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# EDITORIAL

**Dear Colleagues,**

We meet you again in the first issue of the Bezmialem Science Journal in 2019. I would like to inform you that our publisher has changed in this issue. I thank to our previous publisher for their support in getting our journal to this level. We are always looking for how to go one step further, how to create a better quality journal and how to create a journal that reaches more scientists, and includes their work. We are in the hope that our new publisher will make us reach this goal in a shorter time. In addition to the additional issue that involves the abstracts of the presentations presented at the university's student congress in the last year; we intend to publish two special issues by experts in our publication plan. We look forward to the suggestions and support of our esteemed scientists on this subject.

In this issue, the articles entitled "*Interleukins As a Marker of Inflammation in Diabetic Foot Syndrome and Type 2 Diabetes Mellitus*" by KALELİ et al., "*Ultrasonographic Evaluation of Shoulder in Patients with Diabetes Mellitus*" by ÇAĞLAR OKUR et al., "*Effects of Different Fluoride-containing Toothpastes on In Vitro Enamel Remineralization*" by HATİPOGLU et al, "*May Biochemical Variables and Pleural Fluid Cell Count Be Used in the Benign-Malign Differentiation of Pleural Effusions Associated with Lung Cancer?*" by DENİZ et al. can be introduced as articles in the foreground.

I would like to welcome the new associate editors and esteemed scientists who have joined to the editorial board from abroad. Contribution to both the scientific world and to our journal of our growing team will please us.

I would like to thank to all our authors, referees, editorial board and new publisher who contributed to this issue.

Goodbye until we meet in the next issue.

**Prof. Dr. Adem AKÇAKAYA**
**Chief Editor**

Original Article

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# Interleukins As a Marker of Inflammation in Diabetic Foot Syndrome and Type 2 Diabetes Mellitus

Süleyman KALELİ[1], Ceyhun VARIM[2], Ahmet NALBANT[2], Hayrullah YAZAR[3], Mehmet AKDOĞAN[3]

[1]Sakarya University Faculty of Medicine, Department of Medical Biology, Sakarya, Turkey
[2]Sakarya University Faculty of Medicine, Department of Internal Diseases, Sakarya, Turkey
[3]Sakarya University Faculty of Medicine, Department of Medical Biochemistry, Sakarya, Turkey

## ABSTRACT

**Objective:** Diabetic foot ulcers, one of the factors that determine the life time and quality of life in diabetic patients are one of the most frequent causes of hospitalization and surgery. In this study, we aimed to investigate the levels of interleukin (IL)-12 P70, 17, 18, hemoglobin (Hb) A1c, and some parameters in subjects with type 2 diabetic mellitus with diabetic foot and in healthy subjects.

**Methods:** The study was performed on three groups. They were patients with diabetic foot, with diabetes mellitus type 2 and healthy individuals (control). IL-12 P70, IL-17, and IL-18, HbA1c levels and other biochemical parameters were compared between three groups.

**Results:** We found higher IL-17, IL-18, white blood cells, glucose and HbA1c in the diabetic group and diabetic foot group than in the control group. IL-12 P70 levels in the diabetic foot group were significantly higher than the control group. The performances in diagnosing of IL-12 P70, 17 and 18 as a biomarker for diabetic foot were found statistically significant. IL-12 P70, 17 and 18 levels in diabetic patients were not different from the levels in patients with diabetic foot.

**Conclusion:** According to our results, IL-12 P70, IL-17 and IL-18 can be used as biomarkers for diabetic foot. Further studies are needed to show the role of IL-12 P70, IL-17 and IL-18 levels as a biomarker in chronic inflammatory diseases.

**Keywords:** Diabetic foot, diabetes mellitus, chronic inflammatory diseases, interleukins, biomarkers

## Introduction

Diabetes mellitus (DM) type 2 is the most common endocrine disease in the world. DM is a chronic inflammatory disease characterized by high blood glucose levels. Low grade inflammation and immune activation are closely related to the pathogenesis and complications of DM (1).

Diabetic foot syndromes (ulcers) cause decrease in quality of life in diabetic patients. This syndrome is the most common cause of hospitalization and surgery in patients with DM and has a high morbidity and mortality rate. For example, 85% of foot amputations are secondary to diabetic foot ulcers (DFU) (2). The balance between pro- and anti-inflammatory processes is impaired in patients with DFU (3). The most common procedure for diagnosis of DFU is evaluating physical changes such as skin irritation, pain, fever and redness in the foot region (4,5). Also, culturing the sample taken from patient's foot is applied to observe pathogen proliferation (4). As the infected area enlarges, other symptoms are promoted. There is no optimal treatment for diabetic foot most of the treatment modalities are very expensive and it is not easy to control the disease (6). Diagnostic process is the key point for determining the route of treatment.

Interleukin (IL)-12 P70 is a cytokine with an important role in the initiation of native and adaptive immune responses to

**Address for Correspondence:** Süleyman KALELİ, Sakarya University Faculty of Medicine, Department of Medical Biology, Sakarya, Turkey
**Phone:** +90 536 549 11 61 **E-mail:** skaleli@sakarya.edu.tr **ORCID ID:** orcid.org/0000-0002-6043-2521

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many infections (7). IL-12 P70 is a heterodimer cytokine and is released from macrophages, dendritic cells, langerhans cells, B cells, and natural killer cells. It plays an important role in cell-mediated immunity. Production of IL-12 P70 is increased in viral, fungal and bacterial infections. IL-12 P70 contributes to the production and maturation of natural killer cells and pro-inflammatory cytokines such as IL-2, IL-3, and tumor necrosis factor-α (8). There are some studies showing that IL-12 P70 plays a role in pathogenesis of DM type 1 and 2 (9,10). IL-17 is an important pro-inflammatory cytokine. It increases chemokine production and organizes monocytes and neutrophils (11). IL-17 has been shown to play a role in autoimmune diseases such as inflammatory bowel disease, psoriasis, systemic lupus erythematous, allergy, asthma and multiple sclerosis (12). Emamaullee et al. (13) performed a study on non-obese diabetic mice and they showed that IL-17 is involved in pathogenesis and plays an important role in the fight against extracellular pathogens such as *Candida* and *Klebsiella*. IL-18, previously known as interferon-γ-inducing factor, is an immune-regulatory cytokine secreted from activated macrophages and first described in 1989 (14). IL-18 is secreted by monocytes, macrophages and osteoclasts in osteoblasts, epithelial cells, keratinocytes, adrenal cortex, and the pituitary gland, endometrium and ovary (15,16).

Recently, Tuttolomondo et al. (17-19) showed that IL-1, IL-6 and resistin levels in plasma can be used as markers for determining type 2 diabetes with and without diabetic foot syndrome and they found that there was a relation between cardiovascular morbidity and inflammatory cytokines in patients with diabetic foot syndromes.

Skin irritation, symptoms such as redness, pain and fever around the foot region, some imaging methods such as radiograph and magnetic resonance imaging, C-reactive protein level, leucocyte count, erythrocyte sedimentation rate and related tests are all used in diagnosis of DFU currently (5,19,20).

In the literature, there are different ILs evaluated as a marker for diagnosis of patients with DM and DFU. However, there are not conspicuous studies upon IL-12 P70, IL-18 and IL-17, even though DM and DFUs are related with inflammation as IL-12 P70, IL-17 and IL-18 are. The aim of the present study was to investigate serum IL-12 P70, IL-17, IL-18 levels and some biochemical parameters in subjects with type 2 DM and diabetic foot syndromes, and healthy controls, and to demonstrate a relationship between IL parameters and type 2 DM and diabetic foot syndromes.

## Methods

The study was carried out in the Faculty of Medicine of Sakarya University. The patients were provided by the department of internal medicine. The study was approved by the Ethics Committee of Faculty of Medicine of Sakarya University and informed consent was obtained from every subject. An application was made to institutional ethical committee on 22.05.2013 for the study. The study was started after decision dated 18.06.2013 and numbered 71522473.050.01.04/41 from the Ethics Committee of Faculty of Medicine of Sakarya University.

### Subjects

This study included 95 participants: 31 with DFU (group 1), 33 with type 2 DM (group 2) and 31 healthy subjects as a control group (group 3). Group 1 was consisted of 21 males and 10 females aged 51-80 (61.2±8.35) years. Group 2 was consisted of 19 males and 14 females aged 42-75 (60.4±8.81) years and group 3 was consisted of 17 males and 14 females aged 51- 80 (61.2±8.35) years.

Patients with malignancy, pregnancy, cirrhosis, renal failure, or class 3 or 4 heart failure according to the New York Heart Association (NYHA) classification, systemic inflammatory diseases, undergoing immunosuppressive therapy, Wagner grade 4 and 5 diabetic ulcers, or thrombosis were excluded from the study. The presence of purulent secretions or the presence of two or more signs of inflammation (e.g., erythema, warmth, tenderness, heat, and induration) were regarded as evidence of infection. The condition was described in a consensus development conference on diabetic foot wound care (20).

Patients with 18-80 years, type 2 DM, presence of purulent secretions, presence of two or more signs of inflammation, patients who were not pregnant, did not have cancer, did not undergo immunosuppressive therapy, and who did not have class 3 or 4 heart failure according to the NYHA were involved in this study.

### Samples

Blood samples were taken from all groups in tubes containing ethylenediamine tetraacetic acid (EDTA) and non-EDTA after overnight fasting. Blood samples were taken in non-EDTA tubes for human IL-12 P70, IL-17, IL-18, glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglyceride-C, high-density lipoprotein cholesterol (HDL-C), and urea and creatinine analysis, then centrifuged at +4 °C 3000 rpm for 10 min and sera were immediately separated from the cells after centrifugation. Serum samples for the measurement of human IL-12 P70, IL-17, and IL-18 were stored at -80 °C until being used. All measurements were done in the same series after the samples were thawed. Blood samples taken in EDTA tubes for hematological tests, and hemoglobin (Hb) A1c parameters were studied at the same day in routine laboratory.

### Biochemical Parameters

HbA1c, glucose, total cholesterol, LDL-C, triglyceride-C, HDL-C, urea and creatinine analysis and hematological tests were measured using commercial kits in routine biochemistry laboratory. HbA1c from Trinity Biotech (Trinity Biotech Assay and System, USA), glucose, total cholesterol, triglyceride-C, urea and creatinine from Abbott Architect (fully automatic analyzer, Architect System c1600; Abbott Laboratories, Lake Bluff, IL, USA), LDL-C and HDL-C from Archem Diagnostics for Abbott Architect, USA were used. Hematology parameters were measured using the Cell-Dyne 3700 SL hematology analyzer (Abbott Laboratories, North Chicago, IL, USA).

### ELISA Assay

Human IL-12 P70, IL-17 and IL-18 levels were measured with an enzyme-linked immunosorbent assay kit (reference: BMS 238, lot number: 95350039; reference: BMS 2017, lot number: 96656015; reference: BMS 267/2, lot number: 96934032 respectively; ELISA kits manufactured for eBioscience by Bender MedSystems GmbH Campus Vienna Biocenter 2, 1030 Vienna, Austria, www.eBioscience.com). All ELISA assays were performed via an ELISA autoanalyzer (BioTek 800 TS Absorbance Reader, USA).

### Statistical Analysis

Descriptive analyses were performed to provide information on general characteristics of the study population. Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables were normal. ANOVA or Kruskal-Wallis H test was used to compare the continuous data among groups. For multiple comparison of ANOVA; Tukey or Tamhane T square was used. Beside for multiple comparison of Kruskal-Wallis H test, Dunn's test was used. The continuous data were presented as the mean ± standard deviation. Receiver operating characteristics (ROC) curve analysis was used to determine the cut off value of IL-12 P70, 17 and 18 levels in diagnosis of type 2 DM with diabetic foot. Sensitivity and specificity of the test as well as the positive and negative predictive values were calculated for IL-12 P70, 17 and 18. A p value <0.05 was considered significant. Analyses were performed using commercial software (IBM SPSS Statistics, version 23.0; Armonk, NY: IBM Corp.). ROC curves were constructed using MedCalc (MedCalc Statistical Software version 15.8, MedCalc Software bvba, Ostend, Belgium).

## Results

The levels of HbA1c, glucose, total cholesterol, LDL-C, triglyceride, HDL-C, urea and creatinine were shown in Table 1.

As seen in Table 1, no statistically significant difference was found in terms of HbA1c and fasting glucose between group 1 and group 2 (p>0.05). However it was found that there were significant differences between group 1 and group 3 and between group 2 and group 3 (p<0.05) for same variables. No statistically significant difference was found in levels of LDL-C, HDL-C, triglyceride, total cholesterol, urea and creatinine between group 1 and group 2 (p>0.05). However it was found that there were significant differences between group 1 and group 3, between group 2 and group 3 for LDL-C, and also between group 2 and group 3 for total cholesterol (p<0.05).

As seen in Table 2, the highest levels of IL-12 P70, IL-17 and white blood cell were found in group 1. These levels were significantly higher in group 1 than in group 3 (p<0.05), but there was not significant difference between group 1 and group 2 (p>0.05). IL-18 levels in group 1 and group 2 were significantly higher than group 3 (p<0.05), but there was no significant difference between group 1 and group 2 (p>0.05).

**Table 1.** Comparison of the biochemical parameters among groups

| Parameters | Group 1 (n=31) | Group 2 (n=33) | Group 3 (n=31) | p* |
|---|---|---|---|---|
| HbA1c (%) | 10.45±1.14 | 10.66±0.98 | 5.47±0.44 | <0.001[b,c] |
| Glucose (mg/dL) | 194.0±73.8 | 202.15±46.56 | 97.9±11.83 | <0.001[b,c] |
| Total cholesterol (mg/dL) | 175.97±48.23 | 201.39±30.21 | 177.58±30.21 | 0.019[a,c,**] |
| LDL-C (mg/dL) | 121.65±41.22 | 137.09±29.94 | 108.06±32.89 | 0.003[b,c] |
| Triglyceride (mg/dL) | 172.03±71.48 | 180.85±61.06 | 147.42±72.16 | 0.106 |
| HDL-C (mg/dL) | 36.23±10.62 | 43.36±13.67 | 38.90±10.40 | 0.052[**] |
| Urea | 44.23±24.14 | 33.67±11.11 | 31.87±6.68 | 0.079 |
| Creatinine | 1.05±0.47 | 1.19±1.96 | 0.81±0.14 | 0.056 |

HbA1c: hemoglobin A1c; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; group 1: diabetic foot syndromes; group 2: diabetes mellitus type 2; group 3: control
*: results of the Kruskal-Wallis H test; **: results of the ANOVA; [a]: there is a statistically significant difference between group 1 and 2; [b]: there is a statistically significant difference between group 1 and 3; [c]: there is a statistically significant difference between group 2 and 3; data were shown as mean ± standard deviations

**Table 2.** Comparison of the inflammatory parameters among groups

| Parameters | Group 1 (n=31) | Group 2 (n=33) | Group 3 (n=31) | p* |
|---|---|---|---|---|
| WBC ($10^3$/μL) | 10.07±5.38 | 7.88±3.41 | 6.03±1.45 | <0.001[a,b] |
| IL-12 P70 (pg/mL) | 13.61±12.87 | 10.80±10.58 | 6.89±5.83 | 0.007[b] |
| IL-17 (ng/mL) | 7.15±6.99 | 5.87±7.05 | 2.50±1.04 | <0.001[b,c] |
| IL-18 (pg/mL) | 464.84±279.39 | 483.56±232.08 | 280.29±151.87 | <0.001[b,c] |

WBC: white blood cells; IL: interleukin; group 1: diabetic foot syndromes; group 2: diabetes mellitus type 2; group 3: control
*: results of the Kruskal-Wallis H test; [a]: there is a statistically significant difference between group 1 and 2; [b]: there is a statistically significant difference between group 1 and 3; [c]: there is a statistically significant difference between group 2 and 3; data were shown as mean ± standard deviations

The performances of IL-12 P70, 17 and 18 biomarkers in diagnosing DFU and in separating it from healthy controls were statistically significant [respectively; area under the curve (AUC)=0.736, 0.791 and 0.723; p<0.001, p<0.001, p<0.001]. Cut-off values for relevant variables were calculated as >5.42, >3.3, >407.2, respectively (Table 3 and Figure 1).

The performances of IL-12 P70, 17 and 18 in diagnosing type 2 DM and in separating it from healthy controls were statistically significant, but no statistically significant difference was found in terms of IL-17 (respectively; AUC=0.656, 0.678 and 0.785, p=0.030, p=0.085 and p<0.001). Cut-off values for relevant variables were calculated as >5.9, >1.98, >315.58, respectively (Table 4 and Figure 2).

In diagnosing diabetic foot according to DM type 2 group, the performances of IL-12 P70, 17 and 18 in diagnosis of DFU and in separating it from type 2 DM were not statistically significant,

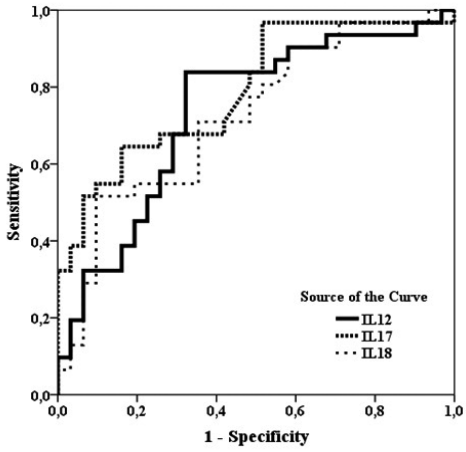


**Figure 1.** Receiver operating characteristics curves of the interleukin-12 P70, 17 and 18 in diagnosing diabetes mellitus type 2 with diabetic foot ulcer group and in separating it from control group
IL: interleukin

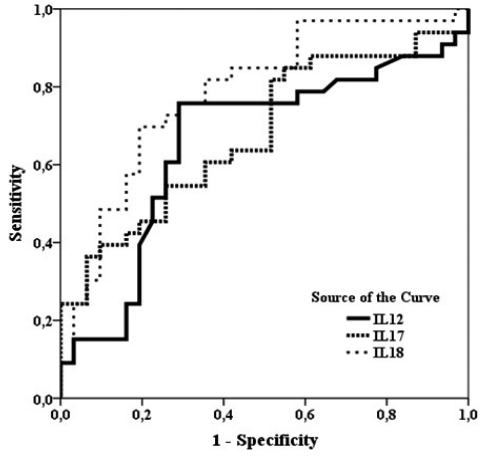


**Figure 2.** Receiver operating characteristics curves of the interleukin-12 P70, 17 and 18 in diagnosing diabetes mellitus type 2 group and separating it from control group
IL: interleukin

**Table 3.** Diagnostic performances of interleukin-12 P70, 17 and 18 in diagnosing diabetes mellitus type 2 with diabetic foot ulcer group and in separating it from control group

| Biomarkers | Cut-off values | AUC | SE of AUC | 95% CI of AUC | p values | Sens. | Spec. | Predictive values (%) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | PPV | NPV |
| IL-12 P70 | >5.42 | 0.736 | 0.0653 | 0.608 to 0.840 | <0.001 | 83.87 | 67.74 | 72.2 | 80.8 |
| IL-17 | >3.3 | 0.791 | 0.0576 | 0.669 to 0.884 | <0.001 | 64.52 | 83.87 | 80.0 | 70.3 |
| IL-18 | >407.2 | 0.723 | 0.0652 | 0.594 to 0.829 | <0.001 | 51.61 | 90.32 | 84.2 | 65.1 |

AUC: area under the curve; SE: standard error; CI: confidence interval; IL: interleukin; Sens.: sensitivity; Spec.: specificity; PPV: positive predictive value; NPV: negative predictive value

**Table 4.** Diagnostic performances of interleukin-12 P70, 17 and 18 in diagnosing diabetes mellitus type 2 group and separating it from control group

| Biomarkers | Cut-off values | AUC | SE of AUC | 95% CI of AUC | p values | Sens. | Spec. | Predictive values (%) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | PPV | NPV |
| IL-12 P70 | >5.9 | 0.656 | 0.0722 | 0.527 to 0.771 | 0.030 | 75.6 | 70.97 | 73.5 | 73.3 |
| IL-17 | >1.98 | 0.678 | 0.0678 | 0.550 to 0.790 | 0.085 | 81.82 | 48.39 | 62.8 | 71.4 |
| IL-18 | >315.58 | 0.785 | 0.0584 | 0.664 to 0.878 | <0.001 | 69.70 | 80.65 | 79.3 | 71.4 |

AUC: area under the curve; SE: standard error; CI: confidence interval; IL: interleukin; Sens.: sensitivity; Spec.: specificity; PPV: positive predictive value; NPV: negative predictive value

**Table 5.** Diagnostic performances of interleukin-12 P70, 17 and 18 in diagnosing diabetes mellitus type 2 with diabetic foot ulcer group and in separating it from diabetes mellitus type 2 group

| Biomarkers | Cut-off values | AUC | SE of AUC | 95% CI of AUC | p | Sens. | Spec. | Predictive values (%) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | PPV | NPV |
| IL-12 P70 | >10.38 | 0.542 | 0.0741 | 0.412 to 0.667 | 0.575 | 41.94 | 75.76 | 61.9 | 58.1 |
| IL-17 | >3.46 | 0.610 | 0.0714 | 0.480 to 0.729 | 0.124 | 64.52 | 60.61 | 60.6 | 64.5 |
| IL-18 | ≤295.4 | 0.556 | 0.0741 | 0.427 to 0.680 | 0.448 | 45.16 | 78.79 | 66.7 | 60.5 |

AUC: area under the curve; SE: standard error; CI: confidence interval; IL: interleukin; Sens.: sensitivity; Spec.: specificity; PPV: positive predictive value; NPV: negative predictive value

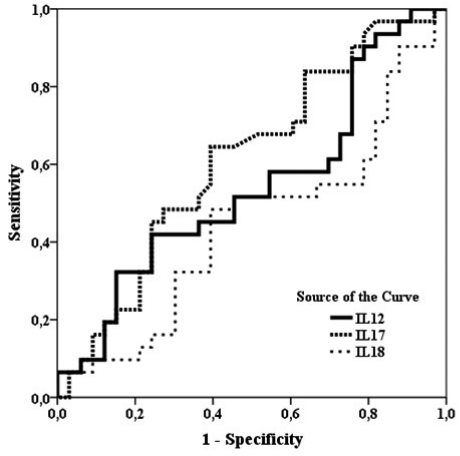


**Figure 3.** Receiver operating characteristics curves of the interleukin-12 P70, 17 and 18 in diagnosing diabetes mellitus type 2 with diabetic foot ulcer group and in separating it from diabetes mellitus type 2 group
IL: interleukin

(respectively; AUC=0.542, 0.610, 0.556 and p=0.575, p=0.124, p=0.448). Cut-off values for relevant variables were calculated as >5.9, >1.98, >315.58, respectively (Table 5 and Figure 3).

## Discussion

Our study demonstrated a relationship between serum IL-12 P70, IL-17, and IL-18 levels and both DM type 2 and DFU.

It was reported that the frequency of cardiovascular diseases increases 2-4 times in diabetic patients with DFU (19). The comparison of biochemical parameters such as LDL, triglyceride and total cholesterol levels between normal and diabetic individuals shows that there is correlation between inflammation and DM (19). Recent studies indicated that the level of inflammatory cytokines IL-1, IL-6 were higher in diabetic patients with cardiovascular diseases (18).

It was reported that cardiovascular diseases are more common in diabetic patients compared with non-diabetic patients (21). Recent studies indicated that the level of inflammatory cytokines IL-1, IL-6 were higher in diabetic patients with cardiovascular diseases (19). However, there is not much study on IL-12 P70, IL-17, and IL-18 levels in diabetic patients.

Studies about DM type 2 and IL-12 P70 were found in the literature (6,7). IL-12 P70 is a pro-inflammatory cytokine which stimulates the proliferation and migration of T cells and natural killer cells (22). Type 2 DM is a chronic inflammatory disease (23,24). High IL-12 P70 levels in patients with type 2 DM are associated with pro-inflammatory cytokines and chronic inflammatory disease. Our results were compatible with this mechanism and the literature.

