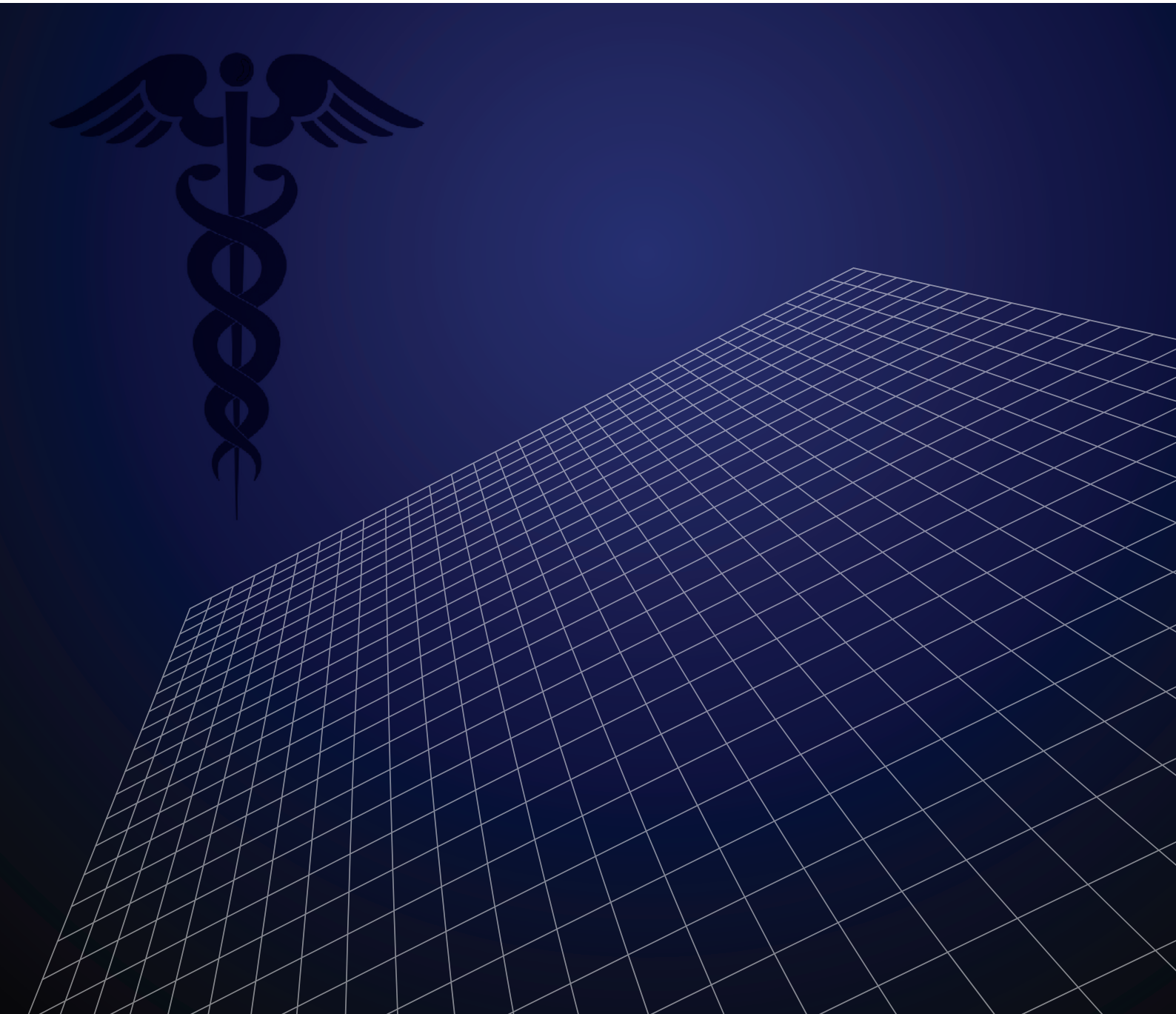
ISSN: e-2149-8296

# Turkish Journal of Clinics and Laboratory

*Türk Klinik ve Laboratuvar Dergisi*

Mart 2018, Cilt:9 Sayı:1



# TURKISH JOURNAL of CLINICS and LABORATORY

Türk Klinik ve Laboratuvar Dergisi





**Franchise Owner / İmtiyaz Sahibi**

Eyüp ÖZEREN

**Manager In Charge / Sorumlu Yazı İşleri Müdürü**

Metin ÖZSOY

E-mail: mozsoy@ada.net.tr

**General Coordinator / Genel Koordinatör**

Cihan SEVİM

**Graphic Design / Grafik Tasarım**

Başak AY KARABAK

E-mail: basakay2510@gmail.com

Yayın İdare Merkezi
DNT ORTADOĞU YAYINCILIK A.Ş.
dntortadoguyayincilik.com
Baskı: Atalay Matbaacılık İskitler/Ankara

TURKISH JOURNAL of CLINICS and LABORATORY
Mart 2018, Cilt: 9, Sayı: 1 Üç Ayda Bir Yayımlanır

Makale gönderim adresi: http://dergipark.gov.tr/tjcl/

# *Editorial* / Editörden

**Değerli Meslektaşlarım ve Sayın Okuyucularımız,**

DNT Ortadoğu Yayıncılık A.Ş. Genel Kurulu tarafından 2018 yılı itibariyle "Turkish Journal Of Clinics And Laboratory" dergisinin yeni sorumlu baş editörü olarak görevlendirilmiş bulunmaktayım.

Benim için çok onurlu bu görevi, aramıza yeni katılan editörler kurulundaki ve danışman havuzundaki arkadaşlarımla daha da güç ve şevk kazanmış olarak yerine getirmeye çalışacağız. Bu vesileyle geçmiş dönemde emek vermiş editörler, editörler kurulu üyeleri ve danışmanlara teşekkürü bir borç bilirim. Hedefimiz onların dergimizi taşıdıkları bu mükemmel noktadan öteye götürmek olacaktır.

Dergimiz kapsam olarak yine tıbbın her dalı ile ilgili Türkçe veya İngilizce yazılmış orijinal klinik, laboratuar veya deneysel çalışmalar, olgu sunumları, derleme, editöre mektup, kısa raporlar ve orijinal görüntüler yayınlamaya devam edecektir. Ulusal platformda TÜBİTAK ULAKBİM TR Dizinindeki varlığımız bize güç katmaktadır.

İlgili alanın çok geniş olması nedeniyle editörler kurulu çok farklı uzmanlardan ve sağlık bilimlerinin hemen her branşını kapsayacak şekilde yeniden düzenlenmiştir. Index Copernicus, DOAJ, DRJI, HINARI, CiteFactor, Infobase Index, International Scientific Indexing gibi uluslararası indekslerde taranan dergimizin bu niteliğine uygun olarak konusunda ünlü uzmanlardan oluşan uluslararası editörler kurulu da devreye sokulmuştur. Bu kapsamdaki dergilerde yayını olmak akademik yükseltmelerde ve performans puanlamasında önem taşımaktadır. Amacımız her zaman dergimizin Index Medicus, SCI gibi en üst indekslere dahil olması olacaktır.

Artan yazı ve hekim sayısı, giderek özelleşen uzmanlık alanlarını göz önüne alarak gönderilen yazıların tüm meslektaşlarımızın oluşturacağı bir danışman havuzu (akran değerlendirmesi -peer review) tarafından değerlendirilmesi ilkesini sürdürme kararındayız. Bu amaçla elektronik altyapımız başta olmak üzere yeniden yapılanma çalışmaları başlatıyoruz. Altyapı hazır olduğunda sizlere dergimize danışman (hakem) olmak için bir davet mektubu gönderilecektir. Sizlere verilen kullanıcı adı ve şifre ile dergi web sitesinden kişisel bilgilerinizi girmeniz ve uzmanlık seçmeniz istenecektir. Danışmanlık mesleğimiz ve meslek grubumuz için gönüllülük esasına dayalı olarak yaptığımız bir görevdir. Bunun yanı sıra kamu hastaneleri ve üniversiteler danışmanlık yapan hekimlere performans ve akademik atanma için puan vermektedir. Danışmanlık yapan meslektaşlarımızın bu çalışmaları için kendilerine -talep ettiklerinde- belge verilecek ve her yılın ilk sayısında bir önceki yılda kararı verilmiş yazılarda danışmanlık yapan kişilerin isimleri dergimizde yayınlanacaktır. Bilimsel Değerlendirme Kurulu'nda yer alacak isimler ise danışmanların yazı değerlendirmedeki sayı, süre ve katkı performansları göz önüne alınarak editörler kurulunun incelemesiyle belli aralıklarla yenilenecektir. Dergimizde görev yapmış tüm danışmanlara içtenlikle teşekkür ederim.

Dergimizin yeni uluslararası indekslere kabulü ya da halen kapsandığı indekslerce kapsanmasının devamı dergimizin bir impakt faktörünün olmasına, yani dergimizde yayınlanmış makalelerin özellikle yurtdışı diğer yayınlarda referans gösterilmesine bağlıdır. Dergimizde yayınlanmış makalelerin tamamını web sitemizden okuyup indirebilir, yine web sitemizdeki ya da TÜBİTAK bünyesindeki ULAKBİM (Türk Tıp Dizini) arama motorlarından anahtar kelimeleri kullanarak ilgili konulara ulaşabilirsiniz.

Gönderilen yazıların kısa sürede değerlendirilmesi ve yayınlanması konusunda en önemli basamak olan danışman değerlendirme süresini kısaltma ve bir baskıdaki makale sayısını artırma gibi değişiklikler uygulamaya geçmiştir. Amacımız siz meslektaşlarımızın göndermiş olduğu yayınların karar ve baskı sürecini en kısa sürede sonuca ulaştırmaktır.

Makalelerin düzeltilmesindeki titiz çalışmaları, zamanında ve kaliteli baskı konusundaki gayretleri nedeniyle yayıncımız DNT Ortadoğu Yayıncılık A.Ş. ve birlikte çalışmaktan büyük mutluluk duyduğumuz yazı işlerindeki değerli arkadaşlarımıza sonsuz teşekkürler etmek isterim.

Dergimizin kalitesini yükseltmek için her zaman önerilere ve eleştirilere açık olduğumuzu ve bu konudaki bildirimlere gereken hassasiyeti mutlaka göstereceğimizi ve eksiklerimiz gidermek için elimizden geleni yapacağımızı vurgulamak isterim.

Bilimsel dergiler meslek grubumuzun ürünlerinin adeta vitrinidir. Bu vitrinin güzelleşmesi için vereceğiniz katkılar için şimdiden teşekkür eder, saygılar sunarım

**Prof. Dr. Serdar Günaydın**
**Baş Editör**

# INDEX

# İÇİNDEKİLER

## Editorial / Editörden

Turkish Journal of Clinics and Laboratory

To cite this article: Hendek MK, Erdemir EO, Kisa U. Advanced oxidation protein products and monocyte chemoattractant protein-1 in periodontal disease. Turk J Clin Lab 2018; 9(1): 1-6

Original Article

# Advanced oxidation protein products and monocyte chemoattractant protein-1 in periodontal disease

## *Periodontal hastalıkta ileri oksidasyon protein ürünleri ve monosit kemoatraktan protein-1*

Meltem KARSIYAKA HENDEK[1]* , Ebru OLGUN ERDEMIR[1] , Ucler KISA[2]

[1]Department of Periodontology, Faculty of Dentistry, Kirikkale University, Kirikkale, Turkey
[2]Department of Biochemistry, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey

## ABSTRACT

**Aim:** The aim of the study was to determine gingival crevicular fluid (GCF) levels of advanced oxidation protein product (AOPP) and monocyte chemoattractant protein (MCP)-1 in subjects with periodontal disease and health.

**Materials and Methods:** A total of 75 non-smokers, including 25 participants with chronic periodontitis (CP), 25 participants with gingivitis (G) and 25 participants with periodontally healthy (H) were included into the present study. The probing depth (PD), clinical attachment level (CAL), plaque index (PI) and gingival index (GI) were recorded. The GCF samples from 4 sites in each individual were collected and GCF AOPP and MCP-1 levels were determined by enzyme-linked immunosorbent assay method.

**Results:** GCF AOPP and MCP-1 levels were the lowest in the H group; followed by the G group and the highest in the CP group. These differences were statistically significant between G and H groups and between the CP and the other groups ($p < .05$). A statistically positive correlation was detected between GCF AOPP and MCP-1 levels.

**Conclusion:** GCF AOPP and MCP-1 levels might play a considerable role during periodontal inflammation and an elevated GCF AOPP and MCP-1 levels are suggested as a potential biomarker for periodontal diseases.

**Key Words:** Advanced oxidation protein products, Gingival crevicular fluid, Monocyte chemoattractant protein, Oxidative stress, Periodontitis

Corresponding Author*: Meltem Karsiyaka Hendek, Department of Periodontology, Faculty of Dentistry, Kirikkale University, Kirikkale, Turkey
E-Mail: mltmkrsyk@yahoo.com
Received 13.07.2017 accepted 13.11.2017
Doi: 10.18663/tjcl.328204

## Öz

**Amaç:** Çalışmanın amacı periodontal hastalıklı ve sağlıklı bireylerde dişeti oluğu sıvısı (DOS) ileri oksidasyon protein ürünleri (AOPP) ve monosit kemoatraktan protein-1 (MCP)-1seviyelerini belirlemekti.

**Gereç ve Yöntemler:** 25 kronik periodontitisli (KP), 25 gingivitisli (G) ve 25 periodontal sağlıklı (S) toplam da 75 sigara içmeyen birey çalışmaya dahil edildi. Sondalanabilir cep derinliği (SCD), klinik ataşman seviyesi (KAS), plak indeksi (Pİ) ve gingival indeks (Gİ) kaydedildi. Her bireyde 4 alandan DOS örnekleri toplandı ve DOS AOPP ve MCP-1 seviyeleri enzim bağlı immunosorbent analizi ile belirlendi.

**Bulgular:** DOS AOPP ve MCP-1 seviyeleri en düşük S grupta; ardından G grubunda ve en yüksek KP grubunda idi. Bu farklılıklar G ve S grupları ile KP ve diğer gruplar arasında istatistiksel olarak anlamlı farklıydı ($p < .05$). DOS AOPP ve MCP-1 seviyeleri arasında pozitif istatistiksel korelasyon bulundu.

**Sonuç:** Periodontal inflamasyon sırasında DOS AOPP ve MCP-1 seviyeleri önemli bir rol oynayabilir ve artmış DOS AOPP ve MCP-1 seviyeleri, periodontal hastalıklar için potansiyel bir biyolojik belirteç olarak önerilebilir.

**Anahtar kelimeler:** İleri oksidasyon protein ürünleri, Dişeti oluğu sıvısı, Monosit kemoatraktan protein, Oksidatif stres, Periodontitis

## Introduction

Oxidative stress is called serious imbalance between the formation of free radical and antioxidant defense mechanism and leads to the tissue damage. The tissue damages of free radicals include many mechanisms such as protein damage, lipid peroxidation, DNA damage, oxidation of important enzymes and stimulation of proinflammatory cytokines [1].

Advanced oxidation protein product (AOPP) has been identified as a novel marker of oxidant-mediated protein damage, the intensity of oxidative stress, and inflammation. AOPP is defined as the cross-linked protein products containing dytrosine and considered to be a reliable marker for determination of protein damage [2]. AOPP was recognized in uremic patients in 1996 and results from activation of the chloronise oxidants with proteins [3]. It is used as a biomarker in several pathological conditions including diabetes mellitus, rheumatoid arthritis, ulcerative colitis, inflammatory bowel disease [4-7]. Furthermore, it is also suggested that AOPP acts as cytokine-like mediator between neutrophils and monocytes by activating mononuclear phagocytes [2,3]. When the relationship between cell activation markers and AOPP was examined, it was found that there was a close correlation with activation markers of monocytes rather than T and B cells' activation markers [2].

Chemokines are a family of polypeptide that activate different cell types and in relationship with them selectively [8]. Monocyte chemoattractant protein (MCP) - 1 is a possible mediator of completion and activation of monocytes. It is a major chemoattractant for specific subsets of lymphocytes, monocytes and macrophages [9]. MCP - 1 can be released by monocytes, endothelial cells, fibroblasts and T cells. It plays a role in the pathogenesis of various diseases, such as atherosclerosis, diabetes mellitus, idiopathic pulmonary fibrosis, tumors, rheumatoid arthritis, osteoarthritis [10-14]. MCP - 1 is also known to be associated with oral infection with monocyte chemotactic ability [15]. Previously, it has been shown that MCP - 1 expression increased in periodontal tissues [9] and gingival crevicular fluid (GCF) of patients with periodontal diseases [16-18].

To the best of the authors' knowledge, there is no study evaluating AOPP level in GCF of subjects with periodontal disease and health as a biomarker of protein oxidation. Therefore, the aims of our study were 1) to determine GCF AOPP and MCP - 1 levels in periodontal disease and health 2) to examine the possible correlation between the GCF AOPP and MCP - 1 levels. We hypothesized that AOPP may be stimulated by periodontal inflammation and there might be a positive correlation between AOPP and MCP - 1 levels.

## Material and Methods

### Study population

Seventy-five non-smokers (12 females and 13 males, aged 27 to 66 years [mean age, 42.28 ± 9.00 years]) with chronic periodontitis [CP], 12 females and 13 males, aged 18 to 45 years [mean age, 28.28 ± 7.25 years] with gingivitis [G], and 15 females and 10 males, aged 20 to 54 years [mean age, 31.80 ± 10.16 years] with healthy [H] participants) were selected from

participants referred to the Department of Periodontology, School of Dentistry, Kirikkale University, Kirikkale, Turkey, from May 2014 to January 2015. After all participants were informed about the procedures, they gave written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committe of Kirikkale University. (31.03.2014 Number: 11/04) The study protocol (NCT02848378) was approved by the Institutional Review Board. Each participant who have ≥ 20 teeth was examined clinically and radiographically. Participants having any systemic and bone diseases, bacterial oral infection, immunologic disorders, hepatitis, pregnant and lactating females, former and current smokers, receiving any periodontal treatment in the last 6 months, taking any antibiotics, anti-inflammatory or antioxidants were excluded.

**Study groups**

Participants were classified into three groups based on their periodontal condition according to criteria proposed by the 1999 International World Workshop for a Classification of Periodontal Disease and Conditions [19]. Participants with CP had moderate to severe alveolar bone loss and clinical attachment level (CAL) ≥ 5 mm and probing depth (PD) ≥ 6 mm in multiple sites of all four quadrants of the mouth but with no evidence of rapid progression. Participants with G had gingival inflammation that was based on the presence of bleeding on probing (BOP) at > 50% of sites in the whole mouth, no clinical and radiographic signs of periodontitis. Participants with healthy periodontium had no sites with PD > 3 mm and CAL > 2 mm, a BOP score of < 15% at the examination, and no alveolar bone loss.

**Clinical periodontal parameters**

The plaque index (PI) [20], gingival index (GI) [21] from four sites per tooth and the PD and CAL from six sites per tooth using a manual periodontal probe (William's periodontal probe, Hu-Friedy, Chicago, IL) in the whole mouth except third molars were identified. All measurements were performed by a calibrated examiner (MKH). The intraexaminer reliability was high as revealed by an intraclass correlation coefficient of 0.82 and 0.80 for PD and CAL measurements, respectively.

**Collection of GCF samples**

Four GCF samples including first incisors and canine teeth in H group; single-rooted teeth with the most inflammation in G group and single-rooted teeth with ≥ 4 and < 7 mm PD and ≥ 30% bone loss in CP group were obtained from buccal aspects of the mesial or distal interproximal sites of all teeth. After the samples sites were isolated with cotton rolls and slightly air-dried, the standardized strips (Periopaper, Ora Flow Inc.,Amityville, NY, USA) were used to collect GCF in 30 seconds and volume was measured on a precalibrated device (Periotron 8000, Oraflow Inc., Plainview, NY, USA). Phosphate-buffered saline (500 mL, pH 7.2) was added to each Eppendorf tube containing four paper strips. Then, tubes were vortexed (Vortex, Velp Scientifica, Usmate Velate, Italy) for 1 minute, mixed for 20 minutes with shaking (Biosan Orbital Shaker OS-10, Riga, Latvia), and centrifuged (Mikro 22 R Hettich Centrifugal Machine, Tuttlingen, Germany) for 5 minutes at 5,800 rpm. All samples were stored at -80°C until analysis. GCF AOPP and MCP - 1 levels were measured by enzyme-linked immunosorbent assay (ELISA) (Sun Red Biotechnology Company, Shanghai, China, eBioscience, Inc. San Diego, CA, USA, respectively) using commercial kits according to the manufacturers' instructions.

## Statistical analysis

Sample size of 25 has been taken which was found to be adequate to achieve more than 80% power at 0.5 level of significance. The normality of the data distribution was examined using the Shapiro-Wilk test. Non-normally distributed data were expressed as median (IQR). The non-parametric Kruskal-Wallis test was used for comparisons among the study groups for levels of AOPP and MCP - 1. Post hoc two-group comparisons were performed with Bonferroni corrected Mann-Whitney U tests for significant differences. Spearman rank correlation analysis was used to observe any correlation between the GCF AOPP and MCP - 1 levels and P < 0.05 was considered to be statistically significant. All data analyses were performed using a statistical package (SPSS for Windows v.15.0, IBM, Chicago, IL) and software (Minitab 16 Statistical Software, Minitab, State College, PA.) was used for the power analyses.

## Results

**Demographic and clinical findings**

The demographic characteristics and clinical data of the study groups are presented in Table 1. There was no significant difference in gender and age among the study groups (p >.05). PI, PD and CAL scores in the CP group were significantly higher than those of the H and G groups (p <.05). GI score in the H group was significantly lower than the CP and the G groups (p <.05). PI and PD scores were significantly higher in the G group than the H group (p <.05).

**Table 1:** Demographic Characteristics and Full-Mouth Clinical Parameters of Study Groups

| Characteristic | H (n=25) | G (n=25) | CP (n=25) |
|---|---|---|---|
| Age (years; mean±SE) | 31.80 ± 10.16 | 28.28 ± 7.25 | 42.28 ± 9.00 |
| Sex | | | |
| Females | 15 | 12 | 12 |
| Males | 10 | 13 | 13 |
| PI | 0.16 ± 0.11 | 1.29 ± 0.27* | 1.80 ± 0.27*,** |
| GI | 0.04 ± 0.05 | 1.75 ± 0.29* | 1.79 ± 0.31* |
| PD (mm) | 1.34 ± 0.49 | 2.17 ± 0.51* | 5.71 ± 0.74*,** |
| CAL (mm) | - | - | 6.35 ± 0.70*,** |

H= Healthy group; G= Gingivitis group; CP= Chronic periodontitis
*p <0.05, significant difference compared with the H group
**p <0.05, significant difference compared with the G group

### Laboratory findings

GCF volume was significantly lower in the the H group than the G and the CP groups and was significantly higher in the CP group than the G group. The total amount of GCF AOPP and MCP - 1 were significantly higher in G and CP groups than the H group.

GCF AOPP and MCP - 1 levels were significantly lower in the G group compared to the CP group (Table 2). The significant positive correlations were found between all clinical parameters and GCF AOPP and MCP - 1 levels. GCF AOPP level was positively correlated with GCF MCP - 1 level (Table 3).

**Table2:** GCF Volume, the total amount of AOPP and MCP-1 in GCF of Study Groups (Median [IQR])

| | H (n=25) | G (n=25) | CP (n=25) | p |
|---|---|---|---|---|
| GCF Volume (µl) | 0.07 ± 0.03 | 0.38 ± 0.13* | 0.48 ± 0.17*,** | <0.05 |
| AOPP (nmol/4 sites) | 1.36 ± 0.63 | 11.11 ± 3.69* | 18.70 ± 7.68*,** | <0.05 |
| MCP-1 (pg/4 sites) | 0.35 ± 0.23 | 9.21 ± 5.84* | 28.77 ± 11.49*,** | <0.05 |

H= Healthy group; G= Gingivitis group; CP= Chronic periodontitis; GCF= Gingival crevicular fluid; AOPP= Advanced Oxidation Protein Product;
MCP= Monocyte Chemoattractant Protein
*p <0.05, significant difference compared with the H group
**p <0.05, significant difference compared with the G group

**Table 3:** Correlations of the gingival crevicular fluid advanced oxidation protein product and monocyte chemoattractant protein-1 levels with clinical parameters

| | PI | | GI | | PD | | CAL | | MCP-1 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | r | P | r | P | r | P | r | P | r | p |
| AOPP | 0.759 | <0.01 | 0.705 | <0.01 | 0.755 | <0.01 | 0.694 | <0.01 | 0.896 | <0.01 |
| MCP-1 | 0.715 | <0.01 | 0.580 | <0.01 | 0.813 | <0.01 | 0.816 | <0.01 | - | - |

PI= Plaque index; GI= Gingival index; PD= Probing depth; CAL= Clinical attachment level; AOPP= Advanced Oxidation Protein Product; MCP= Monocyte Chemoattractant Protein

## Discussion

In this cross-sectional study, we evaluated GCF AOPP level, as a protein damage mechanism's product and GCF MCP - 1 level, as a marker of monocyte function in periodontal disease and health. The data of the present study showed that the levels of AOPP and MCP - 1 in GCF were significantly higher in participants with periodontal disease than periodontally healthy participants and there was a significant positive correlation between GCF AOPP and MCP - 1 levels.

Reactive oxygen species (ROS) act a part in redox-dependent signaling and are necessary for physiological functions. However, excessive generation of ROS and/or reduction of antioxidant defense system against ROS can lead to oxidative stress [1]. Oxidative stress contributes to many diseases and pathologic conditions such as diabetes mellitus [22], cancer [23], chronic renal failure [24], atherosclerotic cardiovascular disease [25], rheumatoid arthritis [26]. Many human studies investigated oxidative stress markers in GCF in periodontitis [27-29].

ROS can cause fragmentation of the peptide chain, alteration of electrical charge of proteins, cross-linking of proteins, and oxidation of specific amino acids and therefore lead to increased susceptibility to proteolysis by degradation by specific proteases [30]. AOPP, as a marker of protein oxidation, is generated during oxidative stress. This product is dependable marker to identify oxidative alteration of proteins. It was shown that in vivo-generated AOPP was able to result in oxidative bursts in neutrophils as well as in monocytes, in this way it was represented to act as inflammatory mediator [31]. Several studies have specified the linkage between AOPP and diabetes mellitus [4,32]. Pan et al. [32] reported a significant increase serum AOPP and protein carbonyl in diabetes mellitus compared with healthy participants. In another study investigating the role of oxidative stress in the pathogenesis of rheumatoid arthritis, it was shown that serum AOPP and the total thiol levels were higher in patients than the control group and protein oxidation has been shown to play an

important role as much as the peroxidation of lipid oxidation in the pathogenesis of rheumatoid arthritis [5]. To the best our knowledge, this is the first study to investigate the AOPP level in GCF in participants with periodontal diseases. In our study, the increment of GCF AOPP level from periodontal health towards periodontal disease supports to use AOPP as a marker of oxidative stress in periodontitis. These results suggest that oxidative protein damage initiates in early stages of periodontal disease and keeps to enhance as the disease progresses and that AOPP is also acceptable marker for determining oxidative stress as a protein damage biomarker in periodontal diseases.

MCP - 1 is a chemokine involved in cell migration during inflammation process. It is secreted from cytokine-activated endothelial cells and vascular smooth muscle cells for the migration of monocytes to inflammation area [18]. Hanazawa et al. [33] evaluated MCP - 1 gen expression in periodontal tissues and monocyte chemotactic activities in GCF in patients with periodontal diseases and they revealed that MCP - 1 gen expression in gingival tissues was significantly higher in patients with chronic periodontitis than periodontally healthy participants and emphasized that MCP - 1 expresssion plays an important role in monocyte infiltration in gingival tissues with periodontal diseases. Yu and Graves [34] examined MCP - 1 expression in chronic inflammed gingival tissues and reported MCP - 1 expression was significantly higher in severe inflamed tissue than moderate and mild inflamed tissues. In a study investigating GCF MCP - 1 level in periodontal health and disease, it was suggested that MCP - 1 level in GCF increased with disease and decreased after periodontal treatment [18]. In an another study, MCP - 1 level in GCF was increased in chronic and aggressive periodontitis compared to periodontally healthy participants [17]. Similarly, in our study, it was shown that MCP - 1 level in GCF was found to be significantly higher in CP and G groups compared to periodontally healthy group. Similarly, these results presented that MCP - 1 level in GCF was parallel to the increase of periodontal clinical parameters and it was determined this increment plays a role in the pathogenesis of periodontal disease.

In this study, we also aimed to examine the possible correlations between AOPP and MCP - 1 levels in GCF and we found that there was a significant positive correlation between AOPP and MCP - 1 levels. In vitro study pointed out MCP - 1 expression at both the protein and mRNA levels was properly increased by AOPP [35]. In rat mesenchymal cells, AOPP can induce MCP - 1 mRNA and protein expression via nuclear factor kappa B activation [36]. A clinical study displayed a relation between AOPP levels and serum markers of monocyte activation [2]. We also found strong positive correlations between the total amount of AOPP and MCP - 1 in GCF. This condition suggests that oxidized proteins may contribute to the inflammatory process that is associated with periodontal inflammation.

## Conclusion

The results of our study suggest that a significant protein damage mechanism's product may occur in periodontal disease. GCF AOPP level may be used as a biomarker to detect the protein damage caused by oxidative stress and the potent positive correlation between GCF AOPP and MCP - 1 levels may provide an elucidation for the mechanisms of inflammatory condition in periodontal diseases. Further, longitudinal prospective studies are needed to affirm the findings of our study.

## Acknowledgements

This work was supported by Research Fund of Kirikkale University Project 2014/17.

## Declaration of conflicting interests

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

## References

1. Chapple IL, Matthews JB. The role of reactive oxygen and antioxidant species in periodontal tissue destruction. Periodontol 2000 2007; 43: 160-232.
2. Witko-Sarsat V, Friedlander M, Nguyen Khoa T, et al. Advanced oxidation protein products as novel mediators of inflammation and monocyte activation in chronic renal failure. J Immunol 1998; 161: 2524-32.
3. Witko-Sarsat V, Friedlander M, Capeillère-Blandin C, et al. Advanced oxidation protein products as a novel marker of oxidative stress in uremia. Kidney Int 1996; 49: 1304-13.
4. Piwowar A, Knapik Kordecka M, Warwas M. AOPP and its relations with selected markers of oxidative/antioxidative system in type 2 diabetes mellitus. Diabetes Res Clin Pract 2007; 77: 188 92.
5. Baskol G, Demir H, Baskol M, et al. Investigation of protein oxidation and lipid peroxidation in patients with rheumatoid arthritis. Cell Biochem Funct 2006; 24: 307–11.
6. Baskol M, Baskol G, Kocer D, Ozbakir O, Yucesoy M. Advanced oxidation protein products: a novel marker of oxidative stress in ulcerative colitis. J Clin Gastroenterol 2008; 42: 687–91.
7. Krzystek Korpacka M, Neubauer K, Berdowska I, et al. Enhanced formation of advanced oxidation protein products in IBD. Inflamm Bowel Dis 2008; 14: 794 802.
8. Bartold PM, Narayanan AS. Molecular and cell biology of healthy and diseased periodontal tissues. Periodontol 2006; 40: 29–49.
9. Tonetti MS, Imboden MA, Gerber L, Lang NP, Laissue J, Mueller C. Localized expression of mRNA for phagocyte-specific chemotactic cytokines in human periodontal infections. Infect Immun 1994; 62: 4005–14.
10. Nelken NA, Coughlin SR, Gordon D, Wilcox JN. Monocyte chemoattractant protein-1 in human atheromatous plaques. J Clin Invest 1991; 88: 1121–27.

11. Kamei N, Tobe K, Suzuki R, et al. Overexpression of MCP-1 in adipose tissues causes macrophage recruitment and insulin resistance. J Biol Chem 2006; 281: 26602–14.
12. Antoniades HN, Neville-Golden J, Galanopoulos T, Kradin RL, Valente AJ, Graves DT. Expression of monocyte chemoattractant protein-1 in mRNA in human idiopathic pulmonary fibrosis. Proc Natl Acad Sci USA 1992; 89: 5371–75.
13. Graves DT, Barnhill R, Galanopoulos T, Antoniades HN. Expression of monocyte chemoattractant protein-1 inhuman melanoma in vivo. Am J Pathol 1992; 140: 9–14.
14. Villiger PM, Terkeltaub R, Lotz M. Production of monocyte chemoattractant protein-1 by inflamed synovial tissue and cultured synoviocytes. J Immunol 1992; 149: 722–27.
15. Gemmell E, Marshall RI, Seymour GJ. Cytokines and prostaglandins in immune homeostasis and tissue destruction in periodontal disease. Periodontol 2000 1997; 14: 112-43.
16. Emingil G, Atilla G, Hüseyinov A. Gingival crevicular fluid monocyte chemoattractant protein-1 and RANTES levels in patients with generalized aggressive periodontitis. J Clin Periodontol 2004; 31: 829-34.
17. Kurtiş B, Tüter G, Serdar M, et al. Gingival crevicular fluid levels of monocyte chemoattractant protein-1 and tumor necrosis factor-alpha in patients with chronic and aggressive periodontitis. J Periodontol 2005; 76: 1849-55.
18. Pradeep AR, Daisy H, Hadge P. Gingival crevicular fluid levels of monocyte chemoattractant protein-1 in periodontal health and disease. Arch Oral Biol 2009; 54: 503-9.
19. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999; 4: 1-6.
20. Silness J, Löe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand 1964; 22: 121-35.
21. Löe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. Acta Odontol Scand 1963; 21: 533-51.
22. Arana C, Cutando A, Ferrera MJ, et al. Parameters of oxidative stress in saliva from diabetic and parenteral drug addict patients. J Oral Pathol Med 2006; 35: 554-59.
23. Bahar G, Feinmesser R, Shpitzer T, Popovtzer A, Nagler RM. Salivary analysis in oral cancer patients: DNA and protein oxidation, reactive nitrogen species, and antioxidant profile. Cancer 2007; 109: 54-9.
24. Akagi S, Nagake Y, Kasahara J, et al. Significance of 8- hydroxy-29-deoxyguanosine levels in patients with chronic renal failure. Nephrology (Carlton) 2003; 8: 192-95.
25. Wolfram R, Oguogho A, Palumbo B, Sinzinger H. Enhanced oxidative stress in coronary heart disease and chronic heart failure as indicated by an increased 8-epi-PGF(2alpha). Eur J Heart Fail 2005; 7: 167-72.
26. Rall LC, Roubenoff R, Meydani SN, Han SN, Meydani M. Urinary 8-hydroxy-29-deoxyguanosine (8-OHdG) as a marker of oxidative stress in rheumatoid arthritis and aging: Effect of progressive resistance training. J Nutr Biochem 2000; 11: 581-84.
27. Hendek MK, Erdemir EO, Kisa U, Ozcan G. Effect of initial periodontal therapy on oxidative stress markers in gingival crevicular fluid, saliva, and serum in smokers and non-smokers with chronic periodontitis. J Periodontol 2015; 86: 273-82.
28. Pradeep AR, Ramchandraprasad MV, Bajaj P, Rao NS, Agarwal E. Protein carbonyl: An oxidative stress marker in gingival crevicular fluid in healthy, gingivitis, and chronic periodontitis subjects. Contemp Clin Dent 2013; 4: 27-31.
29. Liu Z, Liu Y, Song Y, Zhang X, Wang S, Wang Z. Systemic oxidative stress biomarkers in chronic periodontitis: a meta-analysis. Dis Markers 2014; 2014: 931083.
30. Kelly FJ, Mudway IS. Protein oxidation at the air-lung interface. Amino Acids 2003; 25: 375–96.
31. Witko-Sarsat V, Gausson V, Nguyen AT, et al. AOPP-induced activation of human neutrophil and monocyte oxidative metabolism: a potential target for N-acetyl-cysteine treatment in dialysis patients. Kidney Int 2003; 64: 82–91.
32. Pan HZ, Zhang H, Chang D, Li H, Sui H. The change of oxidative stress products in diabetes mellitus and diabetic retinopathy. Br J Ophthalmol 2008; 92: 548-51.
33. Hanazawa S, Kawata Y, Takeshita A, et al. Expression of monocyte chemoattractant protein 1 (MCP-1) in adult periodontal disease: Increased monocyte chemotactic activity in crevicular fluids and Induction of MCP-1 expression in gingival tissues. Infect Immun 1993; 12: 5219-24.
34. Yu XH, Graves DT. Fibroblasts, mononuclear phagocytes, and endothelial cells express monocyte chemoattractant protein-1 (MCP-1) in inflamed human gingiva. J Periodontol 1995; 66: 80-88.
35. Zhao Y, Chen SJ, Wang JC, et al. Sesquiterpene lactones inhibit advanced oxidation protein product-induced MCP-1 expression in podocytes viaan IKK/NF- κB-dependent mechanism. Oxid Med Longey 2015; 2015: 9340-58.
36. Wang JC, Zhao Y, Chen SJ, Long J, et al. AOPPs induce MCP-1 expression by increasing ROS-mediated activation of the NF-κB pathway in rat mesangial cells: inhibition by sesquiterpene lactones. Cell Physiol Biochem 2013; 32: 1867-77.

Turkish Journal of Clinics and Laboratory

To cite this article: Uzunget SB, Maden O, Cabuk G, Uzel E, Balci MM, Golbasi Z. Assessment of the reperfusion success using TIMI Frame score in cases with ante-rior myocardial infarction undergoing thrombus aspiration. Turk J Clin Lab 2018; 9(1): 7-12.

Original Article

# Assessment of the reperfusion success using TIMI Frame score in cases with anterior myocardial infarction undergoing thrombus aspiration

## *Trombüs aspirasyonu yapılan akut anteriyor miyokard infaktüsünde reperfüzyon başarısının TIMI Frame sayımıyla değerlendirilmesi*

Sezen BAGLAN UZUNGET[1*], Orhan MADEN[2], Gizem ÇABUK[3], Eliz UZEL[4], Mustafa Mücahit BALCI[2], Zehra GÖLBAŞI[2]

[1]Department of cardiology, Ufuk University Faculty of Medicine, Ankara, Turkey
[2]Department of cardiology, Turkiye Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey
[3]Department of cardiology, Izmir Buca State Hospital, İzmir, Turkey
[4]Department of cardiology, Adiyaman University, Adiyaman, Turkey

## ABSTRACT

**Aim:** Achieving reperfusion is the key target in the treatment of myocardial infarction with acute ST elevation. In our study, we aimed to compare the improvement in coronary blood flow using corrected TIMI frame score (cTFC) in patients, who presented with acute anterior ST elevated myocardial infarction (AASTEMI), underwent primary percutaneous coronary intervention (PPCI) with manual thrombus aspiration (MTA) and those, who underwent PPCI alone.

**Material and Methods:** We included 30 patients with acute AASTEMI, who underwent PPCI with MTA and 60 patients, who underwent PPCI alone, between June 2009 and August 2013. Coronary angiography images were reviewed after the procedure to evaluate distal embolization, TIMI scores and the corrected TIMI frame scores in both groups. All-cause mortality and stent thrombosis were recorded at hospital admission. All-cause mortality, stent thrombosis, and hospitalization due to cardiac failure, occurring within a month of discharge, were investigated.

**Results:** The mean age was 56.50 ± 16.45 among patients undergoing thrombus aspiration; there were 22 males and 8 females. Among those who did not undergo MTA, the mean age was 56.57 ± 13.21; and there were 44 males and 16 females. The rate of previous myocardial infarction (MI) (23.3 % vs 6.6 %; p = 0.019) and history of percutaneous coronary intervention (PCI) (20.0 % vs 6.7 %, p = 0.040) was higher in patients, who underwent MTA. The mean TIMI frame score was 28.33 ± 7.24 and 26.68 ± 8.22, respectively in the patients, who underwent and did not undergo MTA; however, no statistically significant difference was detected (p = 0.389). Overall time to ischemia was longer in the groups of patients, who underwent MTA (8.23 ± 9.68 vs 3.68 ± 8.22 hours, p = 0.003). Three patients, who underwent MTA (10 %, p = 0.007) died before discharge and 1 patients (13.1 %, p = 0.003) died within a month. No cases of death were detected in the group of patients, who did not undergo MTA, in the hospital and within a month. There were no statistically significant differences between these two groups with respect to hospitalization due to cardiac failure and occurrence of stent thrombosis.

**Conclusion:** The use of MTA in AASTEMI did not have a favorable impact on reperfusion compared to not using MTA.

**Keywords:** Myocardial infarction, thrombus aspiration, acute anterior myocardial infarction, percutaneous coronary intervention

Corresponding Author*: Sezen Bağlan Uzunget , Department of cardiology, Ufuk University Faculty of Medicine, Ankara, Turkey
E-Mail: sezenbaglan@hotmail.com
Recevied 12.03.2017 accepted: 31.05.2017
Doi: 10.18663/tjcl.297580

## ÖZ

**Amaç:** Akut ST yükselmeli miyokard enfarktüsü tedavisinde reperfüzyonun sağlanması temel hedeftir. Bizim çalışmamızda amacımız; akut anteriyor miyokard infarktüsü ile başvuran, manuel trombüs aspirasyonu ile primer perkütan koroner girişim yapılan ve yalnızca primer perkütan koroner girişim yapılan hastalarda, koroner kan akımındaki iyileşmeyi, düzeltilmiş TİMİ frame sayımı ( dTFS ) kullanarak kıyaslamaktır.

**Gereç ve Yöntemler:** Çalışmaya retrospektif olarak akut anteriyor miyokard in-farktüsü olup manuel trombüs aspirasyonu ile birlikte primer perkütan koroner giri-şim uygulanmış 30, yalnızca primer perkütan koroner girişim uygulanmış 60 hasta alındı. Gruplar yaş ve cinsiyet açısından eşleştirdi. Koroner anjiografi filmleri tekrar izlenerek her iki grubta distal embolizasyon, TİMİ skoru ve dTFS değerlendirildi. Hastane yatışı esnasında tüm nedenli ölümler, stent trombozu kaydedildi. Taburcu-luk sonrası bir ay içinde meydana gelen tüm nedenli ölümler, stent trombozu ve kalp yetersizliği nedenli yatışları incelendi.

**Bulgular:** Trombüs aspirasyonu yapılanların, ortalama yaşı 56.50±16.45. Tombüs aspirasyonu yapılmayanların ortalama yaşı 56.57±13.21 idi. Manuel trombüs aspi-rasyonu yapılan grupta dTFS ortalama 28.33±7.24, yapılmayan grupta ortala-ma 26,68±8.22, olarak tespit edildi. Ancak istastistiksel olarak fark tespit edilmedi (p=0.389). İşlem sonrası her iki grupta da EKG'de benzer oranlarda ST segment rezolüsyonu tespit edildi. Manuel trombüs aspirasyonu yapılan 3 hasta (%10, p= 0.007) taburculuk öncesi, 1 hasta (%13.1, p=0.003) bir ay içinde ölmüştür. Trombüs aspirasyonu yapılmayan grupta hastane içinde ve bir ay içinde ölüm izlenmemiştir. Gruplar arasında bir ay içinde kalp yetersizliği nedenli hastane yatışı ve stent trom-bozu görülme oranları açısından istastistiksel fark tespit edilmedi.

**Sonuç:** Çalışma grubumuzda akut anteriyor miyokard infarktüsünde manuel trom-büs aspirasyonun kullanılması, kullanılmamasına göre reperfüzyon üzerine olumlu etki göstermemiştir.

**Anahtar Kelimeler:** Miyokard infarktüsü, trombüs aspirasyonu, akut anteriyor miyokard infarktüsü, perkütan koroner girişim

## Introduction

In case of acute myocardial infarction (AMI), a leading cause of morbidity and mortality worldwide, the best established treatment is rapid complete restoration and maintenance of the coronary flow [1, 2]. Since the objective is to provide and maintain coronary patency, MTA appears to be a low-cost, easily applicable method. However, data on routine use in AASTEMI is not sufficient. Therefore, we aimed to investigate whether there was any difference in achieving post-procedure coronary blood flow by using TIMI frame scores in patients, presenting to our center with AASTEMI, who underwent PPCI alone and those who underwent PCI following MTA.

## Material and Methods

### Patient population demographics

The study sample consists of patients with AASTEMI (30), who were administered MTA and PPCI by different operators from our center and age- and sex-matched AASTEMI patients, who only underwent PPCI (60) between June 2009 and August 2013 at the Turkiye Yuksek Ihtisas Hospital. The demographics of patients included in the study were obtained from by screening of files and one to one telephone calls. Risk factors such as age, sex, diabetes mellitus (DM), hypertension, hyperlipidemia and smoking were recorded. Those with a systolic blood pressure > 140 mmHg, a diastolic blood pressure > 90 mmHg or those with a history of antihypertensive use were considered to be hypertensive patients. Those with a fasting LDL level > 130 mg/dL or history of statin use were considered to be hypercholesterolemic and patients with a fasting blood sugar > 126 mg/dL and those who were on treatment for established DM were considered to be diabetics. Smoking was classified as smoking patients and those with no history of smoking. Height and weight were recorded to calculate the body mass index (BMI). Patients with a TIMI flow of 0 or I following MTA or PPCI, and patients, who used thrombolytics before the procedure, who underwent an unsuccessful PPCI or were observed to have > 50 % left main coronary lesion, developed cardiogenic shock, were detected to have spontaneous recanalization by angiography, met the criteria of left ventricular hypertrophy on ECG as per Sokolow Lyon criteria, or in whom ECG could not be assessed accurately due to left branch block and patients, who had a break in post-procedure aspirin and / or clopidogrel use for any reason were excluded from the study.

