for three seconds than did matched control subjects without peripheral neuropathy [8].

In treatment, various exercise programs should be given to treat the balance impairments identified in the elderly people with peripheral neuropathy. Kinesthetic Ability Trainer (KAT 2000) is a device which consists of two components including a movable platform and a tilt sensor connected to a computer and evaluates and improves the balance ability. In static balance exercises with KAT 2000; patients try to keep the red X symbol located in the center of the computer screen, while in dynamic balance exercises they try to follow the red X symbol moving clockwise or counterclockwise. In this study, we aimed to evaluate the effectiveness of KAT 2000 in the treatment of patients with peripheral neuropathic pain related balance disorder.

METHODS

Experimental Approach to the Problem

This placebo randomized controlled trial was carried out in a university hospital and was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the university ethics committee with 30112015-4 registry number. A total of 60 patients who developed peripheral neuropathic pain-related balance impairment were included into this study and randomized into either balance exercises groups or KAT 2000 exercises groups. All participants were informed about the study and signed written informed consent forms before interventions. Outcome variables were selected to provide scores and before and after treatment these scores were compared.

Subjects

A total of 60 patients who developed peripheral neuropathic pain-related balance impairment in the chronic phase due to lumber disc herniation, lumber spondylosis and gonarthrosis were included in the study. Patients had neuropathic pain for more than 3 months. Neuropathic pain was diagnosed if Douleur Neuropathique 4 (DN4) score was ≥ 4. Balance assessment was done with the Berg Balance Scale. Individuals were included in the study who had DN4 scores ≥ 4 and moderately impaired balance with a score of 21-40 points on the Berg Balance Scale. Individuals were excluded in the study who had history of previous cerebrovascular events; other neurological, musculoskeletal, inner ear or eye disease that may lead to impaired vision or standing balance. Because it may affect balance tests; lower extremity surgery history, knee infection, inflammatory diseases like rheumatoid arthritis and spondyloarthropathies, another cause of polyneuropathy like diabetes mellitus, vitamin B 12 deficiency, toxic or neurological disease like stroke, spinal cord injury, sedative drug use story, heart failure not under active control, malignancy or active systemic disease.

Detailed anamnesis of all patients were obtained. Number of falls, associated systemic diseases and medications were recorded. All patients were examinedin detail with musculoskeletal and neurological examination. After physical examination all patients were received complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and biochemical markers were evaluated. Patients whose test results were within the normal range were included in the study.

By using the website randomizer.org method participants were randomly assigned into two either balance exercises (n = 30) or KAT 2000 balance exercise (n = 30) group [9]. All of the patients were blinded to training allocation but the physiotherapist who applied thebalance training program was aware of the procedure. Also physiatrist who made the examination and evaluations were blinded to training allocation.

Outcome Measures

Patients were evaluated at baseline and 4 weeks later. The outcome measures used in the study are listed below.

Neuropathic Pain

Neuropathic pain was determined by the Douleur Neuropathique 4 (DN4) questionnaire. The DN4 questionnaire was originally developed for neuropathic pain diagnosis [10]. DN4 consists seven items related to symptoms and three related to clinical examination. For each item, a score of "1" is given if the response is "yes" and a score of "0" is given if it is "no". The patient is considered to have neuropathic pain if the total score is calculated to be 4 or more. The reliability and validity study of Turkish version of DN4 was performed by Cevik *et al*. [11].

Pain Intensity

Pain intensity was evaluated on visual analog scale (VAS), where 0 = no pain and 10 = worst possible pain (12). VAS consists of three mean scores; at rest, on movement and pain at night scores. All patients completed this scale.

Quality of Life

The quality of life was assessed using Nottingham Health Profile (NHP). All patients completed the NHP. This contains 38 statements (answered 'yes' or 'no') that assess subjective distress in six sections: physical activity (eight items), pain (eight items), sleep (five items), emotional reactions (nine items), social isolation (five items) and energy level (three items) [13].

O'Brien's method was used in NHP score calculation. In order to calculate the overall score; the item weights for items answered affirmatively are added, and this total score is divided by 600 (the sum of all item weights); the result is subtracted from 1.In order to calculate the score for each section, total weight score of each section is divided by 100, the result is subtracted from 1 [14, 15]. According to these methods, when the evaluation score is close to 'zero', it shows poor health status and when it is close to 'one', it shows good health status. The methods described above were used in NHP score calculation in this study.

Static and Dynamic Balance

Kinesthetic Ability Trainer 2000 (KAT 2000)

The KAT2000 device consists of two components including a movable platform and a tilt sensor connected to a computer. In static balance measurement, patients were instructed to cross their arms against their chest and maintain body equilibrium without changing feet on the platform. During the test, patients were asked to keep the red X symbol located in the middle of the computer screen.In dynamic balance measurement, patients were instructed to follow the red X symbol located in the center of the computer screen. During the test, circling in the clockwise direction, counterclockwise rotation in the clockwise direction, square drawing, eight strokes were performed. All patients performed each test for 30 s and repeated three times. The best of the three scores was considered as the final score. In calculating test scores, low scores indicate that the balance index is good. The reliability of the balance data with the use of the KAT has been explained previously [16].

Berg Balance Scale

Dynamic balance and mobilitywas also evaluated using the Berg Balance Scale (BBS) and Time Up and Go (TUG) test. The BBS consists of 14 simple different balance-related tasks and evaluates the ability of the subject's static, dynamic, and functional balance. The success of each task was evaluated using a scoring scale between zero (unable) and four (independent). Total scores was calculated out of a maximum of 56 points (17). The validity and reliability of the Turkish version of the BBS was studied byŞahin *et al* (18).

Time Up and Go (TUG)

The TUG test is a simple test used to evaluate mobility [19]. Patients were instructed to rise from a chair, walk 3 m on the floor at a normal pace, turn around, walk back to the chair, and sit down [20]. The researcher observed the patient's postural stability, gait and stride length while the participants were walking. One source proposes that scores of 10 seconds (sec) or less indicate normal mobility, 11-20 sec normal limits for frail elderly subjects, and scores of 30 sec or more propose that the subjects may fall [21, 22].

Procedures

Before balance training, warm-up and stretching exercises (paraspinal stretching, gluteus maximus and hip flexors stretching, hamstring stretching,

gastroknemius and soleus stretching 1×10 repetition) were given all patients for 10 minutes.

In group 1, balance exercises contained postures designed to gradually reduce the base of support (2-legged stand, semi-tandem stand, tandem stand, 1-legged stand), dynamic movements to disturb the center of gravity (tandem walk, circle turns), exercises to stress the postural muscle groups (heel or toe stands) and exercises to reduce sensory input (standing with eyes closed) as recommended by the American College of Sports Medicine [22]. Subjects received 45-min individualized training session for three times a week for 4 weeks.

In group 2, balance exercises were given all patients. At the same time, balance exercises were given with Kinesthetic Ability Trainer 2000 (KAT 2000). In static balance exercises with KAT 2000; patients were asked to cross their arms against their chest and maintain body equilibrium without changing feet on the platform. During this time, patients were instructed to keep the red X symbol located in the center of the computer screen. In dynamic balance exercises with KAT2000; patients were instructed to follow the red X symbol located in the center of the computer screen. During this time, circling in the clockwise direction, counterclockwise rotation in the clockwise direction, square drawing, eight strokes are performed. Each test was performed for 30 sec and repeated three times. Increased measurements indicate a poor balance performance. The best of the three scores was accepted as the final score.Patients received 45-min individualized training session for three times a week for 4 weeks.

At the end of the balance training, cool-down exercises were given for 10 minutes, three times a week for 4 weeks in both groups.

Statistical Analysis

The means and standard deviations were given as descriptive statistics. Wilcoxon test was used to calculate the pre and post-treatment value differences. To compare the differences between two groups, Mann Whitney U was used. A level of significance of $p < 0.05$ was accepted. All analyses were performed using the SPSS for Windows 20.0 software program.

Table 1. Demographic characteristics and baseline values of the outcome measures

Variables	Group 1 (n = 30)	Group 2 (n = 30)	*p* value
Age	75.70 ± 6.71	75.43 ± 6.54	0,85
Sex (Female/Male)	25/5	25/5	1.00
DN4 score	7.66 ± 0.71	7.93 ± 0.63	0.14
VAS at rest	4.73 ± 0.98	4.23 ± 1.19	0.50
VAS on movement	7.00 ± 0.87	7.26 ± 0.78	0.25
VAS pain at night	4.83 ± 0.79	4.63 ± 0.66	0.43
Global assessment of patient	7.53 ± 0.68	7.53 ± 0.68	0.84
Global assessment of doctor	7.43 ± 0.67	7.40 ± 0.77	0.96
BBS score	28.00 ± 5.31	30,13 ± 6.18	0.16
KAT 2000 static score	1690.33 ± 520.38	1505,30 ± 556.30	0.18
KAT 2000 dynamic score	2195.26 ± 530.20	2057.30 ± 565.88	0.26
TUG	11.36 ± 2.42	10.9 ± 2.41	0.45
NHP physical activity	0.46 ± 0.20	0.51 ± 0.20	0.32
NHP pain	0.25 ± 0.24	0.25 ± 0.22	0.82
NHP sleep	0.56 ± 0.39	0.70 ± 0.41	0.28
NHP social isolation	0.71 ± 0.33	0.77 ± 0.29	0.46
NHP emotional reactions	0.69 ± 0.18	0.66 ± 0.19	0.40
NHP energy level	0.39 ± 0.39	0.23 ± 0.41	0.10

Data are shown as mean±standard deviation. DN4 = Douleur Neuropathique 4, VAS = visual analog scale, BBS = Berg Balance Scale, KAT 2000 = Kinesthetic Ability Trainer 2000, TUG = Time Up and Go, NHP = Nottingham Health Profile

RESULTS

A total of 60 subjects completed the 4-week exercise program. The demographic characteristics and baseline values of the outcome measures of the patients are presented in Table 1. There were no statistically significant differences between the groups for baseline values ($p > 0.05$) (Table 1).