Development of DFU is multifactorial. Diabetic foot ulcerations occur as a result of complex interactions of factors such as peripheral artery disease, atherosclerotic plaque, changes in the microcirculation, and peripheral neuropathy. Proliferation and migration of T-cell and natural killer cells induced by IL-12 P70 play an important role in the formation of atherosclerotic plaques (25). Atherosclerotic plaques can lead to changes in microcirculation and peripheral arterial disease (26), as well as the production of IL-12 P70 is increased in viral, fungal, and bacterial infections (8). The role of IL-12 P70 in DFU can be explained by the increase in the reproducing rate of bacteria in diabetic ulcer's areas. In our study, the highest levels of IL-12 P70 were found in the DFU group. We think that these levels can be explained in two ways: 1) IL-12 P70 is a pro-inflammatory cytokine, 2) IL-12 P70 can play a role in the development of diabetic foot syndrome.

However, there is not enough data about IL-17, and IL-18 levels in patients with DM in the literature. IL-17 is a pro-inflammatory cytokine released by T cells. There are some studies and animal models which show that IL-17 plays a role in the pathogenesis of DM type 1. Type 1 DM was prevented in the non-obese mice with anti-IL-17 treatment (10). The high presence of IL-17 levels in these studies are related with autoimmune diseases. IL-17 has also been implicated in allergic skin response (27). Gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa,* and *Klebsiella* spp. are more common in severe DFU (28). IL-17 plays an important role in fighting against extracellular pathogens such as *Candida* and *Klebsiella* (12). According to our results, we think that high IL-17 levels in both DFU and DM groups may be attributed to the fact that IL-17 is a pro-inflammatory cytokine. High IL-17 levels in patients with DFU may be due to inflammation in the ulceration, deterioration of skin integrity, and various types of bacteria causing infections. In our study, higher level of IL-17 in both DFU and DM groups compared

with control group gives an idea that IL-17 may be related with diabetic disease and can be used as a marker in diagnosis of DM. Additionally, higher level of IL-17 in DFU group suggests that IL-17 can be used as a pro-inflammatory marker for diabetic foot.

IL-18 is a pro-inflammatory cytokine secreted by epithelial cells, macrophages and dendritic cells; and known as an interferon-γ stimulating factor (14). Elevated IL-18 levels are an independent predictor of type 2 DM and metabolic syndrome (29). In an animal study, IL-18 has been shown to cause β-cell dysfunction and deterioration of insulin secretion (30). IL-18 causes endothelial dysfunction and plays a role in atherosclerosis (31). In another study, the relationship between IL-18 and DFU was examined. IL-18 is a pro-inflammatory cytokine (32). A study showed the correlation between plasma IL-18 levels and plasma fasting glucose; plasma IL-18 levels and insulin levels; plasma IL-18 levels and obesity in females; and plasma IL-18 levels and DFU (16). In our study, high levels of IL-18 in the patients with type 2 DM were consistent with the literature. High levels in patients with DFU are due to the role of IL-18 in atherosclerosis, as IL-18 is pro-inflammatory cytokine. Higher level of IL-18 in both DFU and DM groups suggests IL-18 may be used as a marker in diagnosis of them.

Studies have shown that high LDL level and low HDL-C in type 2 DM patients are related with cardiovascular diseases (33). In our study, higher level of LDL in both patients with type 2 DM and patients with diabetic foot syndrome was supported by these studies. According to the AHEAD Research Group's study, intensive lifestyle intervention or diabetes support and education may help to increase HDL-C level in diabetic patients (33). Nevertheless, there was no significant difference in terms of HDL-C between diabetic foot syndrome, DM and control groups in our study.

HbA1c is the best indicator for glycemic control. It is used as significant parameter to monitor blood glucose level in patients with DM (34). We found high level of HbA1c in patients with type 2 DM and diabetic foot syndrome in our study, which were expected.

### Study Limitations

This study was conducted within a limited period. For this reason, it is considered that increasing the number of patients and studying other IL inflammation markers may be appropriate.

## Conclusion

We think that IL-12 P70, 17 and 18 parameters can be used as biomarkers for diagnosis of DFU and type 2 DM. This study will guide researchers for future studies to find inflammatory biomarkers in DM and DFU. According to our results, further comprehensive studies are needed to investigate specific biomarkers for diagnosis of DFU related with inflammatory.

### Ethics

**Ethics Committee Approval:** This study was approved by the Ethics Committee of Faculty of Medicine of Sakarya University, dated 18.06.2013 and numbered 71522473.050.01.04/41.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: S.K., C.V., A.N., Design: S.K., C.V., Data Collection or Processing: S.K., C.V., A.N., Analysis or Interpretation: S.K., C.V., A.N., H.Y., M.A., Literature Search: S.K., C.V., Writing: S.K., C.V.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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Original Article

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# Ultrasonographic Evaluation of Shoulder in Patients with Diabetes Mellitus

Sibel ÇAĞLAR OKUR[1], Esra ÇİRÇİ[2]

[1]İstanbul Training and Research Hospital, Clinic of Physical Therapy and Rehabilitation, İstanbul, Turkey

[2]İstanbul Training and Research Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Turkey

## ABSTRACT

**Objective:** Shoulder degeneration and rotator cuff tears increase with age and become a frequent cause of shoulder pain. Diabetes mellitus (DM) is the most common endocrine disorder causing pathologies in the musculoskeletal system. In our study, we aimed to evaluate shoulder morphology in diabetic and control groups.

**Methods:** Fifty two diabetic patients (62.4±9.6 years) and 46 non-diabetic patients (66.2±7.8 years) with no shoulder pain were included in the study. Ultrasonographic evaluation was performed on right shoulder using the standard protocol. The examination was performed multiplanar with a linear probe (5-13 MHz).

**Results:** Calcific tendinitis was detected in 8 of diabetic patients (17.4%) and in 7 of control patients (13.5%). Partial tear was detected in supraspinatus tendon in 4 of diabetic patients (8.7%) and in 1 of control patients (1.9%). Full-thickness tears were found in supraspinatus tendon in 8 of diabetic patients (17.4%) and in 2 patients (3.8%). Biceps tendinitis was detected in 10 of diabetic patients (19.0%) and in 6 of control patients (13.0%). There was a significant difference between groups in terms of frequency of calcific tendinitis, presence of supraspinatus tendon tear, and frequency of biceps tendinitis ($p<0.05$).

**Conclusion:** According to the results of our study, DM accelerates shoulder degeneration. Ultrasonography is an inexpensive and reliable imaging method that allows evaluation of shoulder problems.

**Keywords:** Ultrasound, shoulder, diabetes mellitus

## Introduction

Diabetes mellitus (DM) is an endocrine disorder characterized by hyperglycemia due to impaired insulin secretion and/or activity. It is the most common endocrine pathology that causes skeletal system complications and diabetic patients with late diagnosis and who receive medical treatment late can easily be affected by complications such as neuropathy, nephropathy and retinopathy (1,2). In 2004, the American National Health Survey showed that 58% of diabetic patients had functional losses (3). Increased protein glycosylation due to DM in soft tissues and periarticular structures, deterioration of microvascular structure and impaired collagen accumulation are the causes of changes in muscle skeletal system (4).

Musculoskeletal system complications of DM are not only in joints. DM also causes functional loss by the involvement of bones and soft tissues. Ultrasound studies show that findings such as rotator cuff rupture and degeneration in the shoulder increase with age. This rate ranges between 1-15% in patients aged 60 years and ranges between 30-50% in patients aged 80 years (5,6). Studies with magnetic resonance imaging (MRI), which provides the opportunity to evaluate the pathologies of the shoulder, show that shoulder pathologies increase with age as studies with

**Address for Correspondence:** Sibel ÇAĞLAR OKUR, İstanbul Training and Research Hospital, Clinic of Physical Therapy and Rehabilitation, İstanbul, Turkey
**Phone:** +90 533 336 56 51 **E-mail:** sibelcaglarokur@gmail.com **ORCID ID:** orcid.org/0000-0002-4015-5977

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ultrasonography show, but high cost of MRI prevents the use of it as a screening test (7,8).

In this study, we aimed to compare the supraspinatus and biceps tendons (BT) in patients with DM which is the most common endocrine pathology that causes skeletal system complications, with non-diabetic patients in the same age group and to investigate the effect of DM on these muscles.

## Methods

The study was approved by İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (number: 2018-113). All patients were informed about the study and informed consent was taken from all patients.

Right shoulder joints of 52 diabetic patients and 46 controls were evaluated between January 2016 and May 2016 in İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital. Right hand was dominant in all diabetic patients and controls.

### Study Group

Fifty two (20 males, 32 females) asymptomatic patients with DM type 2 with mean age 62.4±9.6 years were evaluated. Mean time of DM diagnosis and follow up duration was 10.3±7.5 years.

The duration of DM in patients and for how many years the patients received treatment were learned. Hemoglobin (Hb) A1c level and body mass index (BMI) were measured in all patients.

### Control Group

Forty six patients (20 males, 26 females) with mean age of 66.2±7.8 years who were admitted to our hospital for other examinations, who did not have DM and who did not have a complaint about shoulder were evaluated. HbA1c level and BMI were measured in all patients.

BMI, comorbid diseases and medications of all participants in both groups were asked and recorded.

### Ultrasonographic Evaluation

Right shoulders of all patients were evaluated with ultrasound in the neutral position while sitting. In ultrasonographic examination, 5-13 MHz lineer prob (Esaote MyLab 5; Genova, Italy) was used. The evaluation was carried out by a specialist experienced in musculoskeletal system ultrasonography. The standard protocol developed by Papatheodorou et al. (9) was used in evaluation.

Supraspinatus tendon (SST) was measured near the lateral head of the humerus in the longitudinal axle, while BT head was measured in the bisipital groove. Subacromial and subdeltoid bursitis were evaluated. Hypo-hyperechoic appearance in tendon, deterioration of fibrillar structure, dishomogeneous fibrillar structures were evaluated in favor of degeneration. While evaluating the tears of SST: 1) partial tears are seen as irregular bordered hypoechoic fields in intratendinous, bursal or articular side and bursal side tears flatten the bursal side and cause a decrease in the superior convexity of the tendon. Tears near the articular side are seen hypo-hyperechoic mix on the articular surface next to the joint cartilage, 2) full thickness tears contain the damaged areas that extend from the bursal surface to the articular surface intratendinously and may be filled with synovial fluid and cause loss in the upper convexity of tendon. Also, when pressed with transducer, it is seen that the deltoid muscle is in contact with the humerus head.

### Statistical Analysis

Statistical analysis was performed with SPSS (SPSS Inc., Chicago, IL) package program version 16. Statistical significance level was accepted as $p<0.05$. Data were expressed as mean ± standard deviation. Age, BMI and HbA1c level were evaluated in the study and control groups. Demographic data were evaluated. Search for calcific tendinitis, tear in SST and biceps tendinitis were made. Percentages of the distribution of data in the groups were given. Supraspinatus and BT thickness were evaluated by ultrasound. Independent sample t-test was used to determine the difference between groups.

## Results

The BMI was 29.6±4.2 kg/m$^2$ in the DM group and 33.6±4.6 kg/m$^2$ in the control group. HbA1c was 8.0%±1.7 in the DM group and 5.7%±0.2 in the control group (Table 1).

There was no difference between groups in terms of age, gender and BMI ($p>0.05$), whereas there was significant difference between groups in terms of HbA1c ($p<0.05$) (Table 1).

Calcific tendinitis was detected in 8 (17.4%) diabetic patients and 7 (13.5%) control patients. Partial tear in SST was detected in 4 (8.7%) diabetic patients and 1 (1.9%) control patients. Full thickness tear in SST was detected in 8 (17.4%) diabetic patients and 2 (3.8%) control patients. Biceps tendinitis was detected in 10 (19.0%) diabetic patients and in 6 (13.0%) control patients.

**Table 1.** Demographic features of the patients

| | Diabetic patients | Control patients | Statistical analysis* |
|---|---|---|---|
| Gender (female/male) | 32/20 | 26/20 | p>0.05 |
| Body mass index (kg/m$^2$) | 29.6±4.2 | 33.6±4.6 | p>0.05 |
| HbA1c (%) | 8.0±1.7 | 5.7±0.2 | p<0.05 |
| Age (years) | 62.4±9.6 | 66.2±7.8 | p>0.05 |

Hb: hemoglobin
*t-test

**Table 2.** Ultrasonographic evaluation of calcific tendinitis, tear in supraspinatus tendon and biceps tendinitis

| | Diabetic patients | Control patients | Statistical analysis* |
|---|---|---|---|
| Calcific tendinitis | 8 (17.4%) | 7 (13.5%) | p<0.05 |
| Partial tear in supraspinatus tendon | 4 (8.7%) | 1 (1.9%) | p<0.05 |
| Full thickness tear in supraspinatus tendon | 8 (17.4%) | 2 (3.8%) | p<0.05 |
| Biceps tendinitis | 10 (19.0%) | 6 (13.0%) | p>0.05 |

Frequency (percentage in the group); *t-test

**Table 3.** Ultrasonographic evaluation of thickness of supraspinatus and biceps tendon

| | Diabetic patients | Control patients | Statistical analysis* |
|---|---|---|---|
| Thickness of supraspinatus tendon at glenoid level (mm) | 7.9±1.4 (4.1-10.2) | 6.6±0.5 (5.2-7.3) | p<0.05 |
| Thickness of supraspinatus tendon at the median level of tendon (mm) | 6.4±1.3 (3.0-9.3) | 5.4±0.8 (3.8-6.6) | p<0.05 |
| Thickness of biceps tendon (mm) | 12.6±4.4 (5.5-22.0) | 12.4±2.4 (8.0-18.0) | p>0.05 |

Mean ± standard deviation (minimum-maximum values); *t-test

There was statistically significant difference between groups in terms of the presence of calcific tendinitis and tear in SST (p<0.05), whereas there was no difference in terms of BT (Table 2).

The thickness of SST was 7.9±1.4 mm at glenoid level in diabetic patients and 6.6±0.5 mm in control patients. SST thickness was 6.4±1.3 mm at the median level of tendon in diabetic patients and 5.4±0.8 in control patients. BT thickness was 12.6±4.4 mm in diabetic patients and 12.4±2.4 mm in control patients. Thickness of SST was increased both at glenoid and at the median level of tendon in diabetic patients than in control patients (p<0.05). There was no difference between groups in terms of BT thickness (p>0.05) (Table 3).

## Discussion

Many studies show that degenerative changes in the shoulder increase with age (9-11). Aging increases degenerative changes in shoulder with or without pain and/or limitation of motion as well as in whole body (6,7).

In addition to degenerative pathologies that are increasing with aging, patients with DM are reported to have more frequent pathologies in the shoulder joint such as frozen shoulder and rotator cuff tear, and the risk of rupture in patients undergoing surgical repair is known to increase (12).

Yamaguchi et al. (13) reported that the pain and limitation of joint motion might occur on the basis of asymptomatic tearing, which could be the result of the degenerative process increasing with age.

As a result of minor or unaware trauma, tendinopathies can be observed in patients with DM due to reactive inflammation following trauma, as well as effusion can be observed in bursas and peritendinous structures, and can show itself with increased tendon thickness (14-18). We found increased SST thickness, more calcific tendinitis and tears in SST in diabetic patients than in control patients which may be explained by the common mechanisms that biochemical age-related degeneration and diabetic degeneration have and by more collagen degeneration in diabetic patients.

The effect of DM on degeneration is thought to be due to the degenerative effect of advanced glycation end products (AGEs) on collagen which develops as a result of non-enzymatic glycosylation of collagen. AGEs are produced by the spontaneous condensation of glucose and the formation of metabolic intermediate products and covalent bonding between free amino acids; arginine, lysine, and hydroxylysine (19-21). AGEs causes changes in the properties of proteins, physically and chemically, hardening of the bonds between collagen, stiffness and ultimately weakening, and tearing of collagen structure (20).

In addition to increasing AGEs with aging, microvascular diseases cause tissue hypoxia, resulting in free oxygen radicals formation and excessive growth factor and cytokine production, which cause increase in tendon thickness and decrease in tissue flexibility, and increase predisposition to damage (22).

### Study Limitations

Studies with high number of patients with evaluation of more joints will provide more informative findings about the early pathologies of DM.

## Conclusion

Our study showed that DM could increase asymptomatic degeneration in supraspinatus and biceps muscles of the shoulder. Ultrasonography is an important and cheap diagnostic tool that assists in diagnosis of pathologies and degeneration during asymptomatic period, does not have radioactive content and makes it possible to assess the patient at the bedside. Ultrasonography in asymptomatic period may give information about possible tendon and muscle pathologies to be encountered.

### Ethics

**Ethics Committee Approval:** The study was approved by İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (number: 2018-113).

**Informed Consent:** All patients were informed about the study and informed consent was taken from all patients.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: S.Ç.O., E.Ç., Concept: S.Ç.O., E.Ç., Design: E.Ç., Data Collection or Processing: S.Ç.O., E.Ç., Analysis or Interpretation: S.Ç.O., E.Ç., Literature Search: E.Ç., Writing: S.Ç.O.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Original Article

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# Effects of Different Fluoride-containing Toothpastes on *In Vitro* Enamel Remineralization

Zerrin HATİPOĞLU[1], Gizem ÖZBAY YAVLAL[2], Betül KARGÜL[2]

[1]Yeditepe University Faculty of Dentistry, Department of Pediatric Dentistry, İstanbul, Turkey
[2]Marmara University Faculty of Dentistry, Department of Pedodontics, İstanbul, Turkey

## ABSTRACT

**Objective:** Fluoride toothpaste is one of the most effective cariostatic product when used as a daily fluoride application. The purpose of this *in vitro* study was to evaluate the effect of a new fluoride-containing toothpaste on enamel surface microhardness (SMH) under a pH-cycling regimen.

**Methods:** Thirty-five sound human enamel samples were randomly divided into five groups (A-E) each containing seven samples as A (fluoride-free control group), B (1000 ppm NaF), C [$KNO_3$ (5%), 1450 ppm NaF], D (1450 ppm sodium monofluorophosphate), and E (1450 ppm NaF). After inducing caries-like lesions, each group was maintained daily for de- and remineralization cycle for seven days. During this cycle, samples were treated by the selected toothpaste for each group. Enamel mineral loss was assessed by SMH and lesion depth was analyzed by polarized light microscopy (PLM). Surface enamel microhardness was determined on the enamel blocks. SMH recovery (%SMHR) among treatments was analyzed by a two-way ANOVA.

**Results:** The highest values of %SMHR were observed for the 1450 ppm NaF (group C). NaF toothpastes significantly increased the microhardness of the lesions ($p<0.001$) when compared to control groups. PLM data revealed a mineral precipitation band on the surface layer of all samples but no difference was found between groups in terms of enamel remineralization layers ($p>0.05$). The results suggest that all toothpastes with similar sources/concentrations of fluoride, provide different levels of remineralization.

**Conclusion:** It can be concluded that new NaF compounds in toothpaste result in a clearly marked remineralization of caries-like enamel lesions.

**Keywords:** pH cycle, toothpaste, remineralization, demineralization

## Introduction

Preventive dentistry is the most preferred research area. Though the progress of *in situ* and *in vivo* research in cariology, laboratory tests are used to examine dental caries, especially the impact of fluoride on prevention of enamel-dentin demineralization and enhancement of remineralization (1-4).

Demineralization, the first step of the decay process with the remineralization process, controls the decay process and reverses the decay. When the acidogenic bacteria reduce pH of the calculus, demineralization occurs. When $Ca^{+2}$ and $PO_4$ ions in saliva increase pH in calculus, the remineralization process begins. Therefore, demineralized lesions are remineralized. However, when the demineralization is equal to or higher than remineralization, decay occurs (5).

The buffer capacity of the saliva has a great deal with $Ca^{+2}$ and $PO_4$ amount inside the saliva. The amount of remineralization increases when the fluoride ions are in the saliva. Therefore, studies about the prevention of caries and reversing the decay or the demineralization process concentrate on the effect of fluoride

**Address for Correspondence:** Zerrin HATİPOĞLU, Yeditepe University Faculty of Dentistry, Department of Pedodontics, İstanbul, Turkey
**E-mail:** zerrin.abbasoglu@gmail.com **ORCID ID:** orcid.org/0000-0002-0077-5581

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ions. In recent *in vivo* and *in vitro* studies, the effect of fluoride on remineralization and demineralization has been researched (5,6).

The pH-cycling test comprises of artificial enamel lesions being treated daily with the products and of cycling in de- and remineralizing solutions to mimic oral pH-fluctuation patterns (7,8).

In studies, pH cycling models provide measurement of the amount of remineralization due to toothpastes containing different concentration of fluoride. The pH cycling model mimics the loss of mineral and the remineralization process, and needs smaller sample dimension and response variables which are performed in pH-cycling models (9,10).

The efficient concentration of $Ca^{+2}$ and $PO_4$ ions and fluoride in saliva stimulate the formation of hidroxiapetite (with $F^-$ as fluorapetite) and accelerate the remineralization. To the cope with these, fluoride is added to toothpastes, mouth rinses and drinking water.

The fluoride toothpastes are the most essential products used as a fluoride application daily (11,12). Fluoride toothpastes contain fluoride salts, such as NaF and sodium monofluorophosphate (NaMFP) (13).

According to the most researchers, toothpastes involving similar dose fluoride (500-1000 ppm) provide approximately same effect on demineralization; but 500 ppm and below fluoride concentrations are accepted as minimum dose and have minimal effect on demineralization (14,15). Higher dose of fluoride can cause fluorosis, on the other hand the lower dose has the insufficient effect on demineralization (14).

The new toothpastes including different formulas which are biocompatible to tooth structure chemically, decrease demineralization, prevent adhesion of bacteria on teeth, provide remineralization and prevent the sensitivity of dentin (6,16).

The aim of the study is to evaluate the ability of a new NaF and $KNO_3$-containing toothpaste on *in vitro* enamel surface microhardness (SMH) by a pH-cycling model.

## Methods

### Enamel Block Preparation

A total of 35 human molar teeth were extracted due to periodontal problems. The soft-tissue debris on the teeth were cleaned and re-inspected for intact surfaces free from caries, hypoplasia and white spot lesions. This study were conducted in 2012 and samples were collected from a biobank and written informed consent was not received due to the nature of this study.

Thirty-five enamel blocks (2x3 mm) which were formed from the extracted human teeth were prepared by using a diamond bur and were kept in 2% formaldehyde solution at pH 7.0 (17). The specimens were embedded in the epoxy resin and the surface of the enamel blocks was grounded flat and was polished to remove 50 µm of the surface layer with 1.2 grit waterproof silicon carbide paper and water-cooled carborundum discs. The prepared samples were submitted to the microhardness test.

**Table 1.** Toothpastes and fluoride concentration

| Toothpastes | Ingredient | Amount |
|---|---|---|
| Sensodyne Mint | Fluoride free | - |
| Colgate® Kids | NaF | 1000 ppm |
| Sensodyne® Pronamel™ for Children | NaF | 1450 ppm |
| Signal White Now | Sodium monofluorophosphate | 1450 ppm |
| Ipana 7 | NaF | 1450 ppm |

### F-Toothpaste Evaluation

Since the treatment with the different experimental dentifrices, enamel blocks were selected randomized into five groups each containing seven blocks; for group A; teeth were treated with Sensodyne Mint as the control group (SENSODYNE® MINT; GSK, USA), for group B; teeth were treated with Colgate® Kids (1000 ppm NaF), (Colgate® Kids; Palmolive Co., New York, USA), for group C; teeth were treated with Sensodyne Pronamel for Children ($KNO_3$ 5%, 1450 ppm NaF) (SENSODYNE® PRONAMEL™; GSK, USA), for group D; teeth were treated with Signal WHITE NOW (1450 ppm NaMFP), (Signal WHITE NOW; Lever Faberge, UK) and for group E; teeth were treated with Ipana 7 (1450 ppm NaF), (Ipana 7; Procter&Gamble Co., Cincinnati, Ohio, USA). The amount of F in the experimental toothpaste was displayed in Table 1. After inducing caries-like lesions, each group was applied daily de- and remineralization cycle period for 7 days. After pH cycling, the surface was assessed and the integrated loss of the hardness of subsurface calculated. Artificial caries-like lesions were formed on specimens of intact human enamel with demineralizing solution for 32 hours.