### Coronary angiography and thrombus aspiration

Coronary angiography was performed through the femoral artery, using the standard Judkins technique. Iopromide (Ultravist 370/100 mL) was used as the contrast agent and 6-8 contrast materials were manually injected for each posture. Coronary arteries were displayed on the right and left oblique planes, at cranial and caudal angles at 25 frames per second (25 fps) and transferred to the CD using DICOM software. Patients were given aspirin (300 mg), heparin (50000 U, intravenous route) and clopidogrel (600 mg) before being transferred to the catheter room and depending on their weight, they were given additional heparin at 100 U/kg in the catheter room.

Manual, double-lumen Export Aspiration Catheter was used for performing thrombus aspiration and these patients were administered coronary stent as required. Those, who did not undergo MTA, were only administered PPCI (balloon and/or stent). Recanalization of the relevant artery was confirmed by angiography following PPCI. A control ECG was performed at the 90th minute in patients, who achieved TIMI II-III flow. Use of glycoprotein IIb / IIIa receptor inhibitor was left to the discretion of the operator. Tirofiban was used as the glycoprotein IIb / IIIa receptor inhibitor.

### ST segment resolution measurement

Without the presence of left ventricular hypertrophy (LVH) and left branch bundle block (LBBB), the diagnosis of AASTEMI was established by detection of ≥ 1 mm (0.1 mV) new and extended (> 20 minutes) ST elevation on DI, aVL, V1-6 on at least two consecutive derivations starting from the J point on V2-V3 derivations, which was ≥ 2.5 mm (0.25 mV) in males below 40 years of age and ≥ 2 mm (0.2 mV) in males above 40 years of age, and ≥1.5 (0.15 mV) in females [3]. Measurements were obtained from ECG samples, recorded right before PPCI and at 90 minutes after TIMI II-III flow was achieved. ST segment elevation was measured in millimeters. The difference between the two measurements was expressed in percentage and was assessed as the ST segment resolution (STR). STR was divided into two groups as below and above 50 %.

### TIMI frame score assessment

Corrected TIMI frame count method was used for quantitative measurement of coronary blood flow as previously described [4]. After administering an opaque material to determine the frame score, the point when the contrast material touched the two sides of the artery and started moving forward was measured as the starting point while the point when the contrast material reached the distal branching point for left anterior descending artery, called moustache, was measured as the final point.

### Endpoints

The primary endpoint was the TIMI frame score. The secondary endpoints included in-hospital mortality, distal embolization, stent thrombosis and 30-day mortality, and hospitalization due to stent thrombosis and cardiac failure. Informed consent was obtained from all patients and the study was approved by the local Ethics Committee.

## Statistical analysis

SPSS for Windows 11.5 packaged software was used for statistical assessment of data. Chi-square test and Fisher's exact test for comparing categorical data, Student's t test for assessing continuous data with normal distribution and Mann-Whitney U tests were used for data without normal distribution. As the descriptive values, number and percentages for categorical data and arithmetic mean ± standard deviations for continuous data were given. The limit of statistical significance was set at 0.05.

## Results

There were 30 patients with AASTEMI, who underwent MTA followed by PPCI and age- and sex-matched 60 patients, who underwent PPCI only.

There were no statistically significant differences between the two groups with respect to age, sex, BMI, smoking, familial history, DM, hypertension, coronary artery bypass grafting surgery (CABG) history. In the group, who received MTA, the rate of previous myocardial infarction (23.3 %; vs. 6.6 %, p = 0.019) and history of percutaneous coronary intervention (PCI) (20.0 % vs. 6.7 %, p = 0.040) was higher. Hyperlipidemia was detected at a higher rate in the group, who did not undergo MTA (68.3 % v.s. 40.0 %, p = 0.005). Other demographics were similar between groups (Table 1).

**Table 1.** Demographics of patients with or without MTA

| | Thrombus aspiration | | | | p |
|---|---|---|---|---|---|
| | Performed (N=30) | | Not performed (N = 60) | | |
| age (years) (mean ± SD) | 56.50 ± 16.45 | | 56.57 ± 13.21 | | 0.832 |
| Body mass index (kg/m2) (mean±SD) | 27.26 ± 4.23 | | 27.30 ± 2.36 | | 0.217 |
| Sex (M /F ) | 22 / 8 | | 44 / 16 | | 0.501 |
| Smoking (%) | 18 | 60.0 % | 40 | 66.9 % | 0.211 |
| Family history (%) | 8 | 26.7 % | 22 | 36.6 % | 0.299 |
| Diabetes Mellitus (%) | 11 | 36.7 % | 14 | 23.3 % | 0.171 |
| Hypertension (%) | 13 | 43.3 % | 21 | 35.0 % | 0.412 |
| Hyperlipidemia (%) | 12 | 40.0 % | 41 | 68.3 % | 0.005 |
| Previous MI (%) | 7 | 23.3 % | 4 | 6.6 % | 0.019 |
| Percutaneous coronary intervention history (%) | 6 | 20. 0 % | 4 | 6.7 % | 0.049 |
| Coronary artery bypass history (%) | 1 | 3.3 % | 0 | 0.0 % | 0.200 |

The results for the laboratory variables of the study population by each group were detected to be similar, except the platelet count and total cholesterol. The group of patients, who underwent MTA, was observed to have a statistically significantly higher mean platelet level and total cholesterol (Table 2). The two groups did not have a statistically significant difference with respect to the number of diseased vessels, and pre- and post-procedure TIMI flow. The mean TIMI frame score was 28.33 ± 7.24 and 26.68 ±8.22, respectively in the group of patients, who underwent and did not undergo MTA Figure1. There was no statistical difference (Table 3). The overall time to ischemia was longer in the group of patients, who received MTA (8.23 ± 9.68 hours vs. 3.68 ± 8.22 hours, p = 0.003). There was no statistical difference between the two groups with respect to application of pre-dilatation during the procedure, the size of the stents used and the stent implantation pressure (Table 5). After the procedure, STR was detected at similar

rates on ECG in both groups. Three patients (10 %, p = 0.007), who underwent MTA, died before being discharged and one patient (13.1 %, p = 0.003) died within one month. There was no in-hospital mortality or deaths within one month in the patients, who did not undergo MTA. There were no statistically significant differences between these two groups with respect to hospitalization due to cardiac failure and occurrence of stent thrombosis (Table 6).

**Table 2.** Hemodynamic and laboratory characteristics of the patients with or without MTA

| | Thrombus Aspiration | | P |
|---|---|---|---|
| | Performed (N = 30) | Not performed ( N = 60) | |
| | Mean ± SD | Mean ± SD | |
| Systolic blood pressure (mmHg) | 119.67 ± 25.40 | 118.35 ± 23.99 | 0.801 |
| Diastolic blood pressure (mmHg) | 72.97 ± 12.81 | 72.68 ± 14.11 | 0.923 |
| Heart rate (beat/minute) | 83.90 ± 12.12 | 84.12 ± 17.40 | 0.832 |
| Hemoglobin (g/dL) | 13.22 ± 1.69 | 13.68 ± 2.88 | 0.055 |
| Platelet (103/mm3) | 277.90 ± 90.34 | 230.11 ± 63.77 | 0.003 |
| White spheres (103/mm3) | 12.90 ± 4.28 | 12.78 ± 4.91 | 0.324 |
| Neutrophils (%) | 78.33 ± 10.75 | 76.31 ± 12.66 | 0.235 |
| Glucose (mg/dL) | 178.63 ± 146.74 | 141.63 ± 76.33 | 0.154 |
| Urea (mg/dL) | 38.77 ± 20.46 | 35.23 ± 11.45 | 0302 |
| Creatinine(mg/dL) | 0.93 ± 0.31 | 0.90 ± 0.39 | 0.621 |
| Potassium (mmol/L) | 4.20 ± 0.32 | 4.21 ± 033 | 0.899 |
| Total cholesterol (mg/dL) | 167.43 ± 36.31 | 155.42 ± 45.01 | 0.032 |
| HDL (mg/dL) | 39.00 ± 11.19 | 40.01 ± 11.24 | 0.502 |
| LDL (mg/dL) | 102.30 ± 30.45 | 100.21±36.89 | 0.701 |
| TG (mg/dL) | 131.73 ± 66.23 | 134.14 ± 105.36 | 0.825 |

HDL: High Density lipoprotein, LDL: Low Density Lipoprotein TG: Triglyceride

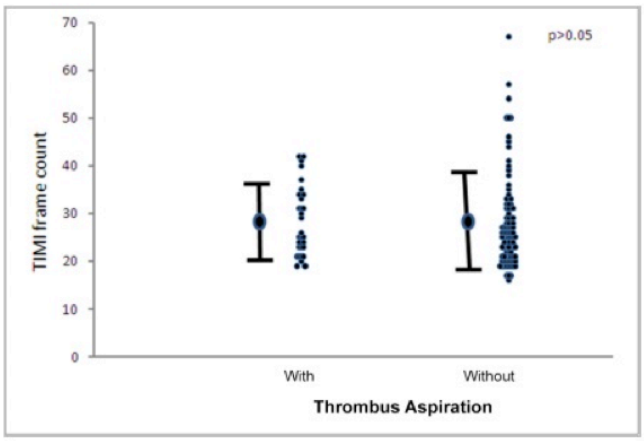



**Figure 1.** TIMI Frame scores in group of patients with or without MTA

**Table 3.** Angiographic characteristics of patients with or without MTA

| | Thrombus Aspiration | | P |
|---|---|---|---|
| | Performed (N = 30) | Not performed (N = 60) | |
| Number of diseased vessels | Median = 3 (min.- max. ; 1-3) | Median = 2 (min.- max. : 1-3) | 0.110 |
| Pre-procedure TIMI flow | Median = 0 (min.- max. ; 0-1) | Median = 0 (min.- max. : 0-1) | 0.354 |
| Post-procedure TIMI flow | Median = 3 (min.- max. ; 1-3) | Median = 3 (min.- max. : 2-3) | 0.210 |
| TIMI Frame Score | 28.33 ± 7.24 | 26.68 ± 8.22 | 0.389 |

**Table 4.** Time to total ischemia in patients with or without MTA

| | Thrombus Aspiration | | P |
|---|---|---|---|
| | Performed (N = 30) | Not performed (N = 60) | |
| | Mean ± SD | Mean ± SD | |
| Time to total ischemia (hours) | 8.23 ± 9.68 | 3.68 ± 8.22 | 0.003 |

**Table 5.** Comparison of the procedures in patient groups with or without MTA

| | Thrombus aspiration | | | | P |
|---|---|---|---|---|---|
| | Performed (N = 30) | | Not performed (N = 60) | | |
| Predilatation (N) | 19 | 63.3 % | 33 | 55.0 % | 0.410 |
| Stentdiameter (mean ±SD) (mm) | 2.92 ± 1.09 | | 3.18 ± 0.29 | | 0.312 |
| Stent length (mean±SD) (mm) | 18.15 ± 5.59 | | 18.78 ± 5.57 | | 0.821 |
| Stentimplantation pressure (mean±SD) (mmHg) | 13.47 ± 4.97 | | 13.98 ± 3.30 | | 0.238 |

**Table 6.** Clinical monitoring characteristics of patients with or without MTA

| | Thrombus Aspiration | | | | P |
|---|---|---|---|---|---|
| | Performed (N = 30) | | Not performed (N = 30) | | |
| ST segment resolution | 21 | 70.0 % | 71 | 58.3 % | 0.306 |
| In-hospital mortality | 3 | 10.0 % | 0 | 0.0 % | 0.007 |
| 1-month hospitalization for cardiac failure | 1 | 3.3 % | 4 | 6.7 % | 0.492 |
| 1-month all-cause mortality | 4 | 13.1 % | 0 | 0.0 % | 0. 048 |
| 1-month stent thrombosis | 2 | 6.7 % | 10 | 16.6 % | 0.212 |

## Discussion

The most significant therapeutic approach in acute ST elevated myocardial infarction (ASTEMI) is preservation of the myocardial viability and function by opening the occluded vessel. Reduced coronary blood flow is associated with cardiac failure and death, therefore the aim is to achieve normal coronary blood flow.

During the reperfusion treatment process, starting with the clear mortality benefit, provided with fibrinolytic treatment, complete reperfusion is achieved only in 50-60% of the patients [5]. Today, reperfusion treatment has taken on another dimension along with new anti-platelet drugs, PPCI-performing sites and technologic advances. One of these important advances is the initiated use of thrombus aspiration devices in reperfusion procedures. Coronary artery thrombus aspiration is an easy, fast and relatively low-cost method that assists PCI. In the recent years, some publications on the use of MTA devices as an additional treatment method in PPCI cases have reported promising results. While it is not a universal finding, it is considered to potentially improve blood flow and ST segment resolution. However despite its morbidity and mortality benefit in PPCI, the clinical benefit of thrombus aspiration is not clear due to different results from studies on thrombus aspiration. Therefore we investigated the efficacy of PPCI in achieving and maintaining vascular patency. To this end, we measured the TIMI frame score to evaluate whether there was a difference in achievement of coronary blood flow after the procedure in patients, presenting with AASTEMI and who underwent MTA followed by PPCI and who underwent PPCI alone. The mean TIMI frame score was 28,33 ± 7,24 and 26,68 ± 8,22 respectively in the patients, who did and did not undergo MTA; however no statistically significant difference was detected. The two methods showed a similar success in improving the blood flow.

Following TAPAS (Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study), a large, randomized, controlled study, published in 2010 [6], use of MTA in ASTEMI was presented as a class IIa recommendation in The American College of Cardiology Foundation/American Heart Association (ACCF\AHA) ST elevation myocardial infarction guideline [7]. In this study, a total of 1071 cases were randomized into two groups, including stenting only or aspiration thrombectomy followed by stenting, and the results investigated. Aspiration was successfully performed in 90 % of the patients and in 72 %, thrombus or atheroma was excised. While the group of patients undergoing aspiration had a significantly better myocardial staining score and STR, these favorable effects on myocardial perfusion also resulted in favorable outcomes in one-year clinical monitoring. During the one-year monitoring period, cardiac mortality was 3.6 % to 6.7 % ($p = 0.02$) and cardiac mortality or myocardial infarction (MI) was reported at 5.6 % to 9.9 % ($p = 0.008$) [6].

In another meta-analysis of 9 randomized studies, a lower level of distal embolization, better staining scores were obtained with thrombus aspiration and a better 30-day mortality rate was observed with STR [8].

In PPCI, aspiration thrombectomy is considered to have two types of potential benefit. The primary benefit is thought to be achievement of a better myocardial perfusion by prevention of the distal embolization. Secondarily, the recent publications have shown that thrombus aspiration reduces the rates of stent thrombosis. Particularly in ASTEMI patients with thrombus load, this risk is known to be increased if drug-eluting stent implantation is performed [9]. Reduction of the thrombus extent would reduce late stent malposition, thereby leading to a better-functioning stent and ensuring a more optimal stent strut distribution and decreasing late thrombosis risk in the long term. Another published study, TASTE (Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction) included 7244 patients from 31 centers and 3621 were randomized to the thrombus aspiration arm and 3623 were randomized to the control arm. During the 30-day follow-up, all-cause mortality, recurrent MI and stent thrombosis were similar between the two arms. Other clinical endpoints were also the same. This study was approximately 10-fold larger than the TAPAS study [10]. On the other hand, 30-day results were used in the TASTE study, and thus, clinical benefit of thrombus aspiration may become clearer after a long period of follow-up. In our study, the rate of patients with DM (36.7 %) was higher in the MTA group relative to the non-MTA group (23.3 %) even if the difference was not statistically significant. On the other hand, total ischemia time was longer in the MTA group compared to the non-MTA group ($p = 0.003$). The higher rates of diabetic patients, patients who presented late and had a high angiographic coronary artery thrombus load may have affected the success of the procedure.

The rate of previous MI (6.6 % versus 22.9 %; $p = 0.019$) and history of percutaneous coronary intervention was (6.7 % versus 20.0 %, $p = 0.040$) was higher in patients, who underwent thrombus aspiration. The presence of patients with a higher-risk and a higher comorbidity in the MTA group may have affected the results.

In a meta-analysis of 13 randomized studies on manual thrombectomy, the myocardial staining score and STR were significantly better while mortality rates were lower [11].

As for our study, we detected similar rates of STR on ECG after the procedure in both groups. In the MTA group, 3 patients

died before being discharges (10 %, p = 0.007) and one patient (13.1 %, p = 0.003) died within a month. In the non-MTA group, no in-hospital mortality or deaths within a month were observed. Although the sample size is not adequate to assess as mortality data, mortality rates were statistically higher in the MTA group.

Despite all these favorable results from studies and meta-analyses, the ability to achieve the same benefit in all patients with ASTEMI is still controversial. It may be appropriate to think that particularly patients with abundant thrombi would benefit more from thrombus aspiration. There are other large-scale ongoing studies on the subject. Use of thrombus aspiration does not appear to be rational until these studies are completed.

**Limitations to the study**

The number of cases that received MTA in the study was small. However, the study includes all AASTEMI patients, who underwent MTA and met the study criteria between June 2009 and August 2013. In this retrospective study, invasive intervention was not performed by a single physician. The decision to perform MTA was made by the operator performing the procedure depending on the thrombus load of the coronary bed. Even if there are some angiographic clues, it is not always easy to detect the presence of thrombus. Generally, thrombi on the coronary bed may be observed as filling defects in different forms, which are mobile or immobile on angiograms of patients, who have shown a recent clinical deterioration. Severity of the thrombus content may be mostly understood after passing through with a guidewire and even after performing a pre-dilatation and displaying the distal vascular bed. However in certain cases, this procedure coincides with distal embolization. Another limitation was the fact that the patients undergoing MTA were clinically more morbid. Additionally, as can be understood from the small number of cases, the little experience of the operator may have affected the results.

## Conclusion

In our study, the use of MTA in AASTEMI did not have a favorable impact on reperfusion compared to not using MTA. The high extent of thrombus that can be observed during coronary artery interventions may affect the success of intervention and long-term results unfavorably. Today, despite the presence of data in support of use particularly in case of lesions with intense thrombi, routine use in all cases is not recommended.

## Declaration of conflicting interests

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

## References

1. Onat A. Eriskinlerimizde kalp hastalıkları prevalansi, yeni koroner olaylar ve kalpten olum sıklığı (TEKHARF). Orhan matbaacılık, istanbul, TR, 2000; 16 – 23.
2. Fuster V. Epidemic of cardiovascular disease and stroke. The three main challenges. Circulation 1999; 99: 1132 – 37.
3. Thygesen K, Alpert JS, Jaffe AS et al. Third universal definition of myocardial infarction . the Writing Group on be half of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Eur Heart J 2012; 33: 2551–67.
4. Gibson CM, Cannon CP, Daley WL et al. TIMI frame count. A quantitative method of assesing coronary artery flow. Circulation, 1996; 93: 879-88. doi.org/10.1161/01. CIR. 93. 5.879
5. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after Acute myocardial infarction. N Engl J Med 1993; 329: 1615-22.
6. Vlaar PJ, Svilaas T, van der Horst IC et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarctions study (TAPAS). A 1-year follow-upstudy. Lancet 2008; 371: 191520.
7. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines doi:10.1016/j.jacc.2012.11.019
8. de Luca G, Dudek D, Sardella G et al. Adjunctive manuel thrombectomy improves myocardial perfusion and mortality in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction. A meta-analysis of randomized trials. Eur Heart J 2008; 29: 3002-10.
9. Sianos G, Papafaklis MI, Daemen J et al. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-elevation myocardial infarction. the importance of thrombus burden. J Am Coll Cardiol. 2007; 50: 573-83.
10. Fröbert O, Lagerqvist B, Gudnason T et al. Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial). A multicenter, prospective, randomized, controlled clinical registry trial based on the Swedish angiography and angioplasty registry (SCAAR) platform. Study design and rationale. Am Heart J 2010; 160: 1042-8.
11. Bavry AA, Kumbhani DJ, Bhatt DL. Role of adjunctive thrombectomy and embolic protection devices in acute myocardial infarction. A comprehensive meta-analysis of randomized trials. Eur Heart J 2008; 29: 3989-4001.

Turkish Journal of Clinics and Laboratory

To cite this article: Kirmusaoglu S. Bactericidal and antibiofilm activities of copper against biofilm producer pathogens colonized on orthopedic implants. Turk J Clin Lab 2018; 9(1): 13-18.

Original Article

# Bactericidal and antibiofilm activities of copper against biofilm producer pathogens colonized on orthopedic implants

## *Ortopedik implantlar üzerinde kolonize olan biyofilm üreten patojenler üzerinde bakırın bakterisidal ve antibiyofilm aktivitesi*

Sahra KIRMUSAOGLU*

Department of Molecular Biology and Genetics, Faculty of Arts and Science, T.C. Haliç University, Sütlüce-Beyoğlu/Istanbul 34445, Turkey

## ABSTRACT

**Aim:** New and alternative antimicrobial and antibiofilm agent discovery has gained attention since antibiotic resistance was easily developed. It has been accepted that metals have antimicrobial activity. Abiotic surfaces such as orthopedic implants that are impregnated with copper can prevent colonization of biofilm producer pathogens, and can detach biofilms produced on implants. In this study, the effects of copper against planktonic bacteria and biofilm embedded bacteria adhered on kirschner wire orthopedic implant were studied.

**Material and Methods:** MICs, MBCs and bMBC of copper against main biofilm producer pathogens such as methicillin resistance *Staphylococcus aureus* (MRSA), methicillin sensitive *Staphylococcus aureus* (MSSA), methicillin resistance *Staphylococcus epidermidis* (MRSE), methicillin sensitive *Staphylococcus epidermidis* (MSSE), *Escherichia coli (E. coli)*, *Klebsiella pneumonia (K. pneumonia), Pseudomonas aeruginosa (P. aeroginosa), Proteus mirabilis (P. mirabilis)* colonized on kirschner wire orthopedic implant were determined.

**Results:** MICs, MBCs, and bMBCs of copper against pathogens were ranged from 0.063 to 0.75 mg/mL. This study revealed that 0.75 mg/mL of copper inhibit all isolates analyzed in this study. The most tolerant pathogen was MRSA. The activities of copper against biofilm embedded bacteria and planktonic bacteria were found to be the same.

**Conclusion:** Indwelling medical devices such as orthopedic wires, prosthetics can be impregnated by copper to overcome colonization and production of matured biofilm on indwelling devices, consequently, implant associated infections.

**Key words:** Biofilm, biofilm embedded pathogens, copper, implants, antibiofilm, antimicrobial.

Corresponding Author*: Sahra KIRMUSAOGLU, Department of Molecular Biology and Genetics, Faculty of Arts and Science, T.C. Haliç University, Sütlüce-Beyoğlu/Istanbul 34445, Turkey
E-Mail: kirmusaoglu_sahra@hotmail.com
Recevied 24.03.2017 accepted:11.04.2017
Doi: 10.18663/tjcl.300359

## ÖZ

**Amaç:** Antibiyotik direnci kolaylıkla geliştiğinden beri, yeni, alternatif antimikrobiyal ve antibiyofilm ajan keşfi dikkat çekmektedir. Metallerin antimikrobiyal aktivitelere sahip olduğu kabul edilmiştir. Bakır ile emdirilmiş ortopedik implantlar gibi abiyotik yüzeyler, biyofilm üreten patojenlerin kolonizasyonunu önleyebilir ve implant üzerinde oluşturulan biyofilmleri ayırabilir. Bu çalışmada, bakırın planktonik bakteriler ve kirschner teli ortopedik implantı üzerine yapışan biyofilme gömülü bakterilere karşı etkisi çalışıldı.

**Gereç ve Yöntemler:** Kirschner teli ortopedik implant üzerinde kolonize olan metisilin dirençli Staphylococcus aureus (MRSA), metisilin duyarlı *Staphylococcus aureus* (MSSA), metisilin dirençli *Staphylococcus epidermidis* (MRSE), metisilin duyarlı *Staphylococcus epidermidis* (MSSE), *Escherichia coli (E. coli)*, *Klebsiella pneumonia (K. pneumonia)*, *Pseudomonas aeruginosa (P. aeroginosa)*, *Proteus mirabilis (P. mirabilis)* gibi ana biyofilm oluşturan patojenler üzerinde bakırın MIK, MBK ve MBEK değerleri belirlendi.

**Bulgular:** Bakırın, patojenlere karşı MIK, MBK ve MBEK değerleri 0.063 - 0.75 mg/mL arasında değişmektedir. Bu çalışma, 0.75 mg/mL bakırın çalışmada analiz edilen tüm izolatları inhibe ettiğini göstermiştir. En dirençli patojen MRSA idi. Bakırın biyofilme gömülü bakteriler ve planktonik bakteriler üzerindeki aktivitesi aynıydı.

**Sonuç:** Ortopedik teller, protezler gibi yabancı medikal cisimler, yabancı cisimler üzerinde kolonizasyon ve olgun biyofilm oluşturulmasını önlemek için bakır ile emdirilebilir

**Anahtar Kelimeler:** Biyofilm, biyofilme gömülü patojenler, bakır, implantlar, antibiyofilm, antimikrobiyal.

## Introduction

Biofilms that are sticky polysaccharides produced by biofilm producer bacteria lead microorganism to adhere biotic and abiotic substances such as host cells and indwelling medical devices, respectively. Biofilm infections become one of the main infection seen in hospitalized and immunosuppressed patients expose the patient to a higher risk of mortality worldwide [1, 2, 3]. Biofilm a place to embed sessile form of microorganism is more resistant to immune defence and antimicrobials such as antibiotics than planktonic microorganisms. Bacterial biofilms make treatment difficult and irresponsive to antibiotics by escaping immune defence of host and making infection recurrent and chronic [1, 2, 4]. Bacterial biofilms have a high risk to lead chronic infections such as indwelling device-associated infections, periodontitis, chronic wound infections, chronic urinary tract infections (UTI), chronic otitis media (OM), cystic fibrosis pneumonia, recurrent tonsillitis, chronic rhinosinusitis [1, 4] and valve-associated endocarditis [5]. Due to irresponsive treatment caused by the development of antibiotic resistance, consequently, functional loss of medical device (such as prosthetic implants, joints, stents, catheters) [6, 7], medical device may be removed out of the place localized [3] to overcome indwelling device-associated infection [1]. When implant-associated infection emerges in patients, the replacement of colonized indwelling device cause high risk of reinfection and bone destruction. Due to the development of antibiotic resistance, surgery fails and amputation may be done [8].

Microorganisms can adhere to surfaces that are made of stainless steel approximately after 28 days [9]. Due to this, in recent years, alternative treatment options such as natural compounds, new chemicals and metals such as copper, platinum and silver have being investigated and used as an antimicrobial compounds to treat resistant isolates caused by biofilms, and eradicate biofilms of microorganisms. Abiotic surfaces that are impregnated with copper such as urinary catheters can prevent colonization of pathogens such as *S. aureus*, MRSA, *Pseudomonas aeruginosa*, *E. coli* O157:H7, *Enterobacter aerogenes*. fungi and viruses on surfaces. Wound dressings containing copper, and paints that are incorporated with copper have been used to overcome rising of microorganism [10]. Inorganic metals such as copper that are toxic to bacteria are used as copper-based antimicrobials in topical balm, disinfectants, surface coatings, cleansers and biocides [11].

The effect of heavy metals such as copper against certain bacteria that were grown in media in vitro, rather than on the orthopedic implants have been studied in most studies. In this study, the activities of copper against bacterial growth and detachment of bacteria from biofilm produced on kirschner wire orthopedic implant were studied.

The aims of this study are to prevent biofilm production and detach mature biofilm produced by pathogens on abiotic medical surfaces such as kirschner wire orthopedic implant by using copper.

## Materials and Methods

### The bacteria.

Biofilm producer isolates of methicillin resistance *Staphylococcus aureus* MRSA (MRSA), methicillin sensitive *Staphylococcus aureus* MSSA (MSSA), methicillin resistance *Staphylococcus epidermidis* (MRSE), methicillin sensitive *Staphylococcus epidermidis*, methicillin sensitive *Staphylococcus epidermidis* (MSSE), *Escherichia coli* (E. coli), *Klebsiella pneumonia* (K. pneumonia), *Pseudomonas aeruginosa (P. aeroginosa)*, *Proteus mirabilis (P. mirabilis)* were used for this study.

### Preparation of bacterial suspension

Bacterial suspensions were prepared and adjusted to 0.5 McFarland ($1.10^8$ cfu/ml). This bacterial suspensions were twenty fold (1/20) diluted to reach $5.10^6$ cfu/ml. Bacterial suspension was adjusted by ten fold dilution (1/10) in such a way as the final concentration become $5.10^5$ cfu/mL.

### Assessment of MRSA and MRSE

Methicillin resistance of *S. aureus* and *S. epidermidis* was determined by cefoxitin by Kirby Bauer disk diffusion method and broth microdilution method according to the Clinical Laboratory Standards Institute criteria 2013 (CSLI). Bacterial suspensions of Staphylococcal strains were prepared in Tryptic soy broth (TSB), and adjusted to 0.5 McFarland ($1.10^8$ cfu/mL). The staphylococcal strains from bacterial suspensions were inoculated by the spread plate method to Mueller Hinton agar, and 30 µg cefoxitin disks were put on the inoculated plate. Zone diameters of cefoxitin were measured after incubation in 24 hours at 37°C. The zone measurements were categorized into sensitive (≥ 22 mm), or resistant (≤ 21 mm for cefoxitin) categories [12].

### Preparation of copper concentrations

1 mg/mL of copper suspension was prepared with sterile distilled water (Merck, Germany). This suspension was double fold diluted (1/2) to reach concentrations extended from 0.063-1 mg/mL. Due to occurrence of long internals between 0.25, 0.5 and 1 mg/mL, the concentrations of 0.375 and 0.75 mg/mL were also prepared.

### The determination of biofilm

### Preparation of orthopedic implant

Kirschner wire orthopedic implant was used for screening antibiofilm activity of copper (1.8 mm diameter, SZO, China). Kirschner wires were cut into 1 cm pieces.

### Qualitative assay for biofilm

### Congo red agar method (CRA).

Isolates were inoculated on Congo red agar media (CRA) (Merck TM) as described by Freeman et al. (1989) to identify whether isolates were biofilm producer or not [13]. The CRA medium was constructed by mixing 0.8 g of Congo red and 36 g of sucrose (Sigma, Missouri, EUA) to 37g/L of BHI (Oxoid, Basingstoke, Hampshire, England). After incubation period that was 24 h at 37°C, morphology of colonies that undergone to different colours were differentiated as biofilm producers or not. Black colonies with a dry crystalline consistency indicated biofilm producers, whereas colonies retained pink were non-biofilm producers.

Tube method (TM). The biofilm formation of isolates were also detected by this method that is described by Christensen et al. (1985). Isolates were inoculated in polystyrene test tube which contained TSB and incubated at 24 h at 37°C [14]. The sessile isolates of which biofilms formed on the walls of polystyrene test tube were stained with saphranin for 1 hour, after planktonic cells were discharged by rinsing twice with phosphate-buffered saline (PBS). Then, saphranin stained polystyrene test tube was rinsed twice with PBS to discharge stain. After air drying of test tube process, the occurence of visible film lined the walls and the bottom of the tube indicates biofilm production [14].

### Determination of MICs and MBCs of copper

Bacterial suspension was prepared and adjusted to 0.5 McFarland ($1.10^8$ cfu/mL) in Mueller Hinton Broth (MHB) containing 2% NaCl [15]. This bacterial suspension was twenty fold (1/20) diluted to gain $5.10^6$ cfu/mL. 180 µl of each copper concentration and 20 µl of bacterial suspensions were dispersed to each well of microplate to obtain $5.10^5$ cfu/mL as a final concentration (ten fold dilution (1/10)). Microplates incubated at 37°C for 24 hours. The lowest concentration of copper in which bacterial growth did not observed visually was determined as minimum inhibitory concentration (MIC) of copper, according to Clinical Laboratory Standards Institute (CLSI) [12].

After incubation of wells, 100 µl inoculum from the wells in which MIC was observed and two of concentrations were higher than MIC inoculated to PCAs to determine minimum bactericidal concentration (MBC) of copper. After incubation of inoculated PCAs at 37°C for 24 hours, the lowest concentration of copper in which bacterial colonies were not occured in PCA was determined as MBC of copper, according to Clinical Laboratory Standards Institute (CLSI) [12]. The studies were repeated in triplicates.

**Formation of biofilm on implant and determination of bMBCs of copper**

In summary, biofilm formation process on abiotic surfaces by bacteria was done. Quantification of biofilm embedded bacteria grew on abiotic surface, and biofilm embedded bacteria remained on abiotic remained on abiotic surface after addition of agent on abiotic surface on which mature biofilms formed determined by plate counting.

Bacterial suspension was prepared and adjusted to 0.5 McFarland ($1.10^8$ cfu/mL) in Mueller Hinton Broth (MHB) containing 2% NaCl [15]. This bacterial suspension was twenty fold (1/200) diluted to gain $5.10^5$ cfu/mL. Kirschner wire orthopedic implants were placed into each test tubes containing $5.10^5$ cfu/mL isolate and incubated at 37°C for 24 hours to lead bacteria to produce biofilm on kirschner wire. After incubation, kirschner wires on which biofilms were produced were discharged and rinsed with phosphate-buffered saline (PBS) (pH 7.2), then, transferred into each test tubes containing copper concentrations. After incubation at 37°C for 24 hours, kirschner wires discharged and placed into test tubes containing sterile MHB and vortexed for 2 minutes. Then, 100 µl samples of each test tubes vortexed were inoculated on plate count agars (PCA), and incubated at 37°C for 24 hours. After incubation at 37°C for 24 hours, the lowest concentration of copper in which colonies of biofilm embedded bacteria were not grown was determined as minimum bactericidal concentration (bMBC) of copper for biofilm that is also defined as minimum biofilm eradication concentration (MBEC) in this case [12], [16]. The studies were repeated in triplicates.

## Results

The effect of heavy metals such as copper against certain bacteria have been studied in most studies. In this study, the activities of copper against bacterial growth and detachment of bacteria from biofilm produced on kirschner wire orthopedic implant were studied. Biofilms of MRSA, MSSA, MRSE, MSSE, *E. coli, K. pneumonia, P. aeruginosa*, and *P. mirabilis* were detached from kirschner wires completely by copper at the concentrations of 0.75, 0.25, 0.5, 0.375, 0.125, 0.125, 0.375 and 0.125 mg/mL, respectively (Table 1).

MICs, MBCs, and bMBC of copper against pathogens were ranged from 0.063 to 0.75 mg/mL. This study revealed that 0.75 mg/mL of copper inhibit all isolates analyzed in this study, whereas there were no bacterial growth and biofilm on kirschner wire orthopedic implants at 1 mg/mL of copper.

The MICs of copper against MRSA, MSSA, MRSE, MSSE, *E. coli, K. pneumonia, P. aeruginosa,* and *P. mirabilis* were 0.5, 0.25, 0.375, 0.375, 0.125, 0.125, 0.25, and 0.063 mg/mL, respectively. The MBCs of copper against MRSA, MSSA, MRSE, MSSE, *E. coli, K. pneumonia, P. aeroginosa,* and *P. mirabilis* were 0.75, 0.25, 0.5, 0.375, 0.125, 0.125, 0.375, and 0.125 mg/mL, respectively (Table 1).

In this study, the most tolerant pathogen was MRSA of which reason may be due to their resistance to methicillin and most antimicrobials [1], [17], [18]. MIC, MBC and bMBC of copper against MRSA were the highest according to other pathogens. This was followed by *S. epidermidis* (MRSE and MSSE), MSSA and *P. aeruginosa, E. coli* and *K. pneumonia*, respectively (Table 1).

*P. mirabilis* was the most sensitive pathogen to copper when compared with the others. It was followed by high sensitivity of *E. coli* and *K. pneumonia* to copper. MICs that were 0.063 and 0.125 mg/mL sufficient to eliminate *P. mirabilis*, and both of *K. pneumonia* and *E. coli,* respectively, whereas bMBCs that were 0.125 mg/mL sufficient to detach mature biofilms of *P. mirabilis, K. pneumonia* and *E. coli* produced on kirschner wires (Table 1).

Although, it is hard to eliminate biofilm embedded bacteria than planktonic ones, the effects of copper against planktonic and sessile bacteria that is also referred biofilm embedded bacteria and adhered on kirschner orthopedic wire were the same after 24 hours incubation (Table 1).

**Table 1.** MICs, MBCs and bMBCs of Copper

| Pathogens | MICs (mg/mL) | MBC (mg/mL) | bMBC (mg/mL) |
|---|---|---|---|
| **MRSA** | 0.5 | 0.75 | 0.75 |
| **MSSA** | 0.25 | 0.25 | 0.25 |
| **MRSE** | 0.375 | 0.5 | 0.5 |
| **MSSE** | 0.375 | 0.375 | 0.375 |
| ***E. coli*** | 0.125 | 0.125 | 0.125 |
| ***K. pneumoniae*** | 0.125 | 0.125 | 0.125 |
| ***P. aeruginosa*** | 0.25 | 0.375 | 0.375 |
| ***P. mirabilis*** | 0.063 | 0.125 | 0.125 |

## Discussion

In this study, the most tolerant pathogen was MRSA due to their resistance to methicillin and most antimicrobials [1, 17, 18]. Researchers had revealed that copper-based antimicrobials that have multitoxicity effect not only effective against sensitive bacteria but also against multi drug resistant (MDR) microorganisms such as methicillin resistant *Staphylococcus aureus* MRSA [11].

Reyes-Jara et al. (2016) contributed a study which determines copper susceptibility of *E. coli,* coagulase negative *Staphylococci* (CNS), *S. aureus* and *Streptococcus uberis (S. uberis)* isolated in milk samples of bovine clinical mastitis. Reyes-Jara et al. (2016) found that *E. coli* was the most sensitive pathogen to copper. Reyes-Jara et al. (2016) revealed that at the concentration of 1000 ppm copper inhibited whole isolates examined. They found that coagulase negative *Staphylococcus* (CNS) that was the most resistant pathogen to copper was followed by *S. aureus*, and *E. coli* was the most sensitive pathogen to copper [19].

Koseoglu Eser et al. (2015) compared antimicrobial activity of copper coupon with stainless steel coupon against multi drug resistant bacteria (MDR) such as MRSA, *P. aeruginosa* and *Acinetobacter baumannii,* and revealed that copper coupon was more effective than stainless steel coupon [20].

It has also demonstrated that copper had an synergistic effect with other certain chemicals [21], [22], such as quaternary ammonium compounds (ex: benzalkonium chloride, cetalkonium chloride, cetylpyridinium chloride, myristalkonium chloride, and Polycide) and Amphotericin B are more effective to eliminate biofilms of certain bacteria such as *P. aeruginosa, E. coli, S. aureus, Salmonella enterica* serovar *Cholerasuis,* and *Pseudomonas fluorescens,* and *Candida albicans* a few times more than sole treatments, respectively [22].

Sole copper and of which combinations with biocides inhibits sessile forms of *P. aeruginosa* ten fold more than planktonic forms. They revealed that metal cations and oxyanions detach biofilms according to increasing concentration and process time [22].

## Conclusion

Indwelling device associated infections that can be untreatable and recurrent can be prevented by metals instead antibiotics to avoid antibacterial resistance. Copper can be used as a bactericidal and antibiofilm substance solely or combinations with antimicrobial agents in solutions. Indwelling medical devices such as orthopedic wires, prosthetics can be impregnated by copper to overcome colonization and production of matured biofilm on indwelling devices, consequently, implant associated infections, and to avoid removal of implants colonized by biofilm producer pathogens out of the body.

## Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

## References

1. Kırmusaoğlu S. Staphylococcal biofilms: Pathogenicity, mechanism and regulation of biofilm formation by quorum sensing system and antibiotic resistance mechanisms of biofilm embedded microorganisms. In: Dharumadurai Dhanasekaran and Nooruddin Thajuddin (ed). Microbial Biofilms - Importance and Applications. Croatia, Eastern Europe: Intech; 2016: 189 -209.
2. Bjarnsholt T, Moser C, Jensen P, Hoiby N. Biofilm Infections. New York Dordrecht Heidelberg London: Springer Science Business Media, LLC; 2011: 215-25.
3. Gandelman G, Frishman WH, Wiese C et al. Intravascular device infections: epidemiology, diagnosis, and management. Cardiology Review. 2007; 15: 13-23.
4. Hall-Stoodley L, Stoodley P. Evolving concepts in biofilm infections. Cellular Microbiology. 2009; 11: 1034-43.
5. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. Clinical Microbiology Reviews. 2002; 15: 167–93.
6. Nablo BJ, Prichard HL, Butler RD, Klitzman B, Schoenfisch MH. Inhibition of implant-associated infections via nitric oxide release. Biomaterials. 2005; 26: 6984–90.
7. Trampuz A, Widmer AF. Infections associated with orthopedic implants. Current Opinion in Infectious Diseases. 2006; 19: 349–56.
8. Stoodley P, Hall-Stoodley L, Costerton B, DeMeo P, Shirtliff M, Gawalt E, Kathju S. Biofilms, Biomaterials, and Device-Related Infections. In: Modjarrad K and Ebnesajjad S (ed). Handbook of Polymer Applications in Medicine and Medical Devices. Elsevier Inc. 2013: 368.
9. Casey AL, Adams D, Karpanen TJ et al. Role of copper in reducing hospital environment contamination. Journal of Hospital Infection.2010; 74: 72–77.
10. Beeton ML, Aldrich-Wright JR, Bolhuis A. The antimicrobial and antibiofilm activities of copper(II) complexes. Journal of Inorganic Biochemistry. 2014; 140: 167–72.

11. Hans M, Erbe A, Mathews S, Chen Y, Solioz M , Mücklich F. Role of Copper Oxides in Contact Killing of Bacteria. Langmuir. 2013; 29: 16160–66.
12. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Third Informational Supplement. CLSI document M100-S23. Wayne PA: Clinical and Laboratory Standards Institute. 2013.
13. Freeman J, Falkiner FR, Keane CT. New method for detecting slime production by coagulase negative staphylococci. Journal of Clinical Pathology. 1989; 42: 872-74.
14. Christensen GD, Simpson WA, Younger JJ et al. Adherence of coagulase-negative staphylococci to plastic tissue culture plates: a quantitative model for the adherence of staphylococci to medical devices. Journal of Clinical Microiology. 1985; 22: 996-1006.
15. Saginur R, Denis MS, Ferris W, Aaron SD, Chan F, Lee C, Ramotar K. Multiple Combination Bactericidal Testing of Staphylococcal Biofilms from Implant-Associated Infections. Antimicrobial Agents and Chemotherapy. 2006; 50: 55-61.
16. Ceri H, Olson ME, Stremick C, Read RR, Morck D, Buret A. The Calgary Biofilm Device: New Technology for rapid Determination of Antibiotic Susceptibilities of Bacterial Biofilms. Journal of Clinical Microbiology. 1999; 37: 1771-76.
17. Novick RP. Staphylococcal plasmids and their replication. Annual Review Microbiology. 1989; 43: 537–65.
18. Plata K, Rosato AE, Wegrzyn G. *Staphylococcus aureus* as an infectious agent: overview of biochemistry and molecular genetics of its pathogenicity. Acta Biochimica Polonica. 2009; 56: 597-612.
19. Reyes-Jara A, Cordero N, Aguirre J, Troncoso M, Figueroa G. Antibacterial Effect of Copper on Microorganisms Isolated from Bovine Mastitis. Frontiers in Microbiology. 2016; 7: 626.
20. Koseoglu Eser O, Ergin A, Hascelik G. Antimicrobial Activity of Copper Alloys Against Invasive Multidrug-Resistant Nosocomial Pathogens. Current Microbiology. 2015; 71: 291–95.
21. Chudzik B, Czernel G, Miaskowski A, Gagoś M. Amphotericin B-copper(II) complex shows improved therapeutic index in vitro. European Journal of Pharmaceutical Sciences. 2017; 97: 9–21.
22. Harrison JJ, Turner RJ, Joo DA et al. Copper and Quaternary Ammonium Cations Exert Synergistic. Antimicrobial Agents and Chemotherapy 2008; 52: 2870-81.
23. Costerton JW. Biofilm theory can guide the treatment of device related orthopaedic infections. Clinical Orthopaedics Related Research. 2005; 437: 7-11.
24. Harrison JJ, Ceri H, Stremick CA, Turner RJ. Biofilm susceptibility to metal toxicity. Environmental Microbiology. 2004; 6: 1220–27.

Turkish Journal of Clinics and Laboratory

To cite this article: Eroglu O, Kocak OM, Buturak SV, Coskun F, Ozpolat AGY, Deniz T. Effects of carbon monoxide poisoning on temperament. Turk J Clin Lab 2018; 9(1): 19-24.

Original Article

# Effects of carbon monoxide poisoning on temperament

## *Karbonmonoksit zehirlenmesinin mizaç üzerindeki etkisi*

Oguz EROGLU[1*], Orhan Murat KOCAK[2], Sadiye Visal BUTURAK[2], Figen COSKUN[1], Ayse Gul YILMAZ OZPOLAT[2], Turgut DENIZ[1]

[1]Kirikkale University Faculty of Medicine, Department of Emergency Medicine, Kirikkale / TURKEY
[2]Kirikkale University Faculty of Medicine, Department of Psychiatry, Kirikkale / TURKEY

## ABSTRACT

**Aim:** The aim of this study was to investigate the effect of carbon monoxide (CO) poisoning on temperament and associated disorders.

**Material and Methods:** The study was conducted in healthy volunteers and patients who presented to the Emergency Department of Kirikkale University Hospital after exposure to CO. Patients with a carboxyhemoglobin level of ≥10% were considered to have CO poisoning. Patients with psychiatric disease or an illness that could increase CO levels and those who smoked or were using medication were excluded. Healthy volunteers were evaluated once, and CO poisoning patients were evaluated at the time of presentation and 3 months after discharge using the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Autoquestionnaire (TEMPS-A) temperament scale. Repeated analysis of variance was applied for comparisons. A p value of <0.05 was considered statistically significant.