At the end of the 4-week treatment periods; VAS at rest ($p < 0.01$ for both groups), VAS pain on movement ($p < 0.01$ for both groups), VAS pain at night ($p = 0.01$ for Group 1, $p < 0.01$ for Group 2), BBS ($p < 0.01$ for both groups), KAT 2000 static ($p < 0.01$ for both groups), KAT 2000 dynamic ($p < 0.01$ for both groups), TUG test ($p < 0.01$ for both groups), NHP physical activity ($p < 0.01$ for both groups), NHP pain ($p < 0.01$ for both groups), NHP social isolation ($p = 0.01$ for Group 1, $p < 0.01$ for Group 2) and NHP emotional reactions ($p < 0.01$ for both groups) scores improved significantly in both groups ($p < 0.05$). At the end of the therapy there were no statistically significant difference forNHP sleep ($p = 0.10$) and NHP energy level ($p = 0.10$) scoresin Group 1; but there were statistically significant difference for these

Table 2. Comparison of the outcome measures in both groups before and after treatment.

Variables		Group 1 (n = 30)	Group 2 (n = 30)	*p* value
VAS at rest				
Before treatment		4.73 ± 0.98	4.23 ± 1.19	0.75
After treatment		3.83 ± 0.94	4.00 ± 1.14	
	***p* value**	**< 0.01**	**< 0.01**	
VAS pain on movement				
Before treatment		7.00 ± 0.87	7.26 ± 0.78	**< 0.01**
After treatment		5.53 ± 1.13	6.66 ± 0.95	
	p value	**< 0.01**	**< 0.01**	
VAS pain at night				
Before treatment		4.83 ± 0.79	4.63 ± 0.66	0.10
After treatment		3.93 ± 0.78	4.23 ± 0.50	
	***p* value**	**0.01**	**< 0.01**	
Global assessment of patient				
Before treatment		7.53 ± 0.68	7.53 ± 0.68	**< 0.00**
After treatment		5.36 ± 0.66	6.73 ± 0.73	
	***p* value**	**< 0.01**	**< 0.01**	
Global assessment of doctor				
Before treatment		7.43 ± 0.67	7.40 ± 0.77	**< 0.01**
After treatment		5.20 ± 0.71	6.56 ± 0.81	
	***p* value**	**< 0.01**	**< 0.01**	
BBS score				
Before treatment		28.00 ± 5.31	30.13 ± 6.18	0.47
After treatment		35.03 ± 5.67	34.00 ± 6.25	
	***p* value**	**< 0.01**	**< 0.01**	
KAT 2000 static score				
Before treatment		1690.33 ± 520.38	1505.30 ± 556.30	0.63
After treatment		1280.10 ± 532.99	1202.76 ± 555.55	
	***p* value**	**< 0.01**	**< 0.01**	
KAT 2000 dynamic score				
Before treatment		2195.26 ± 530.20	2057.30 ± 565.88	0.40
After treatment		1585.60 ± 536.86	1722.70 ± 562.84	
	***p* value**	**< 0.01**	**< 0.01**	

Table 2 Continued.

Variables		Group 1 (n = 30)	Group 2 (n = 30)	*p* value
TUG				
Before treatment		11.36 ± 2.42	10.9 ± 2.41	**0.05**
After treatment		7.66 ± 2.20	8.90 ± 2.39	
	***p* value**	**< 0.01**	**< 0.01**	
NHPphysical activity				
Before treatment		0.46 ± 0.20	0.51 ± 0.20	0.55
After treatment		0.70 ± 0.15	0.72 ± 0.16	
	***p* value**	**< 0.01**	**< 0.01**	
NHP pain				
Before treatment		0.25 ± 0.24	0.25 ± 0.22	0.21
After treatment		0.55 ± 0.14	0.48 ± 0.18	
	***p* value**	**< 0.01**	**< 0.01**	
NHP sleep				
Before treatment		0.56 ± 0.39	0.70 ± 0.41	0.38
After treatment		0.69 ± 0.31	0.74 ± 0.38	
	***p* value**	0.10	**< 0.01**	
NHP social isolation				
Before treatment		0.71 ± 0.33	0.77 ± 0.29	0.52
After treatment		0.87 ± 0.19	0.89 ± 0.18	
	***p* value**	**0.01**	**< 0.01**	
NHP emotional reactions				
Before treatment		0.69 ± 0.18	0.66 ± 0.19	0.37
After treatment		0.91 ± 0.10	0.88 ± 0.11	
	***p* value**	**< 0.01**	**< 0.01**	
NHP energy level				
Before treatment		0.39 ± 0.39	0.23 ± 0.41	**0.01**
After treatment		0.67 ± 0.39	0.28 ± 0.42	
	***p* value**	0.10	**0.01**	

Data are shown as mean±standard deviation. DN4 = Douleur Neuropathique 4, VAS = visual analog scale, BBS = Berg Balance Scale, KAT 2000 = Kinesthetic Ability Trainer 2000, TUG = Time Up and Go, NHP = Nottingham Health Profile

scores in Group 2 ($p < 0.01$ for both scores) (Table 2).

After the treatment, statistical differences in VAS pain on movement ($p < 0.01$), global assessment of patient ($p < 0.01$), global assessment of doctor ($p < 0.01$), NHP energy level ($p = 0.01$) scores were found between the groups ($p < 0.05$) (Table 2). There were no statistical difference in VAS at rest ($p = 0.75$), VAS at night ($p = 0.10$), BBS ($p = 0.47$), KAT 2000 static ($p = 0.63$), KAT 2000 dynamic ($p = 0.40$) TUG test ($p = 0.05$), NHP physical activity ($p = 0.55$), NHP pain ($p = 0.21$), NHP sleep ($p = 0.38$), NHP social isolation ($p = 0.52$) and NHP emotional reactions ($p = 0.37$) scores between the groups at the end of the treatment ($p > 0.05$) (Table 2).

DISCUSSION

Balance is important for daily activities, with increasing age the balance function of older people will decline because of age-related physiological changes, such as decreased muscle strength, increased passive tissue stiffness and decreased nerve conduction velocity [23-25]. The fact that an increased incidence of nerve conduction abnormalities has been found in elderly with a history of balance impairment also suggests that peripheral nerve dysfunction can contribute to balance impairments [7]. Thus, balance exercises are important to maintain and improve balance function in older adults with peripheral

neuropathic pain.

In peripheral neuropathy, patients experience balance impairment during stance and gait because of the sensory proprioception system of the lower extremity that plays a key role in balance control is affected and also the afferent conduction of tactile and proprioceptive information is impaired [26-28].

Balance exercises are important to maintain and improve balance function in older adults with peripheral neuropathic pain. Allet *et al*. [29] reported that strength and balance training significantly improved balance and strength, increased walking speed, and decreased fear of falling in patients with peripheral neuropathy.

In this study, we included the patients with peripheral neuropathic pain-related balance impairment in the chronic phase due to lumber disc herniation, lumber spondylosis and gonarthrosis. Frost *et al*. mentioned that radiculopathy may affect balance control the result of delaying muscle activation timing in patients with low back pain [30]. In the present study,we found that balance exercises and KAT 2000 exercises significantly improved VAS, KAT 2000, BBS, TUG, NHP physical activity, NHP pain, NHP social isolation and NHP emotional reactions scores. In that study, static balance test was performed with the person standing on the dominant leg and the dynamic balance test was performed with the person standing on both feet. It was mentioned that there was a learning effect on balance when the patients were retested, especially in the dynamic test and the greatest differences was seen in the static test. This was explained that standing on one leg was a daily living activity, while the skills required in the dynamic balance test were new because patient must convert a visual task into a set of coordinated movements [16]. On the other hand, there are many different systems that have been used in improvement of balance except KAT 2000. Nardone *et al*. [31] reported that balance training with either specific physical exercises or a powered platform is effective in patients with balance disorders of neuropathic origin; thus, they contribute to improving balance and potentially decreasing the risk of falling in patients with neuropathy. In another study, Lindemann *et al*. [32] compared the effectiveness Biodex stability system (BSS) balance training with a home-based exercise program in nondisabled elderly subjects. At the end of the study, it was shown that computer-assisted balance training, even if focused on one motor skill, was more effective than a home-based exercise program [32].

KAT 2000can also be used as a tool for static and dynamic balance exercises [34]. There are only a few study using the KAT 2000 in balance impairments and in these studies it is used as only a testing device [33-35]. As far as we know there is no other study that KAT 2000 has been used as a tool for static and dynamic balance exercises. Therefore we used KAT 2000 as an exercise program to improve static and dynamic balance in patients with peripheral neuropathic pain.In our study, both balance and KAT 2000 exercises significantly improved KAT 2000 static and dynamic scores. On the other hand, KAT 2000 exercise group did not score better than balance exercise group with KAT 2000. So we can conclude that there is no learning effect.Additionally, there were no statistical difference between the groupsat the end of the 4-week.As a result, we can conclude that the combined use of balance and KAT 2000 exercises does not improve neither static nor dynamic balance further.