### Toothpaste Treatments and the Remineralizing pH-cycling Model

Samples were carried out five pH cycles along 7 days at 37 °C for each group (18). During pH cycling, blocks were put in a demineralization solution [demineralization solution in 75 mmol/L acetate buffer, pH 4.7; 2.2 mL/mm$^2$; 2.0 mmol/L $Ca(NO_3)_2.H_2O$, 2.0 mmol/L $NaH_2PO_4.H_2O$ and 0.04 µg F/mL (NaF)] for 6 hours and in a remineralization solution [remineralization solution, in 0.1 mol/L cacodylate buffer, 7.0 1.1 mL/mm$^2$; 1.5 mmol/L $Ca(NO_3)_2.H_2O$, 0.9 mmol/L $NaH_2PO_4.H_2O$, 150 mmol/L KCl and 0.05 µg F/mL (NaF)] for 18 hours. The treatment consisted of 1 minute soak under the agitation in 2 mL/block of toothpaste/deionized water slurries (1:3 w/w) on a daily basis before the solution was changed from demineralization to remineralization or vice versa twice a day. Deionized water was applied before each step (Figure 1). Samples were kept in the remineralization solution for 2 days.

### Hardness Analysis

The hardness of the enamel surface was determined before and after pH cycling with a Digital Micro-Vickers Hardness Tester (Wilson Wolpert; Europe BV, 401 MVD, Netherlands) being

used for Surface Microhardness Analysis (SMH). It was fitted with a Vickers diamond and 25 gram load was used to make indentations in the enamel surface. The loaded diamond was allowed to rest on the surface for 10 seconds (19).

Three indentations spaced by 100 μm were formed in different parts of the enamel. SMH was determined at the baseline, after the caries-like lesions were formed (after demineralization) and after pH-cycling and percentage of SMH recovery (%SMHR) was calculated %SMHR=[(SMH3-SMH2)/(SMH1-SMH2)]x100 (SMH1: baseline SMH, SMH2: after 32 hours demineralization application, SMH3: after pH-cycling) (20).

**Polarized Light Microscopy Analysis**

Sections were mounted on glass-slides and the artificial caries-like lesion depth and the treatments were analyzed in a polarized light microscope (LEICA; Qwin Image Processing and Analyzing, England) as previously detailed (4). Longitudinal sections of 100±10 μm were obtained from the remaining half of each block.

Lesions were grouped in accordance with their morphological appearance after demineralization and after cycling, and as the each category, a numerical index number was designated as follows: no lesion (1), single porosities (2), interrupted lesion band (3), inhomogeneous lesion (4) and completely homogeneous lesion (5) (21).

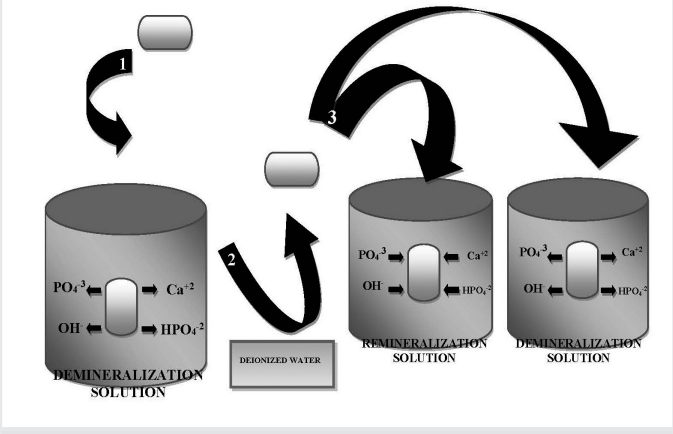


**Figure 1.** pH cycling model according to the flux of minerals

**Statistical Analysis**

Statistical analysis was evaluated by using the SPSS 16.0 software for Windows (SPSS Inc., Chicago, IL, USA). The differences between the F-toothpastes and %SMHR were performed by ANOVA. The datas were compared using the Mann-Whitney U test.

## Results

The mean and standard deviation values of microhardness of the enamel at the baseline, after demineralization and after pH cycling with five different toothpastes were calculated (Table 2). The mean microhardness in group A was found to be 115.96 at baseline, 42.47 after demineralization and 56.32 after remineralization. The mean microhardness in group D was found to be 97.3 at baseline, 58.86 after demineralization and 74.47 after remineralization. There was no difference between group A and D in terms of mean microhardness at baseline, after demineralization and after remineralization (p>0.05) (Figure 2).

There was rehardening of the carious lesions in all groups (%SMHR). The percentage of %SMHR was shown in Table 3. These datas indicated that the percentages of %SMHRs were 96.48%; 67.03%; 63.39%; 60.15% and 57.77%; for groups C, D, E, B and A respectively. The highest %SMHR was found in group C, but statistically significant difference (p=0.946) was not observed for %SMHR regarding the groups.

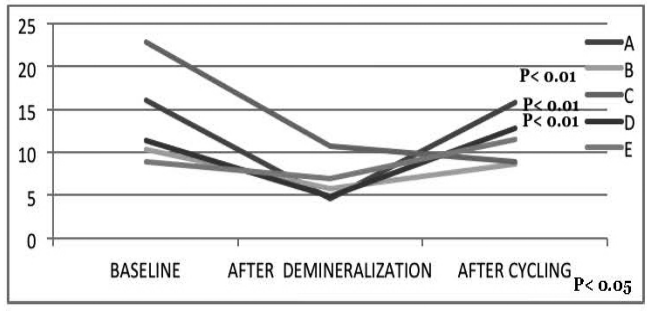


**Figure 2.** The surface microhardness levels of the enamel "baseline, after demineralization and after pH cycling"

**Table 2.** The mean and standard deviation values of surface microhardness at baseline, after demineralization and after pH cycling with five different toothpastes

| Toothpastes | Baseline SMH Mean ± SD | After demineralization SMH Mean ± SD | After cycling SMH Mean ± SD | p values |
|---|---|---|---|---|
| Sensodyne Mint (fluoride free) | 115.96±5.81 | 42.47±2.66 | 56.32±7.54 | p>0.05 |
| Colgate® Kids (NaF-1000 ppm) | 71.7±5.14 | 50.02±4.05 | 69.9±6.43 | p<0.001 |
| Sensodyne® Pronamel™ for Children ($KNO_3$, NaF-1450 ppm) | 165.45±8.60 | 41.24±1.35 | 150.4±13.37 | p<0.001 |
| Signal White Now (NaMF-1450 ppm) | 97.3±9.47 | 58.86±6.53 | 74.47±6.72 | p>0.05 |
| Ipana 7 (NaF-1450 ppm) | 107.44±6.31 | 43.96±1.52 | 116.32±5.54 | p<0.001 |

SMH: surface microhardness; SD: standard deviation

**Table 3.** The percentage of surface microhardness recovery (%SMHR)

| | %SMHR |
|---|---|
| Sensodyne Mint (fluoride free) | 57.77 |
| Colgate® Kids (NaF-1000 ppm) | 60.15 |
| Sensodyne® Pronamel™ for Children ($KNO_3$, NaF-1450 ppm) | 96.48 |
| Signal White Now (NaMF-1450 ppm) | 67.03 |
| Ipana 7 (NaF-1450 ppm) | 63.39 |

SMHR: surface microhardness recovery

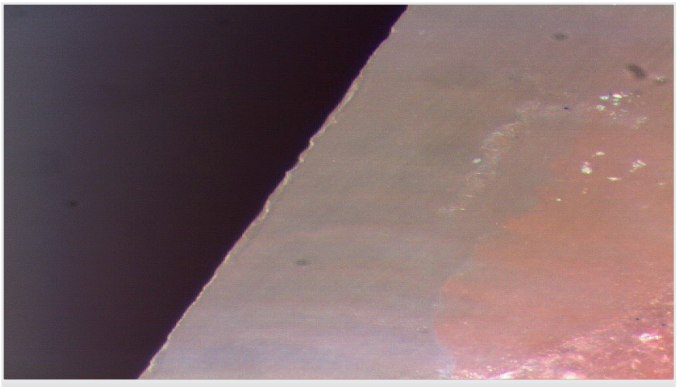

**Figure 3.** Remineralization effect of toothpaste in group A

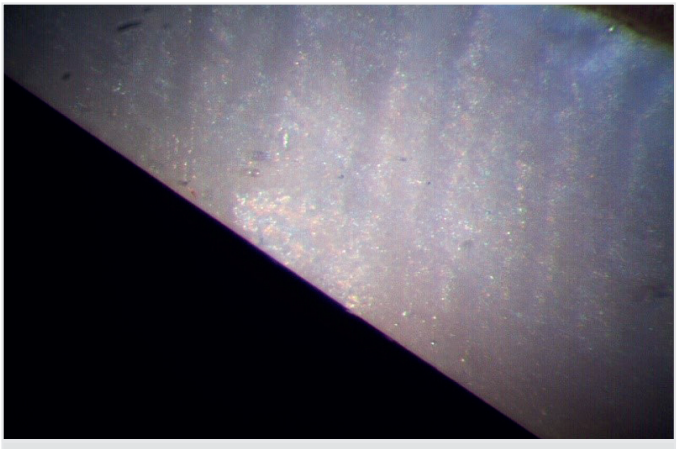

**Figure 4.** Remineralization effect of toothpaste in group B

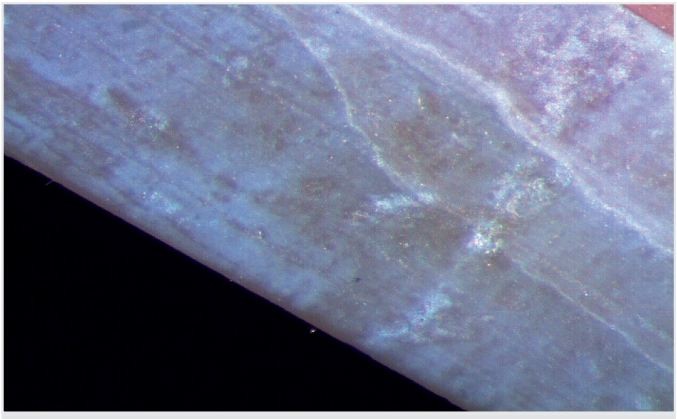

**Figure 5.** Remineralization effect of toothpaste in group C

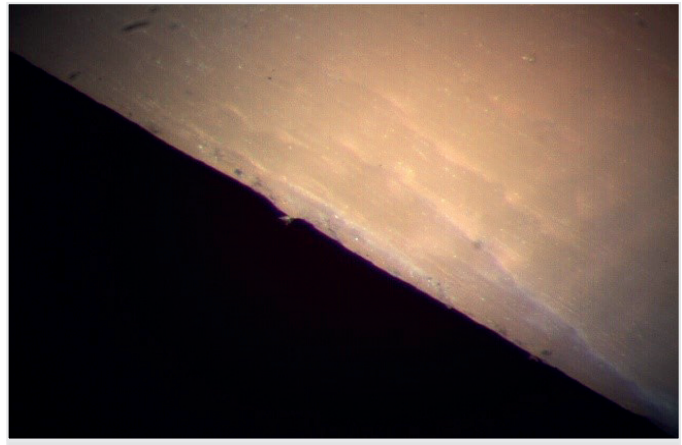

**Figure 6.** Remineralization effect of toothpaste in group D

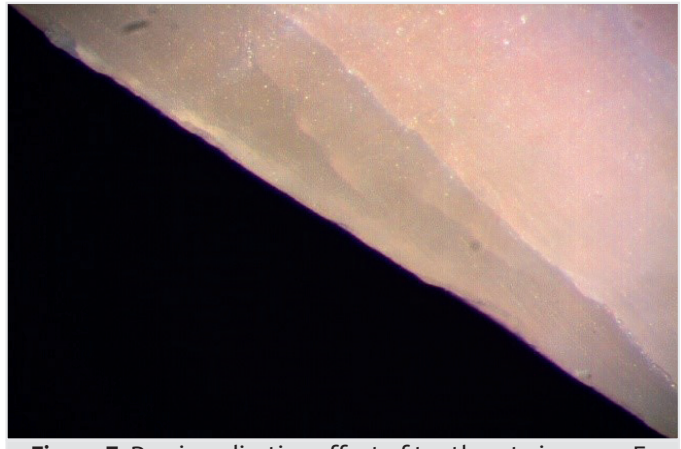

**Figure 7.** Remineralization effect of toothpaste in group E

Polarized light microscope analysis showed the recovery of the enamel surface hardness according to the toothpastes (Figures 3-7).

The irregular enamel surface sign after demineralization and remineralization and after pH cycling regimen were displayed in groups (Figures 8 and 9).

After demineralization; the morphological analysis by using polarized light microscopy showed interrupted bands or inhomogeneous lesions whereas the lesions expressed as single porosities or interrupted lesion bands after pH cycling with five different toothpastes (Table 4). There were no significant differences between the groups ($p>0.05$).

## Discussion

The present study has demonstrated that fluoride toothpastes vary in their capability of enhancing remineralization potential as determined using an established *in vitro* 7 days pH cycling model.

Teeth brushing with F-toothpastes was first used to evaluate the dose-response effect of F on enamel. Recently, the effect of the F on enamel has been identified. However the fluoride toothpastes should be used in natural conditions to prove its usefulness. Therefore, pH cycle regimens were introduced to provide suitable media (4).

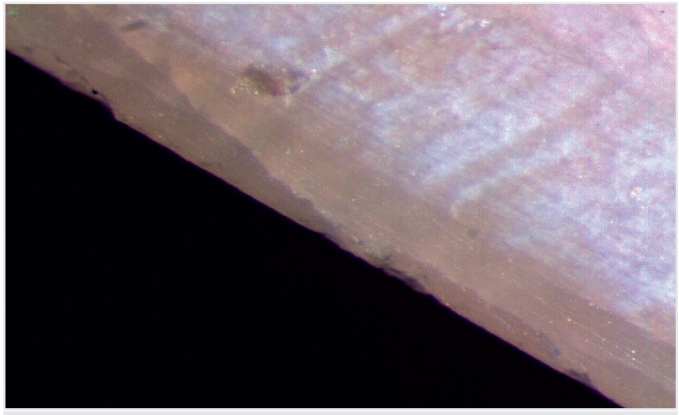

**Figure 8.** Toothpaste C [$KNO_3$ (5%), NaF-1450 ppm]: after demineralization

**Figure 9.** Toothpaste C [$KNO_3$ (5%), NaF-1450 ppm]: after pH cycling

**Table 4.** Number of lesion categories after demineralization and after pH cycling and morphological code numbers in the different groups

| | After demineralization | | | | | After pH cycling | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Sensodyne® Pronamel™ for Children | - | - | 1 | 5 | 1 | - | 3 | 4 | - | - |
| Sensodyne® Mint | - | - | 4 | 3 | - | - | - | 1 | 6 | - |
| Signal White Now | - | - | 4 | 2 | 1 | - | 1 | 5 | 1 | - |
| Ipana 7 | - | - | 2 | 4 | 1 | - | - | 3 | 3 | 1 |
| Colgate® Kids | - | - | - | 4 | 3 | - | - | 4 | 3 | - |

The response variables that can be employed in pH-cycling models are more sensitive than those using in the clinical situation. pH-cycling studies are intended to be extrapolated for the clinical situations. The short period of pH-cycling may produce results that inadequately display the natural process of de- and remineralization. The factors that influence the length of the pH-cycling are the fluoride concentration of the de- and remineralizing solutions (22).

Furthermore Newby et al. (23) demonstrated the importance of formulation effects on driving performance in *in vitro* models.

The findings that the NaMFP toothpaste, which has a definite protective effect, showed less remineralizing efficacy than NaF was not unexpected because pH cycling model consists of only an inorganic solution (24,25). The model choosen to mimic remineralization events is not adequate to estimate the anticaries potential of toothpastes containing NaMFP, because its hydrolysis occurs by phosphatase enzymes, this produced unfavorable results for group C.

The new NaF toothpaste (C-$KNO_3$, NaF 1450 ppm) showed in this model demonstrated the importance of fluoride compound and formulation excipients on driving remineralization *in vitro*.

$KNO_3$ helps reducing tooth sensitivity and it has a neutral pH and a low abrasivity (26). Using an *in situ* erosion remineralization model and a microhardness test, Zero et al. (27) concluded that fluoride toothpaste containing $KNO_3$ dramatically enhanced the remineralization of enamel.

Newby et al. (23) showed that a 1150 ppm NaF test toothpaste protected enamel specimens better (with higher SMH) than a 1100 ppm NaF and a fluoride-free samples at both 10 days and 20 days ($p<0.05$).

Allegrini et al. (28) used polarized light microscopy to determine bone formation in the presence of hydroxyapatite in their study. Similar to our study, Arnold et al. (29) used polarized light microscopy to evaluate crystalline layer of enamel after applying fluoridated milk in their study.

This study demonstrated that fluoride toothpastes can increase the protection of enamel. The present studies also demonstrate the importance of formulation effects on driving performance *in vitro* models.

The *in vitro* model described in the present study should be further used to investigate the effect of enamel SMH of toothpastes.

**Study Limitations**

This study has no limitations.

## Conclusion

This study suggests that the pH-cycling models are enough for studying effect of fluoride on enamel *in vitro* by measuring the change in SMH or performing polarizing microscopy analysis. The average of changes in SMH with $KNO_3$ containing toothpaste was higher than with other toothpastes.

### Ethics

**Ethics Committee Approval:** The study were conducted in 2012 and samples were collected from a biobank.

**Informed Consent:** Written informed consent was not received due to the nature of this study.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: Z.H., G.Ö.Y., Concept: Z.H., G.Ö.Y., B.K., Design: Z.H., G.Ö.Y., B.K., Data Collection or Processing: Z.H., G.Ö.Y., Analysis or Interpretation: Z.H., G.Ö.Y., Literature Search: Z.H., Writing: Z.H.

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Original Article

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# May Biochemical Variables and Pleural Fluid Cell Count Be Used in the Benign-Malign Differentiation of Pleural Effusions Associated with Lung Cancer?

Sami DENİZ[1], Zübeyde GÜLCE[1], Jülide ÇELDİR EMRE[2], Yusuf AYDEMİR[3], Dursun ALİZOROĞLU[1], Ahmet Emin ERBAYCU[1]

[1]University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, Clinic of Chest Diseases, İzmir, Turkey
[2]Turgutlu State Hospital, Clinic of Chest Diseases, Manisa, Turkey
[3]Sakarya University Faculty of Medicine, Department of Chest Diseases, Sakarya, Turkey

## ABSTRACT

**Objective:** Pleural effusion is frequently encountered in patients with lung cancer. Malignant-benign differentiation of the fluid is very important for treatment decision because malignant fluid is considered as the inoperability criterion. However, this distinction is not clinically feasible and may require a cytological examination of the fluid via invasive procedures. The aim of this study was to determine whether there was any difference between laboratory results of malignant and benign pleural fluids.

**Methods:** We retrospectively evaluated 135 patients with cytologically diagnosed lung cancer and underwent benign-malignant differentiation of pleural effusion. Benign and malignant groups were compared in terms of fluid biochemistry, blood gas and cell count.

**Results:** One hundred four patients were male, 31 were female and the mean age was 63.5±11.4 years. Histologically adenocarcinoma was determined as the most common (56%). Right pleural effusion was present in 58.5% of the patients. Malignant effusion rate was higher in females (malign/benign; female: 21/10, male: 48/56). Albumin, protein, erythrocyte count (RBC) and hematocrit (HCT) values in pleural fluid were higher in the malignant group (p=0.001, p=0.018, p=0.009 and, p=0.016, respectively). Cut-off value for albumin: 2.85 and odds ratio (OR): 2.02; for HCT 4.7 and OR: 6.25; for RBC 300 and OR: 6.25; for protein 4.45 and OR: 2.08.

**Conclusion:** In our study, we found that the values of albumin, HCT, RBC and protein in pleural fluid were higher in malignant pleural effusion.

**Keywords:** Pleural effusion, lung cancer, fluid biochemistry

## Introduction

Pleural effusion is a common clinical problem that can occur due to systemic, pulmonary, and pleural pathologies (1). Evaluation of effusion in terms of transudate-exudate helps to differentiate systemic and pulmonary causes. The effusion in the form of transudate is often formed due to systemic causes such as congestive heart failure and liver cirrhosis, while the effusion in the form of exudate can occur during the course of both malignant and benign lung diseases. Approximately 42-72% of all exudative effusions develop secondary to malignant diseases (2,3). All cancers, especially lung cancers, metastasize to pleura and can cause effusion formation. In the initial evaluation of patients with lung cancer, pleural effusion is present in approximately 15% of the patients. During the course of the disease, in 50% of the patients with diffuse lung cancer, pleural effusion develops (4).

**Address for Correspondence:** Sami DENİZ, University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, Clinic of Chest Diseases, İzmir, Turkey
**E-mail:** sami.deniz@saglik.gov.tr **ORCID ID:** orcid.org/0000-0002-8328-295X

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Detection of malignant pleural effusion in a patient with lung cancer is considered as M1a in staging and means stage 4 (inoperable) cancer (5). However, every effusion detected in patients with cancer is not malignant. Pleural effusion can develop due to secondary causes without malignant pleural involvement in lung cancer. These effusions, called as paramalign effusions, are not considered as malignant pleurisy. Paramalign effusion can also be seen due to postobstructive pneumonia, atelectasis, chilotorax, pulmonary embolism and hypoproteinemia (6). Therefore, in a patient with cancer, the differentiation between benign and malign effusion is of great importance. In order to achieve the correct diagnosis, fluid or tissue samples taken from the pleural space should undergo cyto/histopathological examination. However, this distinction is not always easy. The proportion of patients getting a diagnosis with various analyses of pleural fluid sample, including cytological examination, is between 50-60% and it may be necessary to obtain pleural tissue with invasive methods (2).

In this study, it was aimed to investigate the contribution of biochemical tests and cell analysis performed as standard procedures in pleural fluid sample before invasive methods in the separation of paramalign (benign)-malignant pleural effusion.

## Methods

### Patient Selection

The study was designed as a retrospective case series. The study was carried out in patients with lung cancer and pleural effusion who were followed up for the last 5 years. One hundred and thirty five patients with cytologic diagnosis of lung cancer, with an accompanying exudative pleural effusion of which benign-malignant separation was definitively made cytologically (thoracentesis was performed at least 2 times and in addition closed biopsy was performed) and in which biochemical tests, blood gas test and cell count were performed, were included in the study. Patients with chylothorax, pseudochylothorax, pleural effusion in the form of transudate and empyema were excluded: one patient with chylothorax had a history of prior trauma, in 1 patient with pseudochylothorax, it was detected that the patient had pleural fluid before the diagnosis of lung cancer, the content of fluid was intense in patients with empyema, pleural effusion in the form of transudate was related with additional diseases and was not related with lung cancer. Age, sex, type of lung cancer, cytology of fluid, blood gas, biochemistry (albumin, lactate dehydrogenase, protein), erythrocyte count (RBC), hematocrit (HTC) value, and cell count were recorded in all patients. Biochemical tests were performed with Roche-Hitachi Cobas 8000 and 6000, blood gas with Radiometer ABL 700 and hemogram with Beckman-Coulter AV 47160 LH 780 devices. Cytologic examination of fluids was performed as follows: fluid samples, taken by thoracentesis, were centrifuged at 700 rpm in Cytospin 4 device for 5 minutes following being painted with Giemsa and hematoxylin and eosin. This study was approved by the University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, Clinic of Chest Diseases (number: 49109414/806.02.02).

### Statistical Analysis

Statistical analysis was performed using SPSS 18. In all comparisons, type 1 error margin was determined as alpha: 0.05 and was tested in two directions. Chi-square test was used to compare categorical variables and Mann-Whitney U test was used to compare continuous variables. The receiver operating characteristic (ROC) curve analysis was performed and cut-off values were determined for variables of biochemical and cell count tests that were found significant. Specificity and sensitivity values were given in the diagnostic tests, according to these cut-off values.

## Results

One hundred four males and 31 females were included in the study and the mean age of the patients was 63.58±11.45 years. There was no difference between malignant and benign groups in terms of gender and location of pleural effusion (p=0.057 and p=0.20, respectively) (Table 1).

Pleural effusion albumin level [1.91±0.88 vs 2.3±0.61 gr/dL (p=0.001)], protein level [3.7±1.4 vs 4.2±1 gr/dL (p=0.018)], RBC [58.1±174 vs 393±641 (p=0.009)] and HTC level [1.3±3.08 vs 3.79±5.38 (p=0.016)] were significantly higher in the malignant group than in the benign group. There was no significant difference between the benign and malignant groups in terms of other biochemical tests, arterial blood gas, hemogram and age (Table 2).