**Results:** The study included 110 participants: 68 in the CO poisoning group and 42 healthy volunteers. Significant differences between the groups were observed in the TEMPS-A scores for depressive type (p=0.016) and anxious type (p=0.01) at first presentation and for the irritability type (p=0.02) and anxious type (p=0.034) at 3 months after the discharge. When the temperament scale scores of the CO poisoning patients were compared according to evaluation time (first presentation and 3 months after discharge), no significant difference in temperament types was observed.

**Conclusion:** Although the temperament types related to depression and anxiety were affected after CO poisoning, they did not change completely. Further research is needed to better understand the psychiatric effects of CO poisoning.

**Keywords:** Carbonmonoxide poisoning, emergency department, psychiatric disorders, temperament, temperament scale

Corresponding Author*: Oguz Eroglu MD, Kirikkale University Faculty of Medicine, Department of Emergency Medicine, Kirikkale / TURKEY
E-Mail: oguzerogluacil@gmail.com
Received 11.05.2017 accepted 10.08.2017
Doi: 10.18663/tjcl.311874

## ÖZ

**Amaç:** Bu çalışma karbonmonoksit zehirlenmesinin mizaç ve ilişkili olduğu bozukluklar üzerindeki etkisini araştırmak amacıyla yapılmıştır.

**Gereç ve Yöntemler:** Çalışma, Kırıkkale Üniversitesi hastanesi acil servisine karbonmonoksit zehirlenmesi (KZ) sebebiyle başvuran hastalar ve sağlıklı gönüllü (SG) katılımcılarla yapıldı. Karboksihemoglobin düzeyi ≥%10 ölçülen hastalar KZ olarak kabul edildi. Psikiyatrik hastalığı veya ilaç kullanımı olanlar ve CO düzeyini yükseltecek hastalığı veya sigara içiciliği olanlar çalışmaya dahil edilmedi. SG bir kere, KZ olanlar ise acil servise ilk başvuru anında taburcu edilirken ve taburcu olduktan üç ay sonra TEMPS-A (Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Autoquestionaire) mizaç ölçeği ile değerlendirildi. Grupların karşılaştırılmasında Repeated measures ANOVA testi kullanıldı ve $p<0.05$ anlamlı kabul edildi.

**Bulgular:** Çalışmaya KZ (n=68) ve SG (n=42) olmak üzere toplam 110 katılımcı dahil edildi. Gruplar TEMPS-A mizaç ölçeği puanları bakımından karşılaştırıldığında, acil servise ilk başvuru anında Depresif (p=0.016) ve Anksiyöz (p=0.01) mizaç, üçüncü ayda ise Irritable (p=0.02) ve Anksiyöz (p=0.034) mizaç tipi puanlarında anlamlı farklılık saptandı. KZ olan hastaların mizaç ölçeği puanları, değerlendirme zamanına (İlk başvuru zamanı ve üçüncü ay) göre karşılaştırıldığında hiçbir mizaç tipinde fark saptanmadı.

**Sonuç:** KZ sonrası hastaların özellikle depresyon ve anksiyete ile ilişkisi olan mizaç tiplerinde etkilenme olsa da, mizaç özellikleri tamamen değişmemiştir. Karbonmonoksit zehirlenmesinin psikiyatrik etkilerinin daha iyi anlaşılabilmesi için ileri çalışmalara ihtiyaç vardır.

**Anahtar kelimeler:** Karbomonoksit zehirlenmesi, acil servis, psikiyatrik bozukluklar, mizaç, mizaç ölçeği

## Introductıon

Carbon monoxide (CO) is a colorless, odorless, tasteless gas that cannot be easily identified in the environment [1,2]. CO poisoning occurs in developing countries as a result of accidents at home, particularly during winter when heating sources such as wood and coal are incompletely burned. In developed countries, CO poisoning results from accidental or intentional exposure throughout the year [3-5]. CO poisoning can have mild clinical severity; however, when carboxyhemoglobin (COHb) levels exceed 20%, loss of consciousness, severe neurological disorders, coma, and death may occur [4,6]. In cases of CO poisoning, the globus pallidus, other regions of the cerebral cortex, basal ganglia, substantia nigra, thalamus, and cerebellum may be affected. Previous studies have shown that the toxic effects of CO can be accompanied by the development of cognitive disorders (particularly poor memory, loss of concentration, attention deficit, and visual and spatial dysfunctions), gait disorders, urinary and fecal incontinence, dystonia, Parkinsonism, amnesia, obsessive-compulsive disorder, mood disorders (with depressive or manic episodes), irritability, anxiety, anger outbursts, major depression, akinetic mutism, psychosis, hallucinations, delirium, and personality changes [6-13]. Although these neuropsychiatric sequelae can develop acutely, symptoms may appear or improve months or even years later. Although these neuropsychiatric sequelae can develop acutely, symptoms may appear or improve months or even years later [10-13].

Temperament describes the persistent characteristics of emotion, thought, and behavior related to several structural, genetic, and biological factors [14]. The affective temperament model defines 5 temperament categories, including depressive, hyperthymic, cyclothymic, irritable, and anxious [14,15]. The Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Autoquestionnaire (TEMPS-A) temperament scale was developed by Akiskal et al. [18] to evaluate temperament types. This scale was translated into Turkish by Vahip [19].

An acute emergent condition such as CO poisoning can be expected to influence features of the psychological state such as affect and mood. However, whether it has effects on trait characteristics such as temperament is unknown. To the best of our knowledge, no studies have evaluated this question; therefore, the aim of this study was to investigate the effects of CO poisoning on temperament.

## Material and Methods

Approval for this prospective study was granted by the local ethics committee (no. 2014-29/05). The study included a control group of healthy volunteers (HVs) and patients who presented to the emergency department (ED) of Kirikkale University Hospital after CO exposure between 01 October, 2014 and 31 October, 2015. For each patient, we recorded demographic characteristics, physical and neurological examination findings, Glasgow coma scale score (GCS), COHb level, treatments applied, and TEMPS-A temperament scale scores at initial presentation and, for CO poisoning patients, at 3 months after discharge.

### Study design

The study participants were aged >18 years, spoke Turkish as their native language, and had no intellectual deficiencies. CO poisoning was defined as a COHb level of ≥10% at presentation at the ED, as measured with arterial blood gas analysis or a non-invasive pulse CO-oximetry device (Massimo Rad 57, Irvine, CA, USA). Patients were excluded if they had COHb levels of <10%, had a disease that could affect CO levels (chronic obstructive pulmonary disease, asthma, hemolytic anemia), were smokers, had a history of psychiatric disease (major depression according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, or depressive mood, schizophrenia, psychoaffective disorder, epilepsy, dementia, encephalitis, or Parkinson's disease), were taking psychiatric drugs, had recently experienced a life-affecting trauma (e.g., death of a loved one, separation from a partner, loneliness, sexual assault), or were unwilling to participate in the study.

### TEMPS-A temperament scale form

The TEMPS-A temperament scale comprises 109 questions for men and 110 questions for women. The Turkish version of the scale comprises 100 questions to identify depressive (18 questions), cyclothymic (19 questions), hyperthymic (20 questions), irritable (18 questions), and anxious (24 questions) temperaments. Participants answer the questions with Yes or No, with Yes scoring as 1 and No scoring as 0. A threshold value is defined for each temperament type (depressive=13; cyclothymic=18; hyperthymic=20; irritable=13; anxious=18), and values exceeding this threshold are considered to indicate a change in temperament characteristics. The test–retest reliability of the Turkish version is 0.73–0.93, and the Cronbach's α coefficient is 0.75–0.84 [19].

The TEMPS-A temperament scale evaluation of patients with CO poisoning in the ED was performed within 24 h before discharge or, for patients who were hospitalized, within 48 h after full recovery of consciousness (GCS=15, when consciousness, orientation, and cooperation returned to normal). Patients in the CO poisoning group were contacted by telephone 3 months after discharge and re-evaluated using the TEMPS-A temperament scale.

### Statistical analysis

Statistical analyses of the study data were made using SPSS 23.0 software (SSPS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation. Repeated analysis of variance was used in the comparison of the TEMPS-A scores between the groups. The group and sex variables were included in the analysis of variance as "between-subject variables," and the data of the 5 temperaments in the scale as "within-subject variables." A two-tailed p value of 0.05 was considered statistically significant.

## Results

The study initially included 104 patients diagnosed with CO poisoning and a control group of 42 HVs. Thirty-six patients were excluded from the study because TEMPS-A evaluation could not be performed 3 months after discharge or because they wished to withdraw. The study was completed with a total of 110 participants: 68 CO poisoning patients and 42 HVs.

The patient group comprised 36 women (52.9%) and 32 men (47.1%) with a mean age of 38.64 ± 16.61 years. The control group comprised 23 women (54.7%) and 19 men (45.3%) with a mean age of 36.23 ± 7.11 years. No statistically significant difference was found between the groups with respect to age or sex (p=0.376 and p=0.856, respectively).

In the 68 CO poisoning patients, most presentations to the ED occurred in February (n=24), mean GCS was 14.11 ± 2.59, mean COHb level was 23.39 ± 10.37, 40 patients (58.8%) were discharged, 28 (41.2%) were admitted to the intensive care unit for treatment, and 2 (2.9%) received hyperbaric oxygen treatment. At the time of presentation, the GCS value was 3 in 2 patients (2.9%) and ≤12 in 24 patients (35.3%). Evaluation with the temperament scale was performed within 24 h before discharge in the 40 patients managed in the ED and, in the 24 patients admitted to the intensive care unit, within 48 h or after regaining full consciousness. The data recorded for patients in the CO poisoning group are shown in Table 1.

**Table 1.** Data recorded for carbon monoxide (CO) poisoning patients. COHb: carboxyhemoglobin; GCS: Glasgow coma scale; HBT: hyperbaric oxygen treatment; NBT: normobaric oxygen treatment.

| | Carbonmonoxide poisoning (n=68) | |
|---|---|---|
| | **n** | **%** |
| **Gender** | | |
| • Female | 36 | 52.9 |
| • Male | 32 | 47.1 |
| **Poisoning mechanism** | | |
| • Accidental | 68 | 100 |
| • Suicide attempt | - | - |
| **Oxygen treatment** | | |
| • HBT | 2 | 2.9 |
| • NBT | 66 | 97.1 |
| **Months** | | |
| • October | 6 | 8.8 |
| • November | 7 | 10.3 |
| • December | 6 | 8.8 |
| • January | 7 | 10.3 |
| • February | 24 | 35.3 |
| • March | 8 | 11.7 |
| • April | 3 | 4.4 |
| • May | 7 | 10.3 |
| | **mean±SD** | |
| **Age** | 38.64±16.61 | |
| **GCS** | 14.11±2.59 | |
| **COHb levels (%)** | 23.39±10.37 | |
| **Saturation O2 (%)** | 96.1±2.62 | |

A comparison of the distribution of temperament characteristics showed no significant differences between the groups at either of the evaluation times. A comparison of TEMPS-A temperament scale scores in the control group and the CO poisoning group at the time of first presentation showed a significant difference for the depressive type (p=0.02) and the anxious type (p=0.01; Table 2). A comparison of TEMPS-A temperament scale scores between the control group and the CO poisoning patients at 3 months post-discharge showed a significant difference for the irritable type (p=0.02) and the anxious type (p=0.034; Table 2). When the temperament scale scores of the CO poisoning patients were compared according to evaluation time (first presentation and 3 months after discharge), no differences were found for any temperament type (Table 2).

**Table 2.** Comparison of the temperament scores of the groups. AT: anxious type; CT: cyclothymic type; DT: depressive type; FAT: first application time; HT: hyperthymic type; HV: healthy volunteer; IT: irritable type; SD: standard deviation; TM: third month

| Groups | Temperament type | | | | |
|---|---|---|---|---|---|
| | **DT** | **CT** | **HT** | **IT** | **AT** |
| | **mean±SD** | **mean±SD** | **mean±SD** | **mean±SD** | **mean±SD** |
| **FAT vs HV** | 7.50±3.96<br>5.69±3.39 | 7.01±4.29<br>6.71±4.19 | 11.75±3.81<br>11.26±3.03 | 5.16±4.07<br>3.73±3.36 | 6.52±5.72<br>3.88±4.09 |
| **p** | **0.016** | 0.72 | 0.484 | 0.06 | **0.01** |
| **TM vs HV** | 7.04±3.87<br>5.69±3.39 | 7.06±4.18<br>6.71±4.19 | 11.58±3.73<br>11.26±3.03 | 5.51±4.10<br>3.73±3.36 | 6.14±6.04<br>3.88±4.09 |
| **p** | 0.065 | 0.204 | 0.634 | **0.02** | **0.034** |
| **FAT vs TM** | 7.50±3.96<br>7.04±3.87 | 7.01±4.29<br>7.06±4.18 | 11.75±3.81<br>11.58±3.73 | 5.16±4.07<br>5.51±4.10 | 6.52±5.72<br>6.14±6.04 |
| **p** | 0.07 | 0.09 | 0.77 | 0.342 | 0.343 |

## Discussion

The neuropsychiatric sequelae of CO poisoning can occur not only immediately but also weeks, months, or even years later [7,10-13,20]. The most commonly reported psychiatric disorders are depression and anxiety [6-9,27-29]. However, the results of the present study showed no significant difference in temperament characteristics between controls and patients with CO poisoning at either the initial presentation or 3 months later. On the contrary, compared with HVs, CO poisoning patients had higher depressive, anxious, and irritable type temperament scores at both the time of presentation and in the early period after discharge (third month).

Temperament describes persistent emotional, thought, and behavioral characteristics that can directly or indirectly contribute to the development of psychiatric disorders [15-17]. In the current study, a statistically significant difference was found between CO poisoning patients and HVs with respect to depressive and anxious temperament type scores at the time of first presentation. The depressive mood type is related to several psychiatric disorders, primarily depression [21,22]. Rihmer et al. reported that suicide is associated with several temperament types, the most important of which are the depressive and anxious types [23]. Previous studies have

shown that the depressive type is the basic characteristic temperament type of patients with bipolar I disorder and has also often been identified in patients with obsessive-compulsive disorder [21,24,25]. Although the difference in depressive and anxious temperament type scores between groups at the time of presentation in the present study may be explained by the acute toxic effects of CO gas, it could also be explained by the stress, tension, and discomfort felt by patients in the ED environment.

When the scores for the third-month TEMPS-A evaluation were examined, a statistically significant difference was found between patients and controls with respect to the irritable and anxious temperament types. These temperament types underlie anxious personality disorders and suicide, and the irritable type is also closely related to substance abuse [21,23,26]. Previous studies have reported that depression and anxiety are the most frequent psychiatric disorders observed after CO poisoning, and the depressive, anxious, and irritable types are associated with these disorders [6-9,27-29]. Although Gale et al. [27] reported that depression and anxiety are observed at a rate of 95% after CO poisoning [27], Weaver et al. [29] reported the development of depression in 35% in patients with accidental (excluding suicide) CO poisoning despite these patients having no history of depression [29]. Katirci et al. [6] reported an increase in the development of depression at 1 and 3 months post-exposure in CO poisoning patients compared with controls, whereas Karaman et al. [28] reported that symptoms of anxiety emerged 1 month after CO poisoning. In another study, the rates of anxiety and depression were determined to be high at 6 weeks and 6 months after CO poisoning, respectively [9].

Jasper et al. recommended that patients be followed up for at least 1 year after CO poisoning to monitor the development of depression, anxiety, and other psychiatric sequelae [8]. In the current study, the third-month temperament scale evaluations of the CO poisoning patients showed high anxious and irritable temperament type scores, which are related to the development of depression and anxiety as well as to suicide attempts and substance abuse. This finding supports that of other studies that have emphasized that depression and anxiety could develop in patients after CO poisoning. Our results also indicate that it would be useful to evaluate patients for neuropsychiatric disorders in the short and long term periods after CO poisoning.

We found no significant difference in TEMPS-A temperament scale scores between groups at first presentation and at 3 months post-discharge. Furthermore, when the temperament types of the CO poisoning patients were evaluated separately, none of the scores for the 5 temperament types exceeded threshold values. These results show that CO poisoning had only a mathematical effect on the integrity of the emotion, thoughts, and behavior related aspects of temperament, which is a combination of several genetic and environmental factors, and did not wholly change temperament characteristics. Nevertheless, it would be appropriate to evaluate patients for neuropsychiatric disorders that can develop immediately or long after CO poisoning.

## Conclusion

Although temperament types related to depression and anxiety were affected to a small degree in patients with CO poisoning in this study, we found no complete change in any temperament type. Additional studies are needed to more fully elucidate the effects of CO poisoning on temperament.

## Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

## References

1. Guzman JA. Carbon monoxide poisoning. Crit Care Clin 2012; 28: 537-48.
2. Sykes OT, Walker E. The neurotoxicology of carbon monoxide-Historical perspective and review. Cortex 2016; 74: 440-8.
3. Aslan S, Uzkeser M, Seven B et al. The evaluation of myocardial damage in 83 young adult with carbon monoxide poisoning in the East Anatolia region in Turkey. Human Experimental Toxicology 2006; 25: 439-46.
4. Kandis H, Katirci Y, Cakir Z, Aslan S, Uzkeser M, Bilir O. A retrospective analyse of the patients admitted to emergency service for carbon monoxide intoxication. Academic Emerg Med J 2010; 5: 21-25.
5. Quinn DK, McGahee SM, Politte LC et al. Complications of carbon monoxide poisioning: a case discussion and review of the literature. Primary Care Companion to the journal of clinical Psychiatry 2009; 11: 74-79.
6. Katirci Y, Kandis H, Aslan S, Kirpinar I. Neuropsychiatric disorders and risk factors in carbon monoxide intoxication. Toxicol Ind Health 2011; 27: 397-406.

7. Prockop LD. The allegory of a mountain: an environmental introduction to neurotoxicology. J Neurol Sci 2007; 262: 7-14.
8. Jasper BW, Hopkins RO, Duker HV, Weaver LK. Affective outcome following carbon monoxide poisoning: a prospective longitudinal study. Cogn Behav Neurol 2005; 18: 127-34.
9. Chambers CA, Hopkins RO, Weaver LK, Key C. Cognitive and affective outcomes of more severe compared to less severe carbon monoxide poisoning. Brain Inj 2008; 22: 387-95.
10. Weaver LK, Hopkins RO, Elliott G. Carbon monoxide poisoning. N Engl J Med 1999; 340: 1290-92.
11. Smith JS, Brandon S. Morbidity from acute carbon monoxide poisoning at three-year follow-up. Br Med J 1973; 1: 318-21.
12. Choi IS. Delayed neurologic sequelae in carbon monoxide intoxication. Arch Neurol 1983; 40: 433-35.
13. Min SK. A brain syndrome associated with delayed neuropsychiatric sequelae following acute carbon monoxide intoxication. Acta Psychiatr Scand 1986; 73: 80-86.
14. Akiskal HS, Akiskal KK, Haykal RF, Manning JS, Connor PD. TEMPS-A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of te Memphis, Pisa, Paris, and San Diego Autoquestionnaire. J Affect Disord 2005; 85: 3-16.
15. Akiskal HS, Mallya G. Criteria for the soft bipolar spectrum treatment implications. Psychopharmacol Bull 1987; 23: 68-73.
16. Akiskal HS. Toward a definition of generalized anxiety disorder as an anxious temperament type. Acta Psychiatr Scand 1998; 98: 66-73.
17. Eory A, Gonda X, Torzsa P, Kalabay L, Rihmer Z. Affective temperaments: from neurobiological roots to clinical application. Orv Hetil 2011; 152: 1879-86.
18. Akiskal HS, Placidi GF, Maremmani I et al. TEMPS-I: delineating the most discriminant traits of cyclothymic, depressive irritable and hyperthymic temperaments in a nonpatient populaiton. J Affect Disord 2005; 51: 7-19.
19. Vahip S. Affective temperaments in clinically-well subjects in Turkey: initial psychometric data on the TEMPS-A. J Affect Disorders 2005; 85: 113-25.
20. Meert KL, Heidemann SM, Sarnaik AP. Outcome of children with carbon monoxide poisoning treated with normobaric oxygen. J Trauma 1998; 44: 149-54.
21. Rihmer Z, Akiskal KK, Rihmer A, Akiskal HS. Current research on affective temperaments. Curr Opin Psychiatry 2010; 23: 12-8.
22. Aslan AA, Sari BA, Kuruoglu A. From Depressive Symptamotology to Major Depression: Clinical Spectrum. Turkish J Clinical Psychiatry 2012; 15: 56-64.
23. Rihmer A, Rozsa S, Rihmer Z, Gonda X, Akiskal KK, Akiskal HS. Affective temperaments, as measured by TEMPS-A, among nonviolent suicide attempters. J Affect Disord 2009; 116: 18-22.
24. Henry C, Lacoste J, Bellivier F, Verdoux H, Bourgeois ML, Leboyer M. Temperament in bipolar illness: impact on prognosis. J Affect Disord 1999; 56: 103-8.
25. Fistikci N, Hacioglu M, Erek S et al. Differences in affective temperaments in anxiety disorders: comparison of panic disorder and obsessive compulsive disorder. Archives of Neuropsychiatry 2013; 50: 337-44.
26. Moore DJ, Atkinson JH, Akiskal H, Gonzalez R, Wolfson T, Grant I; HNRC Group. Temperament and risky behaviors: a pathway to HIV? J Affect Disord 2005; 85: 191-200.
27. Gale SD, Hopkins RO, Weaver LK, Bigler ED, Booth EJ, Blatter DD. MRI, quantitative MRI, SPECT, and neuropsychological findings following carbon monoxide poisoning. Brain Inj 1999; 13: 229-43.
28. Karaman D, Metin S, Kara K et al. Neuropsychological evaluation of children and adolescents with acute carbon monoxide poisoning. Pediatric Emergency Care 2016; 32: 303-6.
29. Weaver LK, Valentine KJ, Hopkins RO. Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. Am J Respir Crit Care Med 2007; 176: 491-7.

Turkish Journal of Clinics and Laboratory

To cite this article: Kabalci M, Gunal N, Gunal YD et al. Comparison of Elastane Fiber with Polyprolene and Polyglecaprone 25 used as Surgical Suture Material: an experimental preliminary study. Turk J Clin Lab 2018; 9(1): 25-30.

Original Article

# Comparison of Elastane Fiber with Polyprolene and Polyglecaprone 25 used as Surgical Suture Material: an experimental preliminary study

## *Elastan Lif ile Polipropilen ve Poliglekapron 25'in Cerrahi Sütür Malzemesi Olarak Karşılaştırılması: Deneysel Ön Çalışma*

Mehmet KABALCI[1*], Nesimi GUNAL[2], Yasemin DERE GUNAL[3], Mahi BALCI[4], Berkant OZPOLAT[2], Koray DURAL[2], Serap YORUBULUT [5], Erdinc EROGLU[6], Alptekin YASIM[6]

[1] Department of Cardiovascular Surgery, Medicine Faculty of Kirikkale University, Kirikkale, Turkey
[2] Department of Thoracic Surgery, Medicine Faculty of Kirikkale University, Kirikkale, Turkey
[3] Department of Pediatric Surgery, Medicine Faculty of Kirikkale University, Kirikkale, Turkey
[4] Department of Pathology, Medicine Faculty of Kirikkale University, Kirikkale, Turkey
[5] Department of Statistics, Faculty of Science and Letters, Kirikkale University, Kirikkale, Turkey
[6] Department of Cardiovascular Surgery, Medicine Faculty of Kahramanmaras Sutcuimam University, Kahramanmaras, Turkey

## ABSTRACT

**Aim:** Elastane fiber is a synthetic monofilament polymer which is durable and highly flexible. In this preliminary study we compared Elastane fiber with polypropylene and polyglycaprone 25, surching the inflammatory reaction in the rat soft tissue, considering that it could be used for sternal closure because of its properties.

**Material and Methods:** Elastane fiber, polypropylene and polyglycaprone25 sutures were placed in 3 separate areas at 2 cm intervals in the subcutaneous tissue of each 8 male wistar albino rats without any incision, using the seldinger method. After two weeks, the rats were sacrified and tissue specimens, including the suture fragments, were resected. Histopathological scoring in terms of inflammation, vascularization, fibrosis and histiocytic reaction were achieved semiquantitatively.

**Results:** There was no statistically significant difference between three suture materials in terms of inflammation (p=0.513), vascularization (p=0.065), fibrosis (p=0.108) and histiocytic reaction (p=0.630).

**Conclusion:** As a conclusion elastane fiber showed similar inflammatory changes with other suture materials in the rat soft tissue which is thought to be useful for sternal closure due to its high flexibilityand durability.

**Keywords:** Suture material, inflammation, polypropylene, animal experiment,

Corresponding Author*: Mehmet Kabalci, Department of Cardiovascular Surgery, Medicine Faculty of Kirikkale University, Kirikkale, Turkey
E-Mail: kabalci@hotmail.com
Received 15.02.2018 accepted 28.02.2012
Doi: 10.18663/tjcl.395200

## ÖZ

**Amaç:** Elastan lif, dayanıklı ve esnek sentetik bir monofilament polimerdir. Bu ön çalışmada sternum kapatılması için uygun nitelikte olduğunu düşündüğümüz elastan lif ile polipropilen ve poliglekapron 25'i rat yumuşak dokusunda oluşturdukları inflamatuvar cevaplar açısından karşılaştırdık.

**Gereç ve Yöntemler:** Elastan lif, polipropilen ve poliglekapron 25 dikişler 8 adet erkek wistar albino ratın subkutan dokusuna 2 cm aralıklarla 3 ayrı alana herhangi bir kesi yapılmadan seldinger yöntemi ile yerleştirildi. İki hafta sonra ratlar sakrifiye edilerek sütür parçalarını içerecek şekilde doku örnekleri alındı. Enflamasyon, vaskülarizasyon, fibrozis ve histiyositik reaksiyon açısından yarı kantitatif histopatolojik skorlama yapıldı.

**Bulgular:** Her üç sütür materyali arasında inflamasyon ($p = 0.513$), vaskülarizasyon ($p = 0.065$), fibrozis ($p = 0.108$) ve histiyositik reaksiyon ($p = 0.630$) açısından istatistiksel olarak anlamlı fark yoktu.

**Sonuç:** Yüksek esneklik ve dayanıklılığından dolayı sternum kapatılması için faydalı olacağını düşündüğümüz elastan lif, rat yumuşak dokusunda diğer dikiş materyalleri ile benzer inflamatuvar değişiklikler gösterdi.

**Anahtar Sözcükler:** Sütür materyali, inflamasyon, polipropilen, deneysel hayvan çalışması,

## Introductıon

Median sternotomy is the most popular technnique to reach the mediastinum [1]. Postoperative sternal dehiscence and associated mediasinitis are important sources of morbidity and can be seen in 0.5 to 5% of cases [2,3]. There is still a surch search for the ideal closure technique and suture material to overcome this problem [4-9]. Even if sutures provide sufficient stability, recurrent motion pressure such as lying on side or coughing, can damage the bone tissue or even break the steel wire [10].

We planned a study to investigate if sternum dehiscence could be prevented by using a flexible suture material. Lycra® was discovered many years ago and has not been included in almost any research in the last 40 years so we had to test tissue compatibility comparatively before testing the durability of the material.

Monofilament sutures are the most appropriate stitches for contaminated and traumatic injuries due to their resistance to infection, high elasticity, and low inflammatory reaction, slippery, easy to pass through the tissue [11].

Polypropylene suture is a synthetic, monofilament, highly slippery and non-absorbable suture causing minimal acute inflammation in the tissue. It is highly resistant to contamination and infection [12,13]. Polyglyaprone 25 suture is a similar butan absorbable surgical suture [12]. The lowest tissue reaction occurs with stainless steel sutures, followed by polypropylene, polyglactin 910 and poyglecaprone [11].

Lycra® is a synthetic, monofilament, highly slippery, non-absorbable elastane fiber which is commonly used today in textile industry. Owing its strong, durable and highly flexible structure, it was thought that it could be used in surgery as a suture and prosthetic material after the discovery in 1959. However, a suitable area of use was not found [14,15].

Based on our hypothesis that due to the elastic properties of Lycra® during sternal closure, the material may stretch when there is a sudden stress, so not only that the bone damage can be avoided but the suture breakage might be prevented as well. Hence this preliminary study was done to compare the material with the well-known polypropylene and polyglycaprone 25 and to determine the inflammatory tissue response before testing that Lycra® provided the desired strength and stability.

## Material and Methods

This in vivo experimental study was approved by the Ethics Committee of the Local Animal Experiments of the University (15 / 57,2015) and carried out at the animal research laboratory (Kırıkkale University, Kırıkkale, Turkey) between 3 and 17 October 2015.

Lycra®(Lycra, Invista, Maydon, Ireland), was compared with sutures known to be histopathologically compatible with tissues: Polypropylene (Polypropylene tie, Temalar Ltd, Ankara, Turkey) and polyglycaprone 25 (Monocryl®, Ethicon, San Lorenzo, Puerto Rico) which are now routinely used as suture material in a variety of surgical procedures.

A polypropylene tie (Polypropylene tie, Temalar Ltd, Ankara, Turkey) which is also planned to be used for sternal closure was used instead of a polypropylene suture, so polypropylene suture was not preferred to evaluate more real reactions. The material used for sternal closure and also referred to as plastic tie in the literature is compared with Lycra® suture because it does not require a knot, it is locked onto itself and is more elastic than steel sutures [16]. The elastane fiber and polypropylene tie were sterilized with ethylene oxide.

To avoid contact with other suture materials that may occur during skin closure, it was preferred to place the material by seldinger method instead of cutting the abdominal region in the rats. In order to standardize the reactions, it was preferred to place every 3 materials in each rat.

**Animal model**

In this randomized, controlled, experimental study, healthy, 300-350g weight, adult (aged>5 months) male Wistar Albino eight rats were used. After the rats were transferred to the laboratory, they were kept for a week as an adaptation period before surgery. During the entire study, the animals were kept at the Animal Research Laboratory (Kırıkkale University, Kırıkkale, Turkey) under veterinary supervision.

Eight randomly selected Wistar Albino male rats were anesthetized with ketamine (50mg / kg) (ketalar, Pfizer, Turkey) /xylazine (10mg / kg) (rompun, Bayer, Germany) administered intramuscularly. The abdominal region of the rats was shaved and antisepsis was performed with povidone iodine (Batticon, Adeka, Istanbul, Turkey). All of the materials were placed by seldinger method to the abdominal region of rats, subcutaneously. Lycra®, polypropylene and polyglycaprone 25 fragments of 1 cm length and two cm spacing, were placed by seldinger method to the abdominal region of rats, subcutaneously (Figure 1).

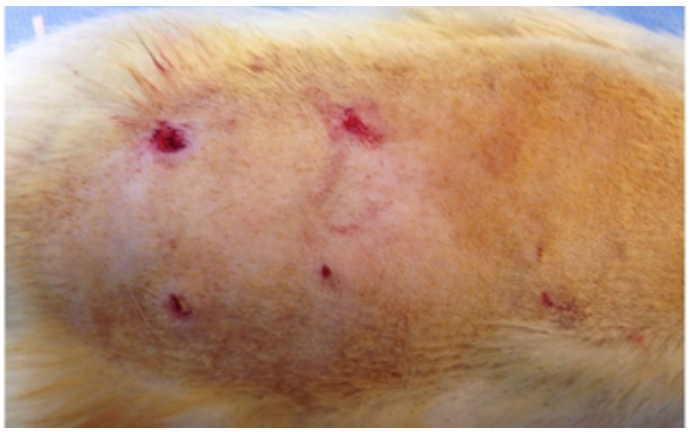


**Figure 1.** Suture pieces of 1 cm length, at intervals of 2 cm, placed on the anterior wall of the abdomen of the rat, subcutaneously.

The rats were followed for 2 weeks in at a room temperature of 25°C ± 1. 9°C and humidity of 52% ± 6%, and received a standard dietas well as water ad libitum during the follow up period. After sacrification full-thickness tissue samples containing each suture material were obtained (Figure 2).

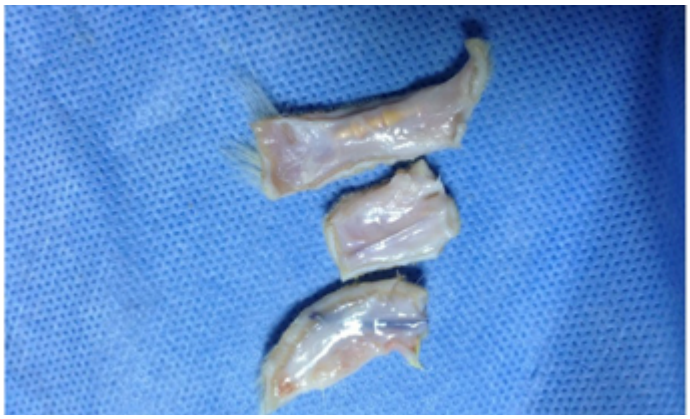


**Figure 2.** Three full-thickness tissue samples were obtained to contain each suture material separately

**Histopatological Examination**

Samples were examined by light microscope (Leica DMI 4000 B, Wetzlar, Germany) and classified semiquantitatively between grade 0 to grade 3 in terms of inflammation, vascularisation, fibrosis and histiocytic reactionas proposed by Hernandez- Richter et al. (Table 1)

**Table 1.** Evaluation of tissue repair response

| | 0 | 1 | 2 | 3 |
|---|---|---|---|---|
| Inflammatory | No | Edema | Intense polymorphonuclear leukocyte and cell infiltration | Intensive mixed inflammatory cell infiltration and tissue necrosis |
| Vascularisation | No | Mild vasodilatation | Severe congestion | Hemorrhage + neovascularization |
| Fibrosis | No | Few fibroblasts | Fibroblastic proliferation and increased collagen | Fibrosis, collagen bundles |
| Histiosis | No | Rare macrophage | High amounts of histiocytes, rare multinucleated giant cells | Granuloma formation |

## Statistical Analysis

The obtained data were analyzed by in SPSS (Version 20. 0, IBM, New York, USA) programme.

The Kruskal-Wallis test was used for nonparametric double-over-group comparisons as the number of observations was not quantified (scale) whether the individual parameters of inflammatory, vascularisation, fibrosis and histiosis differed in the Lycra®, polypropylene and polyglycaprone25 groups. A p value less than 0.05 was considered statistically significant.

## Results

No mortality and local effects such as anorexia, nausea, vomiting, diarrhea or behavioral disturbances were not observed in any group. Macroscopically none of the rats had an abscess or infection findings in the skin and subcutaneous tissue where the sutures were placed. There were no significant differences in the parameters of inflammation, vascularisation, fibrosis and hisitiocitic reaction examined in Lycra®, polypropylene and polyglycaprone25 materials (p> 0,05 for each parameter) (Table 2) (Figure 3-6).

**Table 2.** Evaluation of tissue repair response to suture materials

| | | | | | | |
|---|---|---|---|---|---|---|
| Number of rats and ratio within group | Inflammatory (p=0.649) | 0 | 1 | 2 | 3 | Total |
| | Lycra | 3<br>37.5% | 5<br>62.5% | 0<br>0.0% | 0<br>0.0% | 8<br>100% |
| | Polyproplene | 2<br>25.0% | 5<br>62.5% | 1<br>12.5% | 0<br>0.0% | 8<br>100.0% |
| | Polyglecaprone 25 | 2<br>25.0% | 5<br>62.5% | 1<br>12.5% | 0<br>0.0% | 8<br>100.0% |
| Number of rats and ratio within group | Vascularisation (p=0.073) | 0 | 1 | 2 | 3 | Total |
| | Lycra | 0<br>0.0% | 3<br>37.5% | 3<br>37.5% | 2<br>25.0% | 8<br>100% |
| | Polyproplene | 0<br>0.0% | 1<br>12.5% | 6<br>75% | 1<br>12.5% | 8<br>100.0% |
| | Polyglecaprone 25 | 0<br>0.0% | 0<br>0.0% | 3<br>37.5% | 5<br>62.5% | 8<br>100.0% |
| Number of rats and ratio within group | Fibrosis (p=0.104) | 0 | 1 | 2 | 3 | Total |
| | Lycra | 0<br>0.0% | 2<br>25.0% | 1<br>12.5% | 5<br>62.5% | 8<br>100% |
| | Polyproplene | 0<br>0.0% | 3<br>37.5% | 5<br>62.5% | 0<br>0.0% | 8<br>100.0% |
| | Polyglecaprone 25 | 0<br>0.0% | 1<br>12.5% | 4<br>50.0% | 3<br>37.5% | 8<br>100.0% |
| Number of rats and ratio within group | Histiosis (p=0.562) | 0 | 1 | 2 | 3 | Total |
| | Lycra | 1<br>12.5% | 2<br>25.0% | 4<br>50% | 1<br>12.5% | 8<br>100% |
| | Polyproplene | 0<br>0.0% | 2<br>25.0% | 3<br>37.5% | 3<br>37.5% | 8<br>100.0% |
| | Polyglecaprone 25 | 0<br>0.0% | 3<br>37.5% | 3<br>37.5% | 2<br>25.0% | 8<br>100.0% |

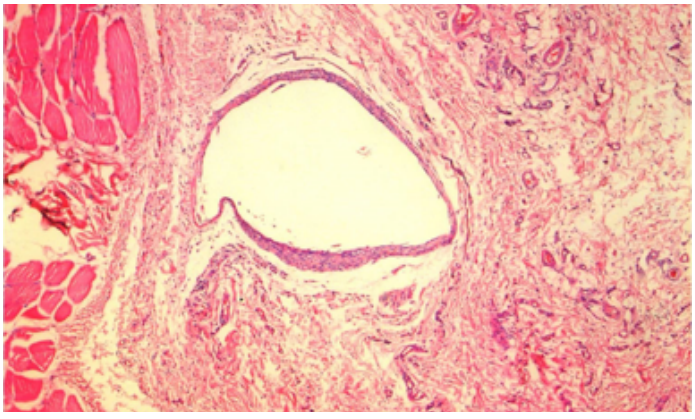


**Figure 3.** Cavitation induced by Lycra® and minimal fibroplasia and angiogenesis around it (Hemotoxylin Eosin x 40).

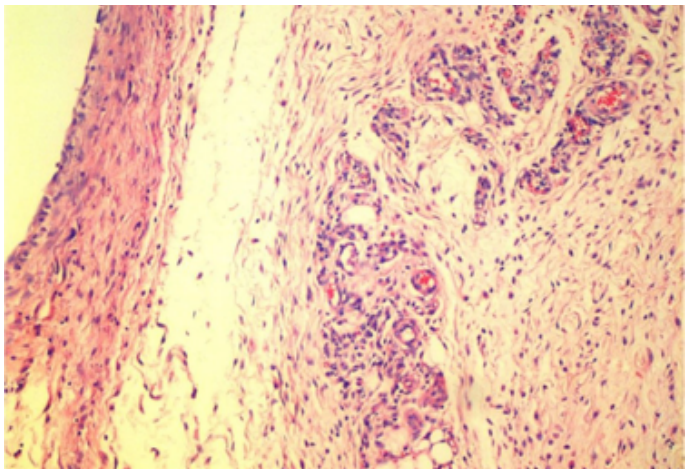


**Figure 4.** Moderate vascularization and fibroblastic response in cavity and surrounding tissue induced by Lycra® (Hemotoxylin Eosin x 40).

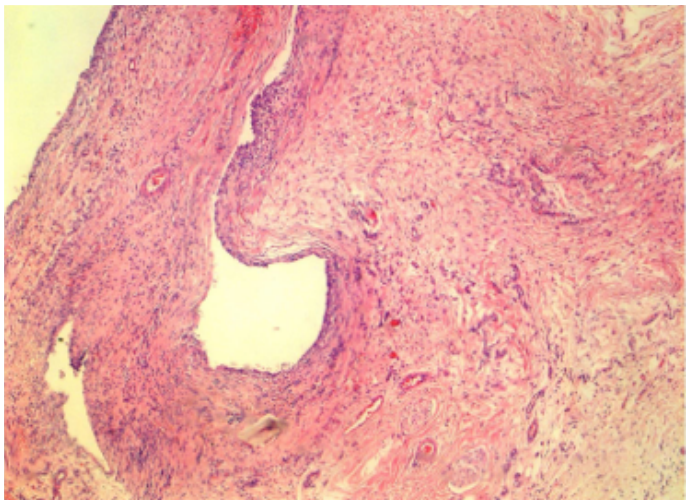


**Figure 5.** Moderate vascularization, fibroblastic and inflammatory response in cavity and surrounding tissue induced by polypropylene. (Hemotoxylin Eosin x 40).

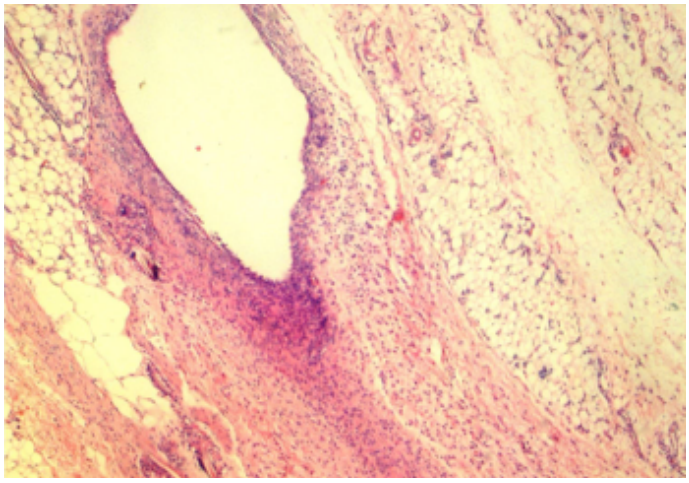


**Figure 6.** Moderate vascularization, fibroblastic and inflammatory response in cavity and surrounding tissue induced by Monocryl®. (Hemotoxylin Eosin x 40).

The result of "intensive mixed inflammatory cell infiltration and tissue necrosis", which is determined asthe most severe inflammatory response level, was not observed in any suture material. Most number of rats at the "0" level, where no inflammatory response was detected, was in the Lycra® group. Inflamatory response was not significant among the groups (p = 0. 513).

In the "Hemorrhage + Neovascularization" phase, which was the most inappropriate level for vascularization, Polyglecaprone 25 group had the worst results with 67.5% (5/8 rat). The difference was not significant (p = 0.065). In the response to fibrosis 67.5% (5 of 8) of the rats in the Lycra® group were at the "Fibrosis, collagen bundles" level, defined as the level in which the worst result was obtained, while none of the rats in the polyproylene group even reached this level. However, this difference was not significant in terms of fibrosis (p = 0.108). At the level where no changes were observed in terms of histiocytic reaction, only Lycra® group was present. There were three rats (37.5%) in the polypropylene group at the level of granuloma formation, the most undesirable level. The difference was not significant (p = 0.630).

## Discussion

Various methods and materials have been investigated to prevent the sternal dehissence after cardiac surgery and may cause severe mortality and morbidity [4-9]. Sutures are still the most appropriate and effective products used for apposition of tissues after a surgical incision is made. Synthetic or organic adhesives and cements mainly developed for dental and orthopedic applications have not been widely used in sternal closure [17]. The recommended method of use for cement and adhesives is an additional reinforcement to routine sternal closure with steel sutures [18]. Although today's technology has developed a wide variety of new alternative materials in the surgical field, new suture materials with flexibility as well as durability for certain specialized tissues and surgical techniques is not yet available.

Although the strength of the steel sutures used for the closure of the routine sternotomy in cardiothoracic surgery is sufficient, various uncontrolled movements of the patients, mainly coughing in the postoperative period, can cause both bone fractures and even suture breakage [10,19]. The search for new techniques and materials concerning the closure of sternum is still ongoing. [20]. The in vitro stability tests of the material we were working on were the subject of another study and positive results were obtained. At this stage, the biocompatibility and tissue response of this material were examined.

For this purpose, we examined the tissue compability of Lycra® and found that the cellular changes caused by Lycra® were similar to polyglecaprone 25 and polypropylene.

Shirazi M. et al reported that more intense vascularization was observed with polyglecaprone 25 than other monofilament and absorbable polydioxanone, polyglactic acid, and polyglactin 910 sutures [21]. Polypropylene and polyglecaprone 25 sutures have been reported to cause low inflammation both in the literature and in our study [12]. The recovery phase in all tissues was consistent with histopathological findings between 1 and 2 weeks.

The major limitation of this study is polypropylene tie and Lycra® used in our work is not a medical product. It has been developed by chemists as a material with superior elastic properties than rubber and used extensively in the textile industry because it is highly elastic as well as oxidation and heat resistant, and does not easily lose this property [15]. However, it is thought that it can be used as a suture and prosthetic material due to these superior features and the possible effects of disinfection and sterilizationprocesses have been studied for this purpose, but no suitable area were found for the medical field in the following years [14, 15].

Although in a few experimental studies where Lycra® was used as a suture material, superior features such as approximating the tissues without applying the tension, self-locking during the knotting and no tendency to open the first knot as opposed to other rigid sutures, were emphasized [14].

Studies have shown that multifilament sutures cause more inflammatory reactions than monofilament [22]. Yaltirik et al showed that polyglactin 910 (Vicryl, Ethicon, New Jersey, USA) was found as the least suture material causing tissue reaction [22]. Gartti-Jardim EC et al examined the effects of different polyglactin derivatives on healing process in rats' skin tissues, poliglecaprone 25 (Monocryl®) was found to havethe best biological response [23]. In our study, the lowest inflammatory response was found in the "poliglecaprone25" suture material, as noted in the literature.