The BBS and TUG tests are most commonly used to predictdynamic and functional balance in the elderly. In the study of Kruse *et al*. [36], efficacy of a home-based exercise program in patients with diabetic neuropathy was evaluated and the balance measurements which included the BBS, TUG and one-leg static stance (OLS) tests were collected at the baseline assessment and after 6 and 12 months of participation. No significant differences were noted between groups in neither BBS nor TUG; only OLS test was better in leg strengthening and balance exercises group than motivational telephone calls group. The training program had a minimal effect on participants' static balance [36]. In another study; Song *et al*. [37] assessed the effects of the balance exercise program on balance and trunk proprioception in the older adults with neuropathies. The BBS and TUG scores which assessed the dynamic balance, significantly increased in the exercise group but did not improve in the controlgruop which did not take exercise program. In that study, balance exercises have shown a positive effect by improving balance and trunk proprioception in older people with neuropathy [37]. In our study, after a 4-week balance training program, patients increased their BBS scores by 7.0

points in balance exercises groupand 3.8 points inKAT 2000 exercises group. The minimum detectable change of the BBS has been reported to be 7 points for older adults with an initial score of 25-34 [38]. Significant improvement in BBS scores was observed in both groups. All patients decreased their TUG time scores below 13.5 sec, a suggested cutoff point for fall risk in the elderly [39]. On the other hand, there were no statistical difference in BBS and TUG time scores between the groups at the end of the 4-week. This situation suggests that the combined use of balanceand KAT 2000 exercises does not improve the dynamic balance further as mentioned before.

Recently, a series of high-quality studies have been published that examine the relationship between neuropathic pain and health-related quality of life. The descriptive studies show that neuropathic pain is reported by patients to have a significant negative impact on sleep, physical functioning, emotional functioning and social functioning [40, 41]. Patients describe pain-related interference in multiple health-related quality of lifeand functional domains, as well as reduced ability to work and reduced mobility due to pain [42]. Disturbed sleep is always among the most common pain-related problems reported by individuals with neuropathic pain [41]. Benbow *et al*. [43] conducted a study on 79 diabetic and 39 non-diabetic patients were assessed using the Nottingham Health Profile (NHP) for the quality of life. Diabetic neuropathy patients had significantly higher scores in 5/6 NHP subgroups than either the other diabetic patients or the non-diabetic control patients. These subgroups were emotional reaction, energy, pain, physical mobility and sleep [43]. In our study, we determined significant improvements at quality of life in both groups except NHP sleep and NHP energy level scores in balance exercise group but this improvement was more significant in KAT 2000 exercise group. There were statistically significant differences in only NHP energy level between the groups. So we can conclude that combined use of balance and KAT 2000 exercises are effective for improvement of sleep and energy level in patients with peripheral neuropathic pain.

There are very few studies on the effect of balance exercise on neuropathic pain. Therefore, it is difficult to compare this study with other studies. In the future, we need to develop different kinds of balance exercises that will improve balance disorder in patients with peripheral neuropathic pain. So research studies should be done continuously to improve the balance and quality of life in patients with peripheral neuropathic pain.

Limitations

Short duration of exercise programs and follow-up were the major limitations of the study. In this study, we analyzed only the short-term effects of balance exercise programs, therefore further studies examining the long-term effects should be considered.

CONCLUSION

The results of our study confirm that 4-week balance and KAT 2000 balance exercise programs are effective in improving pain, static and dynamic balance and quality of life in adults with peripheral neuropathic pain. When combined with the KAT 2000 device, positive effects of balance-coordination exercises on global assessment of patient and doctor, pain on movement and energy level are more evident in patients with peripheral neuropathic pain. So, in an controlled setting; this combined exercise programme improves this burden complication.

Ethical approval

The project was approved by university Ethical Committee. All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its latter amendments.

Informed consent

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

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] Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice AS, et al. A new definition of neuropathic pain. Pain 2011;152:2204-5.
[2] Meacham K, Shepherd A, Mohapatra DP, Haroutounian S. Neuropathic pain: central vs. peripheral mechanisms. Curr Pain Headache Rep 2017;21:28.
[3] Backonja MM, Serra J. Pharmacologic management part 1: Better studied neuropathic pain diseasese. Pain Med 2004;5:528-47.
[4] Gryfe CI, Amies A, Ashley MJ. A longitudinal study of falls in an elderly population: I. Incidence and morbidity. Age Ageing 1977;6:201-10.
[5] Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988;319:1701-7.
[6] Pack DR, Wolfson LI, Amerman P, Whipple R, Kaplan JG. Peripheral nerve abnormalities and falling in the elderly. Neurology 1985;35 Suppl 1:79.
[7] Van de Bosh C, Gilsing MG, Lee SG, Richardson JK, Ashton Miller JA. Peripheral neuropathy effect on ankle inversion and eversion thresholds. Arch Phys Med Rehabil 1995;76:850-6.
[8] Richardson JK, Ashton-Miller JA, Lee SG, Jacobs K. Moderate peripheral neuropathy impairs weight transfer and unipedal balance in the elderly. Arch Phys Med Rehabil 1996;77:1152-6.
[9] www.randomizer.org
[10] Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29-36.
[11] Unal Cevik I, Sarioglu Ay S, Evcik D. A comparison of the DN4 and LANSS questionnaires in the assessment of neuropathic pain: validity and reliability of the Turkish version of DN4. J Pain 2010;11:1129-35.
[12] Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L. Assessment of
pain. Br J Anaesth 2008;101:17-24.
[13] Hunt SM, McEwen J. The development of a subjective health indicator. Sociol Health Illn 1980;2:231-46.
[14] McDowell I. Measuring health: a guide to rating scales and questionnaires. 3rd ed. Oxford University Press. 2006:pp. 780.
[15] O'Brien BJ, Buxton MJ, Ferguson BA. Measuring the effectiveness of heart transplant programmes: quality of life data and their relationship to survival analysis. J Chronic Dis 1987;40:S137-53.
[16] Hansen MS, Dieckmann B, Jensen K, Jakobsen BW. The reliability of balance tests performed on the kinesthetic ability trainer (KAT 2000). Knee Surg Sports Traumatol Arthrosc 2000;8:180-5.
[17] Berg KO, Wood-Dauphinee SL, Williams JI, Maki B. Measuring balance in the elderly: validation of an instrument. Can J Public Health 1992;83(Suppl 2):S7-S11.
[18] Sahin F, Yilmaz F, Ozmaden A, Kotevolu N, Sahin T, Kuran B. Reliability and validity of the Turkish version of the Berg Balance Scale. J Geriatr Phys Ther 2008;31:32-7.
[19] Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39:142-8.
[20] Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. Phys Ther 2000;80:896-903.
[21] Bohannon RW. Reference values for the timed up and go test: a descriptive meta-analysis. J Geriatr Phys Ther 2006;29:64-8.
[22] American College of Sports Medicine, Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exerc 2009;41:1510-30.
[23] Valerio BC, Nobrega JA, Tilbery CP. Neural conduction in hand nerves and the physiological factor of age. Arq Neuropsiquiatr 2004;2:114-8.
[24] Perry MC, Carville SF, Smith IC, Rutherford OM, Newham DJ. Strength, power output and symmetry of leg muscles: effect of age and history of falling. Eur J Appl Physiol 2007;100:553-61.
[25] DeVita P, Hortobagyi T. Age increases the skeletal versus muscular component of lower extremity stiffness during stepping down. J Gerontol Ser A Biol Sci Med Sci 2000;55:B593-600.
[26] Nardone A, Godi M, Artuso A, Schieppati M. Balance rehabilitation by moving platform and exercises in patients with neuropathy or vestibular deficit. Arch Phys Med Rehabil 2010;91:1869-77.
[27] Horlings CG, Kung UM, Bloem BR, Honegger F, Van Alfen N, Van Engelen BG, et al. Identifying deficits in balance control following vestibular or proprioceptive loss using posturographic analysis of stance tasks. Clin Neurophysiol 2008;119:2338-46.
[28] Van Deursen RW, Simoneau GG. Foot and ankle sensory neuropathy, proprioceptionand postural stability. J Orthop Sports Phys Ther 1999;29:718-26.
[29] Allet L, Armand S, de Bie RA, Golay A, Monnin D, Aminian K, de Bruin ED. The gaitand balance of patients with diabetes can be improved: a randomised controlled trial. Diabetologia 2010;53:458-66.
[30] Frost, Lydia R., Brown, Stephen H.M. Muscle activation timing and balance response inchronic lower back pain patients with associated radiculopathy. Clinical Biomechanics 2016;32:124-30.
[31] Nardone A, Godi M, Artuso A, Schieppati M. Balance rehabilitation by moving platformand exercises in patients with neuropathy or vestibular deficit. Arch Phys Med Rehabil 2010;91:1869-77.
[32] Lindemann U, Rupp K, Muche R, Nikolaus T, Becker C. Improving balance byimproving motor skills. Z Gerontol Geriatr 2004;37:20-6.
[33] France P, Derscheid G, Irrgang J, Malone T, Petersen R, Tippett S et al. Preliminary clinical evaluation of the Breg K.A.T.: effects of training in normals. Isokinet Exerc Sci 1992;2:133-9.
[34] Crawford C, Fleming K, Karabatsos P, Volkmann C, Williams K, Newton R. Normative values for healthy young and