**Table 1.** Demographic features and etiologies of the patients

| Variables | | Values |
|---|---|---|
| Number (n) | | 135 |
| Age (mean ± SD) (years) | | 63.58±11.45 |
| Gender (n) (male/female) | | 104/31 |
| Lung cancer (malignant cytologic diagnosis)<br>Squamous cell carcinoma (20%)<br>SCLC (15%)<br>NSCLC (8%) | | Adenocarsinoma (56%) |
| Benign | Male (n) (%) | 56 (53.8%) |
| | Female (n) (%) | 10 (32.3%) |
| Malignant | Male (n) (%) | 48 (46.2%) |
| | Female (n) (%) | 21 (67.7%) |
| Localization of pleural effusion | Right (malignant/benign) (n) | 43/36 |
| | Left (malignant/benign) (n) | 16/24 |
| | Bilateral (malignant/benign) (n) | 10/6 |

SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; SD: standard deviation

**Table 2.** Intra-group means and intergroup comparisons

| Variables | Cytology | Mean ± SD | Median (Minimum-maximum) | p value |
|---|---|---|---|---|
| Age (years) | Malignant | 65.1±11.4 | 66 (40-87) | 0.141 |
| | Benign | 61.9±11.3 | 62.5 (20-84) | |
| Albumin (blood) (g/dL) | Malignant | 3.2±0.44 | 3.3 (2.1, 3, 8) | 0.061 |
| | Benign | 3.1±0.63 | 3.05 (1.8, 4.5) | |
| Glucose (blood) (mg/dL) | Malignant | 127±59 | 112 (57-396) | 0.760 |
| | Benign | 116±31 | 114 (64-214) | |
| Lactate dehydrogenase (blood) (U/L) | Malignant | 368±506 | 259 (115, 3211) | 0.797 |
| | Benign | 347±415 | 259 (115, 3211) | |
| Protein (blood) (gr/dL) | Malignant | 6.5±0.7 | 6.6 (5, 8.2) | 0.226 |
| | Benign | 6.4±0.9 | 6.4 (3.8, 8.1) | |
| Albumin (fluid) (g/dL) | Malignant | 2.3±0.61 | 2.5 (0.6, 3.8) | 0.001 |
| | Benign | 1.91±0.88 | 2 (0, 3.7) | |
| Glucose (fluid) (mg/dL) | Malignant | 100±67 | 92 (1, 386) | 0.215 |
| | Benign | 79±60 | 89 (0, 242) | |
| Lactate dehydrogenase (fluid) (U/L) | Malignant | 1430±3482 | 560 (57, 25781) | 0.772 |
| | Benign | 2056±3522 | 567 (77, 17000) | |
| Protein (fluid) (g/dL) | Malignant | 4.2±1 | 4.4 (1.3, 6.3) | 0.018 |
| | Benign | 3.7±1.4 | 4.05 (0.2, 7.6) | |
| PH (blood gas) | Malignant | 7.43±0.06 | 7.43 (7.24, 7.54) | 0.092 |
| | Benign | 7.44±0.09 | 7.45 (6.9, 7.59) | |
| $pO_2$ (blood gas) (mmHg) | Malignant | 72.4±20.8 | 67.5 (23, 140) | 0.105 |
| | Benign | 83.8±35 | 72 (27, 216) | |
| $pCO_2$ (blood gas) (mmHg) | Malignant | 39±8.4 | 36 (26, 67) | 0.365 |
| | Benign | 37.5±8.7 | 38 (18, 67) | |
| pH (fluid) | Malignant | 7.30±0.15 | 7.36 (6.9, 7.55) | 0.837 |
| | Benign | 7.24±0.29 | 7.36 (6.27, 7.49) | |
| $pO_2$ (fluid) (mmHg) | Malignant | 107±43.6 | 117.5 (20, 181) | 0.262 |
| | Benign | 99.6±40.4 | 105 (0.1, 163) | |
| $pCO_2$ (fluid) (mmHg) | Malignant | 51±16.2 | 50 (17, 92) | 0.528 |
| | Benign | 59.4±51.5 | 46.5 (30, 383) | |
| Leukocyte (blood) (uL) | Malignant | 10024±3745 | 9300 (4400, 20900) | 0.251 |
| | Benign | 11121±5564 | 9600 (1180, 32000) | |
| Erythrocyte (blood) (M/uL) | Malignant | 4296±642 | 4400 (3000, 5700) | 0.101 |
| | Benign | 4106±710 | 4050 (2800, 5800) | |
| Hemoglobin (blood) (gr/dL) | Malignant | 11.9±2 | 12 (7.4, 17.3) | 0.160 |
| | Benign | 11.5±2.1 | 11.35 (8, 16.3) | |
| Hematocrit (blood) (%) | Malignant | 36.3±5.6 | 37.1 (23.4, 45.9) | 0.348 |
| | Benign | 35.5±6.6 | 35.25 (23.8, 55) | |
| Leukocyte (fluid) (uL) | Malignant | 2629±3938 | 1500 (300, 17300) | 0.885 |
| | Benign | 3231±4254 | 1750 (300, 13300) | |
| Erythrocyte (fluid) (M/uL) | Malignant | 393±641 | 30 (0, 1900) | 0.009 |
| | Benign | 58.1±174 | 0 (0, 700) | |
| Hemoglobin (fluid) | Malignant | 1.08±1.51 | 0.3 (0, 5.1) | 0.064 |
| | Benign | 0.38±0.96 | 0.1 (0, 3.9) | |
| Hematocrit (fluid) | Malignant | 3.79±5.38 | 1 (0, 15.6) | 0.016 |
| | Benign | 1.3±3.08 | 0.1 (0, 12.2) | |

$PO_2$: partial oxygen pressure; $PCO_2$: partial carbon dioxide pressure; SD: standard deviation

**Table 3.** Sensitivity and specifity values for albumin, hematocrit, protein and erythrocyte

| Variables | Cut-off value | Sensitivity (%) | Specifity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|
| Albumin | 2.85 | 80.6 | 10.61 | 47.79 | 35.00 |
| Protein | 4.45 | 50.72 | 31.82 | 43.75 | 38.18 |
| Erythrocyte | 300 | 70.59 | 6.25 | 44.44 | 16.67 |
| Hematocrit | 4.7 | 70.59 | 6.25 | 44.44 | 16.67 |

PPV: positive predictive value; NPV: negative predictive value

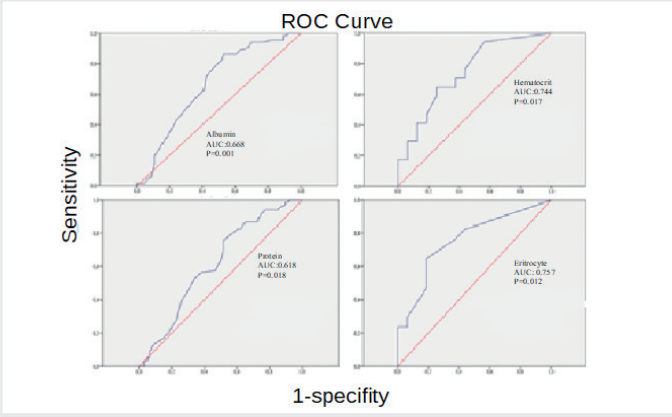


**Figure 1.** Threshold values for albumin, hematocrit, protein and erythrocyte
ROC: receiver operating characteristics

The cut-off value for albumin was 2.85 and odds ratio (OR): 2.02, for HTC 4.7 and OR: 6.25, for RBC 300 and OR: 6.25, for protein 4.45 and OR: 2.08 (Figure 1).

Among determined variables, the highest sensitivity was found in albumin (80.6%) and the highest specifity was found in protein (31.82%) (Table 3).

## Discussion

Malignant pleural effusions are one of the most common causes of exudative pleural fluids; approximately 42-72% of all exudative fluids develop secondary to malignant diseases (2). Lung cancer causes 40-50% of all malignant pleural effusions. Cancer metastasizes to pleura by lymphatic or hematogenous way or by direct invasion. However, it is not yet clear by which mechanism cancer cells cause the formation of fluid in the pleura. The most common accepted mechanisms are increased vascular permeability and impaired drainage (7,8).

Macroscopic features of malignant pleural effusion are not specific. Malignant pleural effusion may be serous, serosanguinous, or hemorrhagic. Hemorrhagic effusions suggest direct pleural involvement. Serous effusion often occurs after lymphatic obstruction or atelectasis due to endobronchial lesion. In all studies conducted to date, tumor markers and other biochemical tests in pleural fluid have been shown to be inadequate in differential diagnosis. Besides, it is stated that biochemical analysis is not reliable in the differentiation between malignant and bening (9). Therefore, cytological examination is used to differentiate malignant from benign pleural effusions. However, in only half of patients, malignant cells are detected in cytological examination (10). Advanced invasive procedures are required for patients who cannot be diagnosed with cytological examination. Although macroscopic appearance of fluid does not have a diagnostic role, it is likely that hemorrhagic and exudative fluids are malignant. Therefore, in patients with lung cancer, exudative and hemorrhagic fluids should be considered as malignant fluids unless proven otherwise (11). In our study, it was found that in pleural fluid, increased albumin and protein levels which were associated with exudate and increased RBC and HTC levels which were associated with hemorrhagic appearance increased the likelihood of malignant effusions. P values for albumin, protein, RBC and HTC were p=0.001, p=0.018, p=0.009 and p=0.016, respectively.

In approximately one-third of patients with malignant pleural effusion, at time of diagnosis, pH of pleural effusion varies from 6.95 to 7.29 and glucose concentration is low (10). In our study, we found that pH was more acidic in malignant effusions but statistically there was no difference between benign and malignant groups in terms of pH of effusion (p=0.837). Also, there was no difference between benign and malignant groups in terms of glucose of effusion.

Although lung cancer is more common in males, malignant pleural effusion is more common in females (12,13). In our study, we found that malignant pleural effusion was more frequent in females than in male patients, although we had more males than females. Malignant effusion was detected in 68% of females and 46% of males in our study.

Pleural effusion associated with malignant disease is usually seen over 50 years of age (14,15). When age trends of patients with malignant effusion were examined, 83% of patients were reported to be over 50 years of age (2). In our study, the mean age was 65 years in patients with malignant effusion, while the mean age was 62 years in patients with benign effusion, but the difference was not significant.

The diagnostic value of cytologic examination of pleural effusion varies according to the type of cancer. The highest diagnostic value was in adenocarcinoma, and this rate was lower in squamous cell carcinoma (16). Adenocarcinoma was found in 56%, squamous cell carcinoma in 20% and small cell carcinoma in 15% of our patients.

When evaluated in terms of the placement of effusion, 62.5% of bilateral effusions, 54.4% of right effusions and 40% of left effusions were found to be malignant. In total, higher rate of malignancy in pleural effusions in the right side could be explained by the fact that much more of lymphatic drainage of the lung is drained to the right side.

In our study, cut-off values were calculated by using ROC curve analysis for albumin, protein, RBC and hemotocrit, which were statistically significant in malignant effusions. As expected, sensitivity and specificity values in all parameters were far from diagnostic efficiency. However, it was confirmed that a fast forward and invasive examination should be performed in exudative and hemorrhagic effusions.

### Study Limitations

The limitation of our study was that it did not contain sufficient information about the etiological causes of benign effusions, arising from its retrospective nature. The knowledge of etiology of benign effusion may guide the detection of false negativity rates. Since the study was retrospective, there were deficiencies in the demographic data (additional diseases, smoking history) of the patients.

The strong aspect of our study was that it contributed to data which are known to be insufficent in our country in this field.

## Conclusion

Pleural effusion in patients with lung cancer is more likely to be malignant in females with an advanced age, with effusion localized in the right, with exudative and hemorrhagic effusion and with adenocarcinoma cell type. Apart from invasive methods, studies investigating biochemical markers that will detect metastatic pleural effusions will contribute to the elimination of diagnostic difficulties in this area.

### Ethics

**Ethics Committee Approval:** This study was approved by the University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, Clinic of Chest Diseases (number: 49109414/806.02.02).

**Informed Consent:** Because this study was a retrospective, informed consent form was not obtained.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: S.D., Design: S.D., Data Collection or Processing: Z.G., Analysis or Interpretation: S.D., Literature Search: J.Ç.E., Y.A., Writing: S.D., D.A., A.E.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Original Article

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# The Effects of Spinopelvic Parameters Such As Lumbar Lordosis and Sacral Slope Angles in the Development of Lumbar Disc Degeneration

Atilla KIRCELLİ[1], İlker ÇÖVEN[2], Pelin ŞEN[3], Osman ORMAN[4]

[1]Başkent University Faculty of Medicine, Department of Neurosurgery, İstanbul, Turkey
[2]Konya Training and Research Hospital, Clinic of Neurosurgery, Konya, Turkey
[3]Bezmialem Vakıf University Faculty of Medicine, Department of Anesthesiology and Reanimation, İstanbul, Turkey
[4]Private Reyap Hospital, Clinic of Orthopedics, İstanbul, Turkey

## ABSTRACT

**Objective:** Spinopelvic parameters were identified and the association between sagittal spinopelvic alignment and lumbar disc diseases have been reported in several studies. The purpose of this study was to evaluate the spinopelvic parameters such as lumbar lordosis (LL) and sacral slope (SS) in normal healthy lumbar spine versus degenerative disc disease group.

**Methods:** We retrospectively identified 140 patients suffered from back pain with/without radiculopathy between 2016-2017 in this study. Of these 70 patients had normal disc morphology and they constituted called control group, and the other 70 patients had lumbar degenerative disc disease and they constituted called disease patient group. All patients' LL, and SS angles were measured on T2 weighted sagittal magnetic resonance imaging and degenerated disc levels were noted. We also recorded LL-SS ratio which was calculated by dividing of LL by SS value in both groups. We compared these parameters between two groups.

**Results:** In disease patient group there was a positive correlation ($r=0.947$, $p<0.0001$) between the LL and SS angles. The mean LL was 45.14±11.01 and the mean SS angle was 35.91±7.67 degrees and there was weak negative correlation between degenerated disc level and SS angle ($r=-0.243$, $p=0.042$). LL-SS ratio was 1.25±0.1. In control group, there was a positive correlation ($r=0.927$, $p<0.0001$) between the LL and SS angles. The mean LL was 49.46±9.07 and the mean SS was 38.45±6.91 degrees. LL-SS ratio was 1.28±0.93. There were significant differences in LL, SS and LL-SS ratio between groups ($p=0.013$, $p=0.041$, and $p=0.025$, respectively).

**Conclusion:** LL, SS angles and LL-SS ratio which are easily measured at in neurosurgery, orthopaedics and physical therapy practice, may be the predictor of disc degeneration.

**Keywords:** Spinopelvic parameters, lumbar lordosis, sacral slope, disc degeneration

## Introduction

The spinal balance is provided by the placement of spine with proper lordosis on pelvis. For this reason, a relationship is tried to be established between the relation of the pelvis with the spine and diseases of the spine. As a result of the studies, spinopelvic parameters were defined by Duval-Beaupere et al. (1-3). Many studies have identified the relationship between degenerative spondylolisthesis and impaired spinopelvic balance. The relationship between sagittal spinopelvic balance and lumbar disc diseases (LDD) has been demonstrated by several studies in recent years (4-7).

**Address for Correspondence:** Atilla KIRCELLİ, Başkent University Faculty of Medicine, Department of Neurosurgery, İstanbul, Turkey
**E-mail:** atillakircelli@gmail.com **ORCID ID:** orcid.org/0000-0003-2109-1274

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Some sagittal spinopelvic parameters were lumbar lordosis (LL) and sacral slope (SS). Pelvic incidence (PI) reaches a permanent fixed value with the completion of growth; it is not affected by position, posture and degenerative diseases of spine and pelvis; it is a fixed morphological parameter (4,8,9). PI consists of the sum of pelvic tilt (PT) and SS and these two values may vary. There is a correct proportional relationship between SS and LL (2).

Increased angle of PI was determined as a predisposing factor in the pathogenesis and development of degenerative spondylolisthesis, resulting in increased PI, increased SS, and increased LL (4,8,9). Increased LL values have been shown in some studies to increase the risk of spondylolisthesis by increasing shear stress in lumbosacral junction. Some authors describe characteristic spinopelvic features in patients with LDD (4-6). Endo et al. (5) and Rajnics et al. (6) and observed decreased SS, decreased LL and anterior-shifted sagittal vertical axis (SVA) in patients with LDD. Although Barrey et al. (4) opposed that asymptomatic individuals might have abnormal spinopelvic angles, Yang et al. (7) showed disc degeneration in magnetic resonance imaging of asymptomatic individuals with abnormal spinopelvic values and revealed the relationship between spinopelvic values and LDD.

The aim of this study was to compare the LL and SS angles, which can be easily calculated from the MRI images between patient and control groups and to find out the relationship between LL and SS angles and the disk levels of degenerative disc disease.

## Methods

Seventy consecutive patients with single or two levels disc degeneration or disc hernias in lumbar MRI, and 70 consecutive patients without disc degeneration or disc hernias, whose disc morphology was completely normal, were retrospectively selected from all the patients who were admitted to our clinic with back and/or leg pain between 2016-2017 for the study. This study was approved by the Başkent University Institutional Review Board (number: KA15/279) and written informed consent form was obtained from each patient. Patients with normal disc morphology were referred as control group, and patients with disk degeneration were referred as the patient group. Patients with 3 or more levels of disc degeneration, spondylosis, spondylolisthesis, spinal stenosis, scoliosis, vertebral fractures, infective processes such as osteomyelitis-discitis, spondyloarthropathies and previously operated patients (patients with discectomy or spinal fusion surgery) were excluded from the study.

The same 1.5 T MRI technique in which the signals are maximized using spine coil (Signa Excite, GE Medical Systems, Milwaukee, WI, USA) was used in all the patients in our radiology department. Lombar MRIs of both groups were investigated, and LL and SS angels were measured by the Clear Canvas program. Although LL is the lordotic angle of the lumbar vertebrae, it is the angle between the parallel line from the L1 vertebra upper end plate and the line tangled to the sacral vertebrae final plate in the T2 sagittal plane of the lumbar MRI (Figure 1A). The angle of the sacral curve is the angle between the parallel line passing through the upper plate of sacrum and the horizontal line in the same MRI cross section (Figure 1B). A radiologist calculated these angles along with the impaired disc levels and recorded them in the patients' medical recordings. Age, gender, and other data were recorded from the patiens' recordings.

A strong correlation was shown in many studies between LL and SS as indicated in the medical literature. In our study, when we divide the LL angle to the SS angle, the resulting value was calculated and recorded in both groups under the name of the LL-SS ratio.

### Statistical Analysis

Correlation between age, gender, degenerated disc levels, LL, SS, LL-SS ratio in the groups was measured by the Pearson correlation test. The mean values of age, LL, SS and LL-SS ratio in both groups were compared by t-test. Descriptive statistics were expressed as mean and standard deviation for variables with normal distribution. P value below 0.05 was accepted as statistically significant. All statistical tests were performed with SPSS software for Windows (version 21.0; IBM, Armonk, NY, USA).

## Results

There were 70 individuals in the control group consisting of 22 males (31.4%) and 48 females (68.6%) and the mean age was 38.17±13.21 years. There were 70 patients with lombar disc degeneration in the patient group consisting of 35 males (50%) and 35 females (50%) and the mean age was 45.58±15.62 years. There was statistically significant difference between the groups in terms of age (p=0.003). Impaired disc levels and demographic features of the patients were given in Table 1.

The mean LL value was 45.14±11.01 degrees and the mean SS value was 35.91±7.67 degrees in the patient group. There was a weak correlation between age and LL and SS (r=0.25, p=0.037 and r=0.245, p=0.041, respectively). There was a proportional strong correlation between LL and SS (r=0.947, p<0.0001). The more caudal disc degeneration levels, the smaller SS angles; however there was a still weak correlation (r=0.243, p=0.042, respectively). The mean LL-SS ration was 1.25±0.1 in the patient group.

The mean LL value was 49.46±9.07 degrees and the mean SS value was 38.45±6.91 degrees in the control group. There

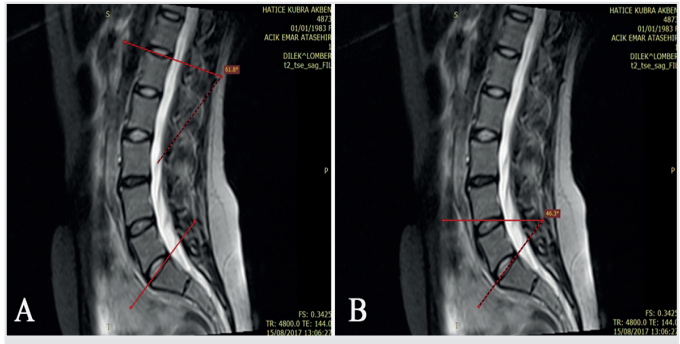


**Figure 1.** T2-weighted sagittal lumbar magnetic resonance imaging shows lumbar lordosis angle (A) and sacral slope angle (B)

**Table 1.** Demographic features

| | Control group | Patient group | p values |
|---|---|---|---|
| Age (years ± SD) | 38.17±13.21 | 45.58±15.16 | 0.003 |
| Gender (n, %) | | | 0.025 |
| Male | 22 (31.4%) | 35 (50%) | - |
| Female | 48 (68.6%) | 35 (50%) | - |
| **Impaired disc levels (n, %)** | | | |
| L2-3 | - | 3 (4.3%) | - |
| L3-4 | - | 7 (10%) | - |
| L3-4 and L4-5 | - | 3 (4.3%) | - |
| L4-5 | - | 23 (32.9%) | - |
| L4-5 and L5-S1 | - | 11(15.7%) | - |
| L5-S1 | - | 23 (32.9%) | - |

SD: standard deviation

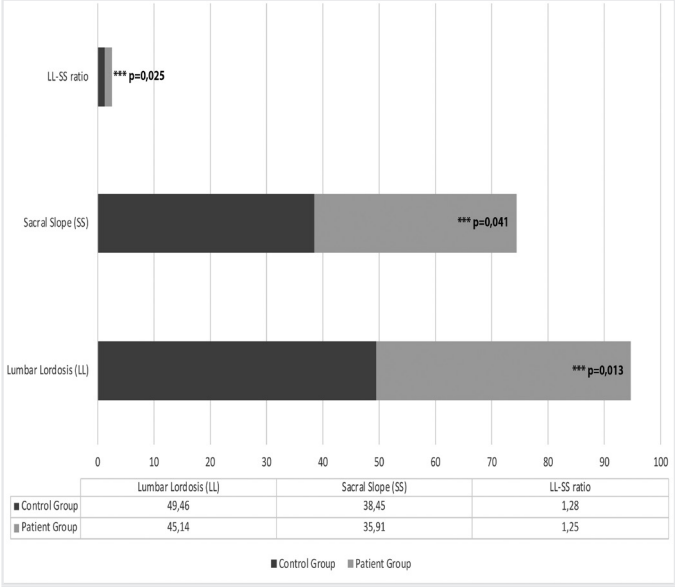


**Figure 2.** Comparison of spinopelvic parameters in control and patient groups

was a strong correlation between LL and SS angles (r=0.927, p<0.0001). The mean LL-SS ration was 1.28±0.93 in the control group.

There were statistically significant differences between the groups in terms of the mean LL and SS angles and LL-SS ratios (p=0.013, p=0.041 and p=0.025, respectively) (Figure 2).

## Discussion

The prevalence of back pain in adults is between 60% and 90%. Discogenic pain is one of the most important causes of low back pain and it is thought that LL and changes in sacral parameters are very important causes of discogenic pain. In many studies on lumbosacral morphology, the relation of back pain with LL and SS angles in isthmic spondylolisthesis has been studied, but this relation in more frequent pathologies such as intervertebral disc degeneration or disc hernias have been less studied (10).

The direct relationship between LL and SS angle has been shown in many studies (11-13). Diseases affecting the lumbar region or sacropelvic junction disrupt the sagittal balance and lead to compensatory changes such as an increase or decrease in thoracic kyphosis. The increase in physiological kyphosis in the thoracic region results in a shift of the sagittal balance line to the front; the decrease in physiological kyphosis in the thoracic region results in a shift of the sagittal balance line to the back. The increase in physiological kyphosis in the thoracic region results in a shift of the sagittal balance line to the front; the decrease in sagittal balance line to the back of the way to change. Anatomical and positional parameters used in the analysis of the sacropelvic compound are available. The main positional parameters are lumbosacral, L5 incidence, PT and SS angles. Although these parameters are used in the evaluation of different regions, they are constantly interrelated. A change in a region or in a parameter results in compansatuary response in other parameters to restore sagittal balance (14).