In 1968, Wagner reported that Lycra®sutures were used on skin, intestines and liver, and almost no foreign body reaction was developed [14].

These limited studies of the medical use of Lycra® indicate

that further work is needed in this regard. We have planned in vitro and in vivo studies to test the endurance and prove that they can be used in practice, there is also a need for studies on the field of use.

## Conclusion

Lycra® which is thought to be used as a suture material for sternal closure due to its flexible property, showed similar inflammatory changes with polypropylene and polyglycaprone 25 in the rat soft tissue.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## References

1. Danter MR, Saari A, Gao, M, Cheung A, Lichtenstein SV, Abel JG. A New Device for Securing Sternal Wires After Median Sternotomy: Biomechanical Study and Retrospective Clinical Assessment. Innovations (Phila) 2018.
2. Schmid C, Akhter SA. Postoperative Sternal Complications. In Cardiac Surgery Springer, Berlin, Heidelberg 2017; 1129-35.
3. Schimmer C, Sommer SP, Bensch M, Bohrer T, Aleksic I, Leyh R. Sternal closure techniques and postoperative sternal wound complications in elderly patients. Eur J Cardiothorac Surg 2008; 34: 132-8.
4. Casha AR, Camilleri L, Manché A, Gauci M, Magri CJ, Agius A, Yang L. Effect of sternal wire twisting on sternotomy closure rigidity. Indian J Thorac Cardiovasc Surg 2018; 34: 25-30.
5. Abbas S, Gul S, Abbas A, Iqbal M, Khan T, Khan JS. Figure-of-8 sternal closure vs simple interrupted sternal closure in reducing sternal dehiscence in patients with coronary artery bypass grafting (CABG). Pakistan Heart J 2017; 50.
6. Park JS, Kuo JH, Young JN, Wong MS. Rigid sternal fixation versus modified wire technique for poststernotomy closures: a retrospective cost analysis. Ann Plast Surg 2017; 78: 537-42.
7. Motomatsu Y, Imasaka KI, Tayama E, Tomita Y. Midterm results of sternal band closure in open heart surgery and risk analysis of sternal band removal. Artif Organs. 2016; 40: 153-8.
8. Allen KB, Thourani VH, Naka Y, Grubb KJ, Grehan J, Patel N, Cohen DJ. Rigid Plate Fixation vs Wire Cerclage: Patient Reported and Economic Outcomes from a Randomized Trial. Ann Tthorac Surg 2018.
9. Hashim S, Chin LY, Krishnasamy S, Sthaneswar P, Mokhtar RAR. Effect of sternal closure with biological bone adhesive on pain visual analogue score and serum cytokine. J Cardiothor Surg. 2015; 10: 32.
10. Wilson RM, Ghareeb PA, McClellan WT, Boustany AN. Biomechanical analysis of the FlatWire Figure 8 sternal fixation device. Plast Surg. 2014; 22: 188-90.
11. Celik F, Kaya MA. "Scientific criterias for surgical suture and needle selection" in Turkish. Ulusal Cerr Derg. 2006; 22: 153-57.
12. Dunn DL. Wound closure manual. Somerwille, NJ: Ethicon inc. ; 2007; 97-102.
13. Birolini C, De Miranda JS, Utiyama EM, Rasslan S. A retrospective review and observations over a 16-year clinical experience on the surgical treatment of chronic mesh infection. What about replacing a synthetic mesh on the infected surgical field?. Hernia 2015; 19: 239-46.
14. Wagner M, Reul G, Teresi J, Kayser KL. Experimental observations on a new and inherently elastic material for sutures and vascular prostheses: Lycra. Am J Surg 1966; 111: 838-41.
15. Boretos JW, Pierce WS. Segmented polyurethane: A polyether polymer. An initial evalution for biomedical applications. J Biomed Mater Res 1968; 2: 121-30.
16. Losanoff JE, Jones JW, Richman BW. Primary closure of median sternotomy: Techniques and principles. Cardiovasc Surg 2002; 10: 102-10.
17. Santos TdeS, Abuna RP, Almedia AL, Beloti MM, Rosa AL. Effect of collagen sponge and fibrin glue on bone repair. J Appl Oral Sci 2015; 23: 623-28.
18. Alhalawani AM, Towler MR. A review of sternal closure techniques. J Biomater Appl 2013; 28: 483-97.
19. Levin LS, MillerAS, Gajjar AH, Bremer KD, Spann J, Milano CA et al. An innovative approach for sternal closure. Ann Thorac Surg 2010; 89: 1995-99.
20. Orhan SN, Ozyazicioglu MH, Colak A. A biomechanical study of 4 different sternum closure techniques under different deformation modes. Interact Cardiovasc Thorac Surg 2017; 25: 750-756.
21. Shirazi M, Noorafshan A, Serhan A. Effects of different suture materials used for the repair of hypospadias: A stereological study in a rat model. Urol Int 2012; 89: 395-401.
22. Yaltirik M, Dedeoglu K, Bilgic B, Koray M, Ersev H, Issever H, et al. Comparison of four different suture materials in soft tissues of rats. Oral Dis 2003; 9: 284-86.
23. Carvalho AC, de Souza AP, de Souza CA, Pereira CC, Okamoto R, Magro FO. Comparative study of the healing process when using Vicryl®, Vicryl Rapid, Vicryl Plus®, and Monocryl® sutures in the rat dermal tissue. Oral Maxillofac Surg 2013; 17: 293-98.
24. Willsallen H, Heller J, Kark L, Hilbert BJ. In vitro mechanical testing of braided polyurethane elastic fiber and braided polyester for equine laryngoplasty. Vet Surg 2015; 44: 223-30.

Turkish Journal of Clinics and Laboratory

To cite this article: Çadırcı K, Olcaysu OO, Yiğit D, Çarlıoğlu A, Arıkan Ş. Tip 2 diabetik hastalarda ortalama trombosit hacmi: mikrovasküler komplikasyonlar ile ortalama trombosit hacmi arasında bir ilişki var mı? Turk J Clin Lab 2018; 9(1): 31-35.

Orjinal Makale

# Tip 2 diabetik hastalarda ortalama trombosit hacmi: mikrovasküler komplikasyonlar ile ortalama trombosit hacmi arasında bir ilişki var mı?

## *Mean platelet volume in type 2 diabetic patient: is there a relationship between mean platelet volume and diabetic microvascular complications?*

Kenan ÇADIRCI[1]*, Osman Okan OLCAYSU[2], Derman YİĞİT[3], Ayşe ÇARLIOĞLU[4], Şenay ARIKAN[5]

[1]Bölge Eğitim ve Araştırma Hastanesi, İç Hastalıkları Kliniği, Erzurum
[2]Bölge Eğitim ve Araştırma Hastanesi, Göz Kliniği, Erzurum
[3]Bölge Eğitim ve Araştırma Hastanesi, Nöroloji Kliniği, Erzurum
[4]Bölge Eğitim ve Araştırma Hastanesi, Endokrinoloji ve Metabolizma Hastalıkları Kliniği, Erzurum
[5]Kırıkkale Üniversitesi, İç Hastalıkları ABD, Endokrinoloji ve Metabolizma Hastalıkları Kliniği, Kırıkkale

## ÖZ

**Amaç:** Diabetik hastaların çoğunda vasküler trombotik ve aterosklerotik komplikasyonlar görülür. Diabetik hastalarda trombosit boyutundaki değişiklikler aterosklerotik komplikasyonlar ile ilişkilidir. Bu çalışmanın amacı, tip 2 diabetik hastalarda ortalama trombosit hacmi (Mean Platelet Volume, MPV) ile mikrovasküler komplikasyonlar arasındaki ilişkiyi saptamaktır.

**Gereç ve Yöntemler:** Bu çalışmaya 115 tip 2 DM tanılı hasta (ortalama yaş 50.4±9.9 yıl ve BMI 31.0±5.3 kg/m$^2$) ve tamamen sağlıklı ve sistemik hastalığı bulunmayan 67 kişide (ortalama yaş 48.8±12.0 yıl ve BMI 30.3±7.3 kg/m$^2$) kontrol grubu olarak dahil edildi. Diabetik grupta kronik diabetik mikrovasküler komplikasyonlar araştırıldı. Nörolojik değerlendirme, oküler fundus muayenesi ve EMG (Elektromyografi) yapıldı. Diabetik hastalarımız öncelikle en az bir mikrovasküler komplikasyonu olan ve olmayan şeklinde ikiye ayrıldı. Daha sonra mikrovasküler komplikasyonu olan hastalar nefropati, nöropati ve retinopatiye göre alt gruplara ayrıldı. Tüm alt gruplarda MPV düzeyi tekrar analiz edildi.

**Bulgular:** En az bir mikrovasküler komplikasyonu olan diabetik hasta grubumuzda 79 hasta mevcutdu. Bu grup da, 44 (%34.7) hastada nöropati, 33 (%26.0) hastada diabetik nefropati ve 13 (%10.2) hastada ise diabetik retinopati tespit edildi. Mikrovasküler komplikasyonu olmayan diabetik hasta grubunda ise 36 kişi mevcutdu. Bu grup ise diabetik kontrol grubu olarak kabul edildi.

Diabetik mikrovasküler grupta MPV düzeyleri sağlıklı kontrol grubundan anlamlı olarak yüksekti (sırasıyla 8.6±0.8fL ve 7.9±0.8fL, p<0.001). Yine diabetik kontrol grubu ile sağlıklı kontrol grupları arasında da MPV düzeyi açısından anlamlı fark mevcutdu (8.3±0.5fL ve 7.9±0.8fL, p=0.005). Diabetik mikrovasküler grup ile diabetik kontrol grubu arasında ise MPV düzeyleri bakımından fark tespit edilmesine rağmen bu fark istatistiki olarak anlamlı değildi (sırasıyla 8.6±0.8fL ve 8.3±0.5fL p=0.06).

Subgrup analizlerinde MPV düzeyleri açısından diabetik nefropati ile sağlıklı kontrol grubu arasında (p=0.006), diabetik nöropati grubu ile sağlıklı kontrol grubu arasında (p=0.001) ve diabetik retinopatili hasta grubu ile sağlıklı kontrol grubu arasında MPV bakımından istatistiki açıdan anlamlı bir fark tespit edildi ( p=0.02).

**Sonuç:** Çalışmamızda, Tip 2 DM hasta grubu MPV düzeyinin sağlıklı kontrollere göre istatistiki açıdan anlamlı yüksek olduğunu tespit ettik. Yine diabetik nefropati, diabetik nöropati ve diabetik retinopatiye sahip hastalarda MPV düzeyinin sağlıklı bireylerden daha yüksek olduğunu tespit ettik. Sıklıkla trombosit aktivitesinin bir göstergesi olarak kullanılmakta olan MPV, tip 2 diabetli hastalarda mikrovasküler komplikasyon gelişmesi riski ile ilişkili olabilir.

**Anahtar kelimeler:** Ortalama trombosit hacmi, diabetik nefropati, diabetik nöropati, diabetik retinopati

Sorumlu Yazar*: Kenan ÇADIRCI, Bölge Eğitim ve Araştırma Hastanesi, İç Hastalıkları Kliniği, Erzurum
E-Posta: doktorcadirci@hotmail.com
Received 21.05.2017 accepted 12.10.2017
Doi: 10.18663/tjcl.315153

## ABSTRACT

**Aim:** Most diabetic patients suffer from vascular thrombotic and atherosclerotic complications. Alteration in platelet size are associated with atherosclerotic complications in patients with diabetes. The aim of present study is to determine the relationship between mean platelet volume (MPV) and microvascular diabetic complications in type 2 diabetic patients.

**Material and Methods:** 115 type 2 diabetic patients [mean age 50.4±9.9 year and body mass index (BMI) 31.0±5.3 kg/m$^2$], and 67 healthy control subjects without any systemic disease (mean age 48.8±12.0 year and BMI 30.3±7.3 kg/m$^2$) were included in this study. Chronic diabetic microvascular complications in diabetic group were researched. Neurological evaluation, ocular fundus examination and EMG (electromyography) were performed. Our diabetic patients were initially divided into two groups with and without at least one microvascular complication. Subsequently, patients with microvascular complications were divided into subgroups according to nephropathy, neuropathy and retinopathy. MPV levels were re-analyzed in all subgroups.

**Results:** There were 79 patients in our diabetic patient group with at least one microvascular complication. In this group, 44 (34.7%) patient neuropathy, 33 (26.0%) patients diabetic nephropathy and 13 (10.2%) patients diabetic retinopathy were detected. There were 36 patients in the diabetic group without microvascular complications. This group was accepted as a diabetic control group.

We determined that mean MPV levels in diabetic microvascular group was significantly different from control group (8.6±0.8 fL and 7.9±0.8 fL, p<0.001). Again we determined that mean MPV levels in diabetic control group was significantly different from control group (8.3±0.5fL ve 7.9±0.8fL, p=0.005)

Despite the difference in MPV between the diabetic microvascular group and the diabetic control group, this difference was not statistically significant ( 8.6±0.8 fL, 8.3±0.5 fL, p = 0.06).

In subgroup analysis, we demonstrated that mean MPV levels in diabetic nephropathy (p=0.006) and in diabetic neuropathy groups (p=0.001) and diabetic retinopathy group ( p=0.02) were higher than control subjects.

**Conclusions:** In our study, we determined mean MPV levels in type 2 diabetic group was significantly highly from control group. Also, we detected MPV level in diabetic patients with nephropathy, neuropathy and retinopathy is more increase than healthy subjects. Although MPV is often used as the marker of platelet activity, elevated MPV levels in patients with type 2 diabetes mellitus may associate with increased microvascular complication risk.

**Key words:** Mean platelet volume, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy

## Giriş

Diabetes Mellitus, kronik hiperglisemi ile seyreden, mikrovasküler ve makrovasküler komplikasyonları ile önemli morbidite ve mortaliteye neden olan bir karbonhidrat metabolizma bozukluğudur. Glukozun damar endotelini hedef alan toksisitesi ile kronik süreçte trombosit aktivasyonu oluşmakta ve trombojenik olaylara eğilim artmaktadır. Bu patojenik mekanizma ile oluşan mikrovasküler ve makrovasküler komplikasyonlar, hastanın morbiditesini artırmakta ve tedavisini güçleştirmektedir.

Ortalama trombosit hacminin otomatik analizörler yardımı ile ölçülen bir değeri olan MPV (Mean Platelet Volume, Ortalama Trombosit Hacmi) son yıllarda trombosit fonksiyonlarının bir göstergesi olarak kabul edilen, kolay ölçülebilen bir değer olarak tespit edilmiştir.

İnvitro aggregometri yöntemi ile yapılan değerlendirmede büyük plateletlerin küçük olanlara göre enzimatik ve metabolik olarak daha aktif oldukları tespit edilmiştir ve bu durumun daha yüksek bir trombotik risk taşıdığı aşikardır (1).

Platelet morfoloji ve fonksiyonlarındaki değişiklikler, mikrovasküler ve makrovasküler hastalıklar için risk faktörü olarak düşünülebilir (2).

Bu çalışmanın amacı, tip 2 diabetik hastalarda ortalama trombosit hacmi (Mean Platelet Volume, MPV) ile mikrovasküler komplikasyonlar arasındaki ilişkiyi saptamaktır.

## Gereç ve Yöntemler

Çalışmaya Erzurum Bölge Eğitim ve Araştırma Hastanesi Endokrinoloji ve Metabolizma hastalıkları polikliniğinde Tip2 DM tanısı ile takip edilen ve herhangi bir karaciğer ve böbrek yetmezliği ile trombosit hacmini değiştiren kan diskrazisi gibi hastalığı olmayan, trombosit sayısı normal aralıkta tespit edilen ve trombosit fonksiyonlarını bozan herhangi bir ilaç kullanım öyküsü olmayan 115 hasta ve herhangi bir sistemik hastalığı olmayan tamamen sağlıklı ve yine trombosit fonksiyonlarını bozan herhangi bir ilaç kullanım öyküsü olmayan 67 kişide kontrol grubu olarak alındı. Diabetik hasta grubunda yer alan kişilerin son 6 ay içerisinde MPV düzeyini etkileyebilecek antihiperlipidemik ve antiagregan ilaç kullanmamış olmasına dikkat edildi. Her iki grup arasında yaş, cinsiyet, vücut kitle

Volume 9 Number 1 p: 31-35

indeksi bakımından istatistiki anlamlı bir fark tesit edilemedi.

Bütün venöz kan örnekleri 12 saatlik açlık sonrası antekübital venden alındı. Çalışmada tam kan sayımı analizi, otomatik hematoloji analizörü Beckman Coulter LH 750 (Beckman Coulter, ABD) ile gerçekleştirildi. Trombosit sayısı (PC) ve ortalama trombosit hacmi (MPV) ölçüldü.

İstatistiksel analiz için SPSS 19 programı kullanıldı. Bütün sonuçlar ortalama±standart deviasyon (SD) olarak ifade edildi. Kontrol ve hasta gruplar arası karşılaştırma için independent-t testi kullanıldı. Değişkenlerin değerlendirilmesinde Pearson's korelasyon testi kullanıldı. p <0.05 değeri istatistiki açıdan anlamlı olarak kabul edildi.

## Bulgular

Çalışmaya Tip 2 DM tanısı ile tedavi almakta olan (hastalar arasında tedavi, diabet süresi, cinsiyet ayrımı yapılmadan) 115 hasta alındı. Diabetik hastalar mikrovasküler komplikasyonu olup olmama özelliklerine dayanılarak 2 gruba ayrıldı. Diabetik mikrovasküler grupta en az bir diabetik mikrovasküler komplikasyonu olan 79 hasta (32 erkek, 47 bayan) ve diabetik kontrol grubunda ise herhangi bir mikrovasküler komplikayonu olmayan 36 diabetik hasta (19 erkek, 17 bayan) çalışmaya dahil edildi. Aynı zamanda herhangi bir sistemik hastalığı olmayan 67 kişide (30 erkek, 37 bayan) sağlıklı kontrol grubu olarak alındı.

Tip 2 DM grubunda yer alan hastaların yaş ortalaması 50.4±9.9 yıl ve BMI 31.0± 5.3 kg/m$^2$ ve kontrol grubunun ise ortalama yaş 48.8±12.0 yıl ve BMI 30.3±7.3 kg/m$^2$ olarak hesaplandı. Her iki grup arasında yaş ve BMI yönü ile istatistiki açıdan anlamlı bir fark tespit edilemedi. Sırası ile p değerleri 0.3 ve 0.5 olarak hesaplandı.

Tip2 DM grubuna ait MPV ortalaması 8.5±0.7fL ve kontrol grubuna ait MPV ortalaması ise 7.9±0.8fL olarak tespit edildi. Aralarında istatistiki açıdan anlamlı bir fark olduğu tespit edildi ( p<0.001).

Diabetik mikrovasküler grupta MPV düzeyleri sağlıklı kontrol grubundan anlamlı olarak yüksekti (sırasıyla 8.6±0.8fL ve 7.9±0.8fL, p<0.001). Yine diabetik kontrol grubu ile sağlıklı kontrol grupları arasında da MPV düzeyi açısından anlamlı fark mevcutdu (sırasıyla 8.3±0.5fL ve 7.9±0.8fL, p=0.005). Diabetik mikrovasküler grup ile diabetik kontrol grubu arasında ise MPV düzeyleri bakımından fark tespit edilmesine rağmen bu fark istatistiki olarak anlamlı değildi (sırasıyla 8.6±0.8fL ve 8.3±0.5fL p=0.06).

Hasta ve kontrol gruplarına ait demografik veriler Tablo 1' de gösterilmiştir.

**Tablo 1:** Hasta ve kontrol grubunun klinik ve demografik özellikleri

| | DMTip2 | | Sağlıklı Kontrol | p1 | p2 | p3 |
|---|---|---|---|---|---|---|
| | Mikrovasküler | Diabetik kontrol | | | | |
| **Hasta sayısı** | 79 | 36 | 67 | | | |
| **Cinsiyet ( E/K)** | 32/47 | 19/17 | 30/37 | | | |
| **Yaş (yıl)** | 51.0±10.8 | 49.3±7.3 | 48.8±12.0 | 0.25 | 0.74 | 0.28 |
| **BMI(kg/ m$^2$)** | 31.0± 5.5 | 31.0±4.9 | 30.3±7.3 | 0.67 | 0.43 | 0.68 |
| **Platelet/µL** | 267.4±71,6 | 288.9±66.7 | 233.7±8.8 | 0.7 | 0.6 | 0.4 |
| **MPV( fL)** | 8.6±0.8 | 8.3±0.5 | 7.9±0.8 | **<0.001*** | **0.005*** | **0.06** |
| **CRP** | 0.7±1.05 | 0.7±0.9 | 0.6±0.9 | 0.9 | 0.4 | 0.3 |
| **Ferritin** | 95.5±98.5 | 88.2±88.8 | 88.8±82.8 | 0.4 | 0.3 | 0.6 |
| **Fibrinojen** | 348.2±81.9 | 320.1±80.9 | 332.2±77.7 | 0.08 | 0.06 | 0.7 |

*Diabetik mikrovasküler grup ile sağlıklı kontrol arasındaki istatistiki ilişki p1
*Diabetik kontrol grubu ile sağlıklı kontrol arasındaki istatistiki ilişki p2
*Diabetik mikrovasküler grup ile diabetik kontrol grubu arasındaki istatistiki ilişki p3 ile gösterildi.
BMI: Body Mass Index( Vücut kitle indeksi), MPV( Mean Platelet Volume): Ortalama Trombosit Hacmi,

Çalışmaya alınan diabetik mikrovasküler grupta yer alan 79 hasta içerisinde birden fazla sayıda mikrovasküler komplikasyonu olanlar, subgrup analizlerinde bulundurdukları komplikasyon türüne göre birden fazla gruba dahil edilerek subgrup analizleri yapıldı. Buna göre diabetik mikrovasküler grupta 44 (%34.7) hastada nöropati, 33 (% 26.0) hastada diabetik nefropati ve 13 (%10.2) hastada ise diabetik retinopati tespit edildi.

Subgrup analizlerinde MPV düzeyleri açısından diabetik nefropati ile sağlıklı kontrol grubu arasında (p=0.006), diabetik nöropati grubu ile sağlıklı kontrol grubu arasında (p=0.001) ve diabetik retinopatili hasta grubu ile sağlıklı kontrol grubu arasında MPV bakımından istatistiki açıdan anlamlı bir fark tespit edildi ( p=0.02).

Subrupların sağlıklı kontrol grubu ile yapılan karşılaştırmalara ait istatistiki veriler Tablo-2' de gösterilmiştir.

**Tablo 2:** Diabetik Mikrovasküler komplikasyonlara ait veriler

| Diabetik Komplikasyon | Hasta sayısı | MPV ( fL) | Sağlıklı kontrol p | Diabetik kontrol p |
|---|---|---|---|---|
| **Nefropati** | 33 | 8.5±0.9 | **0.006*** | **0,5** |
| **Nöropati** | 44 | 8.5±0.8 | **0.001*** | **0,2** |
| **Retinopati** | 13 | 8.5±0.8 | **0.02*** | **0,5** |

Yine MPV düzeyleri açısından diabetik mikrovasküler grup ile diabetik kontrol grubu arasında istatistiki karşılaştırma yapılmıştır. Buna gore diabetik nefropati grubu ile diabetik kontrol grubu arasında (p=0.5), diabetik nöropati ile diabetik kontrol grubu arasında (p=0.2) ve diabetik retinopatisi olan grup ile diabetik kontrol grubu arasında (p=0.5) anlamlı istatistiki fark tespit edilememiştir.

Çalışmamızda diabetik grup ile sağlıklı kontrol grubu arasında platelet miktarı, CRP ve fibrinojen düzeyi arasında anlamlı bir fark tespit edilemedi.

## Tartışma

Diabetes Mellitus, dünyada önemli ve artan oranlarda morbidite ve mortalite sebebidir. Diabete eşlik eden hiperglisemi, toksik ara metabolizma ürünleri ve serbest oksijen radikalleri üzerinden tüm vücudu etkileyen patolojik süreçlere yol açar. Hipergliseminin endotel hücrelerine toksisitesi çok iyi bilinmektedir. Bundan dolayı hastalığın ilerleyen dönemlerinde mikrovasküler ve makrovasküler komplikasyonlar oluşmakta ve önemli morbidite ve mortalite sebebi olmaktadır.

Diabetik mikrovasküler komplikasyonlar (retinopati, nöropati ve nefropati) tip2 diabetli 100 milyonlarca hastayı etkilemektedir. Genellikle uzun süredir devam eden ya da kontrol edilemeyen hastalığı olan insanları etkiler, teşhis sırasında tespit edilebileceği gibi teşhis konmamış kişilerde de olabilir (3).

Diabete bağlı olsun veya olmasın, vasküler aterotrombotik olayların fizyopatogenezinde trombositler anahtar rol oynarlar. Bundan dolayı trombosit fonksiyonlarının kolay ölçülebilen bir göstergesi olarak MPV, ilgi odağı olmuştur.

MPV, platelet aktivasyonu ve fonksiyonları için kabul edilen bir indikatördür (4). Daha büyük platletlerin daha genç olduğu, daha reaktif olduğu ve daha hazır oldukları bilinmektedir. Küçük plateletlere göre daha fazla dens granül taşıdıkları, β tromboglobulin ve serotonin sekrete ettikleri ve daha fazla tromboxan A2 sentezledikleri bilinmektedir (5).

Literatürde diabetik hastalarda tespit edilen MPV değerlerinin normal sağlıklı bireyler ile karşılaştırıldığı çalışmalar vardır (6-8).

Hekimsoy ve arkadaşları tarafından yapılan ve 145 tip 2 DM ve 100 sağlıklı kontrol grubunun dahil edildiği çalışmalarında MPV' nin diabetik grupta non-diabetik gruba kıyasla daha yüksek olduğu ve bunun istatistiki anlamlı olduğu bildirilmiştir (6). Papanas ve arkadaşları tarafından yapılan ve 265 Tip 2 diabetik hastanın alındığı çalışmada MPV kontrol grubuna göre diabetik grupta anlamlı yüksek olarak tespit edilmiştir (7). Yenigün ve arkadaşları da yapmış oldukları ve 48 hasta ve 30 sağlıklı gönüllünün alındığı çalışmalarında diabetik hastalarda MPV değerini non-diabetik gruba göre istatistiki anlamlı yüksek olarak tespit etmişlerdir (8).

Bizim çalışmamızda MPV değerleri, hem Tip2 DM grupta ve hem de Tip2 DM grubu oluşturan mikrovasküler grup ile diabetik kontrol grubunda sağlıklı kontrol grubuna göre istatistiksel olarak anlamlı bir şekilde yüksek bulunmuştur.

Yine mikrovasküler grubu oluşturan alt gruplar olan diabetik nefropati, nöropati ve retinopati grubu MPV ortalamaları, sağlıklı kontrol grubu MPV ortalamasına göre istatistiksel olarak anlamlı bir şekilde yüksek bulunmuştur.

Diyabetin mikrovasküler komplikasyonları ve MPV arasındaki ilişkileri inceleyen pek çok çalışma literatürde dikkati çekmektedir. Bazı çalışmalar MPV' nin mikrovasküler komplikasyonların varlığında arttığını ve anlamlı yükseklikler gösterdiğini ifade ederken (7,9), bazı çalışmalar ise her iki grup arasında anlamlı fark olmadığını ifade etmektedir (6,10,11).

Ünübol ve arkadaşları yapmış oldukları çalışmalarında, 354 DM tip2 tanılı hastayı mikroalbuminüri pozitif ve negatif gruplara ayırarak, gruplar arasında MPV bakımından fark olup olmadığını araştırmışlardır. Bu çalışmada, 124 mikroalbuminüri pozitif hasta ve 230 mikroalbuminüri negatif hasta çalışmaya dahil edilmiş ve mikroalbuminüri pozitif DM' lu hasta grubu lehine, gruplar arasında MPV bakımından istatistiki fark tespit etmişlerdir (9). Papanas ve arkadaşları tarafından, yine DM Tip2 li hastaların dahil edildiği çalışmalarında ise, diabetik hastalar retinopati ve mikroalbuminüri pozitifliğine göre gruplara ayrılarak değerlendirmeye alınmıştır. Retinopati pozitif grup ile negatif grup arasında pozitif grup lehine ve yine mikroalbuminüri pozitif grup ile mikroalbuminüri negatif grup arasında da pozitif grup lehine ortalama MPV değeri açısından anlamlı yükseklik tespit edilmiştir (7).

Hekimsoy ve arkadaşları tarafından yapılan ve yukarıda bahsettiğimiz çalışmalarında, diabetik hasta MPV değerinin sağlıklı kontrollere göre anlamlı yüksek olduğu tespit edilmiş

ve MPV' nin hem makrovasküler ve hem de mikrovasküler diabetik komplikasyonun gelişimindeki rolünü tespit etmeye yönelik olarak da alt grup analizleri yapılmıştır. Buna göre diabetik retinopati mikrovasküler ve koroner arter hastalığının ise makrovasküler komplikasyonlara örnek olarak alınarak değerlendirildiği alt grup değerlendirmelerinde, diabetik retinopatili grup ile retinopatisi olmayan diabetik hasta grubu arasında ve yine diabetik koroner kalp hastalığı olan grup ile koroner arter hastalığı olmayan diabetik grup arasında MPV bakımından anlamlı fark tespit edememişlerdir (6). Jindal ve arkadaşlarının yaptıkları ve 75 diabetik (50 hastada en az bir diabetik mikrovasküler komplikasyon mevcut) ve 50 nondiabetik hastanın dahil edildiği çalışmalarında MPV nin diabetik mikrovasküler komplikasyonları olan hastalar ile mikrovasküler komplikasyonu olmayan diabetik grup arasında anlamlı fark göstermediği belirtilmiştir (10). Kebapçılar ve arkadaşları tarafından yapılan ve 48 tip 2DM tanılı hastanın alındığı çalışmalarında, MPV ile diabetik mikrovasküler komplikasyonlar arasında bir ilişki tespit edemediklerini, bu değerlendirmeyi diabetik mikrovaskler komplikasyonu olan hastalar ile komplikasyonu olmayan hastalar arasında yapıldığını belirtmişlerdir (11).

Sadece mikrovasküler komplikasyonlara sahip diabetik hasta gruplarını değerlendirmeye aldığımız çalışmamızda, diabetik mikrovasküler komplikasyonlara sahip bireylerin MPV ortalamasının sağlıklı birey MPV ortalamasından yüksek olduğunu, ama diabetik birey MPV ortalamasından ise istatistiki anlamlı bir fark taşımadığını tespit ettik.

Sonuç olarak MPV sıklıkla trombosit aktivitesinin bir göstergesi olarak kullanılsa da, tip 2 diabetli hastalarda MPV seviyelerinin artması diyabetik mikrovasküler komplikasyon riski ile ilişkili olabilir. MPV seviyesi diabetik hastalarda trombotik olayların varsayımı için kolay ve erişilebilir basit bir parametre olarak kullanılabilir.

## Çıkar çatışması / finansal destek beyanı

Bu yazıdaki hiçbir yazarın herhangi bir çıkar çatışması yoktur. Yazının herhangi bir finansal desteği yoktur

## KAYNAKLAR

1. Endler G, Klımesch A, Sunder-Plassmann H, et al. Mean platelet volume is an independent risk factor for mycardial infarction but not for coronary artery disease. British Journal of Haematology. 2002; 117: 399-404
2. Biadgo B, Melku M, Abebe SM, Abebe M. Hematological indices ad their correlation with fasting blood glucose level and anthropometric measurements in type 2 diabetes mellitus patients in Gondar, Northwest Ethiopia. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2016; 9: 91-99
3. Valencia WM, Florez H. How to prevent the microvascular complications of type 2 diabetes beyond glucose control. BMJ 2017; 356: 6505
4. Çay S, Bıyıkoğlu F, Cihan G, Korkmaz Ş. Mean platelet volume in the patients with cardiac syndrome X. Journal of Thrombosis and Thrombolysis 2005; 20: 175-78
5. Abalı G, Akpınar O, Söylemez N. Correlation of the coronary severity scores and mean platelet volume in Diabetes mellitus. Adv Ther. 2014 Jan;31(1):140-8
6. Hekimsoy Z, Payzin B, Örnek T, Kandoğan G. Mean platelet volume in type 2 diabetic patients. J Diabetes Complications 2004; 18: 173-76
7. Papanas N, Symeonidis G, Maltezos E, et al. Mean platelet volume in patients with type 2 diabetes mellitus. Platelets 2004; 15: 475-78
8. Yenigün EC, Okyay UG, Pirpir A, Hondur A, Yıldırım İS. Increased mean platelet volume in type 2 diabetes mellitus. Dicle Medical Journal 2014; 41: 17-22
9. Ünübol M, Ayhan M, Güney E. The relationship between mean platelet volume with microalbuminuria and glycemic control in patents with type 2 diabetes mellitus. Platelets, September 2012; 23: 475-80
10. Jindal S, Gupta S, Gupta R, et al. Platelet indices in diabetes mellitus:indicators of diabetic microvascular complications. Hematology. 2011; 16: 86-89
11. Kebapçılar L, Bilgir O, Demirel H, ve ark. Tip2 diyabetik hastalarda ortalama trombosit volümü karşılaştırılması ve mikrovasküler komplikasyonlarla ilişkisinin değerlendirilmesi. Medical Journal of Izmir Hospital 2009; 15: 1-4

To cite this article: Yuceler Kacmaz H, Curuk GN. Healthy lifestyle behaviours and attitudes of relatives of patients with colorectal cancer towards protection from colorectal cancer. Turk J Clin Lab 2018; 9(1): 36-49.

Original Article

# Healthy lifestyle behaviours and attitudes of relatives of patients with colorectal cancer towards protection from colorectal cancer

## *Kolorektal kanserli hasta yakınlarının kolorektal kanserden korunmaya yönelik tutumları ve sağlıklı yaşam biçimi davranışları*

Hatice YUCELER KACMAZ[1], Gulsum Nihal CURUK[2*]

[1]Erciyes University, Faculty of Health Sciences,Department of Nursing, Kayseri
[2]Izmir University of Economics, Faculty of Health Sciences,Department of Nursing, Izmir-TURKEY

## ABSTRACT

**Aim:** This study was conducted in order to determine healthy lifestyle behaviours and attitudes of first degree relatives of patients with colorectal cancer (CRC) towards protection from CRC.

**Material and Method:** The data were collected by the researcher using Colorectal Cancer Screening Attitude Beliefs Scale (CCSAB), and Health Promotion Life-Style Profile II (HPLP).

**Results:** It was found that more than half (56.3%) of the patient relatives did not have knowledge about CRC and 85.2% did not participate early diagnosis/screening programs of CRC. It was found that CCSAB total mean score of the patient relatives was 53.06±8.91 and HPLP' total mean score was 132.46±20.96. Both HPLP' mean score and CCSAB' mean score was higher in patient' relatives who had knowledge about CRC and participated in early diagnosis/screening programs of CRC and the difference was determined to be highly significant. A positive, weak, and statistically significant correlation was found between CCSAB and HPLP scale of patient relatives in the study.

**Conclusion:** The present study showed that the rate of patient relatives to participate in CRC screening participation rates was low, healthy lifestyle behaviours and attitudes towards protection from CRC were moderate. Nurses should raise awareness through protection from cancer and early diagnosis/screening programs especially for cancer patients' relatives in all individuals is at risk primarily first degree relatives of patients with protection from and be guiding to acquire healthy lifestyle behaviours.

**Keywords:** cancer prevention, health lifestyle behaviours, relative, nursing

Corresponding Author*: Gulsum Nihal Curuk, Izmir University of Economics, Faculty of Health Sciences,Department of Nursing, Izmir
E-Mail: guleser38@gmail.com
Received 29.03.2017 accepted 25.04.2017
Doi: 10.18663/tjcl.302608

Volume 9 Number 1 p: 36-49


## ÖZ

**Amaç:** Araştırma, kolorektal kanserli (KRK) hasta yakınlarının KRK'den korunmaya yönelik tutumlarını ve sağlıklı yaşam biçimi davranışlarını belirlemek amacıyla tanımlayıcı olarak yapılmıştır.

**Gereç ve Yöntemler:** Çalışma Haziran 2015-Haziran 2016 tarihleri arasında Erciyes Üniversitesi Sağlık Uygulama ve Araştırma Merkezi genel cerrahi servisinde KRK cerrahisi geçiren 86 hastanın 142 yakını ile tamamlanmıştır. Veriler hasta tanıtım formu, kolorektal kanser taraması tutum inanç ölçeği (KKTTİ) ve sağlıklı yaşam biçimi davranışları II ölçeği (SYBD) kullanılarak, araştırmacı tarafından toplanmıştır.

**Bulgular:** Hasta yakınlarının yarısından fazlasının (%56.3) KRK hakkında bilgi sahibi olmadığı ve %85.2'sinin KRK erken tanı/tarama programlarına katılmadığı belirlenmiştir. Hasta yakınlarının KKTTİ ölçeği toplam puan ortalamasının 53.06±8.91, SYBD ölçeği toplam puan ortalamasının ise 132.46±20.96 olduğu tespit edilmiştir. KRK ile ilgili bilgi sahibi olan ve KRK erken tanı ve tarama programlarına katılan hasta yakınlarının hem KKTTİ ölçeği hem de SYBD ölçeği puan ortalamaları daha yüksek olup, aradaki farkın ileri derecede anlamlı olduğu belirlenmiştir ($p<0.001$). Araştırmada hasta yakınlarının SYBD ölçeği ile KKTTİ ölçeği arasında pozitif yönlü, zayıf düzeyde, istatistiksel olarak anlamlı bir ilişki tespit edilmiştir ($p<0.01$).

**Sonuç:** Çalışmamızda hasta yakınlarının KRK taramalarına katılma oranlarının düşük, KRK'den korunmaya yönelik tutumlarının ve sağlıklı yaşam biçimi davranışlarının ise orta düzeyde olduğu belirlenmiştir. Hemşireler kanserli hastaların birinci derece yakınları başta olmak üzere risk altındaki tüm bireylerde kanserden korunma ve erken tanı/tarama programları ile ilgili farkındalık geliştirmeli ve sağlıklı yaşam biçimi davranışı kazanmalarında yol gösterici olmalıdır.


**Anahtar kelimeler:** Hasta yakını, Hemşire, Kanserden korunma, Sağlıklı yaşam biçimi davranışları

## Introduction

According to 2016 report of American Cancer Society (ACS), the first three most frequent cancer types in the world are prostate/breast, lung and colorectal cancers (CRC), respectively. It is reported in the report that CRC is the third leading cause of cancer deaths in both women and men and approximately 49.190 people will die due to CRC in 2016 [1].

Environmental and genetic factors play an important role in the pathogenesis of CRCs developing with multifactorial reasons. The lifetime prevalence is approximately 5% in CRCs and this rate increases even more with certain risk factors such as genetic, age and environmental factors [2]. Genetic predisposition among those factors is reported to be the most important factor increasing the CRC risk. In CRCs showing a genetic transition of approximately 35%, the number of first-degree relatives with CRC and the age when they are diagnosed with the disease also increase further the possibility of having CRC [3]. While the risk increases two-four times in individuals having first degree relatives with history of CRC, this rate increases three-five times when the person has two first-degree relatives with history of CRC or when they have an age at diagnosis of below 50 years and incidence of CRC increases up to 20-25% [4].

It is reported that the genetic risk factor playing an important role in cancer development can be controlled with some changes in lifestyle [2,4]. It is stated in previous studies that consuming frequently animal fat, red meat and foods meat with high fat content increases the risk of CRC, while nutritional behaviours like consuming foods with high amount of fibre, milk and calcium regularly decrease the formation of CRC and the development of many cancer types including CRC can be controlled in people doing regular exercise. All of these studies indicate that the individuals having genetic predisposition can reduce the risk of CRC if they have healthy lifestyle behaviours [2,5].

In addition to the management of environmental factors, early diagnosis of CRC especially in individuals with genetic predisposition is another important issue. Early diagnosis has resulted in decreased morbidity and mortality rates of CRC and in increased five-year survival chance by 90% [6]. It is stated in the studies that rates of the CRC patients' first degree relatives to participate in recommended screening programs vary between 16-40% and remain below the expected level [7].

Nurses who have an important role to protect and maintain the health should consider the patients' first degree relatives which are in the risk group as well as the patients admitted to the clinic because of surgical intervention that is the first treatment method in almost all cancer types. Nurses should plan and apply appropriate interventions about risky patients to know the disease, to be aware of the false beliefs about the disease and gain positive health behaviours related with the protection from the disease within the scope of primary prevention measures and provide the necessary support by evaluating the results [8].

This descriptive study was conducted to investigate the attitudes of CRC patients' relatives towards protection against CRC and their healthy lifestyle behaviours.

**Preventive Health Model**

A person's health is affected by his beliefs and attitudes at a significant level. Healthcare professionals benefit from various models to describe the person's attitudes and beliefs affecting his health-related behaviours. Models provide significant information related to the factors that are effective in exhibiting a preventive behaviour. Preventive health model (PHM), one of these models, is a psychosocial model developed in order to determine the factors directing the individuals' behaviours and to guide the individuals for displaying positive health behaviours by creating behavioural changes in those individuals [9]. This model which is used in the studies related to mostly cancer screening and particularly CRC screening was developed by Myers et al. in 1994 to determine the factors affecting the individual's CRC screening behaviour and intention [10].

Factors such as health beliefs, attitudes, the effect of the social environment (family, friends, healthcare personnel, etc.), knowledge about the disease, risk perception and screening recommendation of healthcare professionals are involved among the factors affecting the individuals' prevention and early diagnosis/screening behaviours of colorectal cancer [7,11]. In terms of investigating these factors affecting the screening behaviours, PHM is a commonly used model in the studies. One of the scales developed on the basis of PHM is "Colorectal Cancer Screening Attitude and Belief Scale" (CCSABS) determining psychosocial effects including the individual's perceptions and barriers related to CRC screening [9,10].

**Healthy Lifestyle Behaviours**

Healthy lifestyle is for an individual to control all behaviours affecting his health, select and apply the appropriate behaviours for promoting his health during daily activities. Healthy lifestyle behaviours are expressed as an individual's promoting health and increasing his control over his health. Healthy lifestyle behaviours cover all activities performed for increasing the health potential and well-being status (such as adequate and balanced nutrition, stress management, regular exercise, spiritual growth, interpersonal relationships and taking responsibility for preventing and promoting the individual's health). The individual who transforms these behaviours into an attitude can not only maintain a healthy state but also bring his health status to a higher level [12,13].

Current evidences demonstrate that chronic diseases like cardiovascular diseases, diabetes and cancer are related with healthy lifestyle behaviour. While it is reported in Cancer Prevention guideline of World Cancer Research Fund that there is a relationship between lifestyle behaviours and cancer, it is stated in European Prospective Investigation into Cancer and Nutrition that healthy lifestyle behaviours are effective in the prevention of cancer [14,15].

In the previous studies, healthy lifestyle behaviours were revealed to reduce cancer-related morbidity and mortality rates [14]. It is reported that a simple behavioural change would have a strong influence on the incidence of cancer which is a complex multifactorial disease. Cancer prevention policies are emphasized to be built on providing healthy diet and healthy lifestyle habits [16].

It is known that there is a negative correlation between the incidence rate of colorectal cancer and healthy lifestyle behaviours. It was found from a study examining approximately 50.000 individuals that the risk of colon cancer development decreased with the increased healthy lifestyle scores [14].

## Material and Method

**Sample**

The population of the study consisted of first-degree relatives of the patients who underwent surgery in general surgery services of X University Application and Research Centre due to CRC. The study was completed with 142 relatives of 86 patients who underwent CRC surgery between June 2015 and June 2016. Individuals who were first degree relatives (parents, brothers, sisters and children) of the patients undergoing CRC surgery, had no psychiatric disorders, no communication problem, and can speak and understand Turkish are included in the study.

**Measurement**

The data were collected by using Personal Description Form, Colorectal Cancer Screening Attitude and Belief Scale and Health-Promoting Lifestyle Profile II in the study.

**Personal Description Form**

There are a total of 25 questions in the form containing socio-demographic characteristics of the patient relatives, and information about the disease and early diagnosis. The questions of the form were prepared by the researcher by reviewing the literature [7,11].

**Colorectal Cancer Screening Attitude and Belief Scale**

The scale developed by Vernon et al., in 1997 was restructured by Tiro et al., in 2005 [17]. Turkish validity and reliability of the scale was conducted by Koc in 2010. The scale has 16 items and five subscales containing salience and coherence (4 items), perceived susceptibility (4 items), response efficacy (2 items), cancer worries (2 items), and social influence (2 items). Participation in screening is expected to increase when the scale score increases [17].

Items 5, 6, 8, and 12 in the scale are reversed and thus analysed. Minimum-maximum scores to be taken from the scale vary between 4-16 for salience and coherence, 4-16 for perceived susceptibility, 2-10 for response efficacy, 4-16 for social influence, 2-10 for cancer worries and 16-80 in overall scale [17]. While the Cronbach alpha of the scale was 0.80 in the present study, Cronbach alpha values of the subscales were found as 0.79 for salience and coherence, 0.75 for perceived susceptibility, 0.63 for response efficacy, 0.61 for social influence, and 0.77 for cancer worries, respectively.