elderly adult populations on the KAT balance system. Issues Aging 1995;18:10-4.
[35] Johnston RB, Howard ME, Cawley PW, Losse GM. Effect of lower extremity muscular fatigue on motor control performance. Med Sci Sports Exerc 1998;30:1703-7.
[36] Kruse RL, LeMaster JW, Madsen RW. Fall and balance outcomes after an intervention to promote leg strength, balance, and walking in people with diabetic peripheral neuropathy: "Feet First" randomized controlled trial. Phys Ther 2010;90:1568-79.
[37] Song CH, Petrofsky JS, Lee SW, Lee KJ, Yim JE. Effects of an exercise program onbalance and trunk proprioception in older adults with diabetic neuropathies. Diabetes Technol Ther 2011;13:803-11.
[38] Donoghue D; Physiotherapy Research and Older People (PROP) group, Stokes EK. Howmuch change is true change? The minimum detectable change of the Berg Balance Scale inelderly people. J Rehabil Med 2009;41:343-6.
[39] Shumway-Cook A, Brauer S, Woollacott M. Predicting the probabilityfor falls incommunity-dwelling older adults using the Timed Up & Go Test. Phys Ther 2000;80:896-903.
[40] David J. Rowbotham. Neuropathic pain and quality of life. European Journal of Pain 2002;6 (Suppl. B):19-24.
[41] Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-relatedquality of life: review and implications. Neurology 2007;68:1178-82.
[42] O'Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. Pharmacoeconomics 2009;27:95-112.
[43] Benbow SJ, Wallymahmed ME, MacFarlane IA. Diabetic peripheral neuropathy and quality of life. OJM 1998;91:733-7.

The European Research Journal 2019;5(4):707-711 REVIEW

Statin-associated myopathy: a general overview

Allam Harfoush

Department of Cardiovascular Diseases, Tishreen Hospital, Lattakia, Syria

DOI: 10.18621/eurj.416772

ABSTRACT

Among the amazing turn of events in preventing and reducing the risk of cardiovascular diseases since the discovery of statins, thousand of physicians started to prescribe it as a regular life-long treatment, but regarding the expanding number of patients on statin therapy, a wide spectrum of side effects started to appear. Statin-associated myopathy considered as one of the most common side effects and could be subtle for a long time, we performed a review to provide a clinical summary of statin-associated myopathy and to discuss possible mechanisms of risk factors and management of statin-associated myopathy.

Keywords: Statin-associated myopathy, myalgia, myositis, rhabdomyolysis

Received: April 19, 2018; Accepted: August 16, 2018; Published Online: November 6, 2018

Although that cardiovascular diseases considered as the most common cause of death worldwide, but since 2003; death rate has dropped about 38% [1], due to the significant advance in the medical field. However, it has always been the #1 priority is to reduce the incidence and control different risk factors by both life style changes and medical interventions (Drugs, Percutaneous coronary intervention, Surgery).

Guidelines from all over the world (NICE guidelines) consider statins as the drug of choice to control low-density lipoprotein level and reduce the incidence of atherosclerosis which is the most important cause of angina pectoris, myocardial infarction and stroke, but according to the expanding burden of patients with this daily pharmaceutical regime, side effects of this safe groups start to be noticed; as Statin-Associated Myopathy (SAM) considered as one of the most important cause for cessation of the therapy [2].

What is SAM?

Although there is not a universally accepted definition of SAM but it is agreed to refer to any muscular symptoms occurring during therapy despite of creatine level , and resolve on treatment cessation [3, 4]. SAM considered as one of the most common/severe side effects, the clinical spectrum of SAM include: myalgia, myositis, rhabdomyolysis and asymptomatic elevation of CK [5, 6].

Myalgia

It is the most common condition related to SAM, but as myalgia is frequently reported in hospitals and general clinics and it could for many different reasons , thus statin therapy is not necessarily the cause of myalgia even with the patients on statins therapy [7, 8].

The definition of myalgia is unexplained muscle pain or discomfort, may be described as 'flu-like' general symptoms with normal Creatine Kinase (CK) [8, 9]. The wide spectrum of symptoms include: muscle pain, cramps and maybe associated with weakness [7, 9, 10].

Tenderness after the many articles we reviewed is usually proximal, maybe symmetrical with the involve-

Address for correspondence: *Allam Harfoush, MD., Tishreen Hospital, Department of Cardiovascular Diseases, Lattakia, Syria*
E-mail: allamharf@gmail.com

e-ISSN: 2149-3189

ment of the large muscle groups such as: the thighs, back muscles and buttocks [11]. Some patients reported legs cramps, difficulty climbing stairs , getting up after sitting. This symptoms aggravated especially during or after exercise, but predominantly without CK elevation [9, 11]. In a review of a database of 508 patients with familial hypercholesterolemia treated with simvastatin (80 mg/day) for two years , myalgia noted in 45 patients with 8.86% [12].

In another observation study (PRIMO), muscle related symptoms was reported by 832 patients out of 7,942 patients with hyperlipidemia receiving statins in an unselected group , with 10.49%, which is relatively close to the percentage of the past study [13]. In general; discomfort or the associated weakness typically occur within the first month (4-6 weeks) after starting the therapy , or symptoms may occur after increasing the dose in a patient who is already on statins , symptoms maybe more frequent in physically active individuals treated with statins [10, 14].

Myositis

Myositis is defined as a muscle inflammation, it is usually accompanied with serum CK elevation; symptoms include pain and weakness and it is typically generalized and proximal (like myalgia) [7, 9, 10]. Skeletal muscle biopsies shows different findings , such as polymyositis and myolysis, however it is not one of the criteria to diagnosis myositis and biopsy is not a routine procedure [6]; so the diagnosis should be considered in any patient with statin therapy in the presence of CK elevation even without any physical or pathological findings [11].

Rhabdomyolysis

It is a rare, life threatening side effect with severe general devastation of the muscles, elevation of serum CK more than 10× of the normal limit, decreased renal function or even failure, myoglobinuria, disseminated intravascular coagulation and maybe death. Symptoms may include: severe muscle pain , muscle weakness through the entire body, dark urine, vomiting, malaise and tachycardia, however patients with rhabdomyolysis may not report any muscular symptoms.

Pathologically biopsies shows myonecrosis and significant inflammation [7, 9, 10, 15]. In one study that included 252,460 patients showed that the average incidence of hospitalization for rhabdomyolysis was 0.44 per 10,000 patients treated with statins (atorvastatin, pravastatin, simvastatin), however; cerivastatin which was withdrawn in 2001 has a 12 fold increased risk in the incidence of rhabdomyolysis. In USA; reported death due to statins induced rhabdomyolysis was over 0.15 per 1000,000 [14, 16, 17].

However ; this not a standard universal classification of SAM, and it may be difficult to set a final diagnosis because of the similarity of symptoms and laboratory findings between this three types, and also between other differential diagnosis that mimic SAM findings, and could be much more common.

What are the mechanism of SAM?

Although there is a lot of theories to explain the mechanism of SAM, the etiology still poorly understood , and seems to be multifactorial which need more studies and some of the proposed mechanisms [5, 9, 10, 18, 19].

Membrane ion channels theory

This proposed theory is that impaired synthesis of cholesterol may lead to a different changes in the muscle cell membrane, which may affect membrane fluidity altering ion channels behavior (like sodium, potassium and chloride) affecting the muscle membrane excitability. In an animal study results showed a dose-dependent reduction of membrane chloride conductance in rats treated with simvastatin, while the resting membrane was not affected.

Apoptosis theory

Another proposed theory is statin-induced apoptosis; statin interfere with the synthesis of cholesterol, thus may lead to a pre-cholesterol products depletion such as isoprenoid-lipid. Isoprenoid-lipid depletion involves with myofiber apoptosis. In 'in vivo' studies , statin manage to induce apoptosis in myo cells , but it still not established this particular mechanism 'in vitro'.

Ubiquinine theory

As isoprenoid; ubiquinine (CoQ10) considered as one of the products of cholesterol synthesis pathway, and the depletion of ubiquinine could lead to impaired enzymes activity in mitochondria. However; although low serum concentration of ubiquinine have been noted in patients with statin therapy but the concen-

tration of ubiquinine in muscles have not always showed that. In general myocellular concentration of ubiquinine in patients with statins therapy have showed unchanged , increased and decreased levels. In one small randomized blind trial , 41 patient on statin therapy who had muscle pain , divided into two groups first group (21 patients) received ubiquinine, the other group (20 patients) received vitamin E; after one month of therapy results showed that (18 of 21 patients) who received ubiquinine report improvement in muscle symptoms , compared to (3 of 20 patients) who received vitamin E [20]. However; more studies still needed to confirm the important role of ubiquinine.

Other proposed mechanisms

Autoimmune mechanism, calcium homeostasis impairment and genetics interference.

What are the risk factors of SAM?

Determining and detecting risk factors of SAM before starting statin therapy may help physicians to make more effective and efficient decisions considering statin therapy [2, 4, 6, 9-11]. Risk factors categorized into two types: Patients-related risk factors and therapy-related risk factors.

Patients-related risk factors

This group could be categorized into subtypes:

Demographic: The risk of SAM is higher in:

>Elderly patients
>Female sex
>People with heavy exercise
>Low body mass index
>Alcoholism
>Heavy consumption of grape fruit

Genetics: This is considered as a rare risk factor , it includes such as:

>Inherited muscle diseases (McArdle, Pompe)
>Variations in the enzymes system that is responsible of the metabolism of statins (CYP enzymes system)

Co morbidities: Many diseases interfere with statin myotoxicity such as:

>Renal failure
>Hepatic failure
>Hypothyroidism
>Diabetes mellitus
>Infections
>Recent major surgery

Therapy-related risk factors

This type divided into subtypes too:

Statin dose: Although the mechanism is unknown; the incidence of SAM increase gradually among the dose and the concentration of statins. Drugs that interfere with CYP2C9 (responsible for the metabolism of rosuvastatin, fluvastatin) such as ranitidine, fluconazole, amiodaron [9, 19].