It is known that pelvic morphology affects sagittal spinal geometry in particular, LL angle (14). The effect of pelvic morphology on spinal balance in the progression and treatment of spinal deformities should be well understood. PI is the sum of SS and PT. It is accepted that spinopelvic balance changes are compensated by changes in PT and SS angle to keep PI angle stable. Theoretically, PI angle is constant. Mac-Thiong et al. (15) investigated the relationship between toracic kyphosis, LL, PI, SS and PT in children adolescents in 2005. They found mild relation between toracic kyphosis and LL and strong relation between SS and LL. A direct relation between toracic kyphosis and PT was not established. Gottfried et al. (16) showed decrease in LL and increase in PI and PT in patients with iatrogenic flatback. This compensatory mechanism prevents the increase of kyphosis. With these parameters, LL-SS ratio has not been previously reported in the literature. The mean constant value of 1.3 calculated in the control group with normal disc morphology was low and suggested that disc degeneration might develop. This value was lower in the patient group and there was a statistically significant difference between groups in terms of LL-SS ratio.

In patients with degenerative disc disease and disc hernias, there is a more flat spine, characterized by decreased thoracic kyphosis and decreased LL. In these individuals, PI appears to be lower than normal population. Rose et al. (17) suggested that the sum of thoracic kyphosis, LL and pelvic indices should be less than 45 degrees for a healthy spinopelvic balance (18). Yang et al. (7) observed that PI was lower in patients with lumbar degenerative disc, and that the angles of the SS and PT were decreased, and finally, that flatter LL and thoracic kyphosis developed. A flattened spine and more vertically positioned sacrum increases the compressive forces created by gravity and accelerates disc degeneration (6,19-21). On the other hand, the absorption of the shaking loads formed by these vertical forces will decrease and result in the formation of disc hernias. The decrease in LL will shift the SVA line to the fore; and will activate the hip extensors resulting in pelvic backtilts (2,4,5,9,22). It is suggested that lumbar discectomy improves the LL and that SVA approaches to normal limits and thus pain is reduced (5).

We believe that the changes in disc morphology have an effect on many lumbosacropelvic angles and biomechanics of the spinal structure together. Therefore, lumbosacropelvic morphology in male and female patients may be related with the quality of life after lumbar disc herniation surgery.

In the present study, it was shown that LL and SS angles were predisposing factors in the development of degenerative disc disease. In many studies it was shown that there was a relationship between LL and SS (23,24). However, in this study, there was statistically significant difference between the patient group and the control group with normal spinal morphology in terms of LL and SS means. It can also be concluded that the LL and SS angles may be predisposing factors for the development of disc degeneration. However, the patients in the control group were not followed up for many years and it is not known whether controls will develop or not develop disc degeneration over time.

### Study Limitations

Retrospective design based on the medical recordings of the patients, lack of follow-up results of the control group in the study for many years and lack of a prospective or randomized design were the limitations of the study. In addition, patients in both groups did not exhibit similar characteristics in terms of age, gender, occupation and environmental factors, which could be a limitation in determining the development of disc degeneration. The existence of a control group and large number of patients were the strong sides of this study. However, fallibility of these results can be reduced by randomised, controlled and prospective studies.

## Conclusion

The value of LL and SS angles and LL-SS ratio, which can be easily measured in neurosurgery, orthopedics or physical therapy practice, in predicting the development of disc degeneration should not be underestimated.

### Ethics

**Ethics Committee Approval:** This study was approved by the Başkent University Institutional Review Board (number: KA15/279).

**Informed Consent:** Written informed consent form was obtained from each patient.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: A.K., İ.Ç., O.O., Concept: A.K., O.O., Design: İ.Ç., O.O., Data Collection or Processing: A.K., P.Ş., Analysis or Interpretation: A.K., O.O., P.Ş., Literature Search: İ.Ç., P.Ş., Writing: A.K., O.O., İ.Ç.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Original Article

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# Prevalence of Elongated Styloid Process and Eagle Syndrome in East Eagean Population

Fatih ASUTAY[1], Necip Fazıl ERDEM[2], Yusuf ATALAY[3], Ahmet Hüseyin ACAR[4], Hilal ASUTAY[1]

[1]Uzman DentaClinic, Bursa, Turkey
[2]Marmara University Faculty of Medicine, Department of Oral and Maxillofacial Surgery, İstanbul, Turkey
[3]Private Vefa Oral and Dental Health Clinic, Afyon, Turkey
[4]Private Clinic, İstanbul, Turkey

## ABSTRACT

**Objective:** In this study; we aimed to evaluate the prevalence, clinical and radiographic findings of elongated styloid process (SP) and Eagle syndrome (ES) in Eastern Aegean Turkish population.

**Methods:** Recordings of 3678 patients over 18 years of age were examined who were admitted to Afyon Kocatepe University Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, between July 1 and December 31, 2014. Length, elongation type, calcification shape, single or double sided appearance of SP and clinical findings were recorded.

**Results:** In 258 patients (112 male, 146 female), SP were found to be elongated (7.01%). In 9 patients (3 male, 6 female) (0.24%), symptoms were considered as ES. There was no difference between age, sex and elongated SP ($p>0.05$).

**Conclusion:** The elongation of the SP may cause a variety of clinical symptoms. This situation may be confused with many other clinical problems. Elongated SP or ES which can be detected in panoramic radiographs should be consulted with the ear-nose-throat clinic.

**Keywords:** Eagle syndrome, elongated styloid process, prevalence

## Introduction

The styloid process (SP) is a cartilaginous long spine projecting downward from the inferior surface of the temporal bone with an approximate length of 2-3 cm. It is considered elongated when it is longer than 3 cm. Many important neurovascular structures such as the internal jugular vein, internal carotid artery and cranial nerves (10, 11 and 12) locate near the tip of the SP.

Eagle syndrome (ES) which is also known as styloid-carotid artery syndrome, is a rare condition with an elongation of SP or calcification of stylohyoid ligament and clinical symptoms such as neck and cervicofacial pain (1-7). It was first described by an otorhinolaryngologist, whose name was Eagle, in 1937 (8). Elongated process occurs 4% of the population and patients are usually asymptomatic and only 4-5% of them present symptoms with mostly over 30 years of age (9). The elongated SP may be seen as uni- or bilateral and patients may have symptoms related to compression and irritation of cranial nerves (5, 7, 9 and 10) such as dysphagia, tinnitus, otalgia, facial pain while turning the head, foreign body sensation, recurrent orafacial and throat pain, pain on extending tongue and discomfort during chewing (9). It rarely may cause stroke due to the compression of carotid arteries (10). This syndrome is seen most commonly between 30 and 50 years of age. It is more common in women (1:2) according to Bagga et al. (11) and (1:3) according to Alpoz et al. (9). The complaints such as throat pain, unilateral neck pain and tinnitus are classic symptoms of ES. If ES is present, one can palpate the tip of the SP in the back of the throat on the exam, which is normally non-palpable (12). Symptoms may be worsened on

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**Address for Correspondence/Yazışma Adresi:** Fatih ASUTAY, Uzman DentaClinic, Bursa, Turkey
**E-mail:** dt_asutay@hotmail.com **ORCID ID:** orcid.org/0000-0003-3252-5867

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bimanual palpation of the styloid through the tonsillar bed. Patients may be relieved by infiltration of anaesthetic solution into the tonsillar bed. Imaging is important and diagnostic. The enlarged SP may be visible on an orthopantogram or a lateral cephalometry.

There have been several theories on the etiology of the ES but the exact cause is unclear. Local chronic irrigations, endocrine disorders in females at menopause, surgical trauma, mechanical stress, persistence of mesenchymal elements, growth of the osseous tissue or trauma during development of SP could result in calcified hyperplasia of the SP (13-15). Also, women with such elongation may tend to more symptomatic than men according to some studies (16-18).

The aim of this retrospective study is to investigate the prevalence, the clinical symptoms and radiographic location and appearance of the ES in Eastern Aegean Turkish population and its relation with gender and age. The type of elongation and calcification patterns of each elongated SP was classified as elongated, pseudoarticulated and segmented.

## Methods

Recordings of 3678 patients over 18 years of age were examined who admitted to Afyon Kocatepe University Faculty of Dentistry, Department of Oral and Maxillofacial Surgery between July 1 and December 31, 2014 in order to figure out the incidence of ES in Turkish population. There were 1941 males and 1737 females with a mean age of 38.27±15.81. All patients included in this study were prescribed digital panoramic radiographs as a part of their diagnostic and treatment work up. There is no exclusion criteria in this study. All the digital panoramic radiographs (PRs) were taken by a Planmeca ProMax X-ray unit (Planmeca, Helsinki, Finland) according to the manufacturer recommendations. Only diagnostically acceptable images were included in the study. The panoramic radiographs were evaluated and the lengths of SP were measured by the same two oral and maxillofacial surgeons. If they did different measurements, they discussed until they agreed with each other. The measurement of the length was initiated proximally at the point where the SP extended from the tympanic plate to the tip of the process (Figure 1). The ossified stylohyoid ligament that joined to SP was added to the measurements. The SPs were divided into 3 groups; elongated, pseudo-articulated and segmented according to radiographic appearance and also recorded as unilateral or bilateral. Length of SP which was longer than 3 cm was considered as elongated.

Data including atheroma, hypertension, renal problem, osteoporosis, diabetes mellitus, cardiovascular diseases, dysphasia, odynophagia, headache, neckache nausea, sensation of foreign body in throat, pain upon turning head, otalgia and tinnitus were recorded from the patients' medical charts. Patients who experienced recurrent pain in oropharynx and face, dysphagia, foreign body sensation in the throat and one or more of the other symptoms with no other medical reasons but elongated SP were considered as ES.

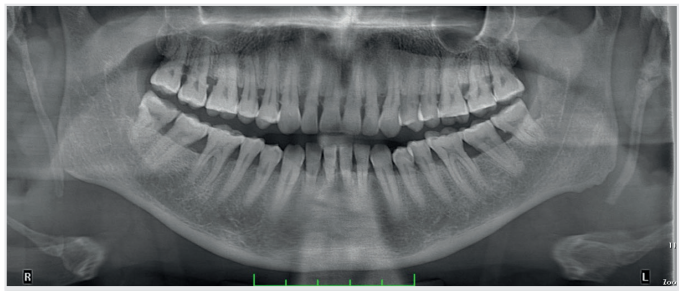

**Figure 1.** A 64-year old male patient with elongated styloid processes

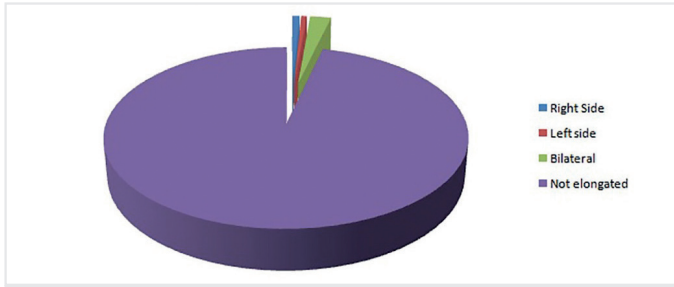


**Figure 2.** Incidence of styloid process elongation

All procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

### Statistical Analysis

The data were analyzed by using chi-square and Continuity (Yates) Correction.

## Results

In a total of 3678 patients, 258 SP elongation cases (7.01%) (112 male and 146 female) were determined. Elongation of the SP was recorded right-sided in 28 patients (10.9%), left sided in 22 patients (8.5%) and bilateral in 208 patients (80.6%) (Figure 2). Number of patients with elongated SP was the highest between the ages of 51-60 and the lowest between the ages of 18-30 in both female and male groups (Table 1). When the relationship between symmetry of the SP elongation and gender was analyzed, we observed symmetry in 84.2% of the female population and in 75.9% of the male population.

The types of SP elongation according to gender were listed in Table 2. The elongated type was the most common type both in males (56.3%) and in females (58.9%) (Table 2). There were no significant differences between the type of SP elongation and gender, age and radiographic location ($p>0.05$).

No statistically significant differences were detected based on atheroma among the genders ($p>0.05$). The privilege of osteoporosis was significantly higher in females (12.3%) compared to males (3.6%) which is statistically significant ($p=0.023$; $p<0.05$). Other clinical and systemic symptoms of ES as listed in Table 3 did not show any statistical difference among genders.

**Table 1.** Styloid process elongation based on age intervals, location and gender

| | Male (n=112) | Female (n=146) | Total | p |
|---|---|---|---|---|
| **Age** | | | | |
| 18-30 | 14 (12.5%) | 14 (9.5%) | 28 (10.9%) | |
| 31-40 | 22 (19.6%) | 29 (19.8%) | 51 (19.7%) | |
| 41-50 | 23 (20.5%) | 35 (24%) | 58 (22.5%) | 0.500 |
| 51-60 | 27 (24.2%) | 47 (32.3%) | 74 (28.7%) | |
| +60 | 26 (23.2%) | 21 (14.4%) | 47 (18.2%) | |
| Total | 112 | 146 | 258 | - |
| **Radiographic location** | | | | |
| Right | 17 (15.2%) | 11 (7.5%) | 28 (10.9%) | |
| Left | 10 (8.9%) | 12 (8.2%) | 22 (8.5%) | 0.135 |
| Bilateral | 85 (75.9%) | 123 (84.2%) | 208 (80.6%) | |
| Total | 112 | 146 | 258 | - |

**Table 2.** Statistical analysis of the types of styloid process elongations

| | Male (n=112) | Female (n=146) | Total | p |
|---|---|---|---|---|
| **Radiographic appearance** | | | | |
| Elongated | 126 (56.3%) | 172 (58.9%) | 298 (57.2%) | 0.545 |
| Pseudoarticulated | 43 (19.2%) | 59 (20.2%) | 102 (19.8%) | 0.775 |
| Segmented | 28 (12.5%) | 38 (13%) | 66 (12.8%) | 0.863 |
| Total | 197 | 269 | 466 | - |

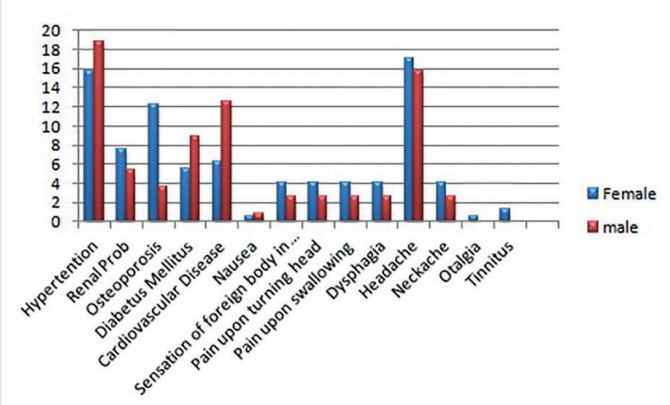


**Figure 3.** The percentage of systemic and clinical complaints of the patients with styloid process elongation

In this study we found out that headache (18.7%), hypertension (17.1%), cardiovascular disease (8.9%), osteoporosis (8.5%) and renal problem (6.6%) were the most common systemic and clinical symptoms that were seen with SP elongation (Figure 3).

## Discussion

Although etiopathogenesis is not clear, mineralization and ossification of the tip of the SP may cause the ES. Local chronic irritations, surgical trauma, endocrine disorders in women at menopause, persistence of mesenchymal elements and trauma or mechanical stress during development are suspected to cause elongation of SP (8,10,19). The stylohyoid ligament is normally composed of dense fibrous connective tissue and has the potential to become partially or completely ossified (9). The resultant abnormal styloid chain may compress or irritate nearby anatomical structures and cause the clinical symptoms of ES. Anatomically, the apex of the SP is located between internal and external carotid arteries. It is also related with the facial nerve, anteromedially and accessory and vagus nerve, medially. Clinicians mostly fail to diagnose the SP elongation. Thus, elongation of the SP should be considered for the diagnosis and treatment of head and neck pain.

**Table 3.** Statistical analysis of systemic and clinical complaints of the patients with styloid process elongation

| | Male (n=112) | Female (n=146) | Total | p |
|---|---|---|---|---|
| **Atheroma** | | | | |
| Absence | 101 (90.2%) | 132 (90.4%) | 233 (90.3%) | 1.000 |
| Presence | 11 (9.8%) | 14 (9.6%) | 25 (9.7%) | |
| Total | 112 | 146 | 258 | |
| **Systemic and clinic situations** | | | | |
| Hipertansion | 21 (18.8%) | 23 (15.8%) | 44 (17.1%) | 0.640 |
| Renal problems | 6 (5.4%) | 11 (7.5%) | 17 (6.6%) | 0.656 |
| Osteoporosis | 4 (3.6%) | 18 (12.3%) | 22 (8.5%) | 0.023* |
| Diabetus mellitus | 10 (8.9%) | 8 (5.5%) | 18 (7%) | 0.406 |
| Cardiovascular disease | 14 (12.5%) | 9 (6.2%) | 23 (8.9%) | 0.121 |
| Nausea | 1 (0.8%) | 1 (0.6%) | 2 (0.7%) | 1.000 |
| Sensation of foreign body in throat | 3 (2.6%) | 6 (4.1%) | 9 (3.4%) | 0.317 |
| Pain upon turning head | 3 (2.6%) | 6 (4.1%) | 9 (3.4%) | 0.317 |
| Pain upon swallowing | 3 (2.6%) | 6 (4.1%) | 9 (3.4%) | 0.317 |
| Dysphagia | 3 (2.6%) | 6 (4.1%) | 9 (0.3%) | 0.317 |
| Headache | 23 (15.8%) | 25 (17.1%) | 48 (18.7%) | 0.624 |
| Neckache | 3 (2.6%) | 6 (4.1%) | 9 (3.4%) | 0.317 |
| Otalgia | 0 | 1 (0.6%) | 1 (0.3%) | 1.000 |
| Tinnitus | 0 | 2 (1.3%) | 2 (0.7%) | 1.000 |

*p<0.05 (significant)

Cervical myofacial pain syndrome, migraine, trigeminal neuralgia, nasopharyngeal lesions, tonsillitis, otitis, neck pain, psychosomatic diseases, nervus intermedius neuralgia, atherosclerosis, dental pains, glossopharyngeal neuralgia and temporomandibular joint disorders should be considered in differential diagnosis (1,11,20). Therefore, a detailed differential diagnosis for SP elongation should be performed. The incidence of the elongated SP ranges between 1.4% and 30% in the literature (1,8,9,11) however, only between 1% and 5% of the patients were reported to be actually symptomatic (9). The pathophysiology of the pain related to elongated SP was thought

to be due to the compression of the nerves such as the lower branch of the trigeminal nerve, glossopharyngeal nerve and/or the chorda tympani. The threshold for elongation is variable in the literature but 30 mm was considered as the threshold by many publications (5,21-23).

PR is mostly used to determine whether the SP is elongated (24). Anbiaee and Javadzadeh (24) used PR for the measurement of SP length and indicated that its length was associated with increasing age, however, in this study we could not find statistically significant correlation between the incidence of SP elongation and age. We used Langlai's classification of elongated SP which is based on three types of complexes; type 1, elongated; type 2, pseudoarticulated; and type 3, segmented. In this study only 7.01% of the studied population was diagnosed as having SP elongation with the most prevalent pattern of elongated type which is in agreement with the previous studies (9). We observed symmetry for the pattern of elongated SP in 84.2% of the female population and in 75.9% of the male population which is in accordance with the literature (25,26). Gender had no statistically significant influence on the type of SP elongations which is also consistent with the literature (18,25).

Headache was the most common clinical symptom in the patients with elongated SP according to this study. Only 9 of the 258 patients with elongated SP declared dysphagia and foreign body sensation in the throat which are the most commonly seen symptoms of ES. Fourty eight of them were complaining from headache whereas only 9 of them reported neckache. Thus we evaluated only 9 (6 female and 3 male) of the 258 patients with elongated SP as true ES. During the clinical examinations of these 9 patients, SPs were easily palpated intraorally. Only 5 (4 female and 1 male) of the patients with ES underwent surgery and other 4 of them did not want to be operated. The reason of high headache privilege could be due to the hypertension and other stress factors.

### Study Limitations

Further studies are needed to clarify the clinical significance between PR and ES. Another limitation of the present study is the relatively small number of subjects.

## Conclusion

Based on this retrospective study, the privilege of elongated SP is 7% in Eastern Eagean Turkish population and only 3.5% of them are actually symptomatic.

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### Ethics

**Ethics Committee Approval:** Not applicable.

**Informed Consent:** Not applicable.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: F.A., Design: F.A., N.F.E., Y.A., Data Collection or Processing: F.A., Y.A., H.A., Analysis or Interpretation: F.A., H.A., A.H.A., Literature Search: F.A., N.F.E., Y.A., Writing: F.A., N.F.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Original Article

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# The Effect of Types of Nasal Septum Deviation on the Eustachian Tube Function

Remzi DOĞAN

Bezmialem Vakıf University Faculty of Medicine, Department of Otorhinolaryngology, İstanbul, Turkey

## ABSTRACT

**Objective:** Nasal septum deviations are divided into six different subtypes in the literature. Because obstruction and nasal airflows in the nasal passages that these types form are different, their effects on the eustachian tube can be different. The effect of different nasal septum deviations on eustachian tube function was investigated in our study.

**Methods:** A total of 80 patients with six different septum types and 15 healthy volunteers were included in the study. We tested eustachian tube function with P1, P2, and P3. P1 is the tympanometric measurement while resting. P2 is the tympanometric measurement after the Toynbee maneuver. P3 is the tympanometric testing after the Valsalva maneuver. To evaluate the functionality of the eustachian tube, we used the P1-P2 >10 daPa or $P_{max}$-$P_{min}$ >15 daPa criteria. Measurements were performed before and 6 months after surgery.

**Results:** Before surgery, there was no difference between types 1, 2, 3, and 5 and healthy volunteers in terms of eustachian tube dysfunction. Before surgery, type 4 and 6 had significant eustachian tube dysfunction compared with healthy volunteers. Type 4 and 6 showed significant improvement in the eustachian tube functions at 6$^{th}$ month after operation.

**Conclusion:** According to the results of our study, applying septoplasty only to patients with type 4 and 6 nasal septum deviations before middle ear surgery would reduce unnecessary cost and increase the success of middle ear surgeries by preventing morbidities.

**Keywords:** Nasal septum type, eustachian tube, septoplasty, middle ear

## Introduction

The eustachian tube (ET) is a small passage between the middle ear and the nasopharynx and its main function is to provide ventilation of the middle ear (1). ET equalizes the pressure in the middle ear with the atmospheric pressure. Nasal pathologies (anatomic, functional) may affect the middle ear ventilation by acting on the ET. The effects of nasal obstruction on the pathophysiology of middle ear diseases and the success rates of the surgeries (tympanoplasty, miringoplasty) performed in this region are debated (2).

The importance of ET for the middle ear is not fully understood, although it is clearly demonstrated that this structure is affected by nasal pathologies. However, whether before all middle ear surgeries, all septal deviations in the nose should be corrected is still controversial. In the literature, there are studies claiming that surgical operation is needed to provide healthy functions of the ET (ETF) and for the successful middle ear surgeries (3-5), as well as there are studies claiming that surgical operation is unnecessary (2,6,7). Because we do not have a common practice, the choice is mostly left to the physician. This choice sometimes leads to unsuccessful tympanoplasty with incomplete treatment and sometimes can lead to increase in cost and additional morbidities with excessive treatment.

Nasal septum deviation (NSD) is divided into several sub-types and different obstructions can occur in nasal passage depending

**Address for Correspondence:** Remzi DOĞAN, Bezmialem Vakıf University Faculty of Medicine, Department of Otorhinolaryngology, İstanbul, Turkey
**E-mail:** dr.remzidogan@gmail.com **ORCID ID:** orcid.org/0000-0001-5627-1342

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on the severity of the deviation. Our goal in our study is to find out what kind of nasal septal deviation affects the ETF. Thus, we suggest that prior to middle ear surgery, incomplete treatment or over-treatment can be avoided.

## Methods

Our study was started after approved by the Ethics Committee of Clinical Research of the Bezmialem Vakıf University Faculty of Medicine with the number 71306642-050.01.04. Eighty patients who were admitted to the otorhinolaryngology out patient clinic with nasal congestion were included in the study. Fifteen healthy volunteers with normal examination were referred as the control group. Patients and healthy controls were informed about the study and informed and oral consents were taken from them.