### Health-Promoting Lifestyle Profile II

The scale developed by Walker et al. in 1987 was revised in 1996 and named as "Health-Promoting Lifestyle Profile II" [18]. The scale whose Turkish validity and reliability were conducted by Bahar et al. in 2008 consists of 52 items [13]. There are 6 subscales in the scale containing health responsibility, physical activity, nutrition, spiritual growth , interpersonal relationship, and stress management. The scale was developed in four-point likert-type as never (1 point), sometimes (2 points), often (3 points), and regularly (4 points). The lowest score to be taken from the overall scale is 52 and the highest score is 208 [13]. While the cronbach alpha coefficient is .92 in the present study, the cronbach values of the subscales are determined as .64 for stress management, 0.85 for health responsibility, .82 for physical activity, .65 for nutrition, .78 for spiritual growth, and .76 for interpersonal relations.

### Ethical Procedure

Attention has been given to comply with ethical principles at every stage of the study. Before starting the application, approval from X University Clinical Trials Ethics Committee and a written permission from the department of General Surgery in X University Medical Application and Research Centre were obtained. Primarily, the patient relatives were informed about the purpose of the study and that their identities would not be disclosed in any way and their informed consents were obtained in written.

## Data Analysis

In the evaluation of the data obtained from the research, independent samples t-test was used for the comparison of two groups and analysis of variance was used for comparing more than two groups. Pearson correlation analysis was performed in order to determine the direction and strength of the correlation between scales.

## Results

The average age of the patient relatives was 40.3±12.7; 66.2% of them were the patients' children, 54.9% were male, 30.3% were primary school graduates, 68.3% were married, and 49.3% had moderate level of income.

It was determined that 56.3% of the patient relatives did not have any knowledge about CRC, 85.2% did not participate in diagnosis/screening program for CRC, 62.0% of those participating in CRC early diagnosis/screening program had colonoscopy, and 51.4% of them wanted to participate in CRC early diagnosis/screening programs.

While CCSABS total mean score of the patient relatives was 53.06±8.91, the subscale mean scores were found as 14.33±3.54 for salience and coherence, 12.00±3.29 for perceived susceptibility, 8.11±1.55 for response efficiency, 12.82±3.13 for social influence, and 5.80±2.27 for cancer worries, respectively (Table 1).

**Table 1.** Total and Sub-scales Scores of Colorectal Cancer Screening Attitude and Belief Scale

| Colorectal Cancer Screening Attitude Belief Scale | Mean ± SD | Min-max |
|---|---|---|
| Salience and coherence | 14.33±3.54 | 4-20 |
| Perceived susceptibility | 12.00±3.29 | 4-20 |
| Response efficacy | 8.11±1.55 | 2-10 |
| Social influence | 12.82±3.13 | 5-20 |
| Cancer worries | 5.80±2.27 | 2-10 |
| Total score | 53.06±8.91 | 26-76 |

Total mean score of HPLP of the patient relatives was 132.46±20.96 and the mean scores of the subscales were determined respectively as 19.50±3.96 for stress management, 21.56±5.81 for health responsibility, 16.13±5.25 physical activity, 21.90±4.50 for nutrition, 26.46±4.85 for spiritual growth, and 26.90±4.46 for interpersonal relationship (Table 2).

**Table 2.** Total and Sub-scales Scores of Health-Promoting Lifestyle Profile II

| Health-Promoting Lifestyle Profile II | Mean ± SD | Min-max |
|---|---|---|
| Stress management | 19.50±3.96 | 12-32 |
| Health self-responsibility | 21.56±5.81 | 9-35 |
| Physical activity | 16.13±5.25 | 8-30 |
| Nutrition | 21.90±4.50 | 13-32 |
| Spiritual growth | 26.46±4.85 | 15-35 |
| Interpersonal relationships | 26.90±4.46 | 17-36 |
| Total score | 132.46±20.96 | 83-179 |

A significant difference was found between CCSABS total mean scores of the patient relatives and gender, educational status, income, and smoking ($p<.05$). According to the table, CCSABS total mean scores of those who were female, had BS and MS degree, had a good income and non-smokers were determined to be higher (Table 3).

**Table 3.** Distribution of Scores of Colorectal Cancer Screening Attitude and Belief Scale according to Descriptive Characteristics of Participants

| Descriptive Characteristics | Sub-scales Scores | | | | | |
|---|---|---|---|---|---|---|
| | Salience and Coherence | Perceived susceptibility | Response efficacy | Social influence | Cancer worries | CCSABS total scores |
| | $\overline{x}$ ± SS | $\overline{x}$ ± SS | $\overline{x}$ ± SS | $\overline{x}$ ± SS | $\overline{x}$ ± SS | $\overline{x}$ ± SS |
| Relationship to patient | | | | | | |
| Parent | 12.62±3.25 | 10.54±1.51 | 7.38±1.50 | 12.31±3.40 | 5.85±2.08 | 48.69±4.84 |
| Sibling | 14.09±3.32 | 12.23±2.34 | 7.66±1.76 | 13.06±2.86 | 5.51±2.27 | 52.54±8.30 |
| Child | 14.66±3.61 | 12.12±3.72 | 8.38±1.41 | 12.80±3.21 | 5.89±2.30 | 53.85±9.43 |
| P | 0.133 | 0.242 | 0.012* | 0.761 | 0.700 | 0.137 |
| Gender | | | | | | |
| Female | 14.91±3.21 | 1.22±3.55 | 8.38±1.34 | 13.19±3.23 | 5.79±2.29 | 54.49±8.74 |
| Male | 13.58±3.82 | 11.71±2.93 | 7.77±1.73 | 12.34±2.96 | 5.81±2.25 | 51.21±8.87 |
| P | 0.026* | 0.357 | 0.021* | 0.109 | 0.961 | 0.029* |
| Age | | | | | | |
| 18-39 | 14.75±3.27 | 12.10±3.58 | 8.16±1.48 | 12.42±2.93 | 5.65±2.27 | 53.09±8.89 |
| 40-59 | 14.12±3.80 | 11.90±3.20 | 8.25±1.61 | 13.25±3.24 | 5.95±2.32 | 53.48±9.25 |
| 60 and above | 13.14±3.57 | 11.93±2.16 | 7.29±1.44 | 12.93±3.60 | 5.86±2.07 | 51.14±7.85 |
| P | 0.252 | 0.939 | 0.102 | 0.322 | 0.759 | 0.681 |
| Educational level | | | | | | |
| Primary school | 13.51±3.85 | 11.09±2.82 | 7.58±1.74 | 12.79±3.46 | 5.93±2.26 | 50.91±9.66 |
| Secondary school | 13.55±3.78 | 13.10±3.82 | 8.21±1.61 | 12.52±3.16 | 5.28±2.27 | 52.66±8.17 |
| High school | 14.69±2.89 | 11.64±3.04 | 8.11±1.35 | 12.75±2.77 | 5.39±2.17 | 52.58±8.42 |
| University | 15.65±3.23 | 12.59±3.38 | 8.71±1.24 | 13.18±3.13 | 6.50±2.26 | 56.62±8.33 |
| P | 0.031* | 0.044* | 0.016* | 0.868 | 0.104 | 0.042* |
| Marital status | | | | | | |
| Married | 14.53±3.50 | 12.29±3.04 | 8.15±1.47 | 13.07±3.17 | 6.00±2.30 | 54.04±8.29 |
| Single | 13.91±3.62 | 11.38±3.75 | 8.02±1.73 | 12.27±3.01 | 5.36±2.13 | 50.93±9.90 |
| P | 0.338 | 0.126 | 0.637 | 0.154 | 0.115 | 0.053 |
| Income level | | | | | | |
| Good | 15.04±3.26 | 12.41±3.29 | 8.43±1.45 | 13.17±2.45 | 5.87±2.30 | 54.92±7.93 |
| Moderate | 13.93±3.77 | 12.16±3.29 | 7.99±1.56 | 12.86±3.63 | 5.93±2.18 | 52.86±9.30 |
| Bad | 13.84±3.29 | 10.26±2.92 | 7.68±1.67 | 11.68±2.69 | 5.11±2.45 | 48.58±8.80 |
| P | 0.185 | 0.042* | 0.122 | 0.206 | 0.359 | 0.027* |

Note. . * p < .05.

Although CCSABS total mean scores of the patient relatives who had knowledge about CRC and the mean scores of all subscales of the scale were higher, the difference between them was determined to be statistically significant in total mean scores of the scale and all subscales except for the subscale of cancer worries (p<.05). CCSABS total mean scores of the patient relatives who participated in early diagnosis/screening programs of colorectal cancer and the mean scores of salience and coherence, perceived susceptibility, and response efficacy among subscales were found to be higher and the difference between them was statistically significant at advanced level (p<.001). It was determined that the CCSABS total mean scores of the patient relatives who were willing to participate in the early diagnosis/screening programs of colorectal cancer, mean scores of salience and coherence, perceived susceptibility, and social influence subscale were higher and the difference between them was statistically significant at advanced level (p<.001)(Table 4).

**Table 4.** Distribution of Colorectal Cancer Screening Attitude and Belief Scale according to Knowledge and Attitudes associated Colorectal Cancer of Participants

| Knowledge and Attitudes associated Colorectal Cancer | Sub-scales Scores | | | | | |
|---|---|---|---|---|---|---|
| | Salience and Coherence | Perceived susceptibility | Response efficacy | Social influence | Cancer worries | CCSABS Total Score |
| | $\bar{x}$ ± SS | $\bar{x}$ ± SS | $\bar{x}$ ± SS | $\bar{x}$ ± SS | $\bar{x}$ ± SS | $\bar{x}$ ± SS |
| Knowledge about CRC | | | | | | |
| Yes | 15.39±3.05 | 12.77±3.33 | 8.87±1.08 | 13.53±2.93 | 5.92±2.33 | 56.48±8.56 |
| No | 13.51±3.69 | 11.40±3.16 | 7.53±1.61 | 12.26±3.18 | 5.70±2.22 | 50.40±8.30 |
| P | 0.002** | 0.013* | <0.001** | 0.016* | 0.569 | <0.001** |
| Participation in the CRC early diagnosis/screening programs | | | | | | |
| Yes | 16.90±2.53 | 14.67±2.78 | 9.10±0.89 | 13.95±3.50 | 5.76±2.61 | 60.38±5.32 |
| No | 13.88±3.51 | 11.54±3.16 | 7.94±1.58 | 12.62±3.03 | 5.80±2.21 | 51.79±8.81 |
| P | <0.001** | <0.001** | 0.001** | 0.072 | 0.941 | <0.001** |
| Willingness to participation in the CRC early diagnosis/screening programs | | | | | | |
| Yes | 15.41±3.50 | 12.95±3.11 | 8.34±1.38 | 13.62±3.32 | 5.96±2.32 | 56.27±8.28 |
| No | 13.19±3.23 | 11.00±3.21 | 7.87±1.69 | 11.97±2.70 | 5.62±2.21 | 49.65±8.33 |
| P | <0.001** | <0.001** | 0.069 | <0.001** | 0.379 | <0.001** |

Note. * p < .05. ** p < .01.

HPLP total mean scores of the patient relatives were found to be higher in those who were female (p<.05), had good income level (p<.001), expressed their current health status as good (p<.001), went health control regularly (p<.05), had history of cancer diagnosis in their family except for CRC (p<.001) and had relatives that died because of cancer (p<.05) and the difference between them was statistically significant (Table 5).

HPLP total score and all subscale mean scores of the patient relatives who had knowledge about colorectal cancer were found to be higher and the difference between them was statistically significant (p<.05), (p<.001). HPLP total mean score (p<.001) of the patient relatives who participated in early diagnosis/screening programs of colorectal cancer and mean scores of health responsibility (p<.001), nutrition (p<.05), Spiritual growth (p<.05), and stress management (p<.05) among the scale subscales were high and the difference between them was statistically significant. It was found that HPLP total and subscale mean scores of the patient relatives who were willing to participate in early diagnose /screening programs of colorectal cancer were slightly higher but this variable did not cause a significant difference (p>.05)(Table 6).

**Table 5.** Distribution of Healthy-Promotion Lifestyle Profile Scores according to Participants' Descriptive Characteristics

| Descriptive Characteristics | Sub-scales Scores | | | | | | |
|---|---|---|---|---|---|---|---|
| | Health Responsibility $\bar{x}$ ± SS | Physical Activity $\bar{x}$ ± SS | Nutrition $\bar{x}$ ± SS | Spiritual Growth $\bar{x}$ ± SS | Interpersonal Relationships $\bar{x}$ ± SS | Stress Management $\bar{x}$ ± SS | HPLP Total Score $\bar{x}$ ± SS |
| Relationship to patient | | | | | | | |
| Parent | 22.08±3.09 | 19.00±5.23 | 21.69±3.77 | 25.15±5.47 | 26.15±3.83 | 20.08±3.86 | 134.15±16.51 |
| Sibling | 20.46±6.32 | 15.17±5.10 | 23.03±4.29 | 24.83±3.99 | 25.51±3.57 | 18.74±3.51 | 127.74±18.93 |
| Child | 21.90±5.90 | 16.09±5.21 | 21.51±4.63 | 27.26±4.91 | 27.52±4.73 | 19.70±4.13 | 133.98±22.11 |
| P | 0.433 | 0.079 | 0.231 | 0.023* | 0.061 | 0.410 | 0.311 |
| Gender | | | | | | | |
| Female | 22.74±5.89 | 15.98±5.00 | 22.74±4.37 | 27.16±4.87 | 28.25±4.37 | 19.89±4.35 | 136.75±21.46 |
| Male | 20.05±5.41 | 16.32±5.57 | 20.82±4.46 | 25.56±4.71 | 25.16±3.97 | 19.00±3.36 | 126.92±19.07 |
| P | 0.006** | 0.697 | 0.011* | 0.051 | <0.001** | 0.187 | 0.005** |
| Age | | | | | | | |
| 18-39 | 20.54±5.95 | 16.84±5.77 | 21.04±4.25 | 27.01±4.85 | 26.99±4.76 | 19.36±4.05 | 131.78±22.25 |
| 40-59 | 22.64±5.64 | 15.10±4.51 | 22.71±4.41 | 26.41±5.10 | 26.96±4.43 | 19.73±4.12 | 133.56±20.98 |
| 60 and above | 22.07±5.36 | 16.93±5.01 | 22.71±5.26 | 24.00±2.83 | 26.21±2.97 | 19.21±2.89 | 131.14±14.22 |
| P | 0.117 | 0.145 | 0.086 | 0.105 | 0.833 | 0.840 | 0.867 |
| Educational level | | | | | | | |
| Primary school | 21.86±5.99 | 15.44±5.12 | 21.95±4.41 | 25.42±4.85 | 27.44±4.15 | 19.91±3.85 | 132.02±20.14 |
| Secondary school | 22.35±6.09 | 15.45±4.81 | 22.93±5.34 | 25.24±5.12 | 25.69±4.93 | 18.59±3.96 | 130.24±23.15 |
| High school | 20.14±5.40 | 16.89±6.00 | 21.33±3.76 | 26.78±4.67 | 26.06±4.09 | 19.81±4.51 | 131.00±21.16 |
| University | 22.03±5.78 | 16.77±5.41 | 21.56±4.58 | 28.50±4.27 | 28.15±4.53 | 19.44±3.51 | 136.44±20.18 |
| P | 0.393 | 0.483 | 0.517 | 0.017* | 0.080 | 0.533 | 0.631 |
| Marital status | | | | | | | |
| Married | 22.05±5.79 | 15.46±4.89 | 22.80±4.48 | 26.41±4.79 | 26.87±4.56 | 19.52±4.00 | 133.11±21.35 |
| Single | 20.51±5.79 | 17.56±5.74 | 19.96±3.91 | 26.58±5.05 | 26.98±4.28 | 19.47±3.92 | 131.04±20.25 |
| Income level | | | | | | | |
| Good | 23.19±5.91 | 17.38±5.02 | 23.23±4.36 | 28.15±4.81 | 28.17±4.44 | 21.02±3.84 | 141.13±20.70 |
| Moderate | 20.83±5.52 | 15.51±4.76 | 21.39±4.39 | 26.14±4.55 | 26.57±4.22 | 19.01±3.82 | 129.46±18.48 |
| Bad | 19.74±5.84 | 14.89±6.95 | 20.11±4.45 | 22.95±4.03 | 24.58±4.44 | 17.05±3.27 | 119.32±21.32 |
| P | 0.027* | 0.081 | 0.013* | <0.001** | 0.007** | <0.001** | <0.001** |

Note. * p < .05. ** p < .01.

**Table 6.** Distribution of Health-Promotion Lifestyle Profile Scores according to Participants' Knowledge, Attitude and Behavior Related to Colorectal Cancer

| Descriptive Characteristics | Sub-scales Scores | | | | | | |
|---|---|---|---|---|---|---|---|
| | Health Responsibility $\bar{x}$ ± SS | Physical Activity $\bar{x}$ ± SS | Nutrition $\bar{x}$ ± SS | Spiritual Growth $\bar{x}$ ± SS | Interpersonal Relationships $\bar{x}$ ± SS | Stress Management $\bar{x}$ ± SS | HPLP Total Score $\bar{x}$ ± SS |
| Knowledge about CRC | | | | | | | |
| Yes | 23.84±5.76 | 17.76±5.22 | 23.24±4.36 | 28.84±4.09 | 28.65±4.45 | 20.68±3.96 | 143.00±20.42 |
| No | 19.80±5.25 | 14.86±4.94 | 20.86±4.35 | 24.63±4.61 | 25.55±3.99 | 18.59±3.74 | 124.29±17.53 |
| P | <0.001** | 0.001** | 0.002** | <0.001** | <0.001** | 0.002** | <0.001** |
| Participation in the CRC early diagnosis/screening programs | | | | | | | |
| Yes | 26.76±3.79 | 17.19±5.09 | 24.57±5.33 | 28.76±4.82 | 28.57±5.46 | 21.62±5.36 | 147.48 |
| No | 20.66±5.64 | 15.94±5.27 | 21.44±4.19 | 26.07±4.82 | 26.61±4.22 | 19.13±3.57 | 129.85 |
| P | <0.001** | 0.316 | 0.003** | 0.018* | 0.063 | 0.008** | <0.001** |
| Willingness to Participation in the CRC early diagnosis/screening programs | | | | | | | |
| Yes | 22.48±5.89 | 15.40±4.94 | 22.27±4.59 | 26.74±4.37 | 27.21±4.76 | 19.63±4.25 | 133.73±20.85 |
| No | 20.59±5.63 | 16.90±5.48 | 21.50±4.39 | 26.17±5.33 | 26.58±4.12 | 19.36±3.67 | 131.12±21.14 |
| P | 0.053 | 0.088 | 0.312 | 0.489 | 0.405 | 0.689 | 0.460 |

Note. * p < .05. ** p < .01

A positive, weak statistically significant correlation was found between HPLP total scores and CCSABS total score, salience and coherence, response efficacy and social influence subscales of patient relatives (p<.01). A positive, weak statistically significant correlation was determined between CCSABS total score and health responsibility, Spiritual growth , interpersonal communication and stress management among the subscales of HPLP scale (p<.01)(Table 7).

**Tablo 7.** Correlation of Colorectal Cancer Screening Attitude and Belief Scale and Health-Promotion Lifestyle Profile Total and Sub-Scales Scores

| Health-Promotion Lifestyle Profile | Colorectal Cancer Screening Attitude and Belief Scale | | | | | | |
|---|---|---|---|---|---|---|---|
| | Salience and Coherence | Perceived Susceptibility | Response Efficacy | Social Influence | Cancer worries | Total Score | Age |
| Total Score | 0.283** | -0.006 | 0.351** | 0.304** | -0.010 | 0.279** | 0.031 |
| Health Responsibility | 0.375** | 0.177* | 0.272** | 0.353** | -0.104 | 0.351** | 0.149 |
| Physical Activity | 0.052 | -0.168* | 0.073 | -0.067 | -0.047 | -0.052 | -0.013 |
| Nutrition | 0.098 | 0.070 | 0.305** | 0.251** | -0.108 | 0.151 | 0.229** |
| Spiritual Growth | 0.279** | 0.013 | 0.427** | 0.228** | 0.100 | 0.281** | -0.146 |
| Interpersonal Relationships | 0.246** | -0.083 | 0.325** | 0.337** | 0.095 | 0.256** | -0.006 |
| Stress Management | 0.298** | -0.034 | 0.233** | 0.250** | 0.024 | 0.235** | -0.010 |
| Age | -0.098 | 0.041 | -0.121 | 0.127 | 0.087 | -0.013 | 1 |

Note. * p < .05. ** p < .01.

## Discussion

### Associations Between Descriptive Characteristics and Colorectal Cancer Screening Attitude and Belief Scale

In Almadi et al's study where they defined many factors affecting the individual's participation in CRC early diagnosis/screening programs, it was reported that having a CRC history in the family was determined as one of the factors affecting the participation in CRC screening programs and the willingness to participate in CRC screening programs; whereas, rate of the willingness to participate in CRC screening tests in people participating in the study was 70% and this rate increased to 83% in those who had CRC history in their family [19]. In the present study, 51.4% of the patient relatives stated that they wanted to participate in early detection/screening programs of CRC. The rate of participation of the society in CRC screening in Turkey varies from 11.9-22.2% [7,20]. It was also determined in the present study similar to the literature that only 14.8% of the individuals stated to participate in CRC screening programs. It was reported in the previous studies that there was a significant difference between the knowledge level about the disease and prevention from disease and participating in CRC screenings [21]. When the result that more than half of the individuals who participated in the present study had no knowledge about CRC was considered, the rate of participation in screenings for the individuals in the present study can be thought to be associated with not having adequate knowledge about the subject.

Gender is evaluated as one of the factors affecting the participation in CRC screening programs [22-24]. In the studies of Larkey et al. and McQueen et al., women were found to have higher rate of participation in CRC screening tests than men [22,23]. Compared to these studies, in a review examining 37 studies conducted in USA, rate of men to participate in screenings was stated to be higher [24]; In the studies of Almadi, Koc and Ait Ouakrim it was found that there was no significant difference between the gender and participation in screenings and willingness to participate in screenings [7,11,19]. In the present study, CCSABS total mean score of the women and the mean scores of the subscales salience and coherence and response efficacy were found significantly high. It was reported that women's level of taking health responsibility was higher and they used health services more [25]. Additionally, it was stated that women benefited more from preventive health services and had more tendency to ask for help in case of illness [26].

It is reported in the literature that there is a significant difference between educational level and the perception that the cancer is a preventable disease. In the present study, CCSABS total mean score and mean score of its subscales in individuals with high educational level were found to be higher. In the studies conducted with first degree relatives of the patients with CRC, no correlation was found between the educational level and the participation in CRC screening programs [7], it was determined in a study conducted by Pollack to investigate the status of the individuals to participate in CRC screening tests that as the educational levels of the participants increased, the rate of participating in the screening programs increased [27]. In their study, McQueen et al., stated that those with higher educational level used screening tests more [23]. When educational level increased, awareness develops in individuals and the individuals with high educational level are thought to consider the behaviours to protect the health more.

In the previous studies, having a high income level was evaluated as one of the factors affecting CRC screening behaviour [23,24]. In the present study, CCSABS total mean score and the mean scores of its subscales were found higher in those who stated their income status as high. Based on the result of the present study, having regular and sufficient income level can be asserted to be important in adoption of behaviours towards health protection.

While having knowledge about the subject is stated to be one of the factors affecting the participation in CRC screening programs [28], a statistically significant difference was found in the present study between the status of having knowledge about CRC and CCSABS total mean score and the mean scores of almost all subscales, which was compatible with the literature. In McCaffery et al.'s study, they report that there was a significant difference between knowledge and participation in CRC screenings and being willing to the participation; whereas, the individuals with low level of knowledge were not willing to participate in screenings and displayed negative attitudes [21]. In another study, the most important factor affecting the participation in CRC screening tests was reported to be the information given by the doctor to the individuals [29]. It could be asserted that having knowledge about the disease creates awareness among individuals and the individuals having knowledge approached more positively to the behaviours towards protecting the health.

It was reported previously that the rate of participation in CRC screening programs in individuals who participated in CRC screening programs [30] and the other cancer screening tests was higher [31]. In the present study, CCSABS total mean score and of

mean scores all subscales except for social influence and cancer worries of the individuals participating in early diagnosis and screening programs of CRC were higher. In a study conducted by Lemon et al., the rates of women, who had mammography, and men, who had prostate specific antigen measurement, to participate in CRC screening programs were higher than those who did not participate in screening programs before [32]. In addition, it was determined that the individuals who participated in CRC screening complied with the doctor's recommendations more, emotional support mean scores of these individuals were higher, and they felt less perceived barrier [29]. It could be asserted that participating in the screening programs affected the individuals' attitudes positively and thus it is important to encourage all individuals in the society starting with the first degree relatives of cancer patients.

According to the preventive health model, one of the most important factors affecting the individual to perform a behaviour is his/her intention to that behaviour. It was found in the present study that CCSABS total mean score and the mean score of most subscales of the scale in individuals expressing that they are willing to participate in screening programs in a way to support the intention understanding of preventive health model were significantly higher.

**Associations Between Descriptive Characteristics and Health Promotion Life-Style Profile**

It was determined that HPLP total mean scores of the individuals participating in the study were 132.46±20.96, mean scores of the subscales Spiritual growth and interpersonal relationships were at moderate level, the mean scores of nutrition, physical activity, heath responsibility, and stress management were below the moderate level. HPLP total mean score was at moderate level in the previous studies similar to the present study; it was determined in a study [33] conducted with the patients diagnosed with cancer that the mean score was 125.43; whereas, it was found as 124.54 in another study conducted with patients with prostate cancer patients [34].

It was determined in the present study that the subscale having the highest score was interpersonal relations (26.90±4.46), the subscale having the lowest score was physical activity (16.13±5.25). Similar to the present study, it was also determined in other studies that the highest score was generally obtained from interpersonal relations and the lowest one was obtained from physical activity [33,34].

There is a reversed correlation between physical activity and colon cancer risk; physical activity reduces the contact time with colon by increasing the passing rate of faeces and carcinogens through large intestine [35]. Therefore, in "Guidelines for Nutrition and Physical Activity" published by ACS in 2003 and updated in 2012, ACS emphasised that physical activity is effective at Evidence I level for the prevention of colon cancer; and suggested at least 150 minutes (2.5 hours) moderate activity or 75 minutes intense activity every week for adults [36]. However, low mean scores of physical activity subscale in individuals in both the present study and in the other related studies revealed that the physical activity habit of the societies is not at sufficient level.

While it was determined in the present study that the women's HPLP total mean score and the mean scores of all subscales were higher compared to men; total mean score of the scale and mean scores of the subscales health responsibility, nutrition, and interpersonal relations were higher in women at a statistically significant level compared to men. Health responsibility mean scores in Karalar's study, health responsibility, interpersonal relations and nutrition mean scores in Johnson's study were found higher among women [33,37]. The results of the present study are in parallel with results of the other study and it is thought that this results is associated with the fact that women can spare more time for interpersonal relations due to the reason that they are generally unemployed, they have more opportunity to participate in health promotion behaviours and to watch health programs, women have more knowledge about nutrition since they mostly take the cooking role in our society.

Being educated is one of the important determinants in making decisions in health subject and turning to positive health behaviours [38]. According to the health development model, a person's tendency in developing health increases when his educational level increases [39]. In the present study, mean score of Spiritual growth from subscales of HPLP was higher and the difference between them was significant.

Previous studies revealed that there was a statistically significant difference between people's marital status and the physical activity and nutrition subscales [37]. Physical activity mean scores of the single individuals and nutrition subscale mean scores of married ones were higher in the present study. Having less responsibilities, opportunities to spare more time for physical activity, being able to afford sports activities may be effective on high physical activity scores for single individuals. On the other hand, as a result of being a family, always having dinner at home may provide contribution for the formation of a regular dietary habits and thus to nutrition mean scores of the married individuals.

In the present study, patient relatives who stated their income level as high had higher score from HPLP total score and from all subscales of the scale and the obtained result was statistically significant in all subscales except for physical activity. In the study conducted by Gök Ugur, it was determined that interpersonal relations, nutrition and HPLP total mean scores were higher in those having equal income and expense than those who had an income less than expense; in Al-Qahtani's study, nutrition subscale mean score was higher in those with high income; and in the study of Topcu, self-realisation, stress coping, interpersonal support mean scores and HPLP total mean scores were higher in those with good income [40,41]. It is also reported that those with a high income have better health promotion behaviours and the economic level is an important factor affecting HPLP [42]. As in other studies, it is also seen from the present study that economic level was effective on people's health promotion behaviours and their healthy lifestyle behaviours increased with increased economic level.

Having knowledge and participation in trainings towards health promotion are one of the factors affecting HPLP. In a study conducted with women in cancer screening centre; healthy lifestyle behaviours of people who were aware of early diagnosis methods of breast and cervical cancer were higher [40]. With effective training techniques, individual's knowledge about healthy life style increases and enables them to take action to apply these behaviours. The result of the present study support the literature, HPLP total mean score and mean scores of all subscales were high at a statistically significant level in those who had knowledge about CRC.

While a significant difference was found between dietary habits and exercise and participation in colonoscopy in one of two studies conducted with first degree relatives of CRC patients [7]. In the present study, HPLP total mean scores and mean scores of all subscales were high in individuals participating in early diagnosis/screening programs of colorectal cancer, this difference was statistically significant in the subscales except for physical activity and interpersonal relations.

**Correlation Between Colorectal Cancer Screening Attitude and Belief Scale and Health Promotion Life-Style Profile**

In the present study, a positive, weak statistically significant correlation was determined between HPLP total mean score and CCSABS total mean score and the mean scores of salience and coherence, response efficacy, and social influence the subscales of CCSABS. Level of the individuals displaying healthy life style behaviours to participate in CRC screening programs was higher in previous studies [7,43]. Compatible with the literature, the results of the present study showed that these two behaviours towards health promotion and prevention are factors affecting each other.

In the study conducted by Koc et al.'s with first degree relatives of CRC patients, it was found that the rate of participation in colonoscopy was higher in individuals in regular physical activity [7]. It was determined in Shapiro et al.'s study that people making regular physical activity participated in CRC screening tests 1.5 times more than the ones with no physical activity [43]. In contrast to the studies in literature, no significant correlation was found between physical activity subscale from HPLP and the total score of CCSABS in the present study. It is reported that 87% of women and 77% of men do not do enough physical activity in Turkey. This result of the present study is in parallel with the country-wide and showed that the physical activity, an important prevention behaviour, was not regarded by sample group of the present study.

In the present study, a positive, weak and statistically significant correlation was found between nutrition a subscale of HPLP and the subscales response efficacy and social influence of CCSABS and age. While no significant difference was found between nutrition and willingness to participate in CRC screening in Almadi et al.'s study; in the study conducted by Koc et al. with first degree relatives of CRC patients, they found a statistically significant difference between nutrition and participation in colonoscopy and they found higher participation rate to the colonoscopy among those with a good and balanced diet [7,19].

Taking responsibility for an individual's own well-being, diligence to his/her health, and benefiting from health services are included in the scope of health responsibility [13]. It was determined in previous studies that the individuals benefiting from health prevention services participated in screening programs more and participation rates of the individuals who have participated in CRC and different cancer screening programs before were higher for CRC screening programs [43,44]. As expected, in the present study a positive statistically significant correlation was found between health responsibility and CCSABS and almost all subscales of the scale. It could be asserted that the individuals participating in the present study undervalued health responsibility subscale from HPLP and they reflected this responsibility to their behaviours.

"Interpersonal relations" subscale of healthy lifestyle behaviour scale is also expressed as an interpersonal support and it is an

important phenomenon that can be obtained as a result of bilateral or group relationships of individuals and effective on improving health [45]. In the present study, a positive statistically significant correlation was determined between interpersonal relations and CCSABS total mean score, and mean scores of salience and coherence, response efficacy, social influence among the subscales of CCSABS scale. In a study conducted by Allen et al. a positive correlation was found between having social support and mammography and participating in clinical breast examination, the individuals feeling more social support were reported to have higher participation rates for screenings [46]. In a socio-ecological study examining the factors affecting the participation to CRC screenings, the relatives of the patients with CRC talking about CRC screenings with people living in social environment (family members, friends, colleagues) were stated to have higher rates of participation in CRC screenings [47].

It is also stated in studies that parameters related to mood are also one of the factors affecting the participation in cancer screenings. Andersen et al. reported that individuals feeling themselves at risk in terms of cancer had better healthy lifestyle behaviours compared to the general population [48]. In Watts et al.'s study, rates of willingness and participation in screening programs were found to be higher among people with high cancer risk perception [49]. However, in Greiner et al.'s study, disease and screening fear were considered as a barrier by the individuals and determined to affect the participation in screening negatively [50]. As seen in the studies, anxiety affects the participation of the individuals in screening differently. Anxiety felt in moderate level increases women's rate of participation to mammography screening but high level of anxiety are reported to decrease rate of participation in screenings [48,50]. In the present study, a positive statistically significant relationship was determined between stress management and salience and coherence, response efficacy and social influence mean scores. This result leads to think that when stress level of the relatives of the patients diagnosed with cancer decreases, their point of view to cancer screening and their rate of participation in these screenings will develop.

## Conclusion

It was found that CCSABS and HPLP of first degree relatives of the patients with colorectal cancer were at moderate level and their rate of participation in CRC screening was at low level. In addition, there was a positive weak correlation between CCSABS and HPLP.

In this study, we wanted to emphasize that it is important to raise awareness about that both cancer patients and their relatives require consultancy among the nurses working in surgical clinics which are clinics where almost all of the cancer patients are treated firstly. Therefore, nurses working in surgical clinics that are the clinics where cancer patients are admitted due to operation should plan and apply trainings about prevention from cancer and early diagnosis/screening programs of cancer to the patients and their relatives and should evaluate their results.

## Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

## References

1. American Cancer Society. Cancer facts & figures 2016. American Cancer Society, Atlanta, 2016: 66.
2. American Cancer Society. Colorectal cancer facts & figures 2014-2016. American Cancer Society, Atlanta, 2014: 28.
3. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins from Sweden, Denmark, and Finland. Eng J Med N 2000; 343:78-85.
4. Lowery JT, Marcus A, Kinney A, Bowen D, Finkelstein DM, Horick N, et al. The Family Health Promotion Project (FHPP): design and baseline data from a randomized trial to increase colonoscopy screening in high risk families. Contemp Clin Trials 2012; 33: 426-35.
5. Johnson CM, Wei C, Ensor JE, Smolenski DJ, Amos CI, Levin B, et al. Meta-analyses of colorectal cancer risk factors. Cancer Causes Control 2013; 24: 1207-22.
6. National Cancer Intelligence Network. Colorectal cancer survival by stage. http://www.ncin.org.uk/publications/data_briefings/colorectal_cancer_survival_by_stage (11.06.16).
7. Koc S, Esin MN. Screening behaviors, health beliefs, and related factors of first-degree relatives of colorectal cancer patients with ongoing treatment in Turkey. Cancer Nursing 2014; 37: 51-60.
8. Kanbur A, Capik C. Cervical cancer prevention, early diagnosis-screening methods and midwives/nurses role. Hacettepe University Faculty of Health Sciences Nursing Journal 2011; 18: 61-72.
9. Bozhüyük A, Ozcan S, Kurdak H, Akpinar E, Saatci E, Bozdemir N. Healthy life style and family medicine. Turkish Journal of Family Medicine and Primary Care 2012; 6: 13-21.
10. Cole SR, Zajac I, Gregory T, Mehaffey S, Roosa N, Turnbull D, et al. Psychosocial variables associated with colorectal cancer screening in South Australia. International Journal of Behavioral Medicine 2011; 18: 302-9.

11. Ait Ouakrim D, Lockett T, Boussioutas A, Keogh L, Flander LB, Hopper JL, et al. Screening participation predictors for people at familial risk of colorectal cancer: A systematic review. American Journal of Preventive Medicine 2013; 44: 496-506.
12. Pender NJ, Walker SN, Sechrist KR. The Health-Promoting Lifestyle Profile: Development and psychometric characteristics. Nursing Research 1987; 36: 76-81.
13. Bahar Z, Beser A, Gördes N, Ersin F, Kissal A. Healthy life style behavior scale II: A reliability and validity study. Cumhuriyet University School of Nursing Journal 2008; 12: 1-13.
14. Romaguera D, Vergnaud AC, Peeters PH, van Gils CH, Chan DS, Ferrari P, et al. Is concordance with World Cancer Research Fund/ American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. Am J Clin Nutr 2012; 96: 150-163.
15. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002; 5: 1113-24.
16. Yarbro CH, Wujcik D, Gobel BH. Cancer Nursing: Principles and Practice, 7 nd ed, Sudbury, Jones and Bardlett publ, 2011: 1931.
17. Tiro AJ, Vernon WS, Hyslop T, Myers RE. Factorial validity and invariance of a survey measuring psychosocial correlates of colorectal cancer screening among African Americans and Caucasians. Cancer Epidemiology, Biomarkers & Prevention 2005; 14: 2855-61.
18. Walker SN, Hill-Polerecky DM. Psychometric evaluation of the Health Promoting Lifestyle Profile II. Unpublished manuscript, University of Nebraska Medical Center.
19. Almadi MA, Mosli MH, Bohlega MS, Al Essa MA, AlDohan MS, Alabdallatif TA, et al. Effect of public knowledge, attitudes, and behavior on willingness to undergo colorectal cancer screening using the Health Belief Model. The Saudi Journal of Gastroenterology 2015; 21: 71-7.
20. Sahin NS, Üner BA, Aydın M, et al. Knowledge of, attitudes toward, and barriers to participation of colorectal cancer screening in Aydın central region. Turkish Journal of Family Practice 2015; 19: 37-48.
21. McCaffery K, Wardle J, Nadel M, Atkin W. Socioeconomic variation in participation in colorectal cancer screening. J Med Screen 2002; 9: 104-8.
22. Larkey LK, McClain D, Roe DJ, Hector RD, Lopez AM, Sillanpaa B, et al. Randomized controlled trial of storytelling compared to a personal risk tool intervention on colorectal cancer screening in low-income patients. Am J Health Promot 2015; 30: 59-70.
23. McQueen A, Vernon SW, Meissner HI, Klabunde CN, Rakowski W. Are there gender differences in colorectal cancer test use prevalence and correlates? Cancer Epidemiol Biomarkers Prev 2006; 15: 782-91.
24. Beydoun HA, Beydoun MA. Predictors of CRC screening behaviors among average-risk older adults in the United States. Cancer Causes Control 2008; 19: 339-59.
25. Erdem R, Pirincci E. Health services utilization and the factors that influence on the utilization. OMU Medical Journal 2003; 20: 39-46.
26. Redondo-Sendino A, Guallar-Castillón P, Banegas RM, Rodríguez-Artalejo F. Gender differences in the utilization of health-care services among the older adult population of Spain. BMC Public Health 2006; 6: 2-9.
27. Pollack LA, Blackman DK, Wilson KM, Seeff LC, Nadel MR. Colorectal cancer test use among Hispanic and non-Hispanic U.S. populations. Prev Chronic Dis 2006; 3: 1-12.
28. Qumseya BJ, Tayem YI, Dasa OY, Nahhal KW, Abu–Limon IM, Hmidat AM, et al. Barriers to colorectal cancer screening in Palestine: A national study in a medically underserved population. Clin Gastroenterol Hepatol 2014; 12: 463-69.
29. Taouqi M, Ingrand I, Beauchant M, Migeot V, Ingrand P. Determinants of participation in colonoscopic screening by siblings of colorectal cancer patients in France. BMC Cancer 2010; 10: 1-10.
30. Sheikh RA, Kapre S, Calof OM, Ward C, Raina A. Screening preferences for colorectal cancer: a patient demographic study. South Med J 2004; 97: 224-30.
31. Christman LK, Abdulla R, Jacobsen PB, Cantor AB, Mayhew DY, Thompson KS, et al. Colorectal cancer screening among a sample of community health center attendees. Health Care Poor Underserved 2004; 15: 281-93.
32. Lemon S, Zapka J, Puleo E, Luckmann R, Chasan-Taber L. Colorectal cancer screening participation: comparisons with mammography and prostate-specific antigen screening. Am J Publ Health 2001; 91: 1264-72.
33. Karalar UY. Defining healthy lifestyle behaviors and variables in patient with cancer diagnosis. Master's thesis, Istanbul University, Institute of Health Science, Internal Medicine Nursing Department, Istanbul 2010: 84.
34. Ardahan M, Temel Bayik A. The relationship between quality of life and healthy life style behavior in patients with prostate cancer Ege University School of Nursing Journal 2006; 22: 1-14.
35. Demark-Wahnefried W, Rock CL, Patrick K, Byers T. Lifestyle interventions to reduce cancer risk and improve outcomes. Am Fam Physician 2008; 77: 1573-78.

36. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention. http://www.cancer.org/acs/groups/cid/documents/webcontent/002577-pdf.pdf (13.07.2016).
37. Johnson RL. Gender differences in health-promoting lifestyles of African Americans. Public Health Nursing 2005; 22: 130-7.
38. Topcu S. Evaluation of health promotion behavior of immigrant and migrant women. Master's thesis, Dokuz Eylül University, Institute of Health Science, Izmir 2006: 82.
39. Kücükberber N, Özdilli K, Yorulmaz H. Evaluation of factors affecting healthy life style behaviors and quality of life in patients with heart disease. Anatol J Cardiol 2011; 11: 619-26.
40. Gök Ugur H. Determination of the effect of attitudes of women who applied the cancer inspection center toward health issues on early diagnosis knowledge and implementations. Master's thesis, On Dokuz Mayıs University, Institute of Health Science, Samsun 2009:121.
41. Al-Qahtani MF. Health-promoting lifestyle behaviors among nurses in private hospitals in Al-Khobar, Saudi Arabia. J Egypt Public Health Assoc. 2015; 90: 29-34.
42. Mirghafourvand M, Sehhati F, Rahimi M. Health-promoting lifestyle and its demographic predictors in infertile couples referred to infertility clinic of Tabriz Al-Zahra Hospital, 2013. J Caring Sci 2014; 3: 175-84.
43. Shapiro JA, Seeff LC, Nadel MR. Colorectal cancer-screening tests and associated health behaviors. Am J Prev Med 2001; 21: 132-7.
44. Griffith KA, McGuire DB, Royak-Schaler R, Plowden KO, Steinberger EK. Influence of family history and preventive health behaviors on colorectal cancer screening in African Americans. Cancer 2008; 113: 276-85.
45. Esin MN. Turkish adaptation of healthy lifestyle behaviors scale. Nursing Bulletin 1999; 12: 87-96.
46. Allen JD, Sorensen G, Stoddard AM, Peterson KE, Colditz G. The relationship between social network characteristics and breast cancer screening practices among employed women. Ann Behav Med 1999; 21: 193-200.
47. Madlensky L, Esplen MJ, Gallinger S, McLaughlin JR, Goel V. Relatives of colorectal cancer patients: factors associated with screening behavior. Am J Prev Med 2003; 25: 187-94.
48. Andersen MR, Smith R, Meischke H, Bowen D, Urban N. Breast cancer worry and mammography use by women with and without a family history in a population-based sample. Cancer Epidemiol Biomarkers Prev 2003; 12: 314-20.
49. Watts BG, Vernon SW, Myers RE, Tilley BC. Intention to be screened over time for colorectal cancer in male automotive workers. Cancer Epidemiol Biomarkers Prev 2003; 12: 339-49.
50. Greiner KA, Born W, Nollen N, Ahluwalia JS. Knowledge and perceptions of colorectal cancer screening among urban African Americans. J Gen Intern Med 2005; 20: 977-83.

To cite this article: Dayangan Sayan C, Sagsoz N, Ozkan ZS, Yeral MI, Tursun S. Comparison of regional neural tube defects with healthy pregnancies. Turk J Clin Lab 2018; 9(1): 50-54.

Orjinal Makale

# Bölgesel nöral tüp defektli gebelerin sağlıklı gebelerle karşılaştırılması

# *Comparison of regional neural tube defects with healthy pregnancies*

Cemile DAYANGAN SAYAN*[1], Nevin SAĞSÖZ[1], Zehra Sema ÖZKAN[1], Mahmut İlkin YERAL[1], Serkan TURSUN[2]

[1]Kırıkkale Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum ABD, Kırıkkale
[2]Kırıkkale Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları ABD, Kırıkkale, TÜRKİYE

## ÖZ

**Amaç:** Nöral tüp defektleri (NTD) nöral tüpün bir bölümünün kapanmasında meydana gelen kusur sonucu ortaya çıkan ve sık görülen konjenital anomalilerdir. Dünya çapında her yıl yaklaşık 300.000 bebek NTD ile doğmaktadır ve NTD konjenital anomalilerle ilişkili neonatal ölümlerin yaklaşık olarak %29'undan sorumlu tutulmaktadır. Bu çalışmada Kırıkkale ilinde 2014-2017 yılları arasında saptanan NTD'li gebeler ile sağlıklı gebelerin demografik özellikleri ve laboratuar bulgularını karşılaştırmayı amaçladık.

**Gereç ve Yöntemler:** Bu retrospektif çalışmaya NTD'i tanısı almış 27 olgu ve 30 sağlıklı gebe dahil edildi. Olguların demografik verileri ve laboratuvar değerleri kayıtlardan tarandı ve kaydedildi. Bulgular NTD'li ve sağlıklı gebelik grupları arasında karşılaştırıldı.

**Bulgular:** NTD'li hastaların 15 tanesi meningomyelosel, 4 tanesi anensefali, 2 tanesi ensefalosel, 2 tanesi eksensefali, 2 tanesi anensefali+ensefalosel, 1 tanesi meningomyelosel+ensefalosel ve 1 tanesi de myeloşizis tanılı idi. NTD grubunun ortalama vücut kitle indeksi kontrol grubuna göre anlamlı olarak yüksekti. Gruplar arasında laboratuvar parametreleri açısından istatistiksel olarak anlamlı bir fark yoktu.