Combination therapy: Some drugs may increase the incidence of SAM if it was administrated with statins such as fibrates, cyclosporine. Using statins therapy at the same time with gemfibrozile (fibrate) may increase the incidence of rhabdomyolysis approximately 10× higher [9].

Pharmacokinetics: In general; hydrophilic statins are less likely to enter different cells such myocytes , and thus may have less risk of myopathy. However, it is known that hydrophilic statins are as likely as lipophilic statins to cause myotoxicity.

Drug interactions: Interactions with the metabolism of statins (CYP enzymes system): Drugs that interfere with CYP3A4 (responsible for the metabolism of lovastatin, atorvastatin, simvastatin) such as protease inhibitors, macrolide, and diltiazem [9, 19].

What should physicians do to manage SAM?

When patients on statins complain muscle symptoms, detailed history should be taken and physical examination should be done; this procedure covers two goals: first to exclude other more common differential diagnosis, second is to determine the risk factors of SAM [3, 21, 22]. Blood tests, CK and thyroid function (TFT) should be done(hypothyroidism may presents with only hypercholesteremia, raised CK and myalgia), renal function and urine analysis. The first line management is to stop statins, monitor CK and observe symptoms. If muscular symptoms are tolerable and CK is raised less than 10× statin therapy may be continued among with a constant observation. But if there is any signs for rhabdomyolysis or CK level is more than 10× statin therapy should be stopped.

Should physicians monitor CK on a regular basis after statin therapy started?

In general, routine monitoring of CK level is not recommended, but it is useful to obtain a baseline CK

level for comparing purposes prior the starting of statin therapy [3, 11, 22]. For patients receiving statin therapy with an interacting medications it may be necessary to monitor CK level, due to the increased risk of SAM. However; serum CK level does not necessarily exclude muscle damage.

CONCLUSION

Although statins considered as a safe group of drugs , and its benefits of reducing cardiovascular diseases morbidity and mortality , it is still associated with muscular side effects ranging from discomfort to the life-threatening rhabdomyolysis; thus it is important to consider the risk factors of SAM, and assess the advantages and disadvantages for each patient individually before initiating the therapy. Management options for statin-intolerant patients include statin switching, especially to low-dose, non-daily doses of long-acting statins, such as rosuvastatin and atorvastatin. In conclusion, statin-induced myopathy is a significant clinical problem that contributes considerably to statin therapy discontinuation. However, there exist multiple and effective management options for statin intolerant patients [9].

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] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation 2016;133:e38-360.

[2] Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.

[3] Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, at al; European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J 2015;36:1012-22.

[4] Hansen KE, Hildebrand JP, Ferguson EE, Stein JH. Outcomes in 45 patients with statin-associated myopathy. Arch Intern Med 2005;165:2671-6.

[5] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA 2003;289:1681-90.

[6] Sathasivam S, Lecky B. Statin induced myopathy. BMJ 2008;337:a2286.

[7] Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel. An assessment by the Statin Muscle Safety Task Force: 2014 update. J Clin Lipidol 2014;8(3 Suppl):S58-71.

[8] Fernandez G, Spatz ES, Jablecki C, Phillips PS. Statin myopathy: a common dilemma not reflected in clinical trials. Cleve Clin J Med 2011;78:393-403.

[9] Abd TT, Jacobson TA. Statin-induced myopathy: a review and update. Expert Opin Drug Saf 2011;10:373-87.

[10] Tomaszewski M, Stępień KM, Tomaszewska J, Czuczwar SJ. Statin-induced myopathies. Pharmacol Rep 2011;63:859-66.

[11] Best tests: Investigating myalgia in patients taking statins, The Best Practice Advocacy Centre New Zealand (bpacnz). August 2014.

[12] de Sauvage Nolting PR, Buirma RJ, Hutten BA, Kastelein JJ; Dutch ExPRESS Investigator Group. Two-year efficacy and safety of simvastatin 80 mg in familial hypercholesterolemia (the Examination of Probands and Relatives in Statin Studies With Familial Hypercholesterolemia [ExPRESS FH]). Am J Cardiol 2002;90:181-4.

[13] Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. Cardiovasc Drugs Ther 2005;19:403-14.

[14] Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. N Engl J Med 2002;346:539-40.

[15] Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004;292:2585-90.

[16] Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004;292:2585-90.

[17] Joy TR, Hegele RA. Narrative review: statin-related myopathy. Ann Intern Med 2009;150:858-68.

[18] Jacobson TA. NLA Task Force on Statin Safety--2014 update. J Clin Lipidol 2014;8(3 Suppl):S1-4.

[19] Vrablik M, Zlatohlavek L, Stulc T, Adamkova V, Prusikova M, Schwarzova L, et al. Statin-associated myopathy: from genetic predisposition to clinical management. Physiol Res 2014;63 Suppl 3:S327-34.

[20] Parker BA, Thompson PD. Effect of statins on skeletal muscle: exercise, myopathy, and muscle outcomes. Exerc Sport

Sci Rev 2012;40:188-94.
[21] Schuster B. Monitorıng of creatine kinase (CK) in patients on statin therapy. The Rx Files: Q&A Summary, March 2002.
[22] Husband A. Managing statin-induced myopathy. Clin Pharmacist 2009;1:319-20.

The European Research Journal 2019;5(4):712-714 CASE REPORT

Mood disorder following traumatic brain injury: a case report

Buket Koparal[1], Behçet Coşar[2]

[1]*Department of Psychiatry, Recep Tayyip Erdogan University Training and Research Hospital, Rize, Turkey*
[2]*Department of Psychiatry, Gazi University School of Medicine, Ankara, Turkey*

DOI: 10.18621/eurj.434311

ABSTRACT

Traumatic brain injury is a clinical situation that generally affects young people aged 45 years or younger and causes mortality and critical functional losses. The most common psychiatric disorder following taumatic brain injury is depression. Although the relationship between depression and organic diseases has been studied a lot, there is less data about mania. Secondary mania differs from primary mania with advanced beginning age, absence of family history, more difficult and slower response to treatment; and secondary mania usually has no recurrence. In this report, secondary mania and its clinical features are discussed in light of a mood disorder following a trauma case. The case is still followed with mood stabilizer treatment and the patient is euthymic.

Keywords: Traumatic brain injury, secondary mania

Received: June 17, 2018; Accepted: September 6, 2018; Published Online: November 7, 2018

Traumatic brain injury (TBI) affects young people aged 45 years and younger and causes mortality and morbidity [1]. The most essential factors that affect quality of life in the long term are cognitive and behavioral changes in these patients. Trauma has primary and secondary impacts; while primary impacts are contusion and diffuse axonal injury emerging at the moment of accident, changes emerging as a response to primary injury are considered secondary impacts (intracranial pressure increase, parenchymal edema, inflammation, glial proliferation, etc.) [2]. Neuronal degeneration and the repair process following trauma cause changes in neuronal activity and neuronal circuits in the long term. Posttraumatic changes in the neurotransmitter system are also associated with mood disorders following trauma [3].

Various psychiatric disorders may develop after trauma depending on the affected region of the brain [1]. The lateral orbitofrontal cortex is associated with irritability, impulsivity and emotional lability; anterior cingulate cortex with apathy and akinetic mutism; temporal lobe with lability, aggression and psychosis; and hypothalamus with sexual behavior and aggression [4]. In one case changes in the right hemisphere were detected on MR imaging of a 17-year-old patient with mania after TBI and in another case left hemisphere lesion was associated with mania. Additionally, a case of mania following bilateral temporal hemorrhage was also reported [5].

In this case report, mood disorders following trauma and clinical features of secondary mania are discussed in the light of a case about a patient with bipolar disorder following trauma.

CASE PRESENTATION

The patient was a 25-year-old single male, working as a salesman in a company. He had graduated from university and lived with his family in

Address for correspondence: *Buket Koparal, MD., Recep Tayyip Erdogan University Training and Research Hospital, Department of Psychiatry, Rize, Turkey*
E-mail: bkt_svnc@hotmail.com

e-ISSN: 2149-3189

a small city.

He was taken to hospital involuntarily by family members with complaints of insomnia, increased self-confidence, and excessive passion for spending money. According to the family members and the patient himself, he had no previous psychiatric disorder and drug use. He had no psychiatric family history. He had subarachnoid hemorrhage after falling from a height two years previously. He was treated in the intensive care unit for a period. After discharge from hospital, he had a period of depression accompanying unhappiness, pessimism, and unwillingness to live which lasted 4-5 months. He was treated with sertraline 50 mg and entered a remission period. He had a period of increased mobility, self-confidence and uncontrolled behaviors thereafter, treatment was completed and medicines were stopped. The patient was treated with low dosage risperidone. In follow-up, he had one more manic period that subsided in a short time. The patient whose complaints recurred in spite of medical treatment in the last 15 days was admitted to our clinic.

In his psychiatric examination psychomotor activity was increased, he exhibited grandiose attitude and he was irritable. He had flighty ideas and his speaking was fast and speed was increased. Young Mania Rating Scale (YMRS) was 32 points. Laboratory studies were in normal range.