The patient group was divided into six groups according to the Baumann and Baumann's (8) classification of nasal septum, one of the most frequently used classifications in the literature (Figure 1):

Group 1 (n=30 ears, 15 patients): NSD type 1,

Group 2 (n=28 ears, 14 patients): NSD type 2,

Group 3 (n=28 ears, 14 patients): NSD type 3,

Group 4 (n=24 ears, 12 patients): NSD type 4,

Group 5 (n=26 ears, 13 patients): NSD type 5,

Group 6 (n=24 ears, 12 patients): NSD type 6,

Group 7 (n=30 ears, 15 patients): Healthy volunteers with no deviation of nasal septum.

Full otolaryngologic examination was performed in the study and control groups. Patients without intact tympanic membrane, with ear history (radical and modified radical mastoidectomy, chronic otitis media, adhesive otitis media), with upper respiratory tract obstructive pathologies (adenoid vegetation, nasal polyposis, nasal synechia, and upper respiratory tract infections) were excluded from the study.

Tympanometric measurements and automated ETF tests (ETFT) were performed with Impedance Audiometry AC40. In the present study, an automated Toynbee test was used to evaluate the ETF in patients with nasal septal deviation and healthy volunteers in the control group.

In these patients, type A tympanogram peaks are between -100 and +100 daPa and this determines normal middle ear function (1 daPa=1.02 mm $H_2O$) (9). P1 is the stable timpanometric measure. P2 is the Toynbee test which is the result of swallowing when the mouth and nose of patients are closed. The P3 is the Valsalva maneuver which occurs when the mouth and nose of the patients are closed. Peak pressure values were recorded as P1, P2 and P3 and the maximum and the minimum pressure values were recorded as maximum pressure difference= $P_{max}$-$P_{min}$. The criteria P1-P2 >10 or $P_{max}$-$P_{min}$ >15 were used to evaluate ET as functional. In these criteria, P1 is the peak point of classic timpanometry, P2 is the peak point of the Toynbee test and P3 is the peak point of the Valsalva test (9).

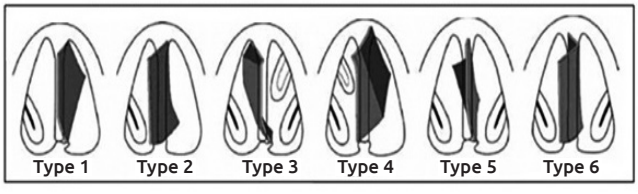


**Figure 1.** Six types of nasal septum deviation

### Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences 16.0 for Windows ile (SPSS Inc.; Chicago, IL, USA). Numeric variables were expressed as mean and standard deviation. The one way ANOVA test was used in comparison between groups. Paired t-test was used for pre- and post-operative comparisons in each group. P<0.05 was considered significant.

## Results

There were no differences between groups in terms of age and gender (p>0.05) (Table 1). The mean values of $P_{max}$-$P_{min}$ in ETFT performed to the right and left ears of the patients and controls in the groups were calculated. $P_{max}$-$P_{min}$ >15 daPa was considered as functional ET. There was no difference between groups 1, 2, 4, 5 and 7 in terms of preop $P_{max}$-$P_{min}$ mean and $P_{max}$-$P_{min}$ mean (Table 2). The mean $P_{max}$-$P_{min}$ values in group 4 and 6 were less than 15 daPa and were 11.41±6.22 and 10.62±5.37, respectively. These values were statistically significantly lower than the mean $P_{max}$-$P_{min}$ value in healthy controls which was 42.63±15.19 (p=0.001 and p=.001, respectively) (Table 2).

**Table 1.** Demographic features of the groups

| Groups | Gender Male/ Female | Statistics p values | Age Mean ± SD | Statistics p values |
|---|---|---|---|---|
| Group 1 (n=25): NSD type 1 | 13/12 | - | 27.34±4.82 | - |
| Group 2 (n=23): NSD type 2 | 11/12 | - | 24.09±7.38 | - |
| Group 3 (n=21): NSD type 3 | 12/9 | - | 31.55±6.19 | - |
| Group 4 (n=20): NSD type 4 | 13/7 | p>0.05 | 29.37±5.03 | p>0.05 |
| Group 5 (n=23): NSD type 5 | 14/9 | - | 33.76±9.16 | - |
| Group 6 (n=19): NSD type 6 | 11/8 | - | 26.01±8.59 | - |
| Group 7 (n=25): Control | 15/10 | - | 30.47±6.23 | - |
| Total (n=156) | 89/67 | - | 28.94±6.77 | - |

NSD: nasal septum deviation; SD: standard deviation
One-way ANOVA test was used in comparison between groups, p<0.05 was considered significant

**Table 2.** Preop eustachian tube function tests in the groups ($P_{max}$- $P_{min}$)

| Groups | $P_{max}$- $P_{min}$ (daPa) Mean ± SD | Statistics p values |
|---|---|---|
| Group 1 (n=25): NSD type 1 | 35.35±9.48 | Group 1 vs group 7: p=0.196 |
| Group 2 (n=23): NSD type 2 | 22.47±7.51 | Group 2 vs group 7: p=0.094 |
| Group 3 (n=21): NSD type 3 | 30.02±11.06 | Group 3 vs group 7: p=0.239 |
| Group 4 (n=20): NSD type 4 | 11.41±6.22 | Group 4 vs group 7: p=0.001 |
| Group 5 (n=23): NSD type 5 | 39.84±12.54 | Group 5 vs group 7: p=0.275 |
| Group 6 (n=19): NSD type 6 | 10.62±5.37 | Group 6 vs group 7: p=0.001 |
| Group 7 (n=25): Control | 42.63±15.19 | - |
| Total (n=156) | - | - |

NSD: nasal septum deviation; SD: standard deviation
One-way ANOVA test was used in comparison between groups, p<0.05 was considered significant

**Table 3.** Comparison of preop-postop $P_{max}$- $P_{min}$ values of the groups

| Groups | $P_{max}$- $P_{min}$ (daPa) Mean ± SD | $P_{max}$- $P_{min}$ (daPa) Mean ± SD | Statistics p values |
|---|---|---|---|
| Group 1 (n=25): NSD type 1 | 35.35±9.48 | 41.01±10.37 | p=0.354 |
| Group 2 (n=23): NSD type 2 | 22.47±7.51 | 31.25±11.66 | p=0.072 |
| Group 3 (n=21): NSD type 3 | 30.02±11.06 | 38.17±13.94 | p=0.238 |
| Group 4 (n=20): NSD type 4 | 11.41±6.22 | 35.72±10.79 | p=0.001 |
| Group 5 (n=23): NSD type 5 | 39.84±12.54 | 42.96±14.01 | p=0.305 |
| Group 6 (n=19): NSD type 6 | 10.62±5.37 | 37.13±12.88 | p=0.001 |
| Total (n=156) | - | - | - |

NSD: nasal septum deviation; SD: standard deviation
Paired t-test was used in comparison in groups, p<0.05 was considered significant

There were no differences between the $P_{max}$-$P_{min}$ mean in the postoperative 6th month and preoperative period in groups 1, 2, 3 and 5 (Table 3). The $P_{max}$-$P_{min}$ means in the postoperative 6th month in group 4 and 6 (35.72±10.79 and 37.13±12.88, respectively) were statistically significantly higher than the $P_{max}$-$P_{min}$ means in the preoperative period (11.41±6.22 and 10.62±5.37, respectively) (p=0.001 and p=.001, respectively) (Table 3).

According to the literature, P1-P2 >10 was considered as functional ET. The ETFT was positive in 27 ears and negative in 3 ears in group 7. The positive/negative ratio was 26/4 in group 1 and was similar to group 7 (p=0.248) (Figure 2). The positive/negative ratio was 21/7 in group 2 and was similar to group 7 (p=0.085) (Figure 2). The positive/negative ratio was 22/6 in group 3 and was similar to group 7 (p=0.168) (Figure 2). The positive/negative ratio was 5/19 in group 4 and was statistically significantly lower than group 7 (p=0.021) (Figure 2). The positive/negative ratio was 23/3 in group 5 and was similar to group 7 (p=0.291) (Figure 2). The positive/negative ratio was 6/18 in group 6 and was statistically significantly lower than group 7 (p=0.011) (Figure 2).

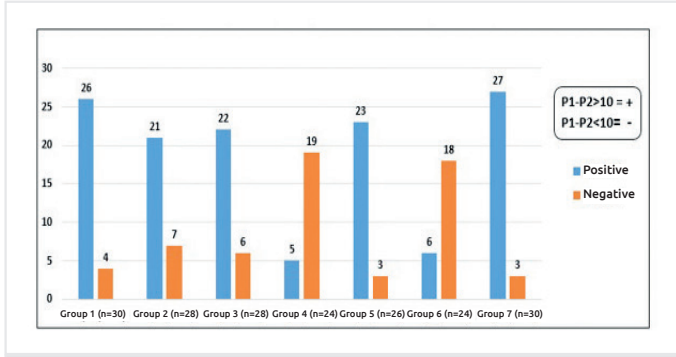


**Figure 2.** Eustachian tube functions of groups before operation

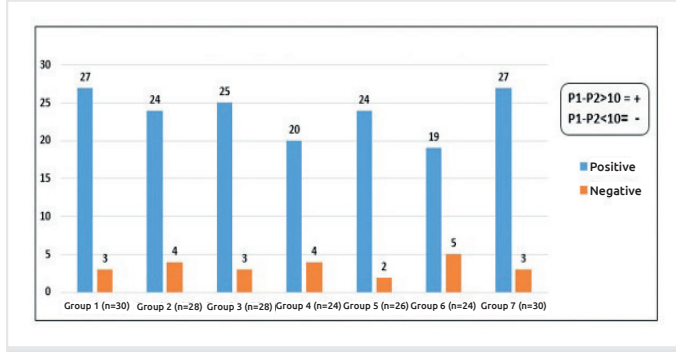


**Figure 3.** Eustachian tube functions of groups after operation

The positive/negative status of ETFT in the postoperative 6 months were summarized in Figure 3. In groups 1, 2, 3 and 5, positive/negative ratios increased (27/3, 24/4, 25/3 and 24/2, respectively), however as preop ratios, they were not different from the ratios of group 7 (p=0.422, p=0.119, p=0.259 and p=.358, respectively) (Figure 3). The positive/negative ratio was 20/4 in group 4 and there was no difference between group 4 and 7 (p=0.163) (Table 3). The positive/negative ratio was 19/5 in group 6 and there was no difference between group 4 and 7 (p=0.094) (Table 3).

## Discussion

We found ET dysfunction (ETD) in type 4 and 6 NSDs which significantly improved in the postoperative 6th month. There was no significant ETD in types 1, 2, 3 and 5 in the preoperative period. We believe that the types of septum deviation that can affect the surgical success in patients undergoing middle ear

surgery are type 4 and 6. In type 1, 2, 3 and 5 deviations, surgery was considered to have no significant effect on ETF. Therefore, we think that operating patients with these types of nasal deviation who will undergo middle ear surgery is unnecessary.

There are many parameters that affect the success of surgical operations of the middle ear. One of the most important of these is that the ET is functional. A non-functional ET causes both middle ear diseases and failure of surgical operations. Schilder et al. (10) defined three subtypes of ETD. These are; dilator ETD, pressure-induced ETD and abnormal patent ETD. Among these, the most common type is the dilator type. The dilator ETD is composed of mucosal inflammation and edema caused by many reasons (upper respiratory tract infection, allergic rhinitis, sinusitis, reflux etc.) (11). It can be concluded that nasal factors have negative effect on middle ear diseases via ET.

It was shown that inflammatory, obstructive and infective pathologies in the nasal and paranasal sinuses could cause ETD (3-6). NSD is the most common of the major anatomical problems in the nose. The NSD may present with different clinical symptoms depending on the type, localization and additional pathologies of the anatomic structures. These symptoms may include nasal obstruction, nasal discharge, facial pain and headache, epistaxis, smell disorders, etc. and many patients may be asymptomatic.

Although there are many studies on the relationship between NSD and ETF, there are still no definitive data about the extent of this relationship. Although it is known that nasal pathologies affect ETF, there is limited information about how NSD affects ETF or whether it affects it. The best known of this information is that NSD affects ETF by affecting the air flow parameters (12). In addition, it is known that infection/inflammation in the nasopharyngeal region due to the conditions formed by NSD, affects ETF (13,14). It is not clear how much ETF is affected in patients with NSD despite these mechanisms are known.

According to the long-known classical data; septoplasty must be performed prior to middle ear surgery (3,5,6). In the studies performed, ETF has been shown to improve after septoplasty (5,10). Low and Willatt (5) concluded that the ipsilateral middle ear pressure in the obstructed nasal passage was negatively correlated with the asymmetry of the openings in the two nasal passages. Deron et al. (15) found that the pressure on the deviated side was higher than on the non-deviated side. Recent studies show that ETF may not be affected by NSD. Akyıldız et al. (2) showed that NSD decreased ETF but not at a level that would affect tympanoplasty results. They concluded that performing septoplasty before tympanoplasty is not necessary (2). Also, Tan et al. (16) did not recommend performing septoplasty before tympanoplasty and they indicated that septoplasty does not have effect on tympanoplasty results. However, in none of these studies, types of NSD were specified. In fact, the type and localization of NSD and additional pathologies affect the severity of the nasal obstruction and can change the air flow in the nasal passage. In our study, significantly more impairment in ETF was found in group 4 and 6 than in healthy volunteers without NSD. In the postoperative 6$^{th}$ month, there was no difference between group 4 and 6 and healthy volunteers without NSD in terms of ETF. There was no difference between NSD type 1, 2, 3 and 5 and healthy volunteers in terms of preoperative ETF and ETF. Eren et al. (17) investigated the satisfaction of the patients after the operation and the success of the operation in different types of NSD. In conclusion, it was found that patients with NSD type 2, 4 and 6 benefited more from the operation and that patient satisfaction was better (17). According to these results, all septum deviations are not required to be operated prior to middle ear surgery. Thus, increase in cost and morbidity will be avoided. We believe that septoplasty may increase the success of middle ear surgery for those with NSD type 4 and 6.

In the study of Maier and Krebs (6), it was reported that ETF was influenced by septal deviation and conchal hypertrophy. However, it was concluded that determining surgery after evaluating the ETF would be appropriate, rather than performing septoplasty for all septum deviations (6). In that study, septoplasty was recommended in severe nasal pathologies (6). According to our results, septoplasty should be performed in patients with severe septal deviation (type 4 and 6). In the study of Maier and Krebs (6), ETF was shown to have not improved in the early postoperative period despite surgery. In our study, postop evaluation was performed in the sixth month. We believe that we have achieved safe results with proper timing.

Harju et al. (18) showed that patients with inferior nasal concha were more associated with ETD compared with healthy controls. In our study, both severe deviation and conchal pathologies were present with type 4 and 6. In type 4, inferior conchal hypertrophy and middle concha bullosa were present whereas in type 6, bilateral inferior conchal hypertrophy were present in the non-deviated side. These additional pathologies accompanying type 4 and 6 in our study also increased ETD and our findings were in line with the literature.

### Study Limitations

The strengths of our study are that for the first time in the literature ETD was examined with septum classification, the number of patients was sufficient and prospective measurements (postop sixth month) were performed. The limitation of our study is the use of a single type of ETFT.

## Conclusion

For the first time in the literature, septums were classified and ETFTs were performed prospectively. As a result, we found that ETF was significanty impaired in type 4 and 6 and was significantly improved in postop 6$^{th}$ month. We recommend that the septoplasty operation be performed in patients with type 4 and 6 before middle ear surgery.

### Ethics

**Ethics Committee Approval:** This study was approved by the Ethics Committee of Clinical Research of the Bezmialem Vakıf University Faculty of Medicine (number: 71306642-050.01.04).

**Informed Consent:** Patients and healthy controls were informed about the study and informed and oral consents were taken from them.

**Peer-review:** Externally peer-reviewed.

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Original Article

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# Straight Proximal Femoral Nails Mismatch with the Anterior Bowing of the Femur

Fatih YILDIZ[1], Yunus GÜZEL[2], Tunay ERDEN[1], Deniz KARA[1], Nuh Memet ELMADAĞ[1]

[1]Bezmialem Vakıf University Faculty of Medicine, Department of Orthopedics and Traumatology, İstanbul, Turkey
[2]Ordu University Faculty of Medicine, Department of Orthopedics and Traumatology, Ordu, Turkey

## ABSTRACT

**Objective:** Increased anterior bow of the femur due to advanced age and osteoporosis impinges with the distal part of the non-anatomic, standard proximal femoral nails (PFN), which is one of the most preferred implant for the fixation of trochanteric fractures (TF) in the elderly. The relation between increased femoral bowing and standard PFN application was investigated.

**Methods:** Radiographs of 111 patients (59 men, 52 women; mean age 74.5 years), who were treated with PFN due to TF between 2011 and 2015, were evaluated retrospectively. Relation between the nail and the anterior cortex was determined by measuring the angle between distal anatomical axes of the nail and the femur (ADA). The patients were divided into two groups according to their ADA (group 1 ADA ≤4° and group 2 ADA >4°). Functional results and pain was evaluated using Harris Hip Score (HHS) and visual analog scale (VAS). Complications were also recorded.

**Results:** The mean amount of ADA was 4.5°±1.5°. Forty-seven patients were classified in group 1 and 64 patients were in group 2. The mean HHSs were 80.6 and 79.3 (p=0.464), and the mean VAS scores were 2.13 and 5.35 (p<0.001) in group 1 and 2, respectively. Five patients were revised due to cut-out of the lag screws (total hip arthroplasty in two patients and revision of the nails in three patients). Union was achieved in all patients without infection.

**Conclusion:** Because straight femoral nails impinges anterior cortex of the femur with increased bowing, new design PFN with anterior curve is needed especially for shorter or osteoporotic people, or Caucasian population.

**Keywords:** Femur, trochanteric fracture, proximal femoral nail, anterior bowing

## Introduction

In the treatment of trochanteric fractures (TF), stable fixation is mandatory to achieve a safe and early mobilization, because it is important for patients to return to their previous activity level (1,2). Although choice of the implant varies according to the type of TFs, many studies report that unstable pertrochanteric fractures of the femur, i.e. 31-A2 without medial support, and 31-A3, i.e. intertrochanteric fractures, can be treated successfully with intramedullary (IM) implants. IM fixation devices have become increasingly popular due to biomechanical advantages in the treatment of unstable TFs compared with extramedullary fixation (3-5).

TFs are common in the elderly population and its incidence increases twice in every decade after the age of 50 (6). Although increase in the anterior femoral bow by advanced age has been proved in the literature, the proximal femoral nails (PFN) in the market have still straight designs on the sagittal plane (7,8). Non-anatomic shapes of the PFNs sometimes make the surgeries difficult or can cause additional intraoperative fractures around the tip of the nail because they may impinge to the anterior cortex of the femur and increase the stress at this area due to increased femoral bowing (7-10). This problem is more apparent in shorter patients with shorter femurs, especially in the Asian or Caucasian population. We hypothesized that non-anatomical, straight PFNs

**Address for Correspondence:** Fatih YILDIZ, Bezmialem Vakıf University Faculty of Medicine, Department of Orthopedics and Traumatology, İstanbul, Turkey
**E-mail:** : yildizfatih@hotmail.com **ORCID ID:** orcid.org/0000-0003-4475-5379

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impinge to anterior femoral cortex and cause anterior tight pain in patients with increased femoral bow due to increased age and osteoporosis.

The primary outcome of this study was to determine the rate of femoral anterior cortical encroachment after stabilization of the proximal femur in a consecutive series of patients using a short straight PFN. Secondary outcome was to discuss whether PFNs need some improvements in their design for the geriatric population.

## Methods

This retrospective study was performed according to Declaration of Helsinki. One hundred and eleven patients with the diagnosis of TF (31-A2.1-3 or 31-A3.1-3 according to Arbeitsgemeinschaft für Osteosynthesefragen/Association for the Study of Internal Fixation's classifications) (11), who had been treated using PFN between 2011 and 2015, were included in the study. The data were collected using files of the patients and the digital database of the hospital. Patients with high-energy trauma, a neoplastic reason for the fractures, open fractures, multiple fractures, the American Society of Anesthesiologists score of 5, inability to walk before the injury, degenerative osteoarthritis/arthritis in the injured hip were excluded from the study. The patients who could not be reached or lost to follow up were also excluded.

The mean age of the patients (59 male and 52 female) was 74.4 (65-95) years. The left hip was involved in 72 cases, and the right hip was involved in 39 cases. The etiologies were simple fall from standing position in 106 patients and pedestrian accident in five patients.

Experienced orthopedic trauma surgeons in a university hospital operated all patients in a standard way. The surgeries were performed using fracture table and under the fluoroscopy. After closed or open reduction (if acceptable reduction could not be achieved by closed reduction techniques), the PFN (InterTAN, Smith&Nephew, Memphis, Tennessee, USA) was inserted in all patients. Its proximal lag screws and distal static locking screws were placed with the appropriate sizes. Final positions of the fractured fragments and the implants were checked under the fluoroscopy before the patients left the operating rooms. On the first postoperative day, an antero-posterior (AP) and lateral X-ray was taken and the patients were allowed walking with weight bearing as they could tolerate.

The digital AP and lateral radiographs taken on the day after surgery and at the 6-month follow up were used for the radiographic measurements. The quality of reduction of the fracture (Garden alignment index) was classified as good, acceptable or poor (12). Position of the proximal screws in the femoral head was calculated by measuring the tip-apex distance (TAD), and the neck-shaft angle (NSA) to evaluate loss in reduction during the follow up (13). Clinical evaluations were performed using Harris Hip Score (HHS) and the visual analog scale (VAS) (14). Loss of reduction, implant failure and complications were recorded.

The angle between the anterior longitudinal axis of the nail and central anatomic axis of the femur at the level of the distal tip of the nail was measured digitally on the lateral radiographs to describe the relation between the anterior of the nail and anterior cortex of the femur. This angle was defined as "angle of distal axes (ADA)". We divided the patients into two groups according to their ADA: group 1 included patients with ADA ≤4° and group 2 included patients with ADA >4°. All of the radiographs were measured by the same orthopedic surgeon.

### Statistical Analysis

Group 1 and 2 were compared in terms of HHS and VAS scores with Kruskal-Wallis test. NSAs on the second postoperative day and at the 6-month follow up radiographs were compared using Wilcoxon signed-ranks test. P<0.05 was accepted as the level of significance.

## Results

Quality of reduction was good in 32 patients, acceptable in 12 patients and poor in three patients in group 1, and good in 43 patients, acceptable in 15 patients and poor in six patients in group 2. The mean TAD were 18.3±8.25 mm and 19.7±7.41 mm in group 1 and group 2, respectively.

In group 1 and group 2, the mean early postoperative NSAs were 128.8°±4.5° and 130.1°±3.7° (p=0.08) and the mean final NSAs were 126.8°±6.8° and 128.7°±4.1° (p=0.078), respectively. The mean NSAs were similar initially and at final follow up in group 1 and 2.