**Sonuç:** Kırıkkale ilinde NTD'li ve sağlıklı gebeleri karşılaştırdığımız çalışmamızda NTD grubunda VKİ'nin kontrol grubuna göre anlamlı daha yüksek olduğunu tespit ettik. Çok merkezli ve artmış popülasyonla yapılacak yeni çalışmalar, Türk toplumunda NTD risklerini ayrıntılı olarak belirlemek açısından faydalı olacaktır.

**Anahtar Kelimeler:** Nöral tüp defekti, gebelik, konjenital anomali

Sorumlu Yazar*: Cemile Dayangan Sayan, Kırıkkale Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum ABD, Kırıkkale, TÜRKİYE
Tel: +905056755247
E-Posta: c.dayangan-sayan@hotmail.com
Recevied 07.02.2018 accepted 11.02.2018
Doi: 10.18663/tjcl.391392

Volume 9 Number 1 p: 50-54


## ABSTRACT

**Aim:** Neural tube defects (NTD) are congenital anomalies that occur as a result of a defect in the closure of a part of the neural tube. Worldwide, approximately 300,000 babies are born with NTD each year, and NTD is responsible for approximately 29% of neonatal deaths associated with congenital anomalies. In this study, we aimed to compare the demographic characteristics and laboratory findings of healthy pregnants with those of NTD in Kırıkkale province between 2014-2017.

**Material and Methods:** This retrospective study included 27 cases with NTD diagnosis and 30 healthy pregnant women. The demographic data and laboratory values of the cases were recorded from the computer records. Findings were compared between NTD and healthy pregnancy groups.

**Results:** Of the NTD patients, 15 were meningomyelocele, 4 were anencephaly, 2 were encephalocele, 2 were exencephaly, 2 were anencephaly + encephalocele, 1 was meningomyelocele + encephalocele and 1 was myeloschisis. The mean body mass index of the NTD group was significantly higher than the control group. There was no statistically significant difference between groups in terms of laboratory parameters.

**Conclusion:** In our study comparing NTD and healthy pregnancies in Kırıkkale province, we found that NTD group had significantly higher body mass index than control group. New studies with multi-centered and increased populations will be useful in detailing NTD risks in Turkish society.


**Keywords:** Neural tube defect, pregnancy, congenital anomaly

## Giriş

Nöral tüp defektleri (NTD) nöral tüpün bir bölümünün kapanmasında meydana gelen kusur sonucu ortaya çıkan ve sık görülen konjenital anomalilerdir [1]. Söz konusu olan bu kapanma defekti genellikle fertilizasyondan sonraki üç ve dördüncü haftalarda yani kişinin henüz gebe olduğunu bilmediği dönemde gerçekleşir. Defekt nöral tübün vertebra, spinal kord, kranium ve/veya beyin gibi herhangi bir kısmını içerebilir [2]. Defekt izole bir malformasyon olarak karşımıza çıkabileceği gibi diğer malformasyonlarla kombine olarak ya da genetik bir sendromun bir parçası olarak da görülebilir [3]. NTD kardiyak malformasyonlardan sonra ikinci en sık görülen konjenital anomalilerdir. Prevelansı coğrafik bölgelere ve çevresel faktörlere göre değişiklik gösterir [4]. Dünya çapında her yıl yaklaşık 300.000 bebek NTD ile doğmaktadır ve NTD konjenital anomalilerle ilişkili neonatal ölümlerin yaklaşık olarak %29'undan sorumlu tutulmaktadır [5]. 2016'da yapılan bir derlemeye göre NTD prevelansı Doğu Akdeniz'de 10.000 doğumda 21,9 iken, Avrupa'da 10.000 doğumda 9,0 ve Amerika'da ise 10.000 doğumda 5,3 olarak bildirilmiştir [4].

Sendromik olmayan NTD'nin etiyolojisi multifaktöriyel düşünülmekte olup; genetik ve çevresel faktörlerin ortak etkileri sonucu geliştikleri kabul edilmektedir . Aile hikayesi, kromozomal anormallik ya da tek gen hastalığı gibi genetik kusurlar, etnik ve coğrafi faktörler, maternal medikal hastalıklar, çeşitli medikasyonlar ve çevresel faktörler NTD ile ilişkilendirilmiştir [2]. NTD'li gebelik hikayesi, maternal ya da paternal NTD varlığı, folik asit eksikliği, pregestasyonel diyabet, maternal hipertermi, valproik asit gibi yüksek riskli antiepileptik kullanımı, radyasyon maruziyeti ve sigara NTD için belirtilen risk faktörlerinin önemli olanlarıdır [6]. Ayrıca düşük sosyoekonomik düzeye sahip toplumlarda NTD sıklığının arttığı bildirilmiştir [7].

NTD'li fetusa sahip olan bir gebeliğin antenatal takibi, yenidoğan bakımı ve etkilenmiş çocuğun uzun dönem bakımı önem arz eder. Her ne kadar NTD'nin ağır formları intrauterin dönemde veya doğumdan hemen sonra ölümle sonuçlansa da yaşamla bağdaşabilen meningomyelosel gibi olgulara yeterli bakım verildiği taktirde bunların %75'inin erken gençlik yaşlarına ulaşabildiği bilinmektedir [8]. Ancak bu hastaları uzun dönemde ciddi nörolojik, ortopedik ve ürolojik sekeller beklemektedir ve yaşam boyu sağlık giderleri önemli mali yüke sebep olmaktadır [9].

Bu çalışmada Kırıkkale ilinde 2014-2017 yılları arasında saptanan NTD'li gebeler ile sağlıklı gebelerin demografik özellikleri ve laboratuar bulgularını karşılaştırmayı amaçladık.

## Gereç ve Yöntem

Bu retrospektif çalışmaya 2014 ile 2017 yılları arasında Kırıkkale Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı'nda rutin antenatal takip sırasında saptanmış ya da ikinci basamak dış merkezlerden refere edilerek takibe alınmış NTD'li 27 olgu (NTD grubu) ile antenatal takipleri aynı klinikte devam etmiş ve sağlıklı bebek doğumu ile sonuçlanmış 30 sağlıklı gebe (kontrol grubu) dahil edildi. Gruplar gebelik haftaları açısından denkleştirildi. Yaş, vücut kütle indeksi (VKİ), gravida, parite, eğitim düzeyi, gebelik haftası, maternal medikal hastalık varlığı, kronik ilaç kullanım öyküsü, NTD'nin lokalizasyonu ve kesin tanısı, gebelik öncesi ve gebelikte folik asit kullanımı, önceki gebelikte NTD öyküsü, maternal ya da paternal NTD öyküsü, gebeliğin ilk trimesterinde ateşli hastalık geçirme öyküsü, sigara kullanımı, hemoglobin (Hb), beyaz küre (WBC), açlık kan şekeri (AKŞ) ve tiroid stimülan hormon (TSH) değerleri kayıtlardan tarandı ve kaydedildi.

Veriler SPSS 16.0 (USA) programı kullanılarak bilgisayar ortamına aktarıldı ve istatistiki değerlendirme yapıldı. Sürekli değişkenler ortanca (minimum–maksimum) veya ortalama ±standart sapma olarak belirtilirken; kategorik değişkenler sayı ve yüzde olarak sunuldu. Gruplar arası verilerin karşılaştırılmasında; sürekli değişkenlerin dağılım özelliğine göre Student t test veya Mann Whitney-U testi kullanılırken, kategorik verilerde ise Ki-kare testi kullanıldı. P<0,05 değeri istatistiki olarak anlamlı kabul edildi.

## Bulgular

NTD grubu kendi içinde incelendiğinde hastaların 15 tanesi meningomyelosel, 4 tanesi anensefali, 2 tanesi ensefalosel, 2 tanesi eksensefali, 2 tanesi anensefali+ensefalosel, 1 tanesi meningomyelosel+ensefalosel ve 1 tanesi de myeloşizis tanılı idi. İki fetal meningomyelosel tanılı gebe dışında geri kalan tüm vakalara tıbbi tahliye işlemi uygulandı. Gebeliğin devamını isteyen iki olgunun birinde 37. gebelik haftasında kliniğimizde 7/9 APGAR skorlu, 3200 gram ağırlığında, canlı bir fetüs doğumu gerçekleşti (Tablo 1).

**Tablo 1.** Nöral tüp defekti paternleri

| | Sayı | Yüzde % |
|---|---|---|
| Meningomyelosel | 15 | 55.6 |
| Anensefali | 4 | 14.8 |
| Eksensefali | 2 | 7.4 |
| Ensefalosel | 2 | 7.4 |
| Anensefali-Ensefalosel | 2 | 7.4 |
| Meningomyelosel+Ensefalosel | 1 | 3.7 |
| Myeloşizis | 1 | 3.7 |

Grupların demografik verilerinin karşılaştırılması Tablo-2' de gösterilmiştir. NTD grubunun ortalama yaşı 27,6 yıl iken kontrol grubunun ortalama yaşı 26,8 yıl idi. VKİ ortalaması NTD grubu için 27,6 kg/m2 iken kontrol grubunda 23,5 kg/m2 olarak hesaplandı. NTD grubunun ortalama VKİ kontrol grubuna göre anlamlı olarak yüksekti (p=0.014). NTD grubundaki hastaların % 29,6'sı ilköğretim, % 55,6'sı lise, %14,8'i üniversite mezunu iken kontrol grubundaki hastaların % 33,3'ü ilköğretim, % 46,7'si lise, %20'si üniversite mezunu idi. NTD grubunda hastalardan bir tanesinde daha önce NTD' li gebelik öyküsü mevcut iken iki tanesinde de gebeliğinin ilk üç ayında üriner sistem enfeksiyonuna bağlı yüksek ateş ve hastaneye yatış öyküsü mevcut idi. NTD grubunun %14,8'inde sigara tüketimi mevcut iken kontrol grubunda bu oran % 10 idi. Her iki grupta da konsepsiyon öncesi folik asit kullanımı bulunmamaktaydı. Konsepsiyon sonrası folik asit kullanma süresi ortalama olarak NTD grubu ve kontrol grubu için sırası ile 3,7 ve 4,1 hafta idi. Gruplar arasında yaş, gravida, parite, gebelik haftası, eğitim düzeyi, konsepsiyon sonrası folik asit kullanımı, NTD öyküsü, gebeliğin ilk üç ayında ateşli hastalık öyküsü ve sigara kullanımı açısından istatistiki açıdan anlamlı bir fark saptanmadı (p<0,05) (Tablo 2).

**Tablo 2.** Grupların demografik özelliklerinin karşılaştırılması

| | NTD grubu (N:27) | Kontrol grubu (N:30) | p değeri |
|---|---|---|---|
| Yaş (yıl) | 27.6±6.6 | 26.8±6.8 | 0,614 |
| Gravida | 2.5 (1-6) | 2.2 (1-4) | 0,660 |
| Parite | 1.2 (0-4) | 1 (0-3) | 0,507 |
| Kilo (kg) | 70.1±15.6 | 68.4±11.5 | 0,491 |
| BMI (kg/boy2) | 27.6±5.1 | 23.5±2.7 | 0,014 |
| Gebelik Haftası | 16.4±2.5 | 16.3±2.5 | 0,860 |
| Eğitim düzeyi<br>• İlköğretim (%)<br>• Lise (%)<br>• Üniversite (%) | <br>8 ( %29.6)<br>15 (%55.6)<br>4 (14.8) | <br>10 (%33.3)<br>14 (%46.7)<br>6 (%20.0) | 0,779 |
| Konsepsiyon sonrası folik asit kullanımı (hafta) | 3.7±2.0 | 4.1±2.2 | 0.783 |
| NTD öyküsü varlığı (%) | 1 (%3.7) | 0 (%0) | 0.474 |
| Sigara kullanımı(%) | 4 (%14.8) | 3 (%10.0) | 0.589 |
| Maternal hipertermi öyküsü varlığı (%) | 2 (% 7.4) | 0 (%0) | 0.476 |

Veriler ortalama ± standart sapma olarak, ortanca (minimum–maksimum) ve yüzde olarak verilmiştir. Sayısal değerler için Mann-Whitney U testi, kategorik veriler için Kİ-kare testi uygulanmıştır.

Laboratuvar parametreleri açısından gruplar karşılaştırıldığında (Tablo 3), NTD grubunda ortalama Hb düzeyi 11,8 g/dL, ortalama WBC düzeyi 10,2x 103/µL, ortalama açlık kan şekeri düzeyi 92,5 mg/dL ve ortalama TSH düzeyi 1,6 µU/mL iken; kontrol grubunda bu parametre düzeyleri sırası ile 11,6 g/dL, 9,9 x103/µL, 89,6 mg/dL ve 1,9 µU/mL idi. Gruplar arasında laboratuvar parametreleri açısından istatistiksel olarak anlamlı bir fark yoktu (p<0.05).

**Tablo 3.** Grupların laboratuvar parametrelerinin karşılaştırılması

| | NTD grubu (N:27) ortalama±SD | Kontrol grubu (N:30) ortalama±SD | p değeri |
|---|---|---|---|
| Hb (g/dl) | 11.8±0.8 | 11.6 ±0.9 | 0.543 |
| WBC (103/µl) | 10.2±2.5 | 9.9±2.5 | 0.695 |
| AKŞ (mg/dl) | 92.5±15.3 | 89.6±12.3 | 0.879 |
| TSH (µU/ml) | 1.6±0.8 | 1.9±1.0 | 0.725 |

Veriler ortalama ± standart sapma olarak verilmiştir. Mann-Whitney U testi uygulanmıştır.

## Tartışma

Çalışmamızda 2014 ile 2017 yılları arasında kliniğimizde tanı konmuş ya da dış merkezden refere edilmiş 27 NTD'li gebe ile 30 sağlıklı gebe demografik veriler ve laboratuvar bulguları açısından karşılaştırıldı. Gruplar arasında demografik veriler açısından istatistiki anlamlı bir fark gözlenmedi. Sadece NTD'li olguların ortalama VKİ kontrol grubuna göre anlamlı olarak

daha yüksek idi. Gruplar arasında Hb, WBC, AKŞ, TSH değerleri açısından anlamlı fark gözlenmemiştir.

NTD genel olarak kraniyal ve spinal olmak üzere iki gruba ayrılır. Kraniyal NTD anensefali, eksensefali, ensefalosel ve inensefali olarak sınıflanırken; spinal NTD ise spina bifida, meningosel, meningomyelosel, myeloşizis, holoraşisisiz, kraniyoraşisisiz olarak sınıflandırılır [2]. Fakat daha sıklıkla NTD açık ya da kapalı defektler olarak sınıflandırılır [4]. Olguların % 80'ini açık NTD olan meningomyelosel, meningosel, ensefalosel ve anensefali oluşturur [2]. Zaganjor ve ark. [4] yakın zamanda yaptıkları derlemede 160 adet çalışmayı incelemişler ve olguların % 2'sinde tek başına spina bifida, % 10'unda spina bifida+anensefali, %1'inde spina bifida+ ensefalosel ve %81'inde ise spina bifida+ensefalosel+anens efalinin birlikte olduğunu bildirmişlerdir. Ayriyeten vakaların % 6'sında tam tanımlamanın yapılamadığını kaydetmişlerdir. Bizim olgularımızda da literatür ile uyumlu olarak vakalarımızın tamamını açık NTD oluşturmakta ve bunların arasında da en sık meningomyelosel olguları yer almakta idi.

NTD'nde maternal yaşın etkisi araştırıldığında literatürde sınırlı sayıda çalışmaya rastlanmaktadır. Frey ve arkadaşları yaptıkları çalışmada maternal yaşın NTD riski üzerinde etkisinin oldukça zayıf olmakla birlikte ileri yaş ve çok genç yaşın NTD risk artışıyla birlikte olabileceğini bildirmişlerdir [10]. Ancak Unusan ve ark. [11] yaptıkları çalışmada folik asit takviyesinin NTD'ni önlemedeki rolünün Türk kadınlarındaki farkındalığını araştırmışlar ve bu farkındalığın en çok 26 ve 35 yaş arasında arttığını bildirmişlerdir. Bu yaş grubundaki artmış farkındalığa bağlı folik asit kullanımı NTD insidansını azaltıyor olabilir. Materna-Kiryluk ve ark. [12] yaptıkları çalışmada genç anne yaşının NTD riskinde bir miktar artışa neden olduğunu bildirmişlerdir. Yavuzcan ve ark. [13] Düzce ilindeki NTD'ni inceledikleri çalışmalarında NTD ile anne yaşı arasında bir ilişki bulmadıklarını belirtmişlerdir. Biz de çalışmamızda NTD'li grup ile kontrol grubu arasında maternal yaş açısından anlamlı bir fark gözlemedik. Maternal yaş arttığında kromozomal anomali sıklığının arttığı düşünüldüğünde, maternal yaşın ileri olduğu NTD vakalarının sendromik NTD olabileceğini düşünmekteyiz.

NTD risk faktörleri incelendiğinde maternal obezitenin NTD riskini arttırdığına dair kanıtlar mevcuttur. VKİ ile NTD arasında pozitif kolerasyon bildirilmiştir [14]. Rasmussen ve ark. [15] yaptıkları derlemede, normal kilolu kadınlarla kıyaslandığında NTD riskinin obez kadınlarda 1,7 kat ve morbid obez kadınlarda ise 3,1 kat artış gösterdiğini bildirmişlerdir. Liu ve ark. [16] yaptıkları retrospektif bir çalışmada ise NTD'nin rekürrens risk faktörlerini incelemişler ve tekrarlayan NTD olgularının VKİ'nin ilk kez NTD tanısı alan gruba göre anlamlı olarak yüksek olduğunu saptamışlardır. Biz de bu çalışmalara benzer olarak NTD' li grupta VKİ değerlerinin kontrol grubuna göre anlamlı derecede yüksek olduğunu tespit ettik.

NTD'nin etiyolojisinde genetik faktörlerin rol oynadığına dair önemli kanıtlardan biri de NTD'li olgularda NTD açısından pozitif aile hikayesinin risk artışına yol açtığının bilinmesidir. Bir kez NTD'li doğum öyküsü olan çiftlerin ikinci çocuğunda NTD rekürrens riski artmıştır [17]. Bir NTD'li çocuk doğurma öyküsünden sonra, NTD'li çocuk doğurma riski %3,2 iken, iki NTD'li çocuk doğurma öyküsünden sonra bu risk %10'a kadar çıkmaktadır [18]. Biz çalışmamızda NTD grubunun özgeçmişini incelediğimizde yalnızca bir olguda NTD'li çocuk doğurma öyküsü olduğunu tespit ettik. Soygeçmişte NTD varlığı açısından gruplar arasında anlamlı bir fark tespit etmedik.

Gebeliğin ilk trimesterinde maternal ateşli hastalık öyküsünün NTD gelişim riskini yaklaşık üç kat arttırdığı bildirilmiştir [9]. Duong ve ark. [20] sıcak küvet ve/veya sauna kullanımı sonucu birinci trimesterde hipertermiye tekrarlayan ve uzun süreli maruziyetin doğumsal defektleri özellikle de anensefali gelişim riskini 1,7 kat arttırdığını bildirmişlerdir. Biz olgularımızı maternal hipertermi açısından incelediğimizde NTD'li iki olgunun ilk trimesterde üriner sistem enfeksiyonuna bağlı yüksek ateş ve hastaneye yatış öyküsünün olduğunu tespit ettik ancak bu açıdan gruplar arasında anlamlı bir fark gözlemedik.

NTD ile folik asit eksikliğinin ilişkisini gösteren çalışmalar oldukça eskiye dayanmaktadır. 1976 yılında Smithells ve ark. [21] folik asit eksikliğinin NTD riskini arttırdığını ilk olarak bildirmişlerdir. 1991'de yapılan çok merkezli, randomize, çift-kör koruma çalışmasında NTD hikayesi olan yüksek riskli 1817 kadın konsepsiyon öncesi ve gebeliğin ilk üç ayında 4 mg folik asit, diğer vitaminler, folik asit+vitaminler ve hiçbiri şeklinde dört grup halinde replasman yapılarak doğuma kadar takip edilmişlerdir. Prekonsepsiyonel ve gebeliğin ilk 12 haftası 4mg/gün folik asit takviyesinin %72 ye varan oranda NTD tekrarlama riskini azalttığını bildirmişlerdir [22]. Bunun devamında yapılan bir plasebo kontrollü çalışmada prekonsepsiyonel folik asit takviyesinin ilk kez ortaya çıkan NTD riskini azalttığı bildirilmiştir [23]. Devam eden yıllarda folik asit takviyesinin NTD riskini azaltma mekanizması kesin olarak aydınlatılamamış olsa da MRC Vitamin Çalışması tüm gebelik planlayan kadınlara konsepsiyon öncesi ve gebelikte ilk üç ay 400 mikrogram/gün ve NTD açısından yüksek risk taşıyan kadınlara da 4 mg/gün folik asit takviyesinin yaygın olarak önerilmesine neden olmuştur [24]. ACOG 2017'de yayınlanan bülteninde NTD riski taşımayan kadınlara konsepsiyon öncesi bir ay ve gebeliğin ilk üç ayında 400 mikrogram/gün folik asit takviyesini önermiştir [2]. Biz çalışmamızda her iki grubumuzda da hastaların tamamının konsepsiyon öncesi folik asit kullanmamış olduğunu saptadık. Konsepsiyon sonrası folik asit kullanma süreleri de gruplarımız arasında anlamlı bir fark göstermedi. Bu durumun hastaların folik asit kullanma sürelerine dair yaptıkları bildirimlerin doğru olmamasından kaynaklandığını düşünmekteyiz. Bazı çalışmalarda maternal eğitim düzeyinin artmasının NTD riskini azalttığı bildirilmiştir. Bu durum, eğitim düzeyi arttıkça maternal beslenme özellikleri, gelir düzeyi ve çevresel faktörlerin konu üzerine etkili olmasıyla açıklanmıştır [13,25]. Ancak biz çalışmamızda gruplar arasında maternal eğitim düzeyleri açısından anlamlı bir fark gözlemedik.

Çeşitli maternal medikal hastalıkların da NTD riskinde artışa yol açabileceği bilinmektedir. Maternal pregestasyonel diyabet bunlar arasında en iyi bilinendir ve kontrolsüz pregestasyonel

diyabetin NTD riskini arttırdığı bilinmektedir [26]. Glukoz dengesinde rol oynayan genlerdeki polimorfizmlerin NTD riskini modifiye ettiği düşünülmektedir [27]. Bizim çalışmamızda pregestasyonel diyabete sahip hasta bulunmamakta idi. Grupları açlık kan şekerleri açısından karşılaştırdığımızda gruplar arasında anlamlı bir fark olmadığını gözledik. Maternal tiroid disfonksiyonunun NTD riski ile ilişkisine ait yeterli veri literatürde mevcut değildir [28]. Biz çalışmamızda maternal TSH düzeylerini gruplar arasında karşılaştırdık ve anlamlı fark olmadığını tespit ettik. Ayrıca gruplar arasında maternal Hb ve WBC düzeyleri açısından da anlamlı bir fark gözlemedik.

Sonuç olarak; Kırıkkale ilinde NTD'li ve sağlıklı gebeleri karşılaştırdığımız çalışmamızda NTD grubunda VKİ'nin kontrol grubuna göre anlamlı daha yüksek olduğunu tespit ettik. Çok merkezli ve artmış popülasyonla yapılacak yeni çalışmalar, Türk toplumunda NTD risklerini ayrıntılı olarak belirlemek açısından faydalı olacaktır.

## Maddi Destek ve Çıkar ilişkisi

Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur.

## Kaynaklar

1. Giordan E, Bortolotti C, Lanzino G, Brinjikji W. Spinal arteriovenous vascular malformations in patients with neural tube defects. AJNR Am J Neuroradiol 2017; 28: 1
2. American College of Obstetrics and Gynecology. ACOG (American College of Obstetrics and Gynecology) Practice Bulletin: Neural tube defects. Obstet Gynecol 2017; 130: 6
3. Moretti ME, Bar-Oz B, Fried S, Koren G. Maternal hyperthermia and the risk for neural tube defects in offspring: systematic review and meta-analysis. Epidemiol 2005; 16: 216-9.
4. Zaganjor I, Sekkarie A, Tsang BL et al. Describing the prevalence of neural tube defects worldwide: a systematic literature review. PLoS One 2016; 11: 11.
5. Christianson A, Howson CP, Modell B. March of Dimesglobal report on birth defects: the hidden toll of dying anddisabled children. White Plains (NY): March of Dimes Birth Defects Foundation 2006; 12.
6. Mitchell LE. Epidemiology of neural tube defects. Am J Med Genet C Semin Med Genet 2005; 135: 88-94.
7. Grewal J, Carmichael SL, Song J, Shaw GM. Neural tube defects: an analysis of neighbourhood and individual-level socio-economic characteristics. Paediatr Perinat Epidemiol 2009; 23: 116-24.
8. Bowman RM, McLone DG, Grant JA, Tomita T, Ito JA. Spina bifida outcome: a 25-year prospective. Pediatr Neurosurg 2001; 34: 114-20.
9. Yi Y, Lindemann M, Colligs A, Snowball C. Economic burden of neural tube defects and impact of prevention with folic acid: a literature review. Eur J Pediatr 2011; 170:1391-400.
10. Frey L, Hauser WA. Epidemiology of neural tube defects. Epilepsia 2003; 44: 4-13.
11. Unusan N. Assesment of Turkish women's knowledge concerning folic acid and prevention of birth defects. Public Health Nutrition 2004; 7: 851-5.
12. Materna-Kiryluk A, Wiśniewska K, Badura-Stronka M, et al. Parental age as a risk factor for isolated congenital malformations in a Polish population. Paediatr Perinat Epidemiol 2009; 23: 29-40.
13. Yavuzcan A, Topuz S, Çağlar M, Dilbaz S, Üstün Y, Kumru S. Düzce ilinde nöral tüp defekti saptanan olguların değerlendirilmesi. JOPP Derg 2013; 5: 125-30.
14. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA 2009; 301: 636–50.
15. Rasmussen SA, Chu SY, Kim SY, Schmid CH, Lau J. Maternal obesity and risk of neural tube defects: a meta-analysis. Am J Obstet Gynecol 2008; 198: 611-9.
16. Liu J, Li Z, Greene NDE, Li H, Ren A. The recurrence risk of neural tube defects (NTDs) in a population with high prevalence of NTDs in northern China. Oncotarget 2017; 8: 72577-83.
17. Nussbaum RL, McInnes RR, Willard HF. Complex inheritance of common multifactorial disorders. In: Thompson & Thompson genetics in medicine. 8th ed. Philadelphia (PA): Elsevier; 2016; 133-53.
18. Bonaiti-Pellie C, Smith C. Risk tables for genetic counselling in some common congenital malformations. J Med Genet 1974; 11: 374-7.
19. Dreier JW, Andersen AM, Berg-Beckhoff G. Systematic review and meta-analyses: fever in pregnancy and health impacts in the offspring. Pediatrics 2014; 133: 674-88.
20. Duong HT, Shahrukh Hashmi S, Ramadhani T, et al. Maternal use of hot tub and major structural birth defects. Birth Defects Res A Clin Mol Teratol 2011; 91: 836-41.
21. Smithells RW, Sheppard S, Schorah CJ. Vitamin deficiencies and neural tube defects. Arch Dis Child 1976; 51: 944–50.
22. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991; 338: 131-7.
23. 23. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med 1992; 327: 1832–5.
24. 24. Wilson RD, Wilson RD, Audibert F, et al. Pre-conception folic acid and multivitamin supplementation for the primary and secondary prevention of neural tube defects and other folic acid-sensitive congenital anomalies. Genetics Committee. J Obstet Gynaecol Can 2015; 37: 534-52.
25. Zhang X, Li S, Wu S, et al. Prevalence of birth defects and risk-factor analysis from a population based survey in Inner Mongolia, China. BMC Pediatr 2012; 12: 125.
26. Wu Y, Wang F, Fu M, Wang C, Quon MJ, Yang P. Cellular stress, excessive apoptosis, and the effect of metformin in a mouse model of type 2 diabetic embryopathy. Diabetes 2015; 64: 2526-36.
27. Lupo PJ, Canfield MA, Chapa C, et al. Diabetes and obesity-related genes and the risk of neural tube defects in the national birth defects prevention study. Am J Epidemiol 2012;1 76: 1101-9.
28. Ceyhan ST, Beyan C, Atay V, et al. Serum vitamin B12 and homocysteine levels in pregnant women with neural tube defect. Gynecol Endocrinol 2010; 26: 578-81.

Turkish Journal of Clinics and Laboratory

To cite this article: Cayci B, Gunaydin B, Yuksel S, Soylemez S, Altundarak C. Acute effect of moderate exercise on oxidative stres in smoker versus non-smokers. Turk J Clin Lab 2018; 9(1): 55-58.

Original Article

# Acute effect of moderate exercise on oxidative stres in smoker versus non-smokers

## *Sigara içen ve içmeyen bireylerde orta derecede egzersizin oksidatif stres üzerine akut etkileri*

Banu CAYCI[1], Berrin GUNAYDIN*[2], Seher YUKSEL[1], Sibel SOYLEMEZ[1], Cagrı ALTUNDARAK[3]

[1]Gazi University, School of Medicine, Department of Clinical Biochemistry
[2]Gazi University, School of Medicine Department of Anesthesiology & Reanimation,
[3]Hacettepe University Faculty of Sports Science

## ABSTRACT

**Aim:** : One of the particular sources of oxidative stress is smoking and thiobarbituric acid reactive substances (TBARS) and malondialdehyde (MDA) have been used as biomarkers of lipid peroxidation of oxidative damage. Therefore, we aimed to investigate the acute effect of moderate exercise on oxidative stress by determining serum MDA levels by TBARS in moderate smoker subjects versus non-smokers.

**Material and Methods:** Fifty healthy subjects performing moderate intensity exercise were assigned to 2 groups as moderate smokers (11-20 cigarettes/day) (Group Smoker, n=25) and non-smokers (Group Non-Smoker, n=25). Venous blood samples were collected from all participants half an hour before exercise (pre-exercise) and immediately after exercise (post-exercise) to determine MDA levels as an indicator of lipid peroxidation in the serum by TBARS/UV (ultra violet).

**Results:** Although no significant differences were observed in pre-exercise MDA levels between the groups, post-exercise MDA levels in smokers were significantly higher than that of non-smokers ($p<0.05$).

**Conclusion:** The MDA determination in serum by TBARS/UV appears to be positively correlated with smoking status in particularly female subjects. Therefore, it can be a promising helpful tool in demonstrating the oxidative stress due to moderate exercise particularly in smokers to reorganize a healthier life style.

**Key words:** Malondialdehyde (MDA), Smoking, Exercise, Oxidative Stress

Corresponding Author*: Berrin GUNAYDIN, MD, PhD, Gazi University, School of Medicine Department of Anesthesiology & Reanimation
E-Mail: gunaydin@gazi.edu.tr
Recevied 14.02.2018 accepted 22.02.2018
Doi: 10.18663/tjcl.394776

## ÖZ

**Amaç:** Oksidatif stresin esas kaynaklarından biri sigara içilmesidir ve tiyobarbitürik asit reaktif türevleri (TBRAT) ve malondialdehit (MDA) oksidatif hasarın biyobelirteci olarak kullanılmıştır. Bu nedenle sigara içen ve içmeyen bireylerde TBART ile serumda MDA seviyelerini belirleyerek orta derecede egzersizin akut etkilerini araştırmayı amaçladık.

**Gereç ve Yöntemler:** Orta derecede egzersiz yapan ve orta derecede sigara içen (11-20 sigara/gün)(Grup Sigara İçen, n=25) ve hiç sigara içmeyen (Grup Hiç Sigara İçmeyen, n=25) 50 sağlıklı birey iki gruba ayrıldı. Tüm bireylerden egzersizden yarım saat önce ve egzersizden hemen sonra TBART/UV (ultra viole) ile serumda lipid peroksidasyonu indikatörü olarak MDA seviyelerini belirlemek için venöz kan örnekleri alındı.

**Bulgular:** Gruplar arasında egzersiz öncesi MDA seviyelerinde anlamlı değişiklik olmamasına rağmen sigara içenlerde egzersiz sonrası MDA seviyeleri, sigara içmeyenlerden istatistiksel olarak anlamlı şekilde yüksek bulundu ($p<0.05$).

**Sonuç:** TBART/UV ile serumda MDA seviyelerinin belirlenmesi, özellikle kadın bireylerde sigara içilmesiyle pozitif ilişki göstermektedir. Bu nedenle özellikle sigara içenlerde daha sağlıklı bir hayat tarzını organize etmek için orta derecede egzersize bağlı oksidatif stresin gösterilmesinde ümit vaad eden yararlı bir araç olabilir.

**Anahtar Kelimeler:** Malondialdehit (MDA), Sigara, Egzersiz, Oksidatif stres

## Introductıon

Oxidative stress is defined as an imbalance between oxidants and antioxidants on the cellular base (1). There are various exogenous oxidative stress inducers including UV (ultra violet), radiation, inflammation, air pollution, physical exercise and smoking which can result in the formation of free radicals (2). Basically, smoking and exercise are two factors result in oxidative stress or damage (3, 4). Tobacco smoke contains gas and tar in addition to some other oxidants that induce oxidative stress (5). Smoking is classified as light, moderate and heavy based on the number of cigarettes consumed per day. Moderate is between 11 to 20 cigarettes, where light is < 11 and heavy is > 20 (3). On the other hand exercise is also graded as mild moderate and vigorous. Moderate intensity workout corresponds to 100 steps/min or 3000 steps/30 min which can be measured either by using pedometers or monitoring O2 uptake during exercise (6).

Based on the theoretical balancing effect between oxidants and either endogenous (SOD:superoxide dismutase or GSH-PX:Gluthatione peroxidase) or exogenous (vitamins E, C or A) antidoxidants in healthy subjects, studies have been done to show the association between malondialdehyde (MDA) levels and oxidative stress (2,7). Thiobarbituric acid reactive substances (TBARS) and MDA have been used as a biomarker of lipid peroxidation and MDA/TBARS seemed to be positively correlated with smoking (2,3). Despite studies on smoking, exercise has not been taken into account as a potential factor until now. Therefore, we aimed to investigate the acute effect of moderate exercise on oxidative stress by determining serum MDA levels in moderate smoker subjects versus non-smokers.

## Material and Methods

Fifty healthy subjects performing moderate intensity exercise were assigned to 2 groups as moderate smokers smoking 11-20 cigarettes/day (Group Smoker, n=25) and non-smokers (Group Non-smoker, n=25). After obtaining ethic committee approval and consents of the participants, venous blood samples were collected to determine MDA levels half an hour before and immediately after moderate exercise according to Helsinki Declaration Rules.

### Biochemical Analysis

As an indicator of lipid peroxidation MDA levels were detected in the serum by TBARS/UV as described in table 1 and calculations were made step by step accordingly (8).

**Table 1.** Detection and calculations for MDA analysis

| | Sample | Std1 (20 nmol/mL) | Std2 (10 nmol/mL) | Std3 (5 nmol/mL) |
|---|---|---|---|---|
| Standard | - | 250 µL | 125 µL | 62,5 µL |
| $dH_2O$ | - | - | 125 µL | 187,5 µL |
| Sample | 250 µL | - | - | - |
| TCA | 1,25 mL | 1,25 mL | 1,25 mL | 1,25 mL |
| TBA | 0,5 mL | 0,5 mL | 0,5 mL | 0,5 mL |

**Step 1:**

- Std1 (20 nmol/mL) → 0.354
- Std2 (10 nmol/mL) → 0.186
- Std3 (5 nmol/mL) → 0.083
- 20/0.354=56.5
- 10/0.186=53.7 56.5+53.7+60.2=170.4
- 5/0.083=60.2 170.4/3=56.8 (common factor)

**Step 2:**

Standard curves were drawn simultaneously with analysis of study groups. Three different concentration were chosen to draw standard graphics.

Absorbance of venous blood sample was multiplied by common factor to obtain MDA:

Sample (abs/Std abs) X std concentration= MDA (nmol/mL)

## Statistical Analysis

The results of the study were expressed as mean±standard deviation (sd). One way ANOVA and unpaired t-test were used to assess differences between pre-exercise and post-exercise MDA levels within smokers and non-smokers as well as between female and male subjects. A p value less than 0.05 was considered as statistically significant.

## Results

There were no significant differences between moderate smokers and non-smokers with respect to demographic properties (age, BMI and gender)(Table 2).

**Table 2.** Demographic properties (mean±sd or n)

| | Group Smoker (n=25) | Group Non-Smoker (n=25) |
|---|---|---|
| Age (year) | 34.0±0.8 | 32.8±1.0 |
| BMI (kg/cm2) | 24.9±0.9 | 22.9±1.2 |
| Gender (male/female) | 12/13 | 11/14 |

Baseline mean pre-exercise serum MDA levels and individually either female or male subjects were comparable between smokers and non-smokers (P>0.05)(Table 3).

**Table 3.** Pre-exercise and postexercise serum MDA levels (nmol/mL) of female and male smoker or non-smoker subjects (mean±sd).

| | Group Smoker (n=25) | Group Non-smoker (n=25) |
|---|---|---|
| Pre-exercise (n=25) | 3.99±0.23 | 2.05±0.75 |
| Female | 3.99±0.33 | 2.09±0.34 |
| Male | 3.97±0.22 | 2.01±0.44 |
| Post-exercise (n=25) | 5.78±0.91* | 3.25±0.88 |
| Female | 5.90±0.54# | 3.20±0.65 |
| Male | 5.66±0.32 | 3.30±0.24 |

*:p<0.05 between pre-exercise vs post-exercise
#:p<0.05 between female vs male subjects

Mean post-exercise MDA levels in smokers were significantly higher than that of mean pre-exercise MDA levels of smokers (p<0.05). Additionally, post-exercise MDA levels of female smokers were significantly higher than that of post-exercise male smokers and preexercise female smokers as well (p<0.05). Whereas there were no significant differences in postexercise MDA levels of nonsmokers between males and females (Table 3).

## Discussion

In the present study, oxidative stress and its relation with smoking and exercise has been demonstrated in terms of MDA. Determination of MDA as a biomarker of lipid peroxidation in serum by TBARS appears to be positively correlated with exercise in particularly female smoker subjects. As anticipated baseline pre-exercise serum MDA levels of moderate smokers in both gender were higher than that of non-smokers and post-exercise MDA levels of smokers were higher than that of non-smokers.

Analysis of MDA can be made by high performance liquid chromatography (HPLC) or TBARS. Although TBARS is a rough estimate of MDA for screening oxidative damage, it is commonly preferred because of its relative simplicity and low cost. Various clinical studies have been conducted to measure MDA levels in body fluids like saliva, urine, plasma and serum by using TBARS either UV/VIS detection (spectrophotometric) or fluorescence (FL) detection (spectrofluorometric) (9-11) (Table 4). In three of these studies, MDA levels were measured in the serum in µmol/L and they were found to be significantly higher than that of non-smokers. However, no comparison was made according to the gender. In our study when we compared serum MDA levels (in nmol/mL rather than µmol/L) between post-exercise versus pre-exercise, post-exercise MDA levels of smokers were significantly higher than that of smokers. When comparison was made with respect to gender, post-exercise serum MDA levels of female smokers were significantly higher than that of male smokers as well.

**Table 4.** Method of analysis of serum MDA (µmol/L) levels in smoker versus non-smokers by TBARS in clinical studies (9-11).

| Total (n) | Male (n) | Female (n) | Non-smoker | Smoker | p | TBARS |
|---|---|---|---|---|---|---|
| 123 | 107 | 14 | 20.7 | 24.0 | <0.01 | UV |
| 100 | 50 | 50 | 1.9 | 2.6 | <0.001 | UV |
| 71 | 48 | 23 | 0.22 | 0.37 | <0.05 | FL |

UV: Ultra violet
FL: Fluoroescence

In contrast to significantly increased MDA levels determined by TBARS in smokers vs non-smokers in many studies, MDA levels increased in non-smoker delivering mothers in a small

cohort study (12). Therefore, our study is the 1st prospective study that shows the increased MDA in female non-smokers after moderate exercise. The reason for this conflicting result could be the powerful effect of exercise on the MDA levels.

We previously studied the possible temporal variation in antioxidant system and MDA as a lipid peroxidation biomarker in isolated erythrocytes of critically ill patients versus healthy volunteers. The MDA levels were found to be significantly higher in critically ill patients than control which was considered a sign of oxidative stress (7).

The limitation of the present study might be the lack of comparison of MDA/TBARS results with HPLC. However, MDA/TBARS is considered relevant on group basis rather than individual.

In conclusion, MDA determination in serum by TBARS/UV can be considered as a promising helpful screening tool in demonstrating the oxidative stress due to moderate exercise particularly in female smokers to reorganize a healthier life style.

## Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

## References

1. Dryden GW, Deaciuc I, Arteel G, McClain CJ. Clinical implications of oxidative stress and antioxidant therapy. Curr Gastroeneterol Rep 2005; 7: 308-16.
2. Lykkesfeldt J. Malondialdehyde as biomarker of oxidative damage to lipids caused by smoking. Clin Chimica Acta 2007; 380: 50-8.
3. Solak ZA, Kabaroglu C, Cok G, Parıldar Z, Bayindir U, Ozmen D, Bayindir O. Effect of different levels of cigarette smoking on lipid peroxidation, gluthathione enzymes and paranoxonase 1 activity in healthy people. Clin Exp Med 2005; 5: 99-105.
4. Mate-Munoz JL, Dominguez R, Barba M, Monroy AJ, Rodriguez B, Ruiz-Solano P, Garnacho-Castano MV. Cardiorespiratory and metabolic responses to loaded half squat exercise executed at an intensity corresponding to the lactate threshold. J Sports Sci Med 2015; 14: 648-56.
5. Pryor WA, Stone K. Oxidants in cigarette smoke. Radicals, hydrogen peroxide, peroxynitrate, and peroxynitrite. Ann N Y Acad Sci 1993; 686: 12-27.
6. Tudor-Locke C, Sisson SB, Collova T, Lee SM, Swan PD. Pedometer-determined step count guidelines for classifying walking intensity in a young ostensibly healthy population. Can J Appl Physiol 2005; 30: 666-76.
7. Gunaydin B, Sancak B, Candan S et al. Temporal variation of oxidant stress in critically ill patients. Minerva Anestesiol 2007; 73: 261-6.
8. Hunter MI, Nlemadim BC, Davidson DL. Lipid peroxidation products and antioxidant proteins in plasma and cerebrospinal fluid from multiple sclerosis patients. Neurochem Res 1985; 10: 1645-52.
9. Miller III ER, Appel LJ, Jiang L, Risby TH. Association between cigarette smoking and lipid peroxidation in a controlled feeding study. Circulation 1997;96:1097-101.
10. Sharma SB, Dwivedi S, Prabhu KM, Singh G, Kumar N, Lal MK. Coronary risk variables in young asymptomatic smokers. Indian J Med Res 2005; 122: 205-10.
11. Kalra J, Chaudhary AK, Prasad K. Increased production of oxygen free radicals in cigarette smokers. Int J Exp Pathol 1991; 72: 1-7.
12. Bolisetty S, Naidoo D, Lui K, Koh TH, Watson D, Montgomery R, Whitehall J. Postnatal changes in maternal and neonatal plasma antioxidant vitamins and the influence of smoking. Arch Dis Child Fetal Neonatal Ed 2002; 86: 36-40.

Turkish Journal of Clinics and Laboratory

To cite this article: Ucan B, Sahin M, Kizilgul M, Ozbek M, Unsal I, Cakal E. The relationship Between Nodular Thyroid Disease and Metabolic Parameters in Patients with Acromegaly. Turk J Clin Lab 2018; 9(1): 59-65.

Original Article

# The relationship between nodular thyroid disease and metabolic parameters in patients with acromegaly

## *Akromegali hastalarında nodüler tiroid hastalığı ve metabolik parametreler ile ilişkisi*

Bekir UCAN*[1], Mustafa SAHIN[2], Muhammed KIZILGUL[1], Mustafa OZBEK[1], Ilknur UNSAL[1], Erman CAKAL[1]

[1]Department of Endocrinology and Metabolism, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey
[2]Department of Endocrinology and Metabolism, School of Medicine, Ankara University, Ankara Turkey

## ABSTRACT

**Aim:** The high prevalence of nodular goiter in patients with acromegaly is well known. Insulin-like growth factor-1 (IGF-1) has been claimed to be one of the etiologic factors. The aim of the study was to evaluate the incidence of thyroid lesions in our acromegalic patients and to analyze possible factors influencing thyroid nodule development, especially insulin resistance and hormonal parameters.

**Material and Methods:** Sixty patients with acromegaly, 32 females, and 28 males, with a mean age of 52.7 ± 10.0 years without known thyroid disease were included. Age and sex matched 100 control subjects also included in the study. Waist and hip circumference, weight, and height, fasting blood glucose, postprandial blood glucose, insulin, thyroid function tests, thyroid autoantibodies, lipid profile, IGF-1, growth hormone, other anterior pituitary hormone levels were measured in all patients. Magnetic Resonance Imaging (MRI) and thyroid ultrasonography (US) was performed in all patients. Thyroid nodule volume and thyroid volume were calculated.

**Results:** Thirty-five (58.3%) patients with acromegaly had thyroid nodules according to (% 25) in control group ($p<0,0001$). There were significant differences in BMI, thyroid volume, fasting glucose and TSH levels between patients and controls. After regression analysis, thyroid volume was associated with insulin, waist circumference, HOMA-IR, LDL-cholesterol and the size of the pituitary adenoma ($p<0.05$) or diabetes occurrence. During the logistic regression analysis, the presence of nodules was strongly associated with luteinizing hormone (LH) ($p<0.02$) and HDL-cholesterol levels ($p<0.05$). Nodule volume were significantly associated with LH level ($p<0.05$), ACTH (beta = -0.51, $p< 0.01$), plasma cortisol (beta= 0.965, $p <0.05$), free T4 (beta= 0.522, $p<0.05$), the size of adenoma (beta= 0.615, $p<0.05$) in the regression analysis.