On MR imaging, posttraumatic sequelae were detected in the right temporal lobe, bilateral basal ganglion levels, right corpus callosum splenium, thalamus, bilateral frontal lobe and subcortical white substance. The patient's treatment was arranged as 30 mg/day olanzapine and 1000 mg/day valproic acid. In the second week of treatment, clonazepam 6 mg/day and haloperidol were added because he did not respond to treatment with olanzapine and valproic acid. Haloperidol was increased to 30 mg and olanzapine was decreased step by step and stopped. The patient subsided and his YMRS regressed to 6 points. The patient was discharged in the end of the fourth week. After discharge from hospital, akathisia occurred due to haloperidol, so haloperidol treatment was stopped and his treatment was resumed with trifluoperazine 2 mg. The patient is still euthymic.

DISCUSSION

Depression is the most common psychiatric disorder after trauma [4]. Anxiety disorders and mania follow depression. Although correlations between depression and organic diseases have been commonly studied, there is less data about mania. In a previous study, the rate of mania was detected as 9% in one-year follow-up of TBI patients [6].

Psychiatric symptoms after trauma vary according to the affected region of the brain. Prefrontal cortex, temporal cortex and hypothalamus are the most common regions associated with psychiatric disorders following trauma [4]. Bilateral orbitofrontal and right temporoparietal, right basal and medial temporal lobe, basal ganglions, thalamus and right frontotemporal lesions have been associated with mania [5-7]. In our case, there were posttraumatic lesions in the right temporal lobe, basal ganglions and bilateral frontal area, in line with literature.

Although mania is usually associated with bipolar disorder, there are many etiological causes [6]. However mania induced by bipolar affective disorder is called primary mania, whereas mania induced by neurological, metabolic or pharmacological causes is called secondary mania [8].

Secondary mania comprises 1.75% of all admissions for psychiatric reasons, and affects 4.67% of all manic patients [9]. It is more prevalent than primary mania in later ages. Usually these patients have no family history of primary or secondary mania. In psychiatric examination of these patients, irritability is more common than euphoria. Even though the response to treatment is more difficult, the total disease period is shorter than primary mania. Treatment protocol is similar to primary mania. For this patient, treatment was started with olanzapine. It is known that in bipolar affective disorder long term use of first generation antipsychotics is associated with increased risk of dyskinesia and neuroleptic malignant syndrome. However, we needed sedation for the patient. Haloperidol was added after insufficient response to olanzapine. Haloperidol was then changed with trifluoperazine because akathisia occurred with haloperidol treatment. Maintenance treatment is not

necessary in secondary mania because secondary mania usually does not recur [10]. In this case, mood stabilizer was used due to both depression and recurrent mania. Valproic acid was selected due to its neuroprotective effect to protect patient from potential epileptic seizures.

CONCLUSION

This case report differs from other cases due to longer disease and treatment period, more difficult response to treatment, recurrence and necessity of maintenance treatment [8]. A confusing factor is whether the use of antidepressants caused mania in this patient.

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] Mortensen PB, Mors O, Frydenberg M, Ewald H. Head injury as a risk factor for bipolar affective disorder. J Affect Disord 2003;76:79-83.
[2] Rutherford GW, Wlodarczyk RC. Distant sequelae of traumatic brain injury: premature mortality and intracranial neoplasms. J Head Trauma Rehabil 2009;24:468-74.
[3] Bhalerao SU, Geurtjens C, Thomas GR, Kitamura CR, Zhou C, Marlborough M. Understanding the neuropsychiatric consequences associated with significant traumatic brain injury. Brain Inj 2013;27:767-74.
[4] Zgaljardic DJ, Seale GS, Schaefer LA, Temple RO, Foreman J, Elliott TR. Psychiatric disease and post-acute traumatic brain injury. J Neurotrauma 2015;32:1911-25.
[5] Starkstein SE, Boston JD, Robinson RG. Mechanisms of mania after brain injury. 12 case reports and review of the literature. J Nerv Ment Dis 1988;176:87-100.
[6] Jorge RE, Robinson RG, Starkstein SE, Arndt SV, Forrester AW, Geisler FH. Secondary mania following traumatic brain injury. Am J Psychiatry 1993;150:916-21.
[7] Starkstein SE, Pearlson GD, Boston J, Robinson RG. Mania after brain injury. A controlled study of causative factors. Arch Neurol 1987;44:1069-73.
[8] Mendez MF. Mania in neurologic disorders. Curr Psychiatry Rep 2000;2:440-5.
[9] Shukla S, Cook BL, Hoff AL, Aronson TA. Failure to detect organic factors in mania. J Affect Disord 1988;15:17-20.
[10] David AFS, Kopelman MD. Lishman's Organic Psychiatry: A Textbook of Neuropsychiatry. 4th edition ed. UK: Wiley-Blackwell; 2009.

The European Research Journal 2019;5(4):715-718 CASE REPORT

Balo's concentric sclerosis: a case report

Meltem Özdemir, Aynur Turan, Alper Dilli

Department of Radiology, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

DOI: 10.18621/eurj.434730

ABSTRACT

Balo's concentric sclerosis is a rare variant of multiple sclerosis which is characterized by lesions consisting rings of demyelination alternating with areas of relatively preserved myelin. These pathological changes are reflected by characteristic magnetic resonance imaging findings. We present the imaging findings of a case of BCS who presented with an acute neurological disturbance, showed a dramatical recovery following corticosteroid therapy, and remained free of relapse for more than 1 year. Although previously considered as a fulminant and fatal disease, characteristic MRI findings of Balo's concentric sclerosis enable earlier diagnosis and treatment, and better prognosis.

Keywords: Balo's concentric sclerosis, multiple sclerosis, demyelination

Received: June 19, 2018; Accepted: August 8, 2018; Published Online: September 19, 2018

Balo's concentric sclerosis (BCS) is a rare variant of multiple sclerosis which is characterized by a lesion formed by alternating rings of demyelination and relatively preserved myelin, reminding an onion ring appearance. Previously BCS was regarded to be an invariably fatal disorder. However, with the advent of magnetic resonance imaging (MRI), the earlier diagnosis and management of the disease offered a better prognosis [1]. On MRI, acute BCS lesions are seen as T2-hyperintense lamellae surrounding a T2-hyperintese core which is called 'storm centre'. The areas of active demyelination within the lesion show restricted diffusion, and the peripheral aspect of the lesion enhances following gadolinium administration [2]. Correct characterization of the lesion enables accurate diagnosis and allows prompt treatment of BCS. Most of the patients who develop symptomatic BCS are shown to make a substantial or complete recovery following convenient treatment [1]. We herein present the imaging findings of a case of BCS who presented with an acute neurological disturbance, showed a dramatical recovery following corticosteroid therapy, and remained free of relapse for more than 1 year.

CASE PRESENTATION

A previously healthy 25-year-old woman presented with acute onset of headache, dysarthria and bilateral upper extremity weakness. MRI demonstrated two round lesions with well-defined borders in the right frontoparietal region and in the corpus callosum (Figure 1). The lesions showed a concentric lamellar appearance on all pulse sequences. The concentric rings were; hypointense and isointense on T1-weighted images (Figures 2a and 3a), hyperintense and isointense on T2-weighted images (Figures 2b and 3b). There was neither surrounding edema nor mass effect accompanying the lesions. On diffusion weighted imaging (DWI); the right

Address for correspondence: *Aynur Turan, MD., Associate Professor, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Radiology, 06010 Ankara, Turkey*
E-mail: aturanrad@gmail.com, Phone: +90 312 3198908

e-ISSN: 2149-3189

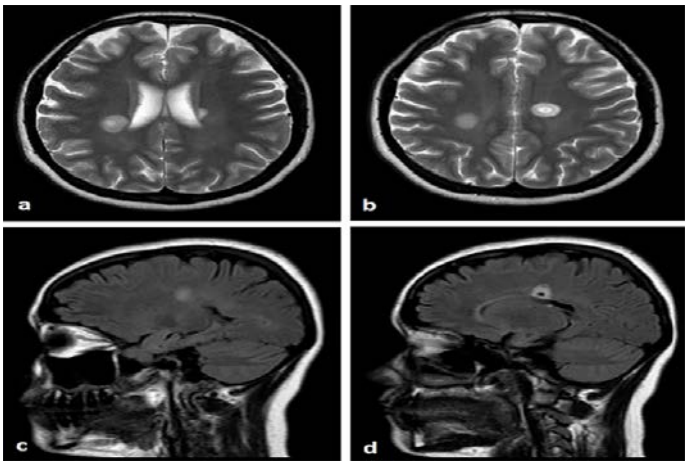


Figure 1. Axial T2-weighted (a, b) and sagittal FLAIR (c, d) images demonstrate a right frontoparietal (a, c), and a callosal (b, d) lesion which show a concentric lamellar appearance, consistent with Balo's concentric sclerosis.