The mean amount of ADA was found as 4.5°±1.5°. Forty-seven patients were classified in group 1 (Figure 1a) and 64 patients were in group 2 (Figure 1b). The mean HHSs were found as 80.6±2.17

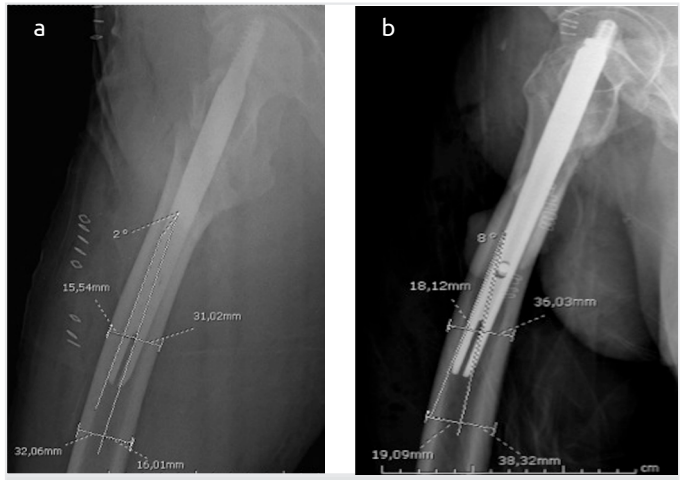


**Figure 1.** Lateral anatomic axis of the femur at the level of the tip of the nail was determined as the line between the two points which were placed three cm distal and proximal to the tip of the nail and placed at the middle of the anterior and posterior cortices of the femur. Lateral longitudinal axis of the nail was drawn as a line along the anterior border of the nail. Angle of distal axes was the angle between the lateral anatomic axis of the femur and the nail. a) Angle of distal axes=2°, b) angle of distal axes=8°

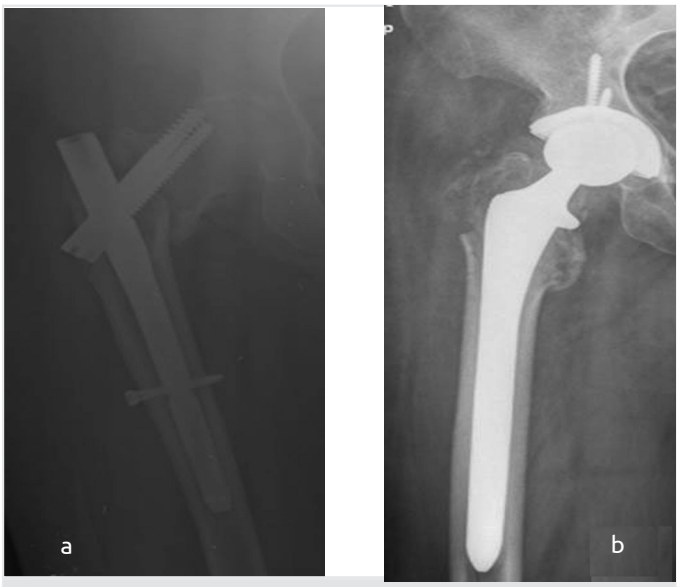


**Figure 2.** a) Cut-out of the lag screw in a 72-year-old female, b) revision with total hip arthroplasty

(78-84) points in group 1 and 79.37±3.26 (72-86) points in group 2 (p=0.464). The mean VAS scores were 2.13±0.62 (1-3) and 5.35±0.78 (4-7) in groups 1 and 2, respectively (p<0.001). Although there was no difference between the groups in terms of the mean HHSs, the VAS scores were found to be significantly lower in group 1 than in group 2.

Cut-out of the lag screws were observed in five patients as complication. In three of these patients, the nails were removed and the fractures were re-reduced and fixed with new PFNs. However, in two patients, the fractures were treated with total hip arthroplasty (Figures 2a and 2b). During the follow up period, union was achieved in all patients including PFN revisions, except two patients with athroplasty. Surgical site infection was not observed in any patient. Intraoperative or postoperative fracture of the femur around the distal tip of the nail did not occur in any patient.

## Discussion

This retrospective study evaluated 111 patients with TFs who were treated with non-anatomic, straight PFNs. The main goal of the study was to investigate whether straight nails impinged with the anterior femoral cortex due to its anatomic bowing or not. Secondary aim of the study was to evaluate the clinical relevance of this possible impingement. The mean ADA was found as 4.9±1.5, and it was >4° (grade 3 to 5) in 64 patients (57.6%) which was considered as anterior cortical impingement.

Success of the IM short nails in the treatment of TFs has already been proved. Especially in unstable fractures, they protect proximal femoral anatomy and reduction against the deforming forces (15,16). It is more preferred than the sliding hip screws in the treatment of unstable fractures, including reverse oblique fractures [A3-the AO Foundation and Orthopaedic Trauma Association (AO-OTA)], because the PFN provides higher stability and its use is easier (16,17). Successful results with PFN in large series have been published although it has some complications such as intraoperative fractures, cut-out of the lag screws and varus collapse, nonunion and malunion (3,5,15,16,18). In the treatment of proximal femoral fractures, anterior cortical encroachment of the cephalo-medullary nails have been described before, however, to our knowledge, the relation between anterior cortical impingement and short PFN have not been reported before (19). Similar to the literature, in the current study, successful results with PFN were obtained in 111 patients with unstable TFs (31-A2.1-3 and 31-A3.1-3 AO-OTA) with a total complication rate of 4.5% (11).

In the treatment of TFs with proximal nailing, the most frequent complications are varus collapse of the proximal femur, cut-out of the lag screw, shortening of the femur, nonunion, secondary fracture of the femur or greater trochanter, thigh pain, screw fracture, and Z-effect or reverse Z-effect of nails with two lag screws (20,21). In our series, cut-out of the lag screw was seen in five patients, two of them were treated with arthroplasty and in three patients the nails were revised. Although the amount of varus collapse at the final radiograph compared to initial radiograph, which was about 2°, was statistically significantly different (p<0.001) in both groups, it did not have clinical or radiological impact on the results. According to alignment index of Garden, quality of reduction was good in 89% of the patients but poor in 9% of the patients (12). ADA was correlated with tight pain and VAS scores, which was higher in group 2 (p<0.001). This result shows the clinical importance of the anterior impingement of the PFN.

It has been well documented that PFN antirotation (PFNA) (Synthes, Switzerland) may cause femoral fractures or valgus impingement of the lateral cortex, especially in the Asian population (9,22-24). Because of these data in the literature, its proximal diameter, lateral bending angle and lateral surface have been revised and improved, and reproduced as PFNA-II which has been shown to be more appropriate for the Asian population. In the treatment of unstable TFs, biomechanical and clinical studies resulted in superiority of InterTan PFN because of its rotational strength and low rate of malunion (25-28). Anterior cortical impingement or destruction of the femoral nails can lead to potential complications such as thigh pain and disability and serve as a stress riser for future fractures (19,29). Similar problems may occur with straight non-anatomic nails on the sagittal plane (PFNA-II or InterTAN) due to mismatch of the anterior femoral bowing. It has been proved that anterior femoral bowing increases with the increased age and osteoporosis in the elderly; therefore short, straight nails can impinge with the anterior cortex, however the design of the PFNs have not been changed, yet (7-10).

Chang et al. (29) treated 158 patients with unstable TFs using PFNA-II and found encroachment of the distal tip of the nail to the anterior cortex in 55 patients (34.8%). Hwang et al. (9) reported mismatch of PFN/PFNA with the anterior and lateral cortices of the femur in four patients in their series. Radiological studies have also reported mismatch between the femoral nails and increased femoral bowing with advanced age (7,8). Our

study showed anterior cortical impingement of the nail in 57.6% of the patients and statistically significantly higher rate of tight pain in this group. In the literature, groin or tight pain after hip nailing is not rare in this group of patients. Inappropriate stress distribution between the femur and the implant is thought to be a reason fortight pain (29-32). Similarly, in our patients, tight pain could be related with increased stress over the anterior cortex of the femur. For this reason, we recommend using shorter or curved nails in order to decrease the stress between the implant and the anterior cortex, which can decrease tight pain and possible fractures around the distal tip of the nail.

### Study Limitations

In this study, we had some limitations. First, evaluation of the anterior tight pain could be more objective. Second, stress distribution over the anterior cortex could be evaluated with a biomechanical study to report a measurable data. Third, standardization of the radiological measurements was difficult. ADA was measured on the lateral radiographs, which might change with the rotation of the femur.

## Conclusion

Straight, non-anatomic femoral nails impinges anterior cortex of the femur due to increased sagittal bowing of the femur by age and these nails are not appropriate for the shorter people, especially in the Caucasian population. New design proximal femoral nails with anatomic bow can solve these problems.

### Ethics

**Ethics Committee Approval:** Retrospective study.

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: F.Y., N.M.E., D.K., Concept: F.Y., N.M.E., Y.G., T.E., Design: F.Y., N.M.E., Y.G., Data Collection or Processing: T.E., D.K., Analysis or Interpretation: F.Y., N.M.E., Y.G., Literature Search: F.Y., N.M.E., D.K., T.E., Writing: F.Y., N.M.E., Y.G.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Original Article

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# Effects of the Valsalva Maneuver on Intraoperative Bleeding During Tonsillectomy

Ömer Faruk ÇALIM

Bezmialem Vakıf University Faculty of Medicine, Department of Otorhinolaryngology, İstanbul, Turkey

## ABSTRACT

**Objective:** We investigated whether the Valsalva maneuver helps detect any further bleeding points following adequate hemostasis in tonsillectomy.

**Methods:** This was a prospective study of consecutive patients who underwent tonsillectomy performed in a tertiary medical center. The data collected included age, gender, method of operation, and hemorrhage (if any) informations. Immediately after completing the surgery, hemostasis was performed by an anesthesiologist using the Valsalva maneuver to identify bleeding points. Intraoperative and postoperative hemorrhage, as well as the treatment applied, were recorded.

**Results:** One hundred twenty patients underwent tonsillectomy (53 males and 67 females). Tonsillectomy was performed using cold dissection in 59 patients (26 males and 33 females) and bipolar diathermy in 61 patients (27 males and 34 females). The differences in intraoperative hemorrhage following Valsalva were significantly higher in the cold dissection group than in the hot (bipolar) group ($p=0.044$). Tonsillectomy using bipolar cautery had a statistically significantly higher postoperative hemorrhage rate than that using cold dissection ($p<0.05$).

**Conclusion:** The Valsalva maneuver is useful for identifying subtle bleeding vessels in tonsillectomy wound bed. We suggest applying the procedure for final verification of hemostasis before ending the surgery.

**Keywords:** Valsalva maneuver, tonsillectomy, bipolar cautery, cold dissection, hemorrhage

## Introduction

Tonsillectomy is one of the most widespread operations applied in pediatric populations (1). Tonsillectomy has important health advantages, such as avoidance of obstructive breathing and behavioral issues, and improving life quality and neuro-cognition in children (1). Recurrent tonsillitis and/or large tonsil-induced snoring and even obstructive sleep apnea are the most common indications for tonsillectomy (1).

Meticulous hemostasis is important for whole surgical techniques. However, the tonsillar area is especially prone to bleeding because of its rich vascular supply. The tonsil is inclined to bleeding, which might have severe sequels such as bleeding aspiration that could lead to a lethal outcome (2). Different methods have been suggested to optimize intraoperative hemostasis, including the Valsalva maneuver, which may display latent bleeding vessels by increasing the venous pressure. This is particularly important in tonsillectomy practice where surgical drains cannot be used.

Tonsillectomy complications include intraoperative and postoperative hemorrhage, respiratory complications, nausea, vomiting, pain, and burn injuries. Post-tonsillectomy hemorrhage, which occurs in 2.7-5% of children (3), can be a life-threatening complication that requires emergent surgery. Furthermore, risks of anesthesia- and opioid-related respiratory depression

**Address for Correspondence:** Ömer Faruk ÇALIM, Bezmialem Vakıf University Faculty of Medicine, Department of Otorhinolaryngology, İstanbul, Turkey
**E-mail:** omercalim@yahoo.com **ORCID ID:** orcid.org/0000-0002-0010-9028

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are other mortal complications that may occur during or after tonsillectomy. Control of post-tonsillectomy hemorrhage usually can be performed easily; however, in a few patients, this may be a challenge (4).

The Valsalva maneuver is performed by forceful attempted exhalation against a closed glottis.

During the maneuver, the intra-thoracic pressure becomes extremely positive and impedes venous return into the thorax. These changes increase the peripheral venous pressure. In our study, the Valsalva maneuver was performed intra-operatively by the attending anesthetist.

We assessed the effectiveness of the Valsalva maneuver for preventing bleeding in the tonsillar wound bed intra-operatively and postoperatively following cold dissection and bipolar diathermy. In addition, we determined whether there was any difference in the intraoperative and postoperative hemorrhage rates between the two methods.

## Methods

A prospective, self-controlled clinical study was conducted to confront the influences of cold towards bipolar electro cautery tonsillectomy procedures in patients with recurrent chronic tonsillitis. One hundred twenty patients aged below 16 years, who were admitted for tonsillectomy were enrolled. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study protocol was confirmed by the Bezmialem Vakıf University Clinical Research Ethics Committee (18.04.2017-8/79). Informed consent was taken from all individual subscribers including the parents of the patients. Patients underwent tonsillar biopsy, tonsillectomy with palatal surgery, pediatric patients with known hematological abnormalities or hypertension and patients in whom general anesthesia was contraindicated were excluded. Before surgery, antibiotic and dexamethasone (0.15 mg/kg) treatments were given parenterally to all patients. Surgery was applied under general anesthesia. Patients were grouped according to the methods of dissection and hemostasis. In the first method, bipolar diathermy was used for both dissection and hemostasis. Both tonsils were dissected together with their capsules and the tonsils were removed using a bipolar electro cautery instrument (ME 411; KLS Martin, Tuttlingen, Germany) set in the cutting mode by power of 20-35 W. The second method involved a cold dissection technique (scissors and raspatory) with hemostasis using packs; however, if bleeding continued, diathermy was used for hemostasis. After the completion of tonsillectomy and performing hemostasis using a bipolar diathermy technique, the Valsalva maneuver was performed, at least twice, for 30 s by applying 30 cm of positive end-expiratory pressure to the ventilator circuit. Meanwhile, bleeding points were identified and treated using bipolar diathermy. Complications included early bleeding within 24 h and late postoperative bleeding causing readmission for surveillance, return to the operation room, or blood transfusion. In addition, on the postoperative first day, the patients were examined to reveal any bleeding before hospital discharge.

All of the patients were hospitalized for one day in the postoperative period. Peroral analgesics and antibiotics were given during 10 days, postoperatively. After discharge, the patients were demanded to return to the hospital if hemorrhage emerged. The patients were examined after 10 days. Patients or their relatives were asked whether any postoperative bleeding had occurred within 10 days after discharge.

### Statistical Analysis

All of the statistical analyses were made using the SPSS 12.0. Descriptive statistics (median, standard deviation, mean, minimum and maximum rates) and frequencies were calculated for numerical and categorical variables, respectively. The Mann-Whitney U test was used to confront intraoperative and postoperative hemorrhage between two methods. Variance analysis was used to evaluate the relationship between hemorrhage and age. A significance level of p less than 0.05 was accepted.

## Results

One hundred twenty patients underwent tonsillectomy during the study period (53 males and 67 females; mean age, 9.4 years). Tonsillectomy was performed using cold dissection in 59 patients (26 males and 33 females; mean age, 9.5±5.2 years) and bipolar diathermy in 61 patients (34 females and 27 males; mean age, 8.9±5.4 years).

The number of females was higher than males, without reaching a statistical significance (p=0.70). No significant difference was considered between the two groups in terms of age and early hemorrhage (first day of surgery). The differences in intraoperative hemorrhage following Valsalva were significantly higher in the cold dissection group than in the hot (bipolar) group (p=0.044; Table 1, Figure 1). Tonsillectomy using bipolar cautery had a statistically significantly higher postoperative hemorrhage rate than that using cold dissection (p<0.05; Figure 2).

## Discussion

Previous studies have shown that, after tonsillectomy, postoperative hemorrhage is higher when using hot dissection (monopolar, bipolar, or coblation) than using cold dissection, and that there is a dose-response relationship between postoperative hemorrhage and the bipolar diathermy power setting (5). The Valsalva maneuver has been used to check bleeding points after hemostasis in thyroidectomy procedures (6); however, a review of the literature revealed no information

**Table 1.** Number of patients with bleeding points identified by the Valsalva maneuver

| | Intraoperative bleeding | Postoperative bleeding (10 days) |
|---|---|---|
| Cold dissection group (n) | 9 | 2 |
| Hot dissection group (n) | 3 | 7 |

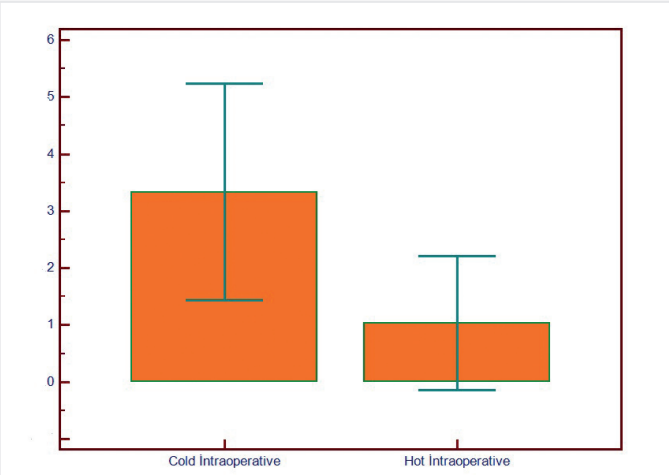


**Figure 1.** After the Valsalva maneuver comparison between two groups in terms of intraoperative haemorrhage rate

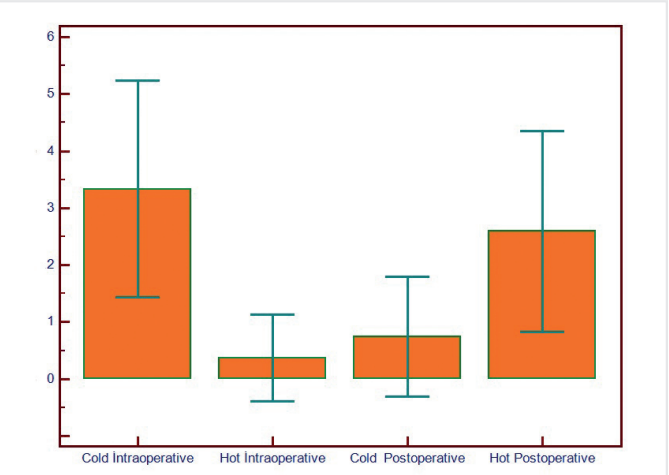


**Figure 2.** The comparison of intraoperative and postoperative haemorrhage rates

concerning the relationship between the Valsalva maneuver and the threat of post-tonsillectomy bleeding. In the present study, after adequate hemostasis, we performed the Valsalva maneuver intra-operatively and compared the risk of hemorrhage between cold and hot dissection tonsillectomy. We found that the risk of intraoperative hemorrhage was statistically significantly higher in the cold dissection group than in the bipolar diathermy group. Conversely, the risk of postoperative hemorrhage was higher in the bipolar diathermy group. The cold dissection group was subjected to the cold dissection technique (scissors and raspatory) with hemostasis using packs; and if bleeding continued, diathermy was used for hemostasis. After hemostasis, the Valsalva maneuver was performed.

Tonsillectomy dissection is commonly applied by cold or diathermy dissections. Hemostasis may be achieved using diathermy, ligature bonds to bleeding vessels, or both of them. Diathermy devices may be unipolar or bipolar. While the reported post-tonsillectomy hemorrhage rates vary with the effort of postoperative examination, the published rates for primary hemorrhage during the first 24 h after tonsillectomy vary from 0.3% to 2.1%, and secondary bleeding rates necessitating at least incoming to the hospital vary from 2% to 10.3% (7). Many publications have defined (8) varied ratios of postoperative hemorrhage in "cold" tonsillectomy procedures and "hot" tonsillectomy procedures, usually identifying lower bleeding rates after cold techniques. In the present study, postoperative hemorrhage was significantly higher in the hot (bipolar) group than in the cold dissection group.

The differences among articles regarding bleeding rates after tonsillectomy using varied procedures need to be discussed. Higher post-tonsillectomy bleeding rates following diathermy techniques may be related to more thermal damage because of extremely high power settings or more frequent or prevalent application of diathermy (5).

The United Kingdom National Prospective Tonsillectomy Audit (NPTA) announced its final survey of tonsillectomies in 2005 (8). According to the NPTA report, cold dissection plus hemostasis using bonds or packs had the lowest risk of post-tonsillectomy bleeding. If the odds ratio for post-tonsillectomy bleeding using this technique is set at 1, then cold dissection plus hemostasis using unipolar or bipolar diathermy has a 1.6 times greater risk for hemorrhage (adjusted odds ratio). Unipolar cautery or bipolar diathermy dissection and hemostasis showed a 2.5- to 3.2-times greater risk for bleeding. All of these differences reached statistical significance. Only diathermy method had a lower risk for primary bleeding than that techniques (9). This present study aimed to reduce intraoperative and postoperative bleeding by performing the Valsalva maneuver. However, similar to other studies reported in the literature, intraoperative hemorrhage was significantly higher in the cold dissection group than in the hot (bipolar) group.

### Study Limitations

Low number of participants and the lack of comparison of other techniques used in tonsillectomy are among the limitations of the study. However, our study is a preliminary study for future research.

## Conclusion

An obvious difference in intraoperative bleeding was observed between the two methods in response to the Valsalva maneuver. Our results show that the Valsalva maneuver is useful for identifying bleeding vessels for thorough tonsillectomy homeostasis. The procedure may become a helpful addition for final verification of hemostasis before ending surgery.

### Ethics

**Ethics Committee Approval:** This study protocol was confirmed by the Bezmialem Vakıf University Clinical Research Ethics Committee (18.04.2017-8/79).

**Informed Consent:** Informed consent was taken from all individual subscribers including the parents of the patients.

**Peer-review:** Internally peer-reviewed.

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Original Article

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# Comparison of Clinical Outcomes and Safety of Single-stage Bilateral and Unilateral Unicompartmental Knee Arthroplasty

Fatih YILDIZ, Tunay ERDEN, Gökçer UZER, İbrahim TUNCAY

Bezmialem Vakıf University Faculty of Medicine, Department of Orthopedics and Traumatology, İstanbul, Turkey

## ABSTRACT

**Objective:** To evaluate the effectiveness and safety of bilateral Oxford medial unicompartmental knee arthroplasty (UKA) in the patients under a single anesthetic procedure.

**Methods:** Between October 2013 and December 2015, 225 knees of 181 (age 67.5 years) patients with at least two years of follow-up were evaluated. They were divided into two groups as unilateral group (group 1, n=137) and one-stage simultaneous bilateral group (group 2, n=44) for the comparisons. The outcome parameters were femoral and tibial component positions measured on the full-length radiographs, clinical outcomes using Oxford Knee Score (OKS), International Knee Documentation Committee Score (IKDC), patient reported satisfaction and complications.

**Results:** Between the groups, the mean follow-up periods (p=0.125), age (p=0.447), preoperative body mass index (p=0.288), OKS (p=0.314) and IKDC (p=0.127) scores were not significantly different. Postoperatively, the mean flexion of the femoral component (p=0.544), posterior slope (p=0.511), varus-valgus angulation of the tibial components (p=0.358) were statistically similar between groups. Although the mean varus-valgus angulation of the femoral components (p=0.033) was statistically different between groups, the difference was too small to make clinical significance. The mean postoperative OKS (p=0.272) and IKDC (p=0.106) were similar between the groups. In group 1, 21 (16.0%) patients reported excellent, 91 (69.5%) good and 4 (3.1%) moderate satisfaction. Fifteen (11.5%) patients reported non-satisfaction. In group 2, patients reported excellent satisfaction in 20 (24.4%) knees, good in 50 (61.0%) knees patients moderate in 2 (2.4%) knees. Patients reported non-satisfaction in 10 (12.2%) knees (p>0.05). Eight (5.8%) complications in group 1 and, 3 (3.4%) complications in group 2 were observed. The number of complications was not statistically different between the groups (p=0.535).

**Conclusion:** One-stage simultaneous bilateral Oxford medial UKA is a safe and effective method with acceptable complication rates compared to unilateral surgery.

**Keywords:** Unicondillar, unicompartmental, knee, artrhroplasty, bilateral

## Introduction

Unicompartmental knee artroplasty (UKA) is a method with high patient satisfaction and successful results, which is used in the surgical treatment of medial joint osteoarthritis accompanied by complete thickness cartilage loss (1,2). It is a less invasive procedure with shorter operation time (3), less blood loss, and without touching cartilage, bone, and ligaments in other parts of the knee, compared with total knee arthroplasty (TKA). In addition, stay in hospital is shorter and rehabilitation of the patients are faster with UKA (4-6). Although long-term results reveal that revision rate is a bit higher in UKA; UKA have important advantages such as lower morbidity and mortality rate and providing a more physiological joint compared with TKA (1,7).

**Address for Correspondence:** Fatih YILDIZ, Bezmialem Vakıf University Faculty of Medicine, Department of Orthopedics and Traumatology, İstanbul, Turkey
**E-mail:** yildizfatih@hotmail.com **ORCID ID:** orcid.org/0000-0003-4475-5379

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It is known that at least 20% of patients with knee arthroplasty due to gonarthrosis have disease in both joints and patients are admitted to the hospital for surgical treatment of other knees after a knee surgery (3,8,9). The advantages of operating two knees in one surgery are decrease in treatment costs, shorter duration of hospitalization and shorter rehabilitation process (10-12). However, it is concerned that operating two knees in one surgery may prolong duration of the operation, increase the amount of bleeding and the need for transfusion, and complications, morbidity and mortality rate may be higher (3,13).