**Conclusion:** The prevalence of nodules in acromegalic patients were found to be higher than usual prevalence. In addition to IGF-1, other hormones and insulin resistance might play an important role in thyroid volume, nodule volume, and nodule formation mechanism in patients with acromegaly.

**Key words:** Acromegaly, thyroid volume, anterior pituitary hormones

Corresponding Author*: Bekir UCAN, MD, Department of Endocrinology and Metabolism, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey
E-Mail: uzm.dr.bekir@hotmail.com
Received 02.05.2017 accepted 19.09.2017
Doi: 10.18663/tjcl.310185

## ÖZ

**Amaç:** Akromegali hastalarında nodüler guatr sık görüldüğü iyi bilinmektedir. İnsülin benzeri büyüme faktörü-1 (IGF-1)'in etiyolojik faktörlerden biri olduğu iddia edilmiştir. Bu çalışmanın amacı akromegali hastalarında tiroid lezyon insidansının değerlendirilmesi ve insülin direnci ve hormonal paramatreler başta olmak üzere tiroid nodül gelişimini etkileyen olası faktörleri değerlendirmektir.

**Gereç ve Yöntem:** Bilinen tiroid hastalığı olmayan ortalama yaşları 52.7±10.0 olan 60 akromegali hastası (32 kadın 28 erkek) çalışmaya dahil edildi. Yaş ve cinsiyet uyumlu 100 kontrol hastası çalışmaya alındı. Tüm hastalarda vücut kitle indeksi (VKİ), bel-kalça çevresi, boy, kilo, açlık kan glukozu, tokluk kan glukozu, insülin, tiroid fonksiyon testleri, tiroid otoantikorları, lipid profili, IGF-1, büyüme hormonu ve diğer ön hipofiz hormonlarının ölçümleri yapıldı. Manyetik rezonans görüntüleme ve tiroid ultrasonografi tüm hastalarda uygulandı. Tiroid volümü ve tiroid nodül volümü hesaplandı.

**Bulgular:** Kontrol grubu (%25) ile kıyaslandığında 35 (%58.3) akromegali hastasında tiroid nodülü mevcuttu (p<0.0001). Hasta ve kontrol grupları arasında VKİ, tiroid volümü, açlık kan şekeri ve TSH düzeyleri açısından anlamlı farklılıklar bulundu (p<0.05). Regresyon analizi sonrasında tiroid volümü ile insülin, bel çevresi, HOMA-IR, LDL-kolesterol ve pituiter adenom boyutu arasında ilişki saptandı (p<0.05). Lojistik regresyon analizinde nodül varlığı ile lüteinizan hormone (LH) (p<0.02) ve HDL-kolesterol (p<0.05) arasında güçlü ilişki bulundu. Regresyon analizinde nodül volümü ile LH düzeyi (p<0.05), ACTH (beta = -0.51, p<0.01), plasma kortizolü (beta= 0.965, p <0.05), serbest T4 (beta= 0.522, p<0.05), adenom boyutu (beta= 0.615, p<0.05) arasında anlamlı ilişki bulundu.

**Sonuç:** Akromegali hastalarında tiroid nodül prevelansı genel populayona göre daha yüksektir. Bununla birlikte IGF-1, diğer hormonlar ve insülin direnci gibi parametreler akromegali hastalarında tiroid volümü, nodül volümü ve nodül formasyon mekanizmalarında önemli rol oynayabilir.

**Anahtar kelimeler:** Akromegali, tiroid nodülü, ön hipofiz hormonları

## Introductıon

Acromegaly is a chronic disease characterized by the presence of growth hormone (GH) hypersecretion caused by a benign pituitary adenoma and increased levels of insulin-like growth factor 1 (IGF-1). Overproduction of IGF-1 by increased secretion of GH leads to a multisystemic disease characterized by disproportionate skeletal, tissue, and organ growth, multiple comorbidities and premature mortality (1,2). The high prevalence of nodular goiter in patients with acromegaly is well known. Thyroid enlargement in acromegaly may be diffuse or multinodular. Cheung et al reported that 92% of patients with acromegaly had an enlarged thyroid gland determined by ultrasound; mean thyroid size was increased more than five times normal (3). According to a recent meta-analysis, approximately 60% of patients with acromegaly had thyroid nodular disease (4). Acromegalic patients have a high risk for the development of thyroid cancer (5,6). It is well documented that IGF-1 is a thyroid growth factor (7). There is a correlation between IGF-1 levels and thyroid volume (TV) in patients with acromegaly (8). Insulin resistance and hyperinsulinemia are common features of patients with active acromegaly (1). Increased lipolysis and free fatty acids concentrations, deterioration of insulin signal pathway, alterations of adipokines and adipose tissue inflammation are possible underlying mechanisms (9,10). Previous studies have demonstrated that patients with insülin resistance (IR) have larger thyroid volumes and a higher prevalence of thyroid nodules (11,12). The possible mechanisms are the concurrent function of insulin with thyroid-stimulating hormone (TSH) as a growth factor and stimulating thyroid cell proliferation, and insulin/IGF-1 signaling pathway modulating the regulation of thyroid gene expression that leads to thyrocyte proliferation and differentiation (13,14).

The aim of the study was to evaluate the incidence of thyroid lesions in our acromegalic patients and to analyze possible factors influencing thyroid nodule occurrence, especially insulin resistance and hormonal parameters.

## Material and Methods

60 acromegaly patients (33 females, 27 males, mean age 47.62 ± 13.27 years), without known thyroid disease, currently managed by the Endocrinology and Metabolism Department of Diskapi Teaching and Research Hospital in Turkey were enrolled to study. Ethics committee approval and written informed consent of participants was obtained prior to the study.

The diagnosis of acromegaly was made on the basis of characteristic clinical features, elevated IGF-1 levels over normal values for age and gender and failure of GH suppression

to <1ng/mL after an oral glucose load (15). All patients had a pituitary adenoma identified clearly by magnetic resonance imaging. All patients were managed according to the recommended guidelines for acromegaly management (15).

All patients underwent an evaluation of thyroid volume (TV) by ultrasound and determination for IGF-1, free T4, TSH, antithyroid peroxidase (anti-TPO) and anti-thyroglobulin (AntiTg). None had a history of thyroid disease, and all were euthyroid on biochemical testing. Growth hormone and IGF-1 levels were analyzed with chemiluminescence method in IMMULITE 2000 Xpi (Siemens Healthcare Diagnostics Inc.). The normal range for GH is 0–0.8 ng/mL. Serum IGF-1 levels were compared with age-gender adjusted normal range. Thyroid stimulating hormone (TSH), free thyroxine (fT4), anti-thyroglobulin (anti-Tg) and thyroid peroxidase antibody (anti-TPO) were measured with specific electrochemiluminescence immunoassays method with a commercially available kit (Immulite 2000, Bio DPC, Los Angeles, CA, USA). The normal range for fT4 as 0.74-1.52 ng/dL. TSH levels ranging between 0.55-4.78 mIU/L was considered normal and normal ranges for anti-Tg and anti-TPO are 0–40 IU/mL and 0–35 IU/mL, respectively. Homeostasis model assessment (HOMA-IR) was used for calculation of IR (16). Serum levels of glucose, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), insulin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol (in women), total testosterone (in men) were also measured. FSH, LH, and estradiol (in women) were measured in pre-ovulatory period if they still menstruate. Blood samples were obtained at 08.00 h to evaluate the basal plasma ACTH and serum cortisol concentration.

Demographic data and medical history of all subjects were recorded; physical examination and anthropometric measurements were performed. Weight, height, waist circumference (WC), hip circumference (HC) and systolic and diastolic blood pressure (BP) were measured. The body mass index (BMI) was measured by dividing the weight by the square of the height (kg/m2). WC was determined by measuring the narrowest point between the costal margin and iliac crest at the end of a normal expiration. The blood pressure (BP) at rest was measured on the right arm using a standard mercury sphygmomanometer, with the patient in the sitting posture for 10 min before the test, and the average of two measurements was recorded.

## Thyroid ultrasound

Thyroid ultrasonography (US) was performed using High-resolution B-mode ultrasound images (EUB 7000 HV; Hitachi, Tokyo, Japan) with a 13-MHz linear array transducer. The volume of each thyroid lobe was calculated by the ellipsoid model formula (length x thickness x width x 0.52) (17). Total TV >18 mL in men and >13 mL in women was considered as goiter. TV was considered as the sum of the volumes of each lobe. Nodule volume was calculated with the same formula. Nodule and thyroid volumes were evaluated at the time of Acromegaly diagnosis.

## Statistical Analyses

All statistical analysis was performed using SPSS (The Statistical Package for Social Sciences) Version 17.0 (SPSS, Inc, Chicago, IL, USA). Whether the distributions of continuous variables were normality or not was determined by using Kolmogorov-Smirnov test. The data obtained by the measurement is given by the arithmetic mean ± standard deviation. Qualitative analysis of the data was performed using. Differences in the groups of patients with and without nodules were analyzed by using Mann-Whitney U test. The relationship between continuous variables in patients' group was determined by using Spearman Correlation analysis; correlation coefficients and p values were calculated. The effects of variables that could be considered as significant on thyroid volume and nodule volume were examined by using multiple linear regression analysis. Multistep regression analysis was performed. Independent variables that may affect the presence of nodules were determined by using Multivariate logistic regression analysis. Adjusted R-squared and statistically significant p-values are presented. A p-value <0.05 was considered statistically significant.

## Results

Thirty-five (58.3%) patients with acromegaly had thyroid nodules when compared to control group (%25) (p<0,0001). Mean thyroid volume was 32.09 ± 33.45 and mean nodule volume was 0.74 ± 0.97 in acromegaly group. BMI was higher in in acromegaly group when compared to controls (29.74 ± 4.58 to 26.06 ± 4.68, p=0.009). There were also significant differences in thyroid volume, fasting glucose and TSH levels between patients and controls (p<0.05). Mean GH and IGF-1 levels were 17.83 ± 13.23 ng/mL and 924.71 ± 446.71 ng/mL, respectively (Table-1). IGF-1 levels were correlated with thyroid volume (r2:0.471, p=0.026) but not with nodule volume (p>0.05). After regression analysis, thyroid volume was associated with insulin, waist circumference, HOMA-IR, LDL-cholesterol and the size of the pituitary adenoma (beta= 0.615, p<0.05). The presence of nodules was strongly associated with LH (p<0.02) and HDL-cholesterol levels (p<0.05) according to the logistic regression analysis. Nodule volume were significantly associated with luteinizing hormone (LH) level (p<0.05), ACTH (beta =-0.51, p<0.01), plasma cortisol (beta= 0.965, p <0.05) and free T4 (beta= 0.522, p<0.05) (Figure 1-2).

**Table 1.** Basic demographics and laboratory values of patients and control group

| | Acromegaly Group | | Control Group | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | P |
| Age (years) | 47.62 | 13.27 | 42.18 | 10.62 | 0,066 |
| Weight (kg) | 83.92 | 16.42 | 69.55 | 13.90 | 0.005 |
| Height (cm) | 167.53 | 8.90 | 163.21 | 7.13 | 0.091 |
| BMI (kg/m2) | 29.74 | 4.58 | 26.06 | 4.68 | 0.009 |
| SBP (mmHg) | 131.42 | 7.51 | 124.36 | 5.43 | 0.007 |
| DBP (mmHg) | 81.12 | 6.32 | 77.82 | 5.21 | 0.012 |
| Glucose (mg/dl) | 107.78 | 27.10 | 84.92 | 7.98 | <0.0001 |
| Insulin (mU/L) | 11.15 | 8.19 | 11.67 | 6.49 | 0.777 |
| HOMA-IR | 1.52 | 1.09 | | | |
| Total Cholesterol (mg/dL) | 185.46 | 42.78 | | | |
| Triglyceride (mg/dL) | 142.15 | 77.71 | | | |
| HDL-C (mg/dL) | 47.05 | 15.86 | | | |
| LDL-C (mg/dL) | 112.78 | 35.22 | | | |
| Free T4 (ng/dL) | 3.45 | 14.04 | 1.02 | 0.14 | 0.210 |
| TSH (mIU/L) | 1.79 | 1.34 | 2.08 | 0.95 | 0.319 |
| FSH (IU/L) | 22.05 | 33.27 | - | - | - |
| LH (IU/L) | 8.43 | 8.64 | - | - | - |
| Prolactin (ng/mL) | 78.96 | 212.07 | - | - | - |
| Estradiol (pg/mL) | 53.66 | 80.17 | - | - | - |
| Total testosterone (ng/dL) | 54.91 | 103.95 | - | - | - |
| Cortisol (mg/dL) | 11.97 | 7.91 | - | - | - |
| ACTH (pg/mL) | 30.49 | 24.89 | - | - | - |
| GH (ng/mL) | 17.83 | 13.23 | - | - | - |
| IGF-1 (ng/mL) | 924.71 | 446.71 | - | - | - |

Abbreviations: SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HOMA-IR: Homeostasis model assessment, TSH: Thyroid stimulating hormone, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, CRP: C-reactive protein FSH: Follicle-stimulating hormone, LH: luteinizing hormone, ACTH: Adrenocorticotroph hormone, GH: Growth hormone, IGF-1: Insulin-like growth factor-1.

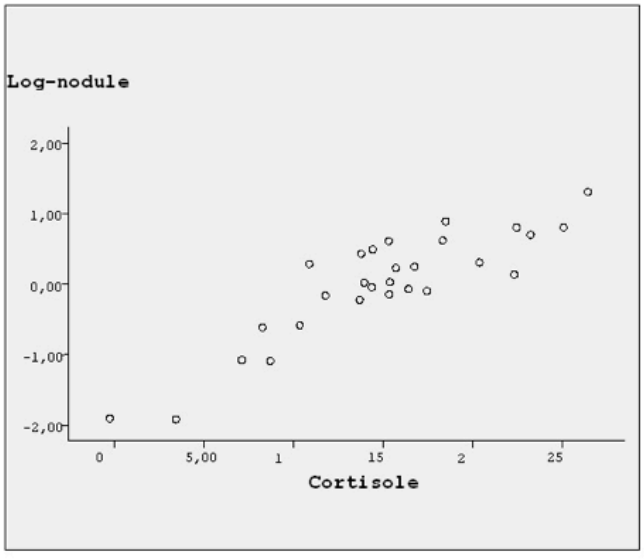



**Figure 1.** Correlation of thyroid nodule volume with Cortisol levels

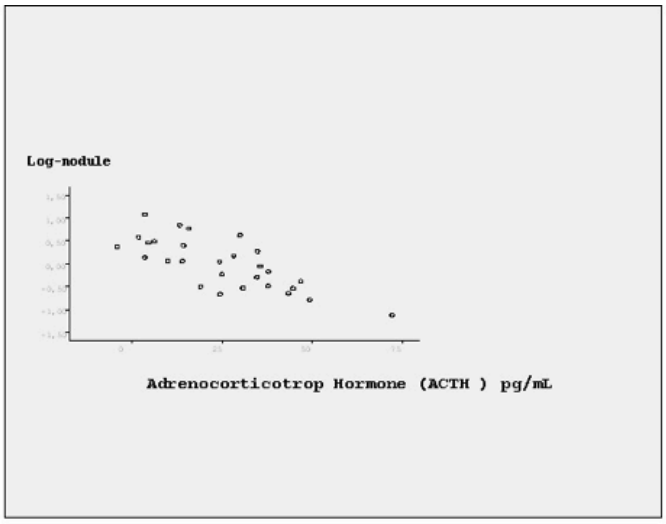



**Figure 2.** Correlation of thyroid nodule volume with ACTH levels

## Discussion

Nodule prevalence in our acromegaly patients (58%) was demonstrated to be significantly higher. Insulin resistance, IGF-1, GH was not associated with nodule prevalence. We found an association between nodule volume and, LH and FSH concentrations.

Insulin resistance is commonly seen in patients with acromegaly. The increased lipolysis induced increased FFAs by GH stimulation may have an impact on insulin sensitivity by competition with glucose for substrate oxidation, deterioration in insulin signal pathway and b-cell function, or triggering adipose tissue inflammation (9,18,19). Mori et al observed that serum IGF-1 levels were associated with insulin resistance in patients with acromegaly and improvement glucose tolerance in was demonstrated after a postoperative decrease in serum IGF-1 levels (20). It may be possible that IGF-insulin hybrid receptors and post receptor pathways cross-talk play role in development of IR in acromegaly patients (21). However, O'Connell et al demonstrated that IGF-1 administration induced by a GH-receptor antagonist decreased blood glucose and insulin resistance in patients with controlled acromegaly (22). Low IGF-1 levels in patients with Laron syndrome are related to insulin resistance that is reversed after IGF-1 treatment (23). These two studies might indicate a GH-independent mechanism may have a role IR in acromegaly patients.

A thyroid nodule is a discrete lesion within the thyroid gland, which can be distinguished from the thyroid parenchyma as (24) increased epithelial hyperplasia and excessive distention of some follicles that have undergone involution are considered to cause of nodule development (25). Genetic factors, iodine deficiency, age, gender, smoking, and goitrogens are well-known etiological factors

for thyroid nodule formation (26,27). IGF-1 stimulates synthesis of protein and DNA in thyrocytes and stimulates the proliferation and differentiation of these cells (13,28). Ongoing exposure to high serum IGF-1 levels may play a role in the development of thyroid nodules in acromegaly patients (29). Völzhe et al reported that high serum IGF-1 levels were associated with thyroid nodules (30). In our study, thyroid volume was associated with IGF-1 levels which are consistent with the literature.

Serum TSH level has been recognized as the main growth factor for thyroid cells. Insulin is a thyroid growth factor act as a co mitogenic factor and it might partly enhance responsiveness to IGFs in response to TSH. This increases the probability of potential role of TSH-insulin interactions in the regulation of thyroid growth and function in vivo (31). Regulation of thyroid gene expression is modulated by insulin/IGF-1 signaling pathway that is an additional important factor in proliferation and differentiation of thyroid cells (13). It is well known that insulin acts as a growth factor that stimulates cell proliferation. IR-induced increased insulin levels decrease Insulin-like growth factor-1 (IGF-1) binding proteins production and consequently increase IGF-1 levels. Antiapoptotic, cell survival and transforming activities are well-known functions of IGFs. Many tissues produce IGFs and most cells express IGFs receptors (13,32,33,34). Heidari et al demonstrated that patients with thyroid nodules had increased HOMA-IR values and there was a relation between HOMA-IR and benign thyroid nodules (35). Rezzonico et al reported that patients with higher circulating levels of insulin due to IR had larger thyroid volumes and a higher risk for the thyroid nodule formation (11). In another study, increased thyroid volume and nodule prevalence were observed in patients with IR due to metabolic syndrome (12). Yasar et al reported that IR may lead to increased thyroid proliferation and nodule formation (36). IR increases visceral fat accumulation via effects on serum leptin concentrations and this visceral fat increases TSH secretion that increase thyroid proliferation (37).

Rezzonico et al demonstrated that patients with differentiated thyroid carcinoma (DTC) had a higher frequency of IR (38). Karimifar et al reported that metformin decreased the size of small solid thyroid nodules via decreasing serum TSH levels and also prevented the thyroid volume increase in patients with prediabetes (39). In another study, metformin therapy was demonstrated to decrease thyroid volume and nodule size in patients with insulin resistance (40). In our study, thyroid volume was associated with insulin and HOMA-IR that may indicate IR may play a role in thyroid nodule formation in patients with acromegaly.

Luteinizing hormone (LH) is a glycoprotein hormone-like TSH and has similar alpha subunit. LH was shown to increase thyroid adenylate cyclase activity 65 times more robustly than human chorionic gonadotropin (hCG) (41). Yoshimura et al also demonstrated that human LH bound to the TSH receptor and stimulated adenylate cyclase more potently than hCG (42). hCG and LH have a proliferative effect on rat and human thyroid cells. Knudsen et al reported that oral contraceptive users had a lower thyroid volume and risk of goiter (43). Oral contraceptive induced LH decrease might have an effect on the decrease in thyroid volume. In our study, thyroid volume was associated with LH that may indicate LH may play a role in thyroid nodule formation in patients with acromegaly.

Glucocorticoids (GCs) are generally considered to increase renal iodide clearance and decrease thyroid iodine uptake hence decrease intrathyroidal iodine availability (44). It was shown that hydrocortisone directly stimulated the function of porcine thyroid cells via glucocorticoid receptor and cAMP pathways (45). GCs, inhibit TSH secretion via acting on both specific receptors located on hypothalamic TRH neurons (46) and pituitary (47). Finally, GCs treatment decrease plasma levels of thyroxine-binding globulin (48) and peripheral conversion of T4 to T3 (49) in vivo. Cushing's disease (CD) and GCs administration in healthy volunteers impair thyrotropin-releasing hormone (TRH) secretion (50,51). Both thyrotropin (TSH) pulses and the nocturnal serum TSH release are disturbed in patients with CD (50) and after GCs infusion (51,52). Invitti et al demonstrated that patients with Cushing's disease had a higher prevalence of nodular thyroid disease (53). In our study, thyroid volume was positively associated with cortisol and negatively associated with ACTH levels that may indicate they may play a role in thyroid nodule formation in patients with acromegaly.

## Conclusion

The prevalence of nodules in acromegalic patients were found to be higher than usual prevalence. In addition to IGF-1, other hormones and insulin resistance might play an important role in thyroid volume, nodule volume, and nodule formation mechanism in patients with acromegaly.

## Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

## References

1. Melmed S. Medical progress: acromegaly. N Engl J Med. 2006; 355: 2558–73
2. Ribeiro-OliveiraAJr, Barkan A. The changing face of acromegaly–advances in diagnosis and treatment. Nat Rev Endocrinol 2012; 8: 605–11

3. Cheung NW, Boyages SC. The thyroid gland in acromegaly: An ultrasonographic study, Clin Endocrinol (Oxf) 1997; 46: 545–49.
4. Wolinski K, Czarnywojtek A, Ruchala M. Risk of thyroid nodular disease and thyroid cancer in patients with acromegaly-meta-analysis and systematic review. PLoS One 2014 14; 9: 88787
5. Gullu BE, Celik O, Gazioglu N, Kadioglu P. Thyroid cancer is the most common cancer associated with acromegaly. Pituitary 2010; 13: 242-48.
6. Dogan S, Atmaca A, Dagdelen S, Erbas B, Erbas T. Evaluation of thyroid diseases and differentiated thyroid cancer in acromegalic patients. Endocrine 2014; 45: 114-21
7. Tramontano D, Cushing GW, Moses AC, Ingbar SH. Insulin-like growth factor-I stimulates the growth of rat thyroid cells in culture and synergizes the stimulation of DNA synthesis induced by TSH and Graves'-IgG. Endocrinology 1986; 119: 940-42
8. Miyakawa M, Saji M, Tsushima T, Wakai K, Shizume K. Thyroid volume and serum thyroglobulin levels in patients with acromegaly: correlation with plasma insulin-like growth factor I levels. J Clin Endocrinol Metab 1988; 67: 973-78
9. Moller N, Jorgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocrine Reviews 2009; 30: 152–77
10. Olarescu NC, Ueland T, Lekva T et al. Adipocytes as a source of increased circulating levels of nicotinamide phosphoribosyltransferase/visfatin in active acromegaly. Journal of Clinical Endocrinology and Metabolism 2012; 97: 1355–62
11. Rezzonico J, Rezzonico M, Pusiol E, Pitoia F, Niepomniszcze H. In-troducing the thyroid gland as another victim of the insulin resistance syndrome. Thyroid 2008; 18: 461 – 64
12. Ayturk S, Gursoy A, Kut A, Anil C, Nar A, Tutuncu NB. Metabolic syndrome and its components are associated with increased thyroid volume and nodule prevalence in a mild-to-moderate iodine-deficient area. Eur J Endocrinol 2009; 161: 599-605
13. Kimura T, Van Keymeulen A, Golstein J, Fusco A, Dumont JE, Roger PP. Regulation of thyroid cell proliferation by TSH and other factors: A critical evaluation of in vitro models. Endocr Rev 2001; 22: 631–56
14. Deleu S, Pirson I, Coulonval K et al. IGF-1 or insulin, and the TSH cyclic AMP cascade separately control dog and human thyroid cell growth and DNA synthesis, and complement each other in inducing mitogenesis. Mol Cell Endocrinol 1999; 149: 41–51
15. Katznelson L, Laws ER Jr, Melmed S et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014 ; 99: 3933-51
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assess¬ment: insulin resistance and beta-cell function from fast¬ing plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-19
17. Vitti P, Rago T, Mazzeo S et al. Thyroid blood flow evaluation by color-flow Doppler sonography distinguishes Graves' disease from Hashimoto's thyroiditis. J. Endocrinol. Invest. 1995:18;857–861
18. Yeop HC, Kargi AY, Omer M et al. Differential effect of saturated and unsaturated free fatty acids on the generation of monocyte adhesion and chemotactic factors by adipocytes: dissociation of adipocyte hypertrophy from inflammation. Diabetes 2010; 59: 386–96
19. Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. Lancet 2010; 375: 2267–77
20. Mori K, Iwasaki Y, Kawasaki-Ogita Y et al. Improvement of insulin resistance following transsphenoidal surgery in patients with acromegaly: correlation with serum IGF-I levels. J Endocrinol Invest 2013; 36: 853-59
21. Benyoucef S, Surinya KH, Hadaschik D, Siddle K. Characterization of insulin/IGF hybrid receptors: contributions of the insulin receptor L2 and Fn1 domains and the alternatively spliced exon 11 sequence to ligand binding and receptor activation. Biochem J 2007; 403: 603–13
22. O'Connell T, Clemmons DR. IGF-I/IGF-binding protein-3 combination improves insulin resistance by GH-dependent and independent mechanisms. J Clin Endocrinol Metab 2002; 87: 4356–60
23. Laron Z. The essential role of IGF-I: lessons from the longterm study and treatment of children and adults with Laron syndrome. J Clin Endocrinol Metab 1999; 84: 4397–404
24. Haugen BR, Alexander EK, Bible KC et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2015; 14
25. H.C. Alpay, T. Kalıdag, E. Keles et al., The effects of fine needle biopsy on thyroid hormone levels. Otolaryngol. Head Neck Surg. 2007; 136: 942–45
26. Gharib H, Papini E. Thyroid nodules: clinical importance, assessment, and treatment. Endocrinol Metab Clin North Am 2007; 36: 707-35
27. Zou Y, Ding G, Lou X et al. Factors influencing thyroid volume in Chinese children. Eur J Clin Nutr. 2013; 67: 1138-41
28. Isozaki O, Santisteban P, Chan J, Grollman E, Kohn L. Insulin and insulin-like growth factor-I (IGF-I) regulate differentiation as well as growth in FRTL5 cells. Acta Endocrinologica 1987; 281: 288–92
29. Tita P, Ambrosio MR C. Scollo C et al. High prevalence of differentiated thyroid carcinoma in acromegaly. Clin. Endocrinol (Oxf) 2005; 63: 161–67

30. Völzke H, Friedrich N, Schipf S et al. Association between serum insulin-like growth factor-I levels and thyroid disorders in a population-based study. J Clin Endocrinol Metab 2007; 92: 4039-45
31. Burikhanov R, Coulonval K, Pirson I, Lamy F, Dumont JE, Roger PP. Thyrotropin via cyclic AMP induces insulin receptor expression and insulin Co-stimulation of growth and amplifies insulin and insulin-like growth factor signaling pathways in dog thyroid epithelial cells. J Biol Chem 1996; 271: 29400-06
32. Pothiwala P, Jain SK, Yaturu S. Metabolic syndrome and cancer. Metab Syndr Relat Disord 2009; 7: 279 – 88
33. Vella V, Sciacca L, Pandini G et al. The IGF system in thyroid cancer: new concepts. Mol Pathol 2001; 54: 121 – 24
34. Kimura T, Dumont JE, Fusco A, Golstein J. Insulin and TSH promote growth in size of PC Cl3 rat thyroid cells, possibly via a pathway different from DNA synthesis: Comparison with FRTL-5 cells. Endocr Rev 2001; 22: 631 – 56
35. Heidari Z, Mashhadi MA, Nosratzehi S. Insulin Resistance in Patients with Benign Thyroid Nodules. Arch Iran Med 2015; 18: 572-76.
36. Yasar HY, Ertuğrul O, Ertuğrul B, Ertuğrul D, Sahin M. Insulin resistance in nodular thyroid disease. Endocr Res 2011; 36: 167-74
37. Mantzoros CS, Ozata M, Negrao AB, et al. Synchronicity of frequently sampled thyrotropin (TSH) and leptin concentrations in healthy adults and leptin-deficient subjects: evidence for possible partial TSH regulation by leptin in humans. J Clin Endocrinol Metab 2001; 86: 3284–91
38. Rezzo´nico JN, Rezzo´nico M, Pusiol E, Pitoia F, Niepomniszcze H. Increased prevalence of insulin resistance in patients with differentiated thyroid carcinoma. Metab Syndr Relat Disord 2009; 7: 375–80
39. Karimifar M, Aminorroaya A, Amini M et al. Effect of metformin on thyroid stimulating hormone and thyroid volume in patients with prediabetes: A randomized placebo-controlled clinical trial. J Res Med Sci 2014; 19: 1019-26
40. Anil C, Kut A, Atesagaoglu B, Nar A, Bascil Tutuncu N, Gursoy A. Metformin Decreases Thyroid Volume and Nodule Size in Subjects with Insulin Resistance: A Preliminary Study. Med Princ Pract. 2015 Nov 30
41. Carayon P, Lefort G, Nisula B. Interaction of human chorionic gonadotropin and human luteinizing hormone with human thyroid membranes. Endocrinology 1980; 106: 1907–16
42. Yoshimura M, Hershman JM, Pang XP, Berg L, Pekary AE. Activation of the thyrotropin (TSH) receptor by human chorionic gonadotropin and luteinizing hormone in Chinese hamster ovary cells expressing functional human TSH receptors. J Clin Endocrinol Metab 1993, 77: 1009–13
43. Knudsen N, Bulow I, Laurberg P, Perrild H, Ovesen L, Jorgensen T. Low goitre prevalence among users of oral contraceptives in a population sample of 3712 women. Clin Endocrinol (Oxf ) 2002; 57: 71–76
44. Saji M, Kohn LD. Effect of hydrocortisone on the abilityof thyrotropin to increase deoxyribonucleic acid synthesis and iodide uptake in FRTL-5 rat thyroid cells: opposite regulation of adenosine 3, 5-monophosphate signal action. Endocrinology 1990; 127: 1867-76
45. Takiyama Y, Tanaka H, Takiyama Y, Makino I. Theeffects of hydrocortisone and RU486 (Mifepristone) on iodide uptake in porcine thyroid cells in primary culture. Endocrinology 1994; 135: 1972-79
46. Cintra A, Fuxe K, Wikstrom AC, Visser TJ. Evidencefor thyrotropin-releasing hormone and glucocorticoid receptorimmunoreactive neurons in various preoptic and hypothalamic nuclei of the male rat. Brain Research 1990; 506: 139-44
47. Rubello D, Sonino N, Casara D, Girelli ME, Busnardo B, Boscaro M. Acute and chronic effects of high glucocorticoid levels on hypothalamic pituitary-thyroid axis in man. Journal of Endocrinological Investigation 1992; 15: 437-41
48. Gamstedt A, Järnerot G, Kågedal B. Dose related effects of betamethasone on iodothyronines and thyroid hormone-binding proteins in serum. Acta Endocrinol (Copenh) 1981; 96: 484-90
49. Cavalieri RR, Castle JN, McMahon FA. Effects of dexamethasone on kinetics and distribution of triiodothyronine in the rat. Endocrinology 1984; 114: 215-21
50. Bartalena L, Martino E, Petrini F et al. The nocturnal serum thyrotropin surge is abolished in patients with adrenocorticotropin (ACTH)-dependent or ACTH independent Cushing's syndrome. Journal of Clinical Endocrinology and Metabolism 1991; 72: 1195–99
51. Samuels M, McDaniel P. Thyrotropin levels during hydrocortisone infusions that mimic fasting-induced cortisol elevations: a clinical research center study. Journal of Clinical Endocrinology and Metabolism 1997; 82: 3700–04
52. Otsuki M, Dakoda M, Baba S. Influence of glucocorticoids on TRF-induced TSH response in man. Journal of Clinical Endocrinology and Metabolism 1973; 36: 95–102
53. Invitti C, Manfrini R, Romanini BM, Cavagnini F. High prevalence of nodular thyroid disease in patients with Cushing's disease. Clin Endocrinol (Oxf) 1995; 43: 359-63

To cite this article: Alpcan A, Tursun S, Acar BÇ. Çocuklarda idrar yolları enfeksiyonları. Turk J Clin Lab 2018; 9(1): 66-69.

Derleme

# Çocuklarda idrar yolları enfeksiyonları

# *Pediatric urinary tract infections*

Ayşegül ALPCAN*[1], Serkan TURSUN[1], Banu ÇELİKEL ACAR[2]

[1] Kırıkkale Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Kırıkkale, Türkiye

[2] Kırıkkale Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Nefroloji Bilim Dalı, Kırıkkale, Türkiye

## ÖZ

İdrar yolu enfeksiyonları çocuklarda oldukça sık görülmektedir. En sık izole edilen ajan EscherichiaColi'dir. İnsidansı kız çocuklarda % 4-8 iken erkeklerde %1-2'dir. Çocuklarda ürosepsis, renal hasar, hipertansiyon, kronik renal yetmezlik ile ilişkili olması sebebiyle endişe vericidir. Bu derlemede çocukluk çağı akut ve kronik idrar yolu enfeksiyonunun tedavisi ve izleminin anlatılması amaçlanmıştır.

**Anahtar Kelimeler:** İdrar yolu enfeksiyonu, teşhis, tedavi

## ABSTRACT

Urinary tract infections are very common in children. The most common pathogens isolated in urinary tract infections are Escherichia coli. The incidence of Urinary tract infections in children 4-8 % in girls and 1-2 % in boys.Urinary tract infections in children is of concern because it can be associated with urosepsis, renal scarring, hypertension, and chronic renal insufficiency.In this review we aim to describe the diagnosis and management of acute and recurrent urinary tract infections in the pediatric population.

**Keywords:** Urinary tract infection, diagnosis, management

Corresponding Author*: Ayşegül Alpcan, Kırıkkale Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Kırıkkale, Türkiye
E-Mail: ozcalk@yahoo.com
Received 24.03.17 accepted 29.05.2017
Doi: 10.18663/tjcl.300336

## Giriş

İdrar yolu enfeksiyonları (İYE) çocuklarda tanı ve tedavisi özel ilgi gerektiren bir hastalık grubudur. Üst İYE çocuklarda kronik böbrek yetmezliği, hipertansiyon gibi kalıcı hasarlar oluşturması bakımından önemlidir[1,2]. Ayrıca mortalitesi yüksek olan ürosepsise de yol açabilmektedir[3]. Yaşamın ilk aylarında erkeklerde daha sık görülürken daha sonraki dönemlerde, üretranın daha kısa olması nedeniyle, kızlarda daha sık görülür. Bunun nedeni erkek çocuklarında üriner sistemin anomalilerinin daha fazla görülmesidir [4, 5]. Genel olarak ilk 6 yaşta sıklığı kızlarda %4-8 iken erkeklerde %1-2'dir[1-4]. İlk enfeksiyondan sonra ise risk %13-20 kat artmaktadır [6-8]. İdrar yolu enfeksiyonları alt İYE (sistit) ve üst İYE (pyelonefrit) olarak iki gruba ayrılır. Hem alt hem üst İYE'nda en fazla izole edilen etken %80 civarında üropatojen Escherichia coli'dir [9,10]. Daha sonra ise Proteus, Klebsiella, Pseudomonas ve Enterobakter türleri İYE'e neden olan etkenler arasında yer alır [11,12]. Mantarlar genelde mesane kateteri ile izlenen hastalarda etken olabilmektedir [13].

## Klinik

Alt İYE semptomları genelde mesane ile sınırlıdır. İdrar yaparken ağrı, suprapubik hassasiyet, sık idrara çıkma, ani idrara çıkma isteği ile ortaya çıkabilir [14]. İki yaşından sonra sistit genel olarak kızlarda daha sık görülmektedir [15].

Pyelonefrit ateş, yan ağrısı, kusma gibi sistemik bulgularla karşımıza gelebilir. Bazen bakteriyemi, sistemik inflamatuar yanıt sendromu, septik şok ile de sonuçlanabilir [16]. İlk 2 ayda emmede azalma, büyüme gelişmede duraksama, kusma, sarılık gibi nonspesifik bulgularla ortaya çıkabilir [17-20]. Eğer fizik muayenede kostovertebral açı hassasiyeti, abdominal hassasiyet, suprapubik hassasiyet, palpable mesane varsa İYE yönünden hasta incelenmelidir [15].

Amerikan Pediatri Akademisi (AAP) 2 ay ile 2 yaş arası ateş yüksekliği ile getirilen her çocukta odak bulunmazsa mutlaka İYE'dan şüphelenilmesi gerektiğini belirtmektedir [20]. Yine küçük çocuklarda karın ağrısı ve kazanılmış tuvalet alışkanlığı olan çocuğun idrar kaçırması olması durumunda, 2 günden uzun süren ateş ve suprapubik hassasiyet varlığında da İYE akılda tutulmalıdır [17-20].

İdrar Yolu Enfeksiyonunda Rol Oynayan Faktörler

Yenidoğan ve infantlarda İYE riski artmaktadır [22,23]. Sünnetin İYE riskini azaltıcı etkisi vardır. İlk 3 ayda sünnetsiz çocuklarda %20 İYE görülürken, sünnetli çocuklarda bu oran %2'lere kadar düşmektedir [24-26]. Kabızlık İYE riskini artırır. Rektumun kronik olarak gaita ile dilate olması sonucu işeme disfonksiyonu oluşur. Buna bağlı olarak da enfeksiyon riski artar[27,28]. Üriner sistem patolojileri, fonksiyonel patolojiler, sistemik hastalıklar, immün yetmezlik İYE riskini artıran nedenlerdir [16-19, 28].

## Tanı

Tanı için hem idrarda piyürinin gösterilmesi hem de idrar kültüründe 100000 CFU/ml tek bir patojenin ürediğinin gösterilmesi gerekmektedir. İdrar tetkikinde lökosit esteraz, nitrit, protein, kan da bakılmalıdır Lökosit esteraz testi İYE'asensitif bir test iken nitrit pozitifliği İYE'de sensitivitesi yüksek olup spesifitesi düşüktür. Bu testler tanıda yol göstermesi açısından önemlidir[14,21].

Piyüri; santrifüj edilen idrarda mikroskopta 40'lık büyütmede, her alanda 5'den fazla lökosit görülmesidir. Tanıda tek başına yeterli değildir [29]. Çünkü tüberküloz, vajinit, ateş yüksekliği, dehidratasyon gibi durumlarda steril piyüri olabilmektedir [26].

Hastalardan idrar alım yöntemi hala tartışmalıdır. 2 yaş altında İYE şüphesi varsa kontaminasyon riskini azaltmak için önerilen yöntem suprapubik aspirasyon (SPA) ve transüretral kataterdir [16,21]. Fakat SPA yöntemi invaziv ve stres verici bir yöntemdir ve her zaman uygulanabilir değildir [14,21]. Esas olarak önerilen yöntem orta akım idrarıdır [30].

Torba ile idrar alma, mesane kontrolü gelişmemiş hastalarda invaziv olmayan kolay bir yöntemdir. Fakat, torba idrarının da yanlış pozitiflik oranı oldukça yüksektir. Torba idrarının tek amacı İYE tanısını ekarte etmektir. Eğer kültür negatif çıkarsa İYE yoktur anlamına gelir, güvenilirdir [21,30]. İdrar kültüründe üretilen koloni sayısı önemlidir. Eğer idrar örneği, suprapubik aspirasyon ile alınmışsa koloni sayısına bakılmaksızın üreme pozitif kabul edilir, mesane katateri ile alınmışsa 103-105CFU/L, orta akım örneği alınmışsa 105CFU/L üreme pozitif kabul edilir [30].

Aşağıdaki durumlardan biri varsa kontaminasyon düşünülmeli ve hastanın semptomu, üriner sistem anomalisi veya İYE öyküsü varsa kültür tekrarlanmalıdır [31].

-Torba idrarında üreme varsa

-Birden fazla koloni türü üremişse

-Deri florasından üreme olmuşsa

-Pozitif sayılan miktardan az sayıda üreme olmuşsa

## Tedavi

Asıl hedef enfeksiyonu tedavi edip, İYE'ye bağlı gelişecek komplikasyonları önlemek olmalıdır. Hastada ateş varsa ampirik tedavi başlanıp daha sonra kültür sonucuna göre tedaviye devam edilmelidir [14]. Tedavi süresi 2007 NICE klavuzuna göre 7-10 gün, Amerikan pediatri akademisi (AAP) verilerine

göre 7-14 gün tedavinin sürdürülmesi önerilmektedir [21,30].

Eğer hastada klinik semptom varsa idrar örneğinde lökosit esteraz ve nitrit pozitif ise veya idrarda bakteriüri görülürse tedaviye hemen başlanması ve idrar kültürüne göre devamı önerilir [21]. Antibiyotik seçimi hastanın yaşı, eşlik eden üriner sistem anomalisi, eşlik eden hastalık ve hastanın genel durumuna göre değişiklik göstermektedir [14]. Başlangıçta oral alımı tolere edemeyen hastalarda 2-3 gün kadar parenteral tedavi verildikten sonra oral antibiyotik ile tedavinin tamamlanması önerilmektedir [21,30]. Septik görünümlü hastalara, 1 ayın altındakilere, oral tedaviyi tolere edemeyenlere, immün yetmezliği olanlara ve ayaktan takip ve tedavisi mümkün olmayan hastalara parenteral tedavi verilmesi uygundur [14,21,30]. Ayrıca tedavide 48 saat içinde yanıt alınamazsa tekrar değerlendirme yapılmalıdır. Antibiyotik seçerken dikkatli olunmalıdır. Lokal bölgesel antibiyotik direncine göre antibiyotik seçilmelidir [14,15].Hasta 3 aydan büyük ve sistit düşünülüyorsa 2-4 günlük tedavi süresi yeterli olacağı düşünülmektedir [30,31]. Etken çoğunlukla E.Coli olduğu için seçilecek tedavi önemlidir. Genelde amoksisilin ve ampisilin direnci görülebilir. Üçüncü kuşak sefalosporinler veya aminoglikozitler seçilecek ampirik tedavide parenteral olarak önerilmektedir Oral tedavide de sefalosporinler tercih edilebilir [19-25].

## Profilaksi

Profilakside amaç İYE'nun tekrarlamasını önlemektir. Tek sefer geçirilmiş İYE sonrası profilaksinin etkinliği kanıtlanmamıştır [14,21]. Amerikan pediatri akademisi ve NICE 2007 verilerine göre profilaksi yüksek dereceli vezikoüreteral reflü (VUR) varsa önerilmektedir [21,30].

## Görüntüleme

Rehberlere göre ateşli İYE geçiren tüm hastalara ve 2 ayın altında İYE geçiren tüm hastalara ultrasonografi (USG) önerilmektedir [14,15,21]. Ultrasonografi noninvaziv olması ve radyasyon riski taşımaması açısından önemlidir. Böbrek hasarını, böbrek boyutlarını göstermede, hidronefroz gibi üriner sistem anomalilerini tespit etmede faydası vardır [15,17,32]. Fakat USG ile böbrek anomalilerinin %60'ı, VUR'un ise%50'si tespit edilmekte olup kalan kısmı gözden kaçmaktadır [16-18]. Hastada VUR tanısı için voiding sistoüretrografi (VSUG) yapılmalıdır. Çocukların yaklaşık %30'nda ilk İYE esnasında VUR tespit edilmektedir [15,33]. Rehberlere göre 2 yaşın altındaki çocukta ateşli İYE ile birlikte USG'de hidronefroz ve renal skar gibi bulgular var ise VCUG istenmesi önerilmektedir [33,34].

Renal parankimal hasar Tc99m ile işaretli dimerkaptosüksinik asit (Tc99m-DMSA) ile görüntülenebilir [34]. Bu tetkik tekrarlayan İYE'da enfeksiyondan 4-6 ay sonra yapılmalıdır[16].

Sonuç olarak İYE'nun çocuklarda görülme sıklığı oldukça fazladır. Özellikle üst İYE çocukluk çağında morbiditesi yüksek bir hastalıktır. Bu nedenle erken tanı, doğru tedavi ve düzenli izlem önem taşımaktadır.