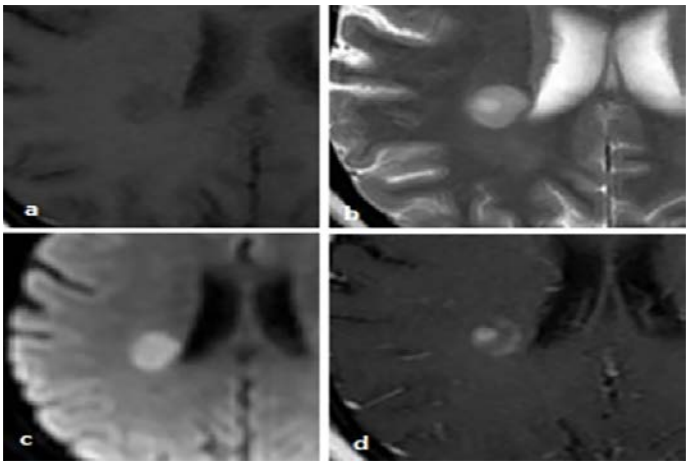


Figure 2. The right frontoparietal lesion is iso/hypointense on T1-weighted (a), iso/hyperintense on T2-weighted (b), hyperintense on diffusion weighted (c) images, and its T2-hyperintens areas show enhancement after gadolinium administration (d).

frontoparietal lesion was completely hyperintense (Figure 2c), whereas hypointense central core of the left callosal lesion was surrounded by a hyperintense ring (Figure 3c). T1 hypointense rings of the right frontoparietal lesion showed enhancement following gadolinium administration (Figure 2d), whereas the callosal lesion showed a minimal enhancement which was difficult to distinguish (Figure 3d). The whole spine MRI was normal. The patient was diagnosed as having BCS and given a high-dose oral corticosteroid therapy. She showed a significant improvement in her clinical symptoms in the first 7 days following the treatment and a complete clinical recovery was obtained in a 2 months' time.

Nine months after the initial MRI, a follow-up MRI was performed. Both lesions exhibited remarkable reduction in size. The lamellae seemed shrunken on both T1 and T2-weighted images (Figure 4). T2-hyperintense rings changed to be focal, milimetric, irregular hyperintense areas (Figure 4b). There was neither contrast enhancement nor restriction of diffusion in either lesions. The repeat whole spine MRI was normal. The patient has had no more clinical relapses at 12 month follow-up and is presently asymptomatic.

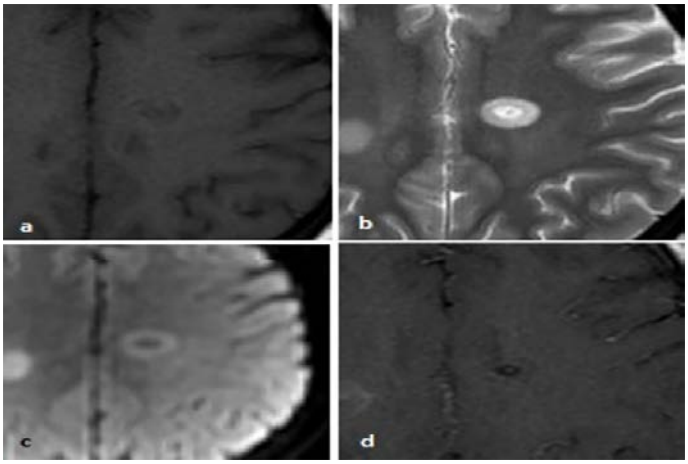


Figure3. Callosal lesion is iso/hypointense on T1-weighted (a) and iso/hyperintense on T2-weighted (b) images. On diffusion weighted image (c), hypointense central core of the lesion is surrounded by a hyperintense ring. Following gadolinium administration, the lesion shows a minimal enhancement which is difficult to distinguish (d).

DISCUSSION

Cerebral white matter oligodendrocyte loss and demyelination are histopathological characteristics of BCS. Cortical grey matter is typically reserved. The lesions characteristically show alternating lamellar pattern of demyelinated and relatively preserved white matter, reminding a union bulb appearance. They usually present as a solitary mass, less commonly, multiple lesions may be detected. BCS lesions occur predominantly in the cerebral white matter, but also basal ganglia, pons, and cerebellum lesions have been reported [3, 4].

With an average age at onset of 34 years (range;

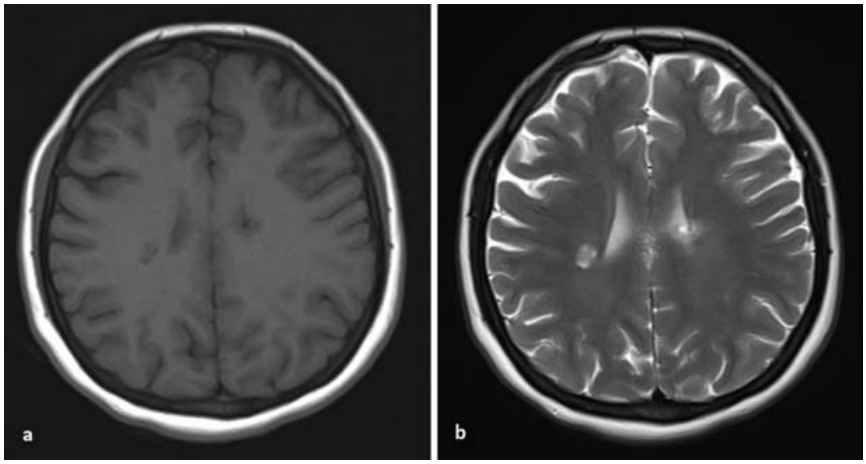


Figure 4. Follow-up MRI shows remarkable reduction in size of both lesions. The lamellae seems shrunken on both T1 (a) and T2-weighted (b) images. T2-hyperintense rings of acute stage appears to be changed to focal, milimetric, hyperintense areas (b).

3-62 years), BCS mainly occurs in young adults. The most common symptoms of the entity are similar to those of any intracerebral mass: headache, seizures, cognitive deficiency, behavioral changes, aphasia, hemiparesis and urinary incontinence. Some patients with BCS can present with classic focal symptoms of multiple sclerosis, [1]. Similar to the most of the previously reported cases of BCS, our patient presented with headache, dysarthria, and bilateral upper extremity weakness.

Histopathological characteristics of the BCS lesions are typically reflected on MRI imaging. In acute lesions; T1-weighted images show alternating isointense (areas of preserved myelin) and hypointense (areas of demyelination) concentric rings. In a similar fashion, T2-weighted images show hyperintense rings (areas of demyelination) surrounding a T2 hyperintense core. In the sites of demyelination rings, increased blood brain barrier permeability and inflammation causes enhancement following gadolinium administration [1, 2]. Both lesions of our patient showed these characteristic findings of an acute BCS lesion, except for the relatively reduced gadolinium enhancement in the callosal lesion. This might be due to either the older age of this lesion than the right frontoparietal one, or relatively preserved blood brain barrier permeability (Figure 3d). In the follow-up MRI, neither of the lesions enhanced, suggesting the lack of active inflammation within the lesions.

DWI can be used for the confirmation of the presence of BCS. On DWI, areas of active demyelination show restricted diffusion, whereas myelinated areas show fascilitated diffusion. Thus, on DWI, BCS lesions demonstrate alternating rings of high and low signal intensity, representing demyelinated and myelinated areas, respectively [2, 5, 6]. In our case; the right frontoparietal lesion was completely hyperintense on DWI (Figure 2c), whereas hypointense central core of the left frontal lesion was surrounded by a hyperintense ring (Figure 3c), probably reflecting the two different stages in which the two lesions were.

The characteristic magnetic resonance spectroscopy pattern of acute BCS lesions is; a decreased N-acetylaspartate peak (reflecting neuronal damage), elevated choline and lipid peaks (suggesting increased membrane turn-over), and elevated lactate peak (consistent with impaired aerobic metabolism) [7, 8]. On fluorodeoxyglucose positron emission tomography (FDG-PET), BCS lesions do not show increased uptake, while the main differentials of BCS including other acute demyelinating lesions and high-grade neoplasms do. This makes FDG-PET a useful adjunct to MRI in characterization of equivocal lesions [1, 8].

For the treatment of acute BCS lesions, corticosteroids and plasma exchange are recommended as the first and second line therapy respectively. Although some authors recommend multiple sclerosis disease-modifying therapy as an ongoing therapy in patients who have developed a

BCS lesion, a standard ongoing treatment guide has not been established yet. The prognosis of the patients with BCS lesion varies. Complete clinical and radiological recovery is possible; however, aggressive BCS lesions could be fatal. [1, 9]. Fortunately, after the corticosteroid therapy, our patient showed a dramatical recovery and remained asymptomatic for the following 1 year.

CONCLUSION

Although previously considered as a fulminant and invariably fatal disease, characteristic MRI findings of BCS enable earlier diagnosis and treatment, and better prognosis.

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] Hardy AT, Miller DH. Balo's concentric sclerosis. Lancet Neurol 2014;13:740-746.
[2] Darke M, Bahador FM, Miller DC, Litofsky NS, Ahsan H. Balo's concentric sclerosis: imaging findings and pathological correlation. JRCR 2013;7:1-8.
[3] Popescu BF, Lucchinetti CF. Pathology of demyelinating diseases. Annu Rev Pathol 2012;7:185-217.
[4] Karaarslan E, Altıntas A, Senol U, Yeni N, Dincer A, Bayindir C, et al. Balo's concentric sclerosis: clinical and radiologic features of five cases. AJNR Am J Neuroradiol 2001;22:1362-7.
[5] Kavanagh EC, Heran MK, Fenton DM, Lapointe JS, Nugent RA, Graeb DA. Diffusion-weighted imaging findings in Balo's concentric sclerosis. Br J Radiol 2006;79;e28-31.
[6] Ripellino P, Khonsari R, Stecco A, Filippi M, Perchinunno M, Cantello R. Clues on Balo's concentric sclerosis evolution from serial analysis of ADC values. Int J Neurosci 2016;126:88-95.
[7] Khiat A, Lesage J, Boulanger Y. Quantitative MRS study of Balo's concentric sclerosis lesions. Magn Reson Imaging 2007;25:1112-5.
[8] Bolcean J, Acou M, Mertens K, Hallaert G, Van den Broecke C, Achten E, et al. Structural and metabolic features of two different variants of multiple sclerosis: a PET/MRI study. J Neuroimaging 2013;23:431-6.
[9] Scott T. Balo's concentric sclerosis. Accessed on 28.4.2016 at http://www.medmerits.com/index.php/article/balo_concentric_sclerosis/P5

The European Research Journal 2019;5(4):719-721 LETTER TO THE EDITOR

Spinal malignant triton tumor in a patient with neurofibromatosis type 1

Sevgi Kulaklı[1], Fazıl Kulaklı[2], İlker Fatih Sarı[2], Samet Tatlı[2], İlker İlhanlı[2], Canan Çelik[2]

[1]Department of Dermatology, Giresun University School of Medicine, Prof. Dr. İlhan Özdemir Training and Research Hospital, Giresun, Turkey
[2]Department of Physical Medicine and Rehabilitation, Giresun University School of Medicine, Prof. Dr. İlhan Özdemir Training and Research Hospital, Giresun, Turkey

DOI: 10.18621/eurj.464297

Received: September 26, 2018; Accepted: February 26, 2019; Published Online: March 21, 2019

Dear Editor,

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with 100 % penetrance that affects approximately 1 in 3500 people [1]. Malignant triton tumor (MTT) is a rare malignant peripheral nerve sheath tumor (MPNST) with rhabdomyoblastic differentiation. Malignant triton tumor is commonly seen in the head, neck, extremities, and trunk and only 2-3% of all MPNSTs arise from the spinal nerves. MTT has an aggressive biological behavior, being 50% of cases associated with NF1 and has worse prognosis than MPNST without rhabdomyoblastic differentiation [2, 3]. In this study, we aimed to present a

patient with MTT. Although MTT is an aggressive tumor, it is possible to detect it asymptomatically and incidentally, so we think that, doctors should be careful in this regard, especially in patients with NF1.

A 59-year-old male patient with neurofibromatosis, was admitted to our inpatient clinic with weakness in both lower extremities. One month ago, the patient falled down from a high place and weakness in lower extremities started after this fall. Thoracal 10 vertebra pathologic fracture and significant spinal cord pressure were detected after the evaluations and the patient was operated urgently. During the operation, the surgeon saw a mass ingrained in the spinal cord and he excited this mass and sent it to pathology department. The mental function of the patient was normal. However, the mental function has begun to deteriorate after a traffic accident. His sister stated that the same illness was also in her, her mother and sister. The general condition and consciousness of the patient was good but cooperation and orientation were not enough. Multiple neurofibromas were observed on the skin (Figure 1). Neurofibromas began to form in the skin of the patient in childhood and he was diagnosed with neurofibromatosis. Cranial nerves and upper extremity examination were normal. Range of motions of lower extremity joints were normal. Proximal and distal muscle strength of right lower extremity was 4/5, left lower extremity was 1/5. Sensory examination failed due to lack of cooperation. Deep tendon reflexes were normoactive and no pathological reflex was detected. The patient was diagnosed with incomplete paraplegia and the rehabilitation program was started. During the rehabilitation program, it was learned that the pathology result of the patient was MTT. The pathology result was evaluated by oncology unit and it was decided that the patient should continue the treatment in the

Address for correspondence: *Fazıl Kulaklı, MD., Assistant Professor, Giresun University School of Medicine, Prof. Dr. İlhan Özdemir Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Giresun, Turkey*
E-mail: drfzl46@gmail.com

e-ISSN: 2149-3189

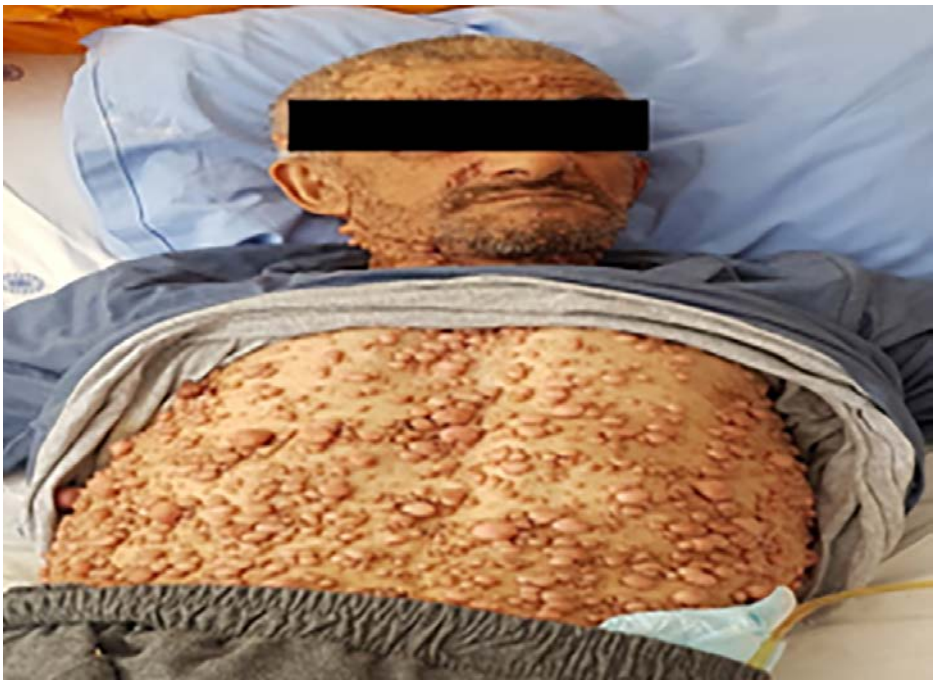


Figure 1. Multiple neurofibromas images

oncology unit.

Neurofibromatosis type 1 is characterized by cutaneous neurofibromas, café-au-lait spots, skeletal dysplasias, Lisch nodules, and sometimes malignant tumors [5]. Patients with NF1 at a significantly higher risk for benign and malignant tumors. MTT is an aggressive and rare MPNST with rhabdomyoblastic differentiation. MTT is commonly seen in the head, neck, extremities, and trunk and only 2-3% of all MPNSTs arise from the spinal nerves. In our case, MTT arised from the spinal nerve. In a review of 124 cases of MTT reported from 1973 to 2010, 38% of patients had NF1, and the median age at diagnosis was 33 years [4]. Patients with NF1 have a larger tumor size and worse disease outcomes than patients with sporadic disease. The 5-year specific survival rate is 54% to 75% in MTT patients with NF1 [6]. Patients may present with enlarging mass. It may cause pain and neurological symptoms such as paraestesia, motor weakness and radicular pain [3, 6]. Although MTT is an aggressive and symptomatic tumour in patients with NF1, our patient was asymptomatic and the tumor was detected incidentally unlike other cases in the literature. Depending on the location of mass, complete resection is the primary treatment method of MTT [7]. Radiotherapy is the other treatment that can be used when necessary [8]. Although the use of chemotherapy in MPNST is not clear, its use in therapy has been accepted [9]. In conclusion, patients with neurofibromatosis generally have a high risk of tumors. MTT is an agressive and rare tumor which is more common in patients with neurofibromatosis. Unlike other cases in the literature, MTT clinic was asymptomatic in our patient, it was detected incidentally and it arised from spinal nerve which was seen very rarely. Even if the patients are asymptomatic, physicians should be careful in terms of MTT especially in patients with NF1.

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] Jouhilahti EM, Peltonen S, Heape AM, Peltonen J. The pathoetiology of neurofibromatosis 1. Am J Pathol 2011;178:1932-9.
[2] Engel EE, Brassesco MS, Valera ET, Barbosa MHN,Yamashita MEAS, Scrideli CA, et al. Clinico-genetic aspects of a pediatric non-neurofibromatosis type 1 malignant triton tumor with loss of chromosome X. Pediatr Blood Cancer 2012;59:1320-3.
[3] Kamran SC, Howard SA, Shinagare AB, Krajewski KM. Malignant peripheral nerve sheath tumors: prognostic impact of rhabdomyoblastic differentiation (malignant triton tumors), neurofibromatosis 1 status and location. EJSO 2013;39:46-52.
[4] McConnell YJ, Giacomantonio CA. Malignant triton tumors--complete surgical resection and adjuvant radiotherapy associated with improved survival. J Surg Oncol 2012;106:51-6.
[5] Lee MJ, Stephenson DA. Recent developments in neurofibromatosis type 1. Curr Opin Neurol 2007;20:135-41.
[6] Stucky CC, Johnson KN, Gray RJ, Pockaj BA, Ocal IT, Rose PS, et al. Malignant peripheral nerve sheath tumors (MPNST): the Mayo Clinic experience. Ann Surg Oncol 2012;19:878-85.
[7] Grobmyer SR, Reith JD, Shahlaee A, Bush CH, Hochwald SN. Malignant peripheral nerve sheath tumor: molecular pathogenesis and current management considerations. J Surg Oncol 2008;97:340-9.
[8] Ferner RE, Gutmann DG. International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis 1. Cancer Res 2002;62:1573-7.
[9] Moretti VM, Crawford EA, Staddon AP, Lackman RD, Ogilvie CM.. Early outcomes for malignant peripheral nerve sheath tumor treated with chemotherapy. Am J Clin Oncol 2011;34:417-21.

THE ASSOCIATION OF HEALTH
RESEARCH AND STRATEGY