This study was planned based on the hypothesis that bilateral medial unicondylar procedure is as reliable and effective as unilateral procedure. The aim of this study was to compare radiological prosthesis alignments, clinical functional scores, patient satisfaction and complications in patients with unilateral UKA and bilateral UKA in one surgery for medial joint osteoarthritis.

## Methods

A total of 181 patients with primary medial joint osteoarthritis who underwent medial unicondylar knee arthroplasty between October 2013 and December 2015 due to the pain and functional limitation that did not improve despite conservative treatment were included in the study. Data were obtained retrospectively. Patients with at least two-year follow-up who had adequate documentation prior to and after the operation were included in the study. Patients who underwent UKA due to posttraumatic osteoarthritis or osteonecrosis and who had body mass index (BMI) higher than 40 kg/m$^2$ were excluded from the study. Patients who underwent bilateral UKA in different sessions were also excluded from the study. Patients were divided into two groups as unilateral UKA (group 1) and bilateral UKA in the same session (group 2).

In the preoperative period, the patients were asked about the localization of pain, the relationship between pain and activity and the presence of pain in front of knee and the presence of an underlying inflammatory disease. Height and weight of the patients were recorded to determine BMI. In physical examination, the knee range of motion was examined and valgus stress test for the presence of medial collateral ligament contracture was used to open the medial joint and to test the passive correctability of the varus deformity in the knee.

Informed consent was taken from all patients before the operation. Surgery was performed by two different surgeons working in the same orthopedic clinic under general or spinal anesthesia. Standard procedures were applied to all patients. About 30 minutes before incision, intravenous 2 grams cefazolin sodium was administered for prophylaxis against infection. The patients were prepared in arthroscopy position allowing knee movement 0-120 degrees on the sides that would be operated. After skin disinfection with betadine, patients were covered sterile. All patients underwent tourniquet as standard and the tourniquet pressure was inflated to be 300 mmHg. Capsulotomy was performed with approximately 8 cm medial parapatellar incision. After evaluating the stability of cartilage surfaces of lateral condyl, trochlea and patella, and anterior collateral ligament, the indication was also confirmed intraoperatively. In all patients, using the microplasty kit for the implantation of the cementless Oxford phase 3 prosthesis, appropriate tibial and femoral incisions were made and prostheses were placed. After the floors were properly closed, the tourniquet was opened. All patients walked with full load on the day after surgery and knee movements were started. Patients were discharged on the postoperative second day. Patients were called for follow-up at postoperative 3 weeks, 3 months, 1 year and later annually and were evaluated radiologically and functionally.

Preoperative and postoperative radiographic evaluations were performed with anterior-posterior and lateral knee radiographs and full-length leg radiographs while standing. Mechanical axis deviation (MAD) was measured on full-length leg radiograph before surgery; MAD, flexion of the femoral component, varus-valgus angulation of the femoral component, posterior tibial slope and varus-valgus angulation of the tibial component were measured on full-length leg radiograph after surgery.

The patients were evaluated with the International Knee Documentation Committee Score (IKDC) and the Oxford Knee Score (OKS) in the preoperative and postoperative controls. In the last control, patients were asked to choose one of the options that were very satisfied, satisfied, uncertain or not satisfied. Complications developed in the follow-ups were noted.

### Statistical Analysis

Data were analyzed using the SPSS statistical program. Comparisons between groups were made using Mann-Whitney U and Pearson chi-square tests. A p value of $<0.05$ for 95% confidence interval was considered statistically significant.

## Results

The mean age of the patients in group 1 consisting of 137 patients was 64.9 (44-86) years and the mean age of the patients in group 2 consisting of 44 patients with 88 knees was 66.1 (51-81) years. A total of 255 knees were evaluated. There was no difference between the groups in terms of mean age (p=0.447), gender distribution (p=0.588), height (p=0.964) and weight (p=0.256) (Table 1).

Preoperative mean MAD decreased from 31.5 mm (0-86 mm) to 16.1 mm (0-44 mm) in group 1 after surgery (Table 2). Preoperative mean MAD decreased from 34.5 mm (0-90 mm) to 15.3 mm (0-41 mm) in group 2 after surgery. There was no difference in terms of decrease in mean MAD between groups (p=0.807). There was no statistically significant difference between groups in terms of postoperative prothesis alignment in radiographs such as flexion of the femoral component (p=0.544), posterior tibial slope (p=0.511) and varus-valgus angulation of the tibial component (p=0.358). However, varus-valgus angulation of the femoral component was measured as a mean of 10° (1°-19°) in group 1, whereas it was 9° (0°-21°) in group 2 (p=0.033). Although there was a statistically significant difference between groups, a mean of 1° difference was not clinically significant.

There was no difference between groups in terms of functional evaluation with IKDC scores before (p=0.127) and after surgery (p=0.106) (Table 3). There was no difference between groups in terms of functional evaluation with OKS before (p=0.315) and after surgery (p=0.272). In terms of patient satisfaction; in group 1, 21 (16.0%) patients were very satisfied, 91 (69.5%) satisfied, 4 (3.1%) uncertain and 15 (11.5%) dissatisfied. In group 2, patients were asked about satisfaction for each knee individually and they were very satisfied for 20 (24.4%) knees, satisfied for 50 (61.0%) knees, uncertain for 2 (2.4%) knees and dissatisfied for 10 (12.2%) knees. There was no difference between groups in terms of satisfaction ratio (p>0.05).

**Table 1.** Demographic data

| | Group 1 (n=137) | Group 2 (n=44) | p |
|---|---|---|---|
| Mean follow-up (months) | 26.1 | 29.3 | 0.125 |
| Mean age (years) | 64.9 | 66.1 | 0.447 |
| Mean preoperative BMI (kg/m$^2$) | 32.0 | 33.1 | 0.288 |
| Females | 110 (80.3%) | 34 (77.3%) | 0.617 |
| Males | 27 (19.7%) | 10 (22.7%) | 0.351 |

BMI: body mass index

**Table 2.** Radiological evaluation of leg alignments and implant placements

| | | Group 1 | Group 2 | p |
|---|---|---|---|---|
| MAD difference between preoperative and postoperative periods (mm) | | 22.4±15.6 | 23.7±17.7 | 0.807 |
| Femoral component (angulation) | Flexion | 12.7±8.4 | 11.4±7.2 | 0.544 |
| | Varus/valgus | 10.0±4.0 | 8.5±4.2 | 0.033 |
| Tibial component (angulation) | Posterior slope | 7.8±3.3 | 7.3±3.2 | 0.511 |
| | Varus/valgus | 3.5±3.8 | 3.5±2.7 | 0.358 |

MAD: mechanical axis deviation

**Table 3.** Functional results before and after surgery

| | Group 1 | Group 2 | p |
|---|---|---|---|
| OKS before surgery | 26.9±2.4 | 26.6±1.9 | 0.314 |
| OKS after surgery | 38.5±2.6 | 39.6±5.2 | 0.272 |
| IKDC before surgery | 38.6±6.1 | 37.3±4.8 | 0.127 |
| IKDC after surgery | 70.3±7.5 | 71.8±7.8 | 0.106 |

OKS: Oxford Knee Score; IKDC: International Knee Documentation Committee Score

In group 1, 8 (5.8%) patients and in group 2, 3 (3.4%) patients and a total of 11 (4.9%) patients had complications. There was no statistically significant difference between the groups in terms of complication (p=0.535). Polyethylene liner dislocation was encountered in 3 patients; 2 spontaneously in group 1 and 1 due to trauma in group 2. In one patient, a thicker polyethylene liner was placed and in two patients, revision was made with primary knee prosthesis. In one patient, loosening due to early and severe osteolysis was observed around the implants and hypersensitivity was detected against cobalt and it was revised with primary TKA produced from oxinium and titanium. In one patient, in follow-up, varus collapse was encountered and was revised with knee prosthesis. Three patients were revised with primary knee arthroplasty in the first year due to pain of unknown. In group 2, acute prosthesis infection was seen and was treated by irrigation and debridement in one patient. Polyethylene liner dislocation was encountered in two patients, a thicker polyethylene liner was placed in one patient and revision was made with primary total knee prosthesis in the other patient.

## Discussion

It is known that duration of anesthesia, hospitalization and rehabilitation are shorter in bilateral TKA or UKA application in the same session and it is also more economical for the patients and health system compared with bilateral TKA or UKA application in different session (11,14-16). However, there are also those who claim that the complication rates are higher (17,18). In this retrospective study, clinical and radiological results of the patients with medial joint osteoarthritis in whom unilateral UKA and bilateral UKA in the same session were performed, were evaluated and compared with each other. Thus, it was aimed to see whether the risk of complications and bad clinical results were increased in bilateral UKA application. According to our findings; the radiographic and functional results and satisfaction of the patients with at least two years follow-up who had similar age, gender distribution, BMI and functional scores before surgery, were similar in those who underwent unilateral UKA and who underwent bilateral UKA. More importantly, the complication rates in patients with bilateral UKA were not higher than in those with unilateral UKA. For this reason, bilateral UKA should not be avoided in appropriate patients with indication to reduce treatment costs, to reduce patients' admission to hospital and to complete all rehabilitation process at once. In a similar study by Romagnoli et al. (3), complication rate and revision need of 220 patients with bilateral UKA in the same session and 347 patients with unilateral UKA were evaluated at the end of at least two years follow-up. Although it was found that blood loss and allogenic blood transfusions rates were higher in the patients treated with bilateral UKA, complication and revision rates were similar between groups. In that study, although patients underwent surgery without using tourniquet, intravenous or intraarticular tranexamic acid was not administered and although they were asymptomatic patients, patients with hemoglobin values below 8 mg/dL received transfusion which could explain the relatively high blood loss and transfusion rates in the bilateral UKA group (11).

Similar to our results; complication (3.5% vs 3%; p=0.83) and revision rates (approximately 1% in both groups; p=0.27) were similar in patients treated with bilateral and unilateral UKA in the study by Romagnoli et al. (3). Complication rate was 5.8% in group 1 and 3.4% in group 2 in our study. The lower revision rates in the series of Romagnoli et al. (3) can be explained by the fact that they had a very high number of patients (more than 2500) and had more experience and that single surgeon's surgical series were examined. In our series, although the revision rate in unilateral UKA was higher than expected, there was no statistically significant difference between groups (p=0.535). However, regardless of surgical technique, revision was made in one patient due to metal allergy and in three patients due to "pain of unknown" in whom radiographic and physical examinations were normal; which could explain the relative high revision rate in this group (19).

In a study that assessed the safety of bilateral UKA in same session by searching early postoperative complications, no major complication was found in patients who underwent bilateral UKA in different sessions, however major complications (deep vein thrombosis in 10 patients and myocardial infarction in one patient) were observed in 8.2% of the patients who underwent bilateral UKA in same session (p=0.005) (13). Therefore, it was recommended to be careful when applying bilateral UKA in the same session. In our study, no symptomatic deep vein thrombosis, cardiac or neurological complaints were encountered in any patient.

When we examined our radiographic results, we saw that the implants were placed within the desired and acceptable limits in both patients with bilateral and unilateral UKA. Although the placement of the implants in the left and right knee of the same patients was not compared, we think that bilateral UKA procedure does not result in poor implant placement.

A significant improvement was observed in functional results such as IKDC and OKS in both groups in the postoperative period compared with the preoperative period. OKS was above 39 points in both groups in the postoperative period in our study. Mohammad et al. (20) reported an average of 40 points in OKS in 10-year follow-up in a recent meta-analysis of more than 8.000 patients with UKA.

### Study Limitations

Having a retrospective design is a limitation of our study. Comparison of similar patient populations in prospective studies may give more accurate results. In addition, the fact that bilateral UKA applications in the same session and different sessions were not compared in our study, which is another limitation of the study. There was low number of patients, short duration of follow-up and no evaluation with patient satisfaction scale in our study, which are other limiting factors. The number of publications containing large series is also very low in the literature. There was no comparison between groups in terms of bleeding volume, blood replacement need, hospitalization period and total treatment costs in this study, which is also a limitation of the study.

## Conclusion

Although the number of patients was limited, the data of our study showed that bilateral UKA was as safe as unilateral UKA, and that there was no difference between bilateral and unilateral UKA in terms of patient satisfaction, functional and radiographic results, complication and revision rates.

### Ethics

**Ethics Committee Approval:** Retrospective study.

**Informed Consent:** Informed consent was taken from all patients before the operation.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: F.Y., G.U., İ.T., Concept: F.Y., İ.T., Design: F.Y., G.U., Data Collection or Processing: F.Y., T.E., Analysis or Interpretation: F.Y., G.U., İ.T., T.E., Literature Search: F.Y., T.E., Writing: F.Y., T.E.

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Review

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# Diabetes, Oxidative Stress and Endothelial Dysfunction

Zeynep ÖZTÜRK

İzmir Atatürk Training and Reserach Hospital, Clinic of Clinical Pharmacology and Toxicology, İzmir, Turkey

**ABSTRACT**

Cardiovascular diseases are the most common causes of morbidity and mortality in diabetic patients. Oxidative stress plays an important role in diabetic endothelial dysfunction. Under conditions of oxidative stress, free oxygen radicals may increase insulin resistance and affect pancreatic beta cells. Several experimental animal models to understand the pathogenesis of diabetes mellitus have been developed, and the model including high fat diet which leads to insulin resistance is the best animal model to mimic type 2 diabetes mellitus. In diabetes mellitus, it is well known that there is an increase in lipid peroxidation. This condition is also associated with oxidative stress. Endothelial dysfunction creates imbalance between vasoconstriction and vasodilatation. In large arteries, nitric oxide plays a main role in endothelium-dependent vasodilatation. Abnormal production or response of nitric oxide contributes vascular and endothelial dysfunction in diabetes mellitus. Oxidative stress reduces the levels of nitric oxide and diminishes endothelium-dependent vasodilatation. Therefore, in recent years, the studies to treat the diabetic complications have focused on antioxidant agents. The goal of the treatment is to decrease oxidative stress, as well as lipid and glucose levels. Thus, endothelial dysfunction may be ameliorated and diabetic vascular complications can be avoided.

**Keywords:** Antioxidant, diabetes, endothelial dysfunction, oxidative stress

## Introduction

Diabetes mellitus (DM) is a common chronic metabolic disease that causes disturbances in the metabolism of carbohydrates, fats, proteins and electrolytes. It can also be defined as a syndrome that is associated with chronic hyperglycemia, resulting from lack of insulin secretion from the pancreas, or lack of insulin effect (1).

Factors such as decrease in the release of insulin into the blood, reduction in the use of blood glucose and increase in production of blood glucose may cause glucose levels to remain high in DM. Considering the blood glucose level is high in DM, there is a pathology that concerns all organs and systems, especially the heart and arteries. The main cause of renal failure, adult blindness and non-traumatic lower extremity amputations is DM, according to studies conducted in developed countries (2).

In all types of DM, the main finding is hyperglycemia, but the mechanism that causes hyperglycemia is different. DM can be divided into two types: type 1 and 2 (3). Type 1 DM is characterized by a deficiency in insulin secretion and develops due to viral, toxic or autoimmune damage to the B cells of pancreas. This type is also known as juvenile DM and accounts for about 10% of all diabetic patients, and the likelihood of developing it increases in the second decade of life (4). Type 2 DM is characterized by impaired insulin secretion and peripheral target tissue resistance to insulin, and usually occurs with the loss of beta cell function. A decrease in the number of insulin receptors present in target cells may result in no response to insulin (5,6).

The classification of DM is gradually evolving with the better understanding of etiology and pathogenesis of DM. In addition to the two main types of DM; the World Health Organization has

**Address for Correspondence:** Zeynep ÖZTÜRK, İzmir Atatürk Training and Research Hospital, Clinic of Clinical Pharmacology and Toxicology, İzmir, Turkey
**E-mail:** dr.zeyneb@hotmail.com **ORCID ID:** orcid.org/0000-0002-7186-0775

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started to classify special types of DM including malnutrition-related DM, DM accompanying certain conditions and syndromes, the type along with impaired glucose tolerance and gestational DM (7). The most common type among these special types is gestational DM. This particular type is similar to type 2 DM and is related to insulin resistance. Insulin resistance develops in pregnant women due to pregnancy hormones.

In patients with diabetes, structural, biochemical and functional changes occur in tissues and organs. Acute complications can be life threatening. Long-term vascular pathologies cause loss of function in the organs. In the early stage, control of blood glucose can prevent progression of vascular complications and coronary artery disease and diabetic nephropathy can be prevented (8).

**Experimental Models of Diabetes Mellitus**

Experimental animal models are the methods used to examine the mechanisms of the formation of diseases, to investigate the prevention and treatment possibilities of diseases. Some of the *in vivo* experiments in drug research are carried out in representative animal models, if possible. Some models are made by changing the animal's diet or by making a lesion with toxic substances in specific target organs. Experimental DM can be made by pancreotectomy or the destruction of pancreatic beta cells. Experimental animals such as mice, rats, rabbits, guinea pigs, hamsters, monkeys, pigs, dogs and cats can be used to create experimental DM (Figures 1 and 2). Experimental DM can be done with chemical agents (9,10), spontaneously (11,12) or through the virus (13). Although there are many experimental animal models defined today, none of these models can be fully equivalent to human DM.

There has been a significant increase in frequency of DM as frequency of obesity has increased throughout the world and type 2 DM constitutes 95% of DM worlwide. Therefore, there is a need to develop new approaches and to find better methods for the treatment of type 2 DM. In this way, the pathogenesis of vascular and neuronal lesions, and the mechanisms of action of therapeutic agents are tried to be clarified to prevent complications and risks associated with type 2 DM. Although there are various animal models on this subject, they generally do not match the course of type 2 DM and its clinical presentation in humans. For this reason, researchers are trying to create new animal models or combined models for type 2 DM. A successful model should include cheap, easy-to-apply and practically testable parameters aimed at the treatment of type 2 DM.

Diet with high fat content [high fat diet (HFD)] is thought to be quite a good way to produce insulin resistance, which is an important feature of type 2 DM. Although various studies on rats has reported that HFD does not cause hyperglisemia or DM, it causes insuline resistance (14-17). Streptozotocin (STZ) is the most widely used agent in animals to form experimental DM. STZ causes death in pancreatic β cells. High-dose STZ severely impairs insulin secretion and creates a pathology similiar to type 1 DM. It is known that low doses of STZ cause a moderate deterioration in insulin secretion, which is similar to the late phase of type 2 DM (18-20).

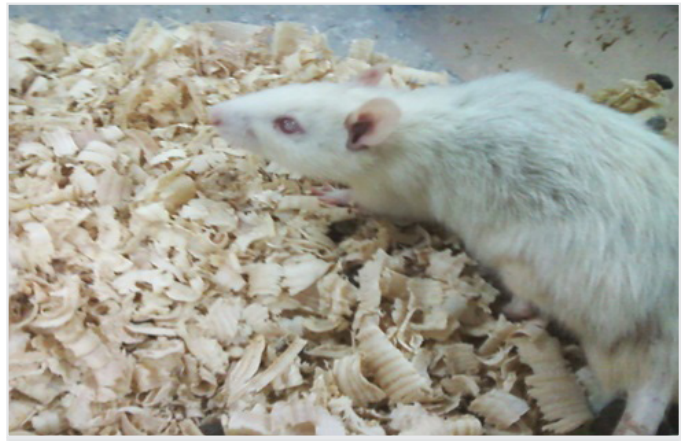

**Figure 1.** Non-treated diabetic rat appearance, significant weight loss and cataract formation in the eye

**Figure 2.** Normal rat appearance

A new rat model with low dose STZ administration following HFD, which is in line with the metabolic characteristics and the natural course of type 2 DM has been tried to be established. Studies on DM with this model are quite high in recent years (14,18-21).

In addition to this combination, there are studies that indicate that repeated low-dose STZ administration can be performed. It is reported that repeated low-dose STZ administration, instead of one single high-dose STZ administration, may lead to gradual and autoimmune destruction of beta cells in rats (21-23).

**Diabetes Mellitus and Oxidative Stress**

Although oxygen is very important and necessary for human life, some exogenous and endogenous reactive oxygen species have the potential to harm the organism (24). Many of them are free radicals and they are reactive oxygen species with high chemical reactivity. Free oxygen radicals (FOR) are formed by adding one or more unpaired electrons to the outer orbit of oxygen. Because these compounds contain unpaired electron in their final orbits, they form compounds that can easily react with other molecules and destroy them and cause very effective damage to the organism (25). They can damage many biological materials,

**Table 1.** Oxidant sources and antioxidant defence systems

| Oxidants | Antioxidant defence |
|---|---|
| Cigarette smoke | Superoxide dismutase |
| Environmental pollutants | Catalase |
| Radiation | Glutathione peroxidase |
| Carsinogens | Glutathione |
| Pesticides | Selenium |
| Exercise | Vitamin E |
| Febrile diseases | Vitamin C |
| Ischemia | Ubiquinol |
| A diet rich in polyunsaturated fatty acids | Uric acide |
| | β-carotene ve diğer carotenoids |

including proteins, lipids, DNA, and nucleotide coenzymes. This damage accelerates aging and also may cause many diseases such as cardiovascular diseases, various types of cancer, cataract, attenuation of immune system and degenerative diseases of the nervous system (26).

Oxygen metabolism in living cells and many factors such as environmental pollutants, radiation and pesticides inevitably lead to the formation of oxygen free radicals. The main ones of these radicals are single oxygen, superoxide anion, hydroxy, peroxy and alkoxy radicals. In response to the damage of reactive oxygen species, different natural defense systems in the body control free radicals (Table 1).

Substances that prevents oxidation events due to free radicals and that have the ability to stabilize free radicals are referred as antioxidants (27). Antioxidants are divided into two types according to the mechanisms: primary and secondary antioxidants. Primary antioxidants are compounds that react with radicals to prevent them from becoming more harmful and forming new free radicals. Enzyme systems such as superoxide dismutase, glutathione peroxidase and catalase are primary antioxidants and are capable of destroying free radicals. In general, these enzymes can prevent the passage of free radicals from one cell to another by limiting the damage to cellular components such as DNA, proteins and lipids (24). Secondary antioxidants are compounds such as vitamin E, vitamin C, bilirubin, uric acid, and polyphenols that capture oxygen radicals and break radical chain reactions.

Oxidative stress is described as an important mechanism in the emergence of diabetic complications (28). The rate at which free radicals are formed and the rate at which they are eliminated are in a balance and this balance is called oxidative stability. In cases where oxidative stability is impaired, the organism is affected by free radicals. A decrease in the rate of elimination or increase in the rate of formation of free radicals can cause this. Oxidative stress reflects an important imbalance between antioxidant defense mechanism and free radical formation, resulting in tissue damage.

Mechanisms that increase oxidative stress in DM include; non-enzymatic glycosylation, autooxidative glycosylation, activity of sorbitol path, metabolic stress resulting from changes in energy metabolism, levels of inflammatory mediators, tissue damage that occurs as a result of changes in antioxidant defense system (29).

In hyperglycemia, free radicals are produced inside the cell. Pancreatic beta cells are one of the most sensitive structures to oxidative stress and the damage to them is thought to be due to a toxic effect of hyperglycemia. The expression rate of antioxidant enzymes such as glutathione peroxidase, superoxide dismutase and catalase in pancreatic islet cells is the lowest compared to other tissues (30). It has been reported that the levels of malondialdehyde (MDA) and glutathione pexidase, commonly used as an oxidative damage index, increase in liver, kidney and mitochondria in rats with DM produced by STZ. Diabetic rats have been shown to have increased MDA levels in their kidneys.

Hydrogen peroxide converts into hydroxyl radicals, a product of reactive oxygen species with high reactivity. It is believed that hydroxyl radicals have an important effect on insulin receptor signal pathway and signal transduction (31).

In various cell culture studies, free radical formation was observed when endothelial and smooth muscle cells were incubated in an environment containing high concentration of glucose (30). There is evidence that STZ, which is used to create experimental model of DM, also causes oxidative stress when damaging the pancreas and disrupts the responses of nitric oxide (NO) and leads to DM (31).

It is believed that not only increased level