## Çıkar çatışması / finansal destek beyanı

Bu yazıdaki hiçbir yazarın herhangi bir çıkar çatışması yoktur. Yazının herhangi bir finansal desteği yoktur

## Kaynaklar

1. Bachur R, Harper MB. Reliability of the urinalysis for predicting urinary tract infections in young febrile children. Arch Pediatr Adolesc Med 2001; 155: 60–65.
2. Byington CL, Rittichier KK, Bassett KE, Castillo H, Glasgow TS, Daly J, Pavia AT. Serious bacterial infections in febrile infants younger than 90 days of age: the importance of ampicillin resistantpathogens. Pediatrics 2003; 111: 964–68.
3. Spencer JD, Schwaderer A, McHugh K, Hains DS. Pediatric urinary tract infections: an analysis of hospitalizations, charges, andcosts in the USA. Pediatr Nephrol 2010; 25: 2469–75
4. American Academy of Pediatrics. The diagnosis ,treatment and evaluation of the initial urinary tract infection febrile infants and youngchildren. Pediatrics 1999; 103: 843-52.
5. Miyazaki Y, Ichikawa I. Ontogeny of congenitalanomalies of the kidney and urinary tract, CAKUT Pediatr Int. 2003; 45: 598–604.
6. The RIVUR Trial Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med 2014; 370: 2367–76
7. Conway PH, Cnaan A, Zaoutis T et al. Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. JAMA 2007; 298: 179–86
8. Harmsen M, Wensing M, Braspenning JCC et al. Management of children'surinarytractinfections in Dutchfamilypractice: a cohortstudy. BMC Fam Pract 2007; 8: 9
9. Chowdhury P, Sacks SH, Sheerin NS. Minireview: functions of the renal tract epithelium in coordinating the innate immuneresponse to infection. Kidney Int 2004; 66: 1334–44.
10. Mulvey MA, Schilling JD, Martinez JJ, Hultgren SJ. Bad bugs and beleaguered bladders: interplay between uropathogenic Escherichia coli and innate host defenses. Proc Natl Acad Sci 2000; 97: 8829–35.
11. Chakupurakal R, Ahmed M, Sobithadevi DN, Chinnappan S, Reynolds T. Urinary tract pathogens and resistance pattern. J Clin Pathol 2010; 63: 652-54.
12. Lutter SA, Currie ML, Mitz LB, Greenbaum LA. Antibiotic resistance patterns in children hospitalized for urinary tract infections. Arch Pediatr Adolesc Med 2005; 159: 924-28

13. Edlin RS, Shapiro DJ, Hersh AL, Copp HL. Antibiotic resistance patterns of out patient paediatric urinary tract infections. J Urol 2013; 190: 222–27.
14. Becknell B, Schober M, Korbel L, Spencer JD. Thediagnosis, evaluation and treatment of acute and recurrent pediatric urinary tract infections. Expert Rev Anti Infect Ther 2015; 13: 81-90
15. Donna J. Pediatric Urinary Tract Infection. Updated: Aug 01, 2016 http://emedicine.medscape.com/article/969643-overview#a5
16. Bitsori M, Galanakis E. Pediatric urinary tract infections: diagnosis and treatment. Expert Rev Anti Infect Ther 2012; 10: 1153–64.
17. Tanaka ST, Brock JW 3rd. Pediatric urologic conditions, including urinary infections. Med Clin North Am 2011; 95: 1–13
18. Bhat RG, Katy TA, Place FC. Pediatric urinary tract infections. Emerg Med Clin North Am 2011; 29: 637–53
19. Afzal N, Qadir M, Qureshi S, Ali R, Ahmed S, Ahmad K. Urinary tract infection presenting as jaundice in neonates. J Pak Med Assoc 2012; 62: 735–37.
20. Pashapour N, Nikibahksh AA, Golmohammadlou S. Urinary tract infection in term neonates with prolonged jaundice. Urol J 2007; 4: 91-94
21. Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2011; 128: 595–610
22. Chang SL, Shortliffe LD. Pediatric urinary tract infections. Pediatr Clin North Am 2006; 53: 379–400.
23. Hanson LA. Esch. Coli infections in childhood. Significance of bacterial virulence and immune defence. Arch Dis Child 1976; 51: 737–43
24. Conway PH, Cnaan A, Zaoutis T, Henry BV, Grundmeier RW, Keren R. Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. JAMA 2007; 298: 179–86.
25. Circumcision Policy Statement. American Academy of Pediatrics. Pediatrics 1999; 103: 686-93
26. Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. Pediatr Infect Dis J. 2008; 27: 302-8
27. Kayaba H, Tamuta H, Kitajima S, Fujiwara Y, Kato T. Analysis of shape and retractibility of the prepuce in 603 Japanese boys. J Urol 1996; 156: 1813-15.
28. Romańczuk W, Korczawski R. Chronicconstipation: a cause of recurrent urinary tract infections. Turk J Pediatr 1993; 35: 181-88.
29. Hansson S, Jodal ULF. Urinary tract infection. In: Barratt TM, Avner ED, Harmon WE (eds). Pediatric Nephrology. Lippincott Williams&Wilkins, Baltimore 1999; 835–50.
30. NICE Clinical Guidelines (2007). Urinary tract infection in children: Diagnosis, treatment and long-term management. Retrieved May 23, 2014, from http://publications.nice.org.uk/urinary-tract-infection-in-children-cg54.
31. McTaggart S, Danchin M, Ditchfield M at all. KHA-CARI guideline: Diagnosis and treatment of urinary tract infection in children. Nephrology 2015; 20: 55-60.
32. Tekgül S, Riedmiller H, Hoebeke P, Kočvara R, Nijman RJ, Radmayr C, Stein R, Dogan HS; European Association of Urology. EAU guidelines on vesicoureteral reflux in children. Eur Urol 2012; 62: 534-42.
33. McDonald A, Scranton M, Gillespie R, Mahajan V, Edwards GA. Voiding cystourethrograms and urinary tract infections: how long to wait? Pediatrics 2000; 105: 50.
34. Mahant S, To T, Friedman J. Timing of voiding cystourethrogram in the investigation of urinary tract infections in children. J Pediatr 2001; 139: 568-71

To cite this article: Demirel S, Yildiz K, Cadirci K, Senocak E. An etiological searching for multiple displaced metatarsal stress fractures . Turk J Clin Lab 2018(9); 1: 70-72.

Case Report

# An etiological searching for multiple displaced metatarsal stress fractures

## *Çoklu yer değiştirmiş metatarsal stres kırığının etiyolojik araştırması*

Esra DEMIREL[1], Kadri YILDIZ*[2], Kenan CADIRCI[3], Eyüp SENOCAK[2]

[1]Erzurum Training and Research Hospital, Department of Orthopedics and Traumatology, Erzurum
[2]Palandoken State Hospital, Department of Orthopedics and Traumatology, Erzurum
[3]Erzurum Training and Research Hospital, Department of Internal Medicine, Erzurum, TURKEY

## ABSTRACT

Metatarsal fracture that is improved by using low-dose cortico-steroid for a long time due to secondary osteoporosis reason by rheumatoid arthritis. 53 year-old female patient use low-dose cortico-steroid for 12 years due to Rheumatoid Arthritis. At the last clinicak trials, multiple metatarsal fractures occured before 3 months. Multilpe metatarsal fracture were fixed by conservative treatment on the serial clinical trials for 3 month. In patients which have used corticosteroid, even if low-dose, fractıres can be seen on the unusual bones.

**Keywords:** Secondary osteoporosis, multiple metatarsal faractures, corticosteroids, stress fractures

## ÖZ

Romatoid artrite bağlı olarak uzun süreli düşük doz kortikosteroidlerle yapılan tedavi sonucu gelişen sekonder osteoporozla oluşan çoklu metatarsal kırık sunulmaktadır. Elli üç yaşında kadın hasta 12 yıldır romatoid artrit nedeniyle düşük doz kortikosteroid kullanmaktadır. Son klinik kontrollerde yaklaşık 3 ay önce çoklu metatarsal kırıklar meydana gelmiştir. Yapılan 3 aylık seri poliklinik kontrollerinde hastanın çoklu metatars kırığı konservatif tedavi ile iyileşmiştir. Romatoid artritli hastalarda uzun süreli, düşük doz olsa bile, kortikosteroid kullanılan hastalarda, alışılmadık kemiklerde kırıklar açısından görülebilmektedir.

**Anahtar kelimeler:** Sekonder osteoporoz, çoklu metatarsal kırık, kortikosteroidler, stres kırığı

## Introduction

Some multiple factors are effective on stress fractures of metatarsal bones. This type of fracture was seen occasionally on women, especially at the menopausal period due to bone resorption. Stress fractures occured on sportive people, dancers by repetetive micro-traumas. Fracture type is generally away from metatarsal basement at this type [1]. Generally, prodromal pain episodes during weeks are the point of discussion. Differential diagnosis is hard and important [2].

In rheumatological diseases have been observed in a rate of 0.8% of non-traumatic insufficiency fractures. The most common sites of insufficiency fractures are pelvis, sacrum, tibia, the sections

Corresponding Author*: Kadri YILDIZ, Palandoken State Hospital, Department of Orthopedics and Traumatology, Erzurum
E-Posta: drkadri1980@hotmail.com, drkadri1980@gmail.com
Received 23.01.2017 accepted 13.03.2017 Doi: 10.18663/tjcl.286960
Doi: 10.18663/tjcl.286960

near to the insertion of the fibula, calcaneus and buttocks. Generally, bone-joint involvement in rheumatic diseases and osteoporosis connected with prolonged use of corticosteroids prepares the ground for these insufficiency fractures [3].

In this paper, present the metatarsal fractures which we have identified in an unexpected localization in a patient the diagnosis of rheumatoid arthritis who has been secondary osteoporosis for a long time use of low-dose steroids were presented.

## Case Report

53-year-old male patient admitted to orthopaedic policlinic because of the starting complaints pain and swelling in his left foot since 25 days. At the anamnesis, he has been diagnosed as Rheumatoid Arthritis approximately for 12 years. The patient was using low-dose corticosteroids without a break since approximately the last two years. In the verified surveys, performed in and was verified avascular necrosis of the talus and common arthritic changes depend on Rheumatoid Arthritis foot-ankle involvement, there were sensitiveness with palpation and swelling in the metatarsal region of the patient's examination. In radiography, it was seen the displaced of 2nd, 3rd, 4th metatarsal basis' and nondisplaced fracture line in his 5th metatarsal basis, but it was intact of lisfranc joint (Figure 1).

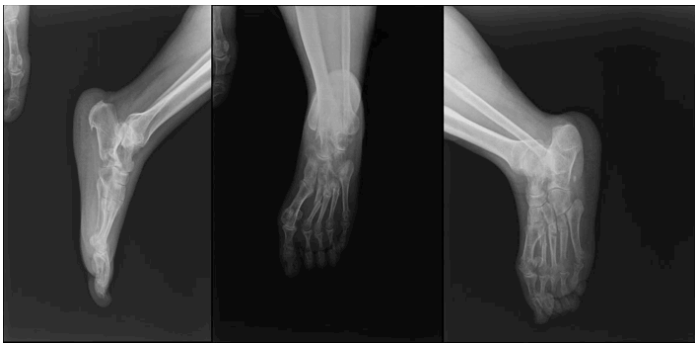


**Figure 1:** The patient's AP, oblique and lateral X-ray image.

At the diferential diagnosis, trauma was first searching progress; the patient's anamnesis was not compatible. Bone tumor or pathologic fracture due to malignancy was an other diagnostic parameter. But there was no malignancy or tumor on the clinical examination and laboratory outcomes of patient. And also, patient were not defining long-time walking. Patient have a unclear chronic minor trauma story just. Positive aspects for stress fractures at the patient were sedantary life-style, long-time walking story, Rheumatoid Arthritis and long-term corticosteroid use. Negative aspects were absence of any major trauma story and malignancy.

The patient's L1-L4 T-Score was found of -3.2. Patient have not received any treatment for osteoporosis. 25(OH)D levels was under 20 ng/Ml (18.7).

Patient's corticosteroid drug were stopped immediately. And patient's low extremity were take in rest by cast and ambulation by walking were inhibited. The patient which treated of orthopedic aspects, was started Alendronate sodium 70 mg and 2800 IU Vitamin $D_3$ treatment.

## Discussion

Stress fractures described in athletes and soldiers with an incidence of 5–30% [2]. At the clinical stress fracture there is a mismatch between the strength of the bone and the amount of mechanical stress. It is mainly found in weight-bearing bones such as the tibia, metatarsals, and calcaneus 3. Iimmobilization, joint deformities, and steroid treatment are associated with rheumatoid arthritis and are also known risque factors for fractures.

Stress fractures are classified into two type: insufficiency and fatigue fractures. Insufficiency fracture is a type of stress fracture which is the result of normal load on abnormal bone and is especially seen in osteoporosis. Common seen body regions are the vertebrae, tibia, the sacrum, and the femur. A fatigue fracture is a type of stress fracture that is the result of abnormal or chronic repeatetive stresses on normal bone. The "march fractures" of the metatarsal bones are well known.

Stress fractures are well recognised complication in arthritic patients.1-6. Osteopenia (juxta- articular or generalised) caused by extensive rheumatoid involvement, corticosteroid treatment, or relative immobility is a predisposing factor. Deformations, flexion contractures and increased mobility after arthroplasties leading to increased stress on juxta-articular bone also contribute to this type of stress fractures. And also; stress fractures in rheumatoid arthritis (RA) preferentially affect the long bones of the legs, the neck of the femur, and the pelvis 2.

Symptoms of stress fractures included osteoporosis, bone pain, and insufficiency fractures, especially at the lower extremity. At the condition of drug stopping, pain of stress fractures reduced and the fracture healed. There is no evidence of loss of bone density is seen in patients with rheumatoid arthritis [8]. At the insufficiency fracture conventional radiographics may no demonstrate abnormalities. Magnetic resonance imaging or bone scintigraphy can prove the diagnosis. In the insufficiency fractures are more common in patients with joint diseases such as rheumatoid arthritis. If stress fracture of a long bone is suspected but not shown by plain radiology, either computerized tomography, magnetic resonance imaging or bone scintigraphy is recommended, depending on the medical community.

Stress fractures must be considered at the arthritic patients when there is pain in the foot, aggravated by weight. Symptoms caused by stress fractures, especially of the lower extremity, should be discriminated from active synovitis.

The clinical aspects of pain, aggravated by weight, in the leg should lead to a consideration of stress fractures. If the radiographic x-ray studies do not provide a diagnosis an adequate diagnostic procedure should be applicated. Although 99mTc bone scintigraphy is sensitive for bone disorders which correlate with increased osteoblast activity. But this procedure is not specific for this condition. Both computed tomography and magnetic resonance imaging (in later stages of the disease) can provide a definite diagnosis 2.

The frequency of osteoporosis in patients with rheumatoid arthritis ranges from 4 to 24% and the frequency of osteopenia ranges from 28 to 61.9%. Glucocorticoid use was associated with decreased bone mass in 56.2% of subjects with RA. The rate of non-union was 7-28% even though immobilization treatment for 6 or 8 weeks. O'Malley, Hamilton, Muniak, DeFranco described metatarsal stress fractures on the 51 ballets.

There are multiple risque factors for insufficiency fractures. The pain had an acute onset after a minimal trauma. The patient had been immobile for a week because of the pain. Reduced mobility increases the risque of insufficiency fractures. It is described that chronic use of low- dose corticosteroids can also negatively affect the bone metabolism and increase the risque of fractures[10]. Rheumatoid arthritis can cause local and systemic osteoporosis and abnormal bone turn-over[11]

Cortico-steroids are possible risque factors for insufficiency fractures in patients with rheumatoid arthritis, although a causal link between cortico-steroid and insufficiency fractures is debatable. Osteopathy due to cortico-steroids should be considered .Withdrawal of the drug may be the best option in case of a proven fracture for stress fractures.

On the other hand, Dequekere and friends reported a study in which a cumulative, dose dependent, cortical bone loss at the radius in patients with rheumatoid arthritis treated with low dose methotrexate was found[12]. One must be careful to attribute this positive effect to the discontinuation of the drug, as fracture healing is dependent on multiple factors.

Corticosteroids are drugs of first choice in the treatment of inflammatory joint disorders such as rheumatoid arthritis and psoriatic arthritis. The drug may be responsible for insufficiency fractures in rheumatoid arthritis because of low bone turn over due to osteoblast inhibition. Its role remains debatable due to multiple risque factors for fractures, such as disease activity, immobilization, or corticosteroid use. Stop corticosteroids therapy is advisable to to enhance fracture healing.

## Declaration of conflicting interests

The author declared no conflicts of interest with and no financial support respect to the authorship and/or publication of this article.

## References

1. Hooghof J, Mellema JJ, Marcel D et al. A.Woman with Rheumatoid Arthritis and a Bilateral Fracture of the Proximal Tibia Case Report in Orthopaedics. 2016; Article ID. 5094906. Pages:4.
2. Matthew B Dobbs, Joseph Buckwalter, Charles Saltzman. Osteoporosis: The Increasing Role of the Orthopaedist Iowa Orthop J 1999; 19: 43–52.
3. Dennis M. Black. N. Bisphosphonates and Fractures of the Subtrochanteric or Diaphyseal Femur Engl J Med 2010; 362: 1761-71.
4. Esbrit P, Alcaraz MJ. Current perpective on parathyroid hormone (PTH) and PTH related protein (PTHrP) as bone anabolic therapies. Biochem Pharmacol 2013; 85: 1417-23.
5. Baer GJ. Ractures in chronicsarthritis . Ann Rheum Dis 1940; 2: 269-73.
6. Schneider R, Kaye JJ. Insufficiency and stress fracture of the long bones occuring in patients with rheumatoid arthritis. Radiology 1975;116:595-9.
7. Ansell G, Evans S, Jackson CT, Lewis-Jones S. Cytotoxic drugs for non-neoplstic disease. BMJ 1983; 287: 762.
8. S. Terry Canale. Campell Operative Orthopaedics. Turkish Edition. Volume 4, 10 th Edition, page: 4271.
9. Lems WF, Van Veen GJM, Gerrits MI et al. Effect of low-dose prednisone (with calcium and calcitriol supplementation) on calcium and bone metabolism in healthy volunteers. British J Rheumatol 1998; 37: 27-33.
10. Geusens P and Lems WF. Osteoimmunology and osteoporosis Arthritis Research Ther 2011; 13: 242.
11. Avacini-Dobrovic V, Vrbanic TS, Kukuljan M, Stamenkovic D, CicvaricT, Jurdana H, Dubrovic D. Spontaneous serial fractures of metatarsal bones in famele patient with rheumatoid arthritis on long –term steroid therapy. Coll Antropol 2012; 34: 1123-6.
12. Dequeker J, Maenaut K, Verwilghen J, Westhovens R. Osteoporosis in rheumatoid arthritis. Clin Exp Rheumatol. 1995; 13: 21-6.
13. Rademaker M. Low dose oral steroids can increase fracture risk. Prescriber-Update 2002; 23: 6-7

Turkish Journal of Clinics and Laboratory

To cite this article: Yalcinkaya S. A case of foreign body aspiration diagnosed 5 years after the incident. Turk J Clin Lab 2018 (9); 1: 73-75.

Case Report

# A case of foreign body aspiration diagnosed 5 years after the incident

## *Oluşundan 5 yıl sonra tanı konmuş yabancı cisim aspirasyonu*

Serhat YALCINKAYA*

Dumlupinar University Medical School, Department of Thoracic Surgery, Kutahya, Turkey

**ABSTRACT**

Foreign body aspiration is rare in adult patients. The aspirated materials may be of various kinds and may not be diagnosed for a long period of time. The patients sometimes are even misdiagnosed and may be treated as asthma, pneumonia, and chronic obstructive pulmonary disease patients. A 72-year-old male patient treated as such was discovered to have a foreign body aspiration 5 years after the incident. The clinical presentation, history, and treatment are presented.

**Keywords:** Aspiration, bronchoscopy, speaking valve.

**ÖZ**

Erişkinlerde yabancı cisim aspirasyonu nadir olup çeşitli maddelerle gelişebilir. Şikayetlerin azlığı nedeniyle uzun süre fark edilmeyebilir. Hastalar bazen yanlışlıkla astım, pnömoni ve kronik obstrüktif akciğer hastalığı var sanılarak tedavi edilebilir. Benzer şekilde takip ve tedavi edilen 72 yaşında bir erkek hastada gerçekleştikten 5 yıl sonra tespit edilen bir yabancı cisim aspirasyonu olgusunun klinik bulguları, öyküsü ve tedavi sonuçları paylaşılmaktadır.

**Anahtar kelimeler:** Aspirasyon, konuşma protezi, bronkoskopi.

Corresponding Author[a]: Serhat Yalcinkaya, Dumlupinar University Medical School, Department of Thoracic Surgery, Kutahya, Turkey
E-Mail: serhat.yalcinkaya@dpu.edu.tr
Recevied 30.03.2017 accepted: 21.04.2017
Doi: 10.18663/tjcl.302667

## Introduction

Foreign body (FB) aspiration is rare in adults [1]. The reported FBs include bone, pins, plant particulates, and speaking valves [2-6]. Usually these patients need urgent medical attention after aspiration. Yet, there are late diagnosed FB cases reported in literature as late as 10 years, indicating FB aspiration in adults may be surprising [2]. These patients may be misdiagnosed and treated as asthma, pneumonia, and or chronic obstructive pulmonary disease (COPD) patients [1, 6]. In this report, we would like to share a patient with a late diagnosed FB aspiration in the light of clinical presentation, history, and treatment of patient in our department.

## Case Report

A 72 year-old male patient was referred to our Thoracic Surgery Department with a possible diagnosis of bronchial tumor in the right main stem bronchus. From his medical history a total laryngectomy due to larynx epidermoid carcinoma with tracheostomy 5 years ago was noted. During follow-up controls, he complained of cough and dyspnea for the last year. His physician ordered a chest computed tomography (CT) scan and discovered a mass lesion on the right lung (Figure 1). He was receiving maximum bronchodilator therapy due to COPD diagnosis. Since tracheostomy patients maybe not be suitable for rigid bronchoscopy, the patient was referred to the local pulmonology hospital for fiberoptic bronchoscopy. The intervention revealed an unknown FB in the right main stem bronchus. The patient was referred back to us for a session of rigid bronchoscopy. We performed rigid bronchoscopy using a size 6.5 Storz bronchoscope (KARL STORZ GmbH & Co., Tuttlingen, Germany) tube under general anesthesia. During the procedure a FB was seen in the right main stem bronchus with a prominent granulation tissue surrounding it (Figure 2). Using an alligator grasping forceps two pieces of plastic material were removed, later understood to be parts of a speaking valve (Figure 3). The patient was transferred to the ward after the procedure. On the following day while questioning his medical past in detail, the relatives of the patient told that he had a hard time using and declined to use the valve right after the laryngectomy operation. Neither he nor the physicians followed him noticed the device parts were aspirated. His respiratory symptoms recovered right after the procedure, and the patient was discharged on day two without any bronchodilators.

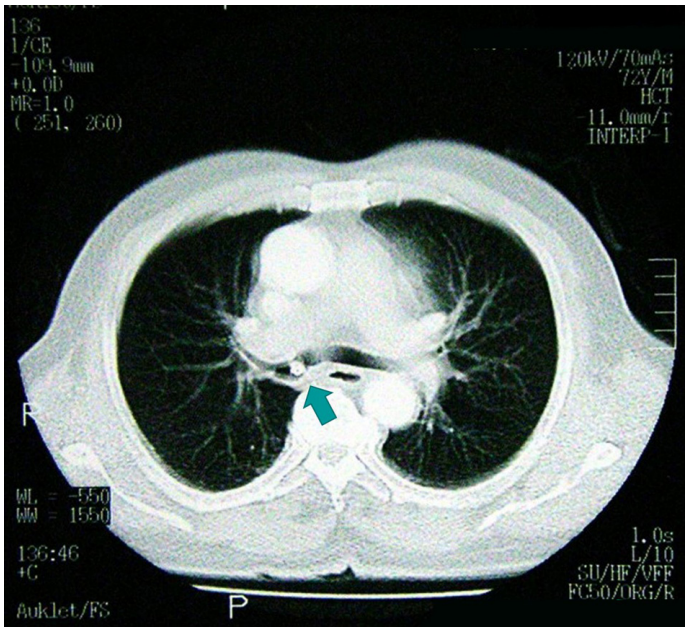


**Figure 1.** Chest computed tomography scan showing a mass lesion (arrow) in the right main stem bronchus.

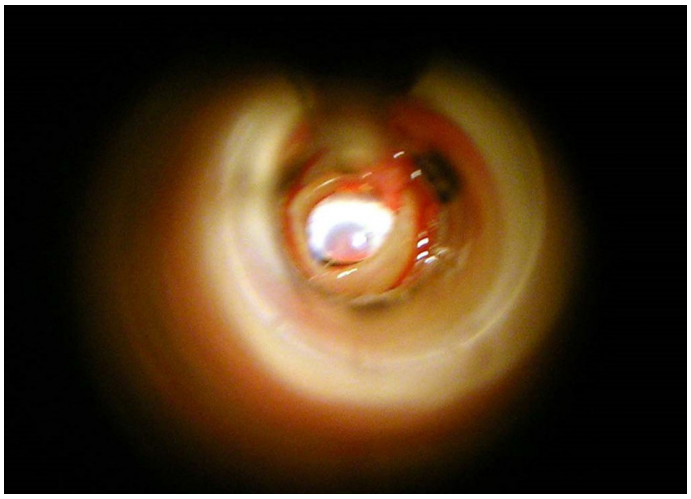


**Figure 2.** Rigid bronchoshopy revealed a foreign body with surrounding granulation.

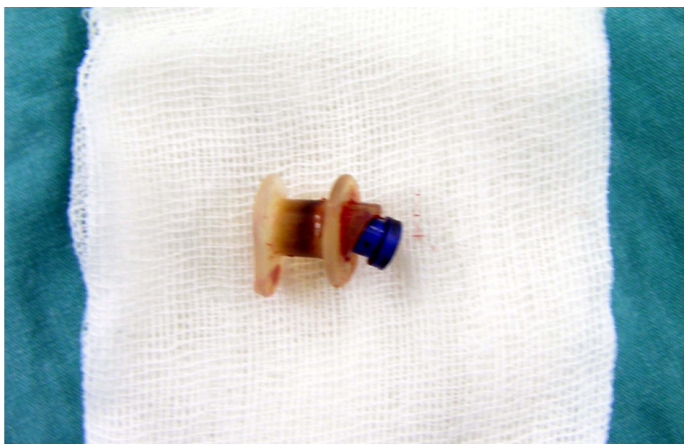


**Figure 3.** The plastic materials removed were parts of a speaking valve.

## Discussion

FB aspiration is common in children, especially under 3 years of age [6]. In the adults, however, it is rare and the patients usually have accompanying physical and mental issues, as well as alcoholism [1, 6]. While the classical triad of cough, dyspnea, and cyanosis is frequent in children, they occur in only few adult patients [1]. This lack of acute symptoms may be due to the larger caliber of airways, leading most FBs placing and obstructing more distal airways [2]. The most common symptoms of a FB aspiration are: cough, choking, dyspnea, fever, and hemoptysis [1, 6]. Our patient had cough and dyspnea.

FBs are placed more frequently in the right bronchial tree [1, 6]. Various materials are reported and may be classified as organic (e.g. bone fragments (especially chicken), fish bones, pieces of vegetables or fruits), and inorganic (e.g. pins, screws, rivets or plastic devices) substances. It may be advisable to name a third group of substances as iatrogenic including pieces of speaking devices, tracheostomy cleaning brushes or dental bridges [1]. Recently some investigators reported on speaking valve aspiration in tracheostomy patients [3-5].

In 2010 Kadam et al reported on a 73-year-old male patient underwent total laryngectomy and received radiotherapy 18 years earlier than the administration to the hospital due to a sudden onset of respiratory distress symptoms including sitting upright, looking pale, having stridor and unable to vocalize [3]. Emergency flexible nasoendoscopic examination unveiled the aspirated speaking valve. They removed the valve using a rigid bronchoscope. Schembri et al reported on a 70-year-old male patient underwent laryngectomy operation some 12 years ago and had dyspnea on minimal exertion and he was also noted to have a chronic cough. Chest CT revealed an opacity in the right main stem bronchus. Although flexible bronchoscopy was preferred, the FB was implanted within the granulation tissue, so the investigators had to use the rigid bronchoscopy to stabilize the flexible bronchoscopy under general anesthesia. They removed the speaking valve probably been there for 12 years [4]. Quinn et al reported on a 75 year-old male patient with treated larynx and lung carcinoma presented with weight loss, general malaise, dyspnea and cough present for 2 months [5]. As he had previous malignancies and weight loss, a chest CT was ordered. The CT revealed a little soft tissue change in the right main stem bronchus taken as related to retained secretions. During rigid bronchoscopy, the speaking valve was seen and removed with success. Our patient was 72 years old and had a history of laryngectomy due to larynx carcinoma 5 years ago. Because of his medical history and complaints, a chest CT was ordered and a lesion then thought to be a malignancy was discovered in the right main stem bronchus.

Age group effects the kind of the bronchoscope preferred in FB removal, as well. In children, rigid bronchoscope is accepted as the safest way, whereas in the adult flexible bronchoscopy is widely used [1]. Yet, in situations like abundant granulation tissue surrounding the FB, large FBs, sharp edged FBs, and unsuccessful attempts with flexible bronchoscopy leads to use of rigid instead of flexible bronchoscope [1]. We preferred to use rigid bronchoscope as the attempts with the flexible bronchoscopy were unsuccessful, due to abundant granulation tissue.

Recovery following removal of the FB is usually complete and fast [2]. The patients reported in literature usually recovered totally and are discharged from the hospital within few days without any complications [3-5]. We discharged our patient without any complications on day two following bronchoscopic removal. On the first day following removal, he didn't need any bronchodilators, as well.

We conclude that FB aspiration in the adults can only be recognized if kept in mind. Reports of cases in the literature suggest this view. In case of suspicion, a chest thorax CT may be preferred over chest x-ray, and rigid bronchoscopy should be the treatment of choice.

## Declaration of conflicting interests

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

## Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

## References

1. Blanco Ramos M, Botana-Rial M, Garcia-Fontan E, Fernandez-Villar A, Gallas Torreira M. Update in the extraction of airway foreign bodies in adults. J Thorac Dis. 2016;8(11):3452-6.
2. Wang L, Pudasaini B, Wang XF. Diagnose of occult bronchial foreign body: A rare case report of undetected Chinese medicine aspiration for 10 long years. Medicine (Baltimore). 2016;95(31):e4076.
3. Kadam VR, Lambert P, Pant H, O'Reilly M. 'Speaking valve' aspiration in a laryngectomy patient. Anaesthesia and Intensive Care. 2010;38(1):197-200.
4. Schembri J, Cortis K, Mallia Azzopardi C, Montefort S. Aspiration of a speaking valve. BMJ Case Rep. 2013;2013.
5. Quinn K, Rowan SA, Rendall J. An unusual cause of pneumonia: seen but not heard. BMJ Case Rep. 2013;2013.
6. Cobanoglu U, Yalcinkaya I. Tracheobronchial foreign body aspirations. Turkish Journal of Trauma & Emergency Surgery. 200;15(5):493-9.

TURKISH JOURNAL of CLINICS and LABORATORY

Türk Klinik ve Laboratuvar Dergisi

Turkish Journal of Clinics and Laboratory - Türk Klinik ve Laboratuvar Dergisi

Tıp dergilerine gönderilecek makalelerin standart gereksinmeleri ile ilgili tüm bilgileri www.icmje.org internet adresinde bulabilirsiniz

**Amaç ve kapsam:** "Turkish Journal of Clinics and Laboratory", hakemli, açık erişimli ve periyodik olarak çıkan, DNT Ortadoğu Yayıncılık A.Ş. ye ait bir dergidir. Hedefimiz uluslararası bir tabanda hastalıkların teşhis ve tedavisinde yenilikler içeren yüksek kalitede bilimsel makaleler yayınlamaktır. Yılda dört kez çıkan bir bilimsel bir tıp dergisidir. Hakemli bir dergi olarak gelen yazılar konsültanlar tarafından, öncelikle, biyomedikal makalelere ait Uluslararası Tıp Dergileri Editörleri Komitesi (www.icmje.org adresinden ulaşılabilir) tarafından tanımlanan standart gereksinimler ile ilgili ortak kurallara uygunluğu açısından değerlendirilir. Tıbbın her dalı ile ilgili retrospektif/prospektif klinik ve laboratuar çalışmalar, ilginç olgu sunumları, davet üzerine yazılan derlemeler, editöre mektuplar, orijinal görüntüler, kısa raporlar ve cerrahi teknik yazılarıları yayımlayan bilimsel, uluslar arası hakemli bir dergidir. Başka bir dergide yayımlanmış veya değerlendirilmek üzere gönderilmiş yazılar veya dergi kurallarına göre hazırlanmamış yazılar değerlendirme için kabul edilmez.

On-line makale gönderimi: Tüm yazışmalar ve yazı gönderimleri dergipark üzerinden http://dergipark.gov.tr/tjcl yapılmalıdır. Yazı gönderimi için detaylı bilgi bu internet adresinden edinilebilir. Gönderilen her yazı için özel bir numara verilecek ve yazının alındığı e-posta yolu ile teyid edilecektir. Makalelerin "full-text" pdf formuna http://dergipark.gov.tr/tjcl linkinden ulaşılabilir.

**Açık erişim politikası:** Turkish Journal of Clinics and Laboratory açık erişimi olan bir dergidir. Kullanıcı lar yazıların tam metnine ulaşabilir, kaynak gösterilerek tüm makaleler bilimsel çalışmalarda kullanılabilir.

Aşağıdaki rehber dergiye gönderilen makalelerde aranan standartları göstermektedir. Bu uluslararası format, makale değerlendirme ve basım aşamalarının hızla yapılmasını sağlayacaktır.

**Yazarlara Bilgi:** Yazıların tüm bilimsel sorumluluğunu yazar(lar)a aittir. Editör, yardımcı editör ve yayıncı dergide yayınlanan yazılar için herhangi bir sorumluluk kabul etmez.

**Dergi adının kısaltması:** Turk J Clin Lab

Yazışma adresi: Yazılar e-mail yoluyla sorumlu yazar tarafından, Dergipark ta yer alan Turkish Journal of Clinics and Laboratory linkine girip kayıt olduktan sonra gönderilmelidir.

**Makale dili:** Makale dili Türkçe ve İngilizcedir. İngilizce makaleler gönderilmeden önce profesyonel bir dil uzmanı tarafından kontrol edilmelidir. Yazıdaki yazım ve gramer hataları içerik değişmeyecek şekilde İngilizce dil danışmanı tarafından düzeltilebilir. Türkçe yazılan yazılarda düzgün bir Türkçe kullanımı önemlidir. Bu amaçla, Türk Dil Kurumu Sözlük ve Yazım Kılavuzu yazım dilinde esas alınmalıdır.

**Makalenin başka bir yerde yayımlanmamıştır ibaresi:** Her yazar makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, editöre sunum sayfasında belirtmelidirler. 400 kelimeden az özetler kapsam dışıdır. Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal, vb.) yazarlara aittir.

**Değerlendirme:** Dergiye gönderilen yazılar format ve plagiarism açısından değerlendirilir. Formata uygun olmayan yazılar değerlendirilmeden sorumlu yazara geri gönderilir. Bu tarz bir zaman kaybının olmaması için yazım kuralları gözden geçirilmelidir. Basım için gönderilen tüm yazılar iki veya daha fazla yerli/yabancı hakem tarafından değerlendirilir. Makalelerin değerlendirilmesi, bilimsel önemi, orijinalliği göz önüne alınarak yapılır. Yayıma kabul edilen yazılar editörler kurulu tarafından içerik değiştirilmeden yazarlara haber verilerek yeniden düzenlenebilir. Makalenin dergiye gönderilmesi veya basıma kabul edilmesi sonrası isim sırası değiştirilemez, yazar ismi eklenip çıkartılamaz.

**Basıma kabul edilmesi:** Editör ve hakemlerin uygunluk vermesi sonrası makalenin gönderim tarihi esas alınarak basım sırasına alınır. Her yazı için bir doi numarası alınır.

**Yayın hakları devri:** http:/www.dergipark.ulakbim.gov.tr/tjclinlab adresi üzerinden online olarak gönderilmelidir. 1976 Copyright Act'e göre, yayımlanmak üzere kabul edilen yazıların her türlü yayın hakkı yayıncıya aittir.

**Makale genel yazım kuralları:** Yazılar Microsoft Word programı (7.0 ve üst versiyon) ile çift satır aralıklı ve 12 punto olarak, her sayfanın iki yanında ve alt ve üst kısmında 2,5 cm boşluk bırakılarak yazılmalıdır. Yazı stili Times New roman olmalıdır. "System International" (SI) unitler kullanılmalıdır. Şekil tablo ve grafikler metin içinde refere edilmelidir. Kısaltmalar, kelimenin ilk geçtiği yerde parantez içinde verilmelidir. Türkçe makalelerde %50 bitişik yazılmalı, aynı şekilde İngilizcelerde de 50% bitişik olmalıdır. Türkçede ondalık sayılarda virgül kullanılmalı (55,78) İngilizce yazılarda nokta (55.78) kullanılmalıdır. Derleme 4000, orijinal çalışma 2500, olgu sunumu 1200, editöre mektup 500 kelimeyi geçmemelidir. Özet sayfasından sonraki sayfalar numaralandırılmalıdır.

**Yazının bölümleri**

**1. Sunum sayfası:** Yazının Turkish Journal of Clinics and Laboratory 'de yayınlanmak üzere değerlendirilmesi isteğinin belirtildiği, makalenin sorumlu yazarı tarafından dergi editörüne hitaben gönderdiği yazıdır. Bu kısımda makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, maddi destek ve çıkar ilişkisi durumu belirtmelidir.

**2. Başlık sayfası:** Sayfa başında gönderilen makalenin kategorisi belirtilmedir (Klinik analiz, orijinal çalışma, deneysel çalışma, olgu sunumu vs).

**Başlık:** Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir. Tüm yazarların ad ve soyadları yazıldıktan sonra üst simge ile 1'den itibaren numaralandırılıp, unvanları, çalıştıkları kurum, klinik ve şehir yazar isimleri altına eklenmelidir.

Bu sayfada "sorumlu yazar" belirtilmeli isim, açık adres, telefon ve e-posta bilgileri eklenmelidir.

Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir.

**3. Makale dosyası: (Yazar ve kurum isimleri bulunmamalıdır)**

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir.

**Özet:** Türkçe ve İngilizce yazılmalıdır. Orijinal çalışmalarda özetler, Amaç (Aim), Gereç ve Yöntemler (Material and Methods), Bulgular (Results) ve Sonuçlar (Conclusion) bölümlerine ayrılmalı ve 250 sözcüğü geçmemelidir. Olgu sunumları ve benzerlerinde özetler, kısa ve tek paragraflık olmalıdır (150 kelime), Derlemelerde 300 kelimeyi geçmemelidir.

**Anahtar kelimeler:** Türkçe ve İngilizce özetlerin sonlarında bulunmalıdır. En az 3 en fazla 6 adet yazılmalıdır. Kelimeler birbirlerinden noktalı virgül ile ayrılmalıdır. İngilizce anahtar kelimeler "Medical Subject Headings (MESH)" e uygun olarak verilmelidir. (www.nlm.nih.gov/mesh/MBrowser.html). Türkçe anahtar kelimeler "Türkiye Bilim Terimleri' ne uygun olarak verilmelidir (www.bilimterimleri.com). Bulunamaması durumunda birebir Türkçe tercümesi verilmelidir.

**Metin bölümleri:** Orijinal makaleler; Giriş, Gereç ve Yöntemler, Bulgular, Tartışma olarak düzenlenmelidir. Olgu sunumları; Giriş, Olgu sunumu, Tartışma olarak düzenlenmelidir. Şekil, fotoğraf, tablo ve grafiklerin metin içinde geçtiği yerler ilgili cümlenin sonunda belirtilmeli metin içine yerleştirilmemelidir. Kullanılan kısaltmalar altındaki açıklamada belirtilmelidir. Daha önce basılmış şekil, resim, tablo ve grafik kullanılmış ise yazılı izin alınmalıdır ve bu izin açıklama olarak şekil, resim, tablo ve grafik açıklamasında belirtilmelidir. Tablolar metin sonuna eklenmelidir. Resimler/fotoğraf kalitesi en az 300dpi olmalıdır.

**Etik kurallar:** Klinik araştırmaların protokolü etik komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda, "Yöntem ve Gereçler" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklerasyonuna (www.wma.net/e/policy/b3.htm) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm insanların bilgilendirilmiş onam formunu imzaladığı metin içinde belirtilmelidir. Turkish Journal of Clinics and Laboratory gönderilen yazıların Helsinki Deklarasyonuna uygun olarak yapıldığını, kurumsal etik ve yasal izinlerin alındığını varsayacak ve bu konuda sorumluluk kabul etmeyecektir.

Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntemler bölümünde Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır.

**Teşekkür yazısı:** Varsa kaynaklardan sonra yazılmalıdır.

Maddi destek ve çıkar ilişkisi: Makale sonunda varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve varsa bu kuruluşların yazarlarla olan çıkar ilişkileri belirtilmelidir. (Olmaması durumu da "Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur" şeklinde yazılmalıdır.

**Kaynaklar:** Kaynaklar makalede geliş sırasına göre yazılmalıdır. Kaynaktaki yazar sayısı 6 veya daha az ise tüm yazarlar belirtilmeli, 7 veya daha fazla ise ilk 3 isim yazılıp ve ark. ("et al") eklenmelidir. Kaynak yazımı için kullanılan format Index Medicus'ta belirtilen şekilde olmalıdır (www.icmje.org). Kaynak listesinde yalnızca yayınlanmış ya da yayınlanması kabul edilmiş veya DOI numarası almış çalışmalar yer almalıdır. Dergi kısaltmaları "Cumulated Index Medicus" ta kullanılan stile uymalıdır. Kaynak sayısının araştırmalarda 25 ve derlemelerde 60, olgu sunumlarında 10, editöre mektupta 5 ile sınırlandırılmasına özen gösterilmelidir. Kaynaklar metinde cümle sonunda nokta işaretinden hemen önce köşeli parantez kullanılarak belirtilmelidir. Örneğin [4,5]. Kaynakların doğruluğundan yazar(lar) sorumludur. Yerli ve yabancı kaynakların sentezine önem verilmelidir.

Şekil ve tablo başlıkları: Başlıklar kaynaklardan sonra yazılmalıdır.

**4. Şekiller:** Her biri ayrı bir görüntü dosyası (jpg) olarak gönderilmelidir.

Makalenin basıma kabulünden sonra "Dizginin ilk düzeltme nüshası" sorumlu yazara e-mail yoluyla gönderilecektir. Bu metinde sadece yazım hataları düzeltilecek, ekleme çıkartma yapılmayacaktır. Sorumlu yazar düzeltmeleri 2 gün içinde bir dosya halinde e-mail ile yayın idare merkezine bildirecektir.

**Kaynak Yazım Örnekleri**

Dergilerden yapılan alıntı;

Özpolat B, Gürpınar ÖA, Ayva EŞ, Gazyağcı S, Niyaz M. The effect of Basic Fibroblast Growth Factor and adipose tissue derived mesenchymal stem cells on wound healing, epithelization and angiogenesis in a tracheal resection and end to end anastomosis rat model. Turk Gogus Kalp Dama 2013; 21: 1010-19.

Kitaptan yapılan alıntı;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Tek yazar ve editörü olan kitaptan alıntı;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams&Wilkins; 1996: 46-60.

Çoklu yazar ve editörü olan kitaptan alıntı;

Schulz JE, Parran T Jr: Principles of identification and intervention. In:Principles of Addicton Medicine, Graham AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams&Wilkins; 1998:1-10.

Eğer editör aynı zamanda kitap içinde bölüm yazarı ise;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag;1988:45-67.

Doktora/Lisans Tezinden alıntı;

Kılıç C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Bir internet sitesinden alıntı;

Sitenin adı, URL adresi, yazar adları, ulaşım tarihi detaylı olarak verilmelidir.

DOI numarası vermek;

Joos S, Musselmann B, Szecsenyi J. Integration of Complementary and Alternative Medicine into Family Practice in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

Diğer referans stilleri için "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References" sayfasını ziyaret ediniz.

Bilimsel sorumluluk beyanı: Kabul edilen bir makalenin yayınlanmasından önce her yazar, araştırmaya, içeriğinin sorumluluğunu paylaşmaya yetecek boyutta katıldığını beyan etmelidir. Bu katılım şu konularda olabilir:

a. Deneylerin konsept ve dizaynlarının oluşturulması, veya verilerin toplanması, analizi ya da ifade edilmesi;

b. Makalenin taslağının hazırlanması veya bilimsel içeriğinin gözden geçirilmesi

c. Makalenin basılmaya hazır son halinin onaylanması.

Yazının bir başka yere yayın için gönderilmediğinin beyanı: "Bu çalışmanın içindeki materyalin tamamı ya da bir kısmının daha önce herhangi bir yerde yayınlanmadığını, ve halihazırda da yayın için başka bir yerde değerlendirilmede olmadığını beyan ederim. Bu, 400 kelimeye kadar olan özetler hariç, sempozyumlar, bilgi aktarımları, kitaplar, davet üzerine yazılan makaleler, elektronik formatta gönderimler ve her türden ön bildirileri içerir."

Sponsorluk beyanı: Yazarlar aşağıda belirtilen alanlarda, varsa çalışmaya sponsorluk edenlerin rollerini beyan etmelidirler:

1. Çalışmanın dizaynı

2. Veri toplanması, analizi ve sonuçların yorumlanması

3. Raporun yazılması

**Kontrol listesi:**

1. Editöre sunum sayfası (Sorumlu yazar tarafından yazılmış olmalıdır)

2. Başlık sayfası ( Makale başlığı/kısa başlık Türkçe ve İngilizce, Yazarlar, kurumları, sorumlu yazar posta adresi, tüm yazarların e-mail adresleri, sorumlu yazarın telefon numarası)

3. Makalenin metin sayfası (Makale başlığı/kısa başlık Türkçe ve İngilizce, Özet/anahtar kelimeler, Summary/keywords, makale metni, kaynaklar, tablo ve şekil başlıkları, tablolar, şekiller)

4. Tablo ve grafikler metin içinde olmalıdır.

5. Şekiller (En az 300 dpi çözünürlükte) ayrı bir veya daha fazla dosya halinde gönderilmelidir.

Özel Ortadoğu Hastanesi


*Sevgiyle, Bilgiyle, Güvenle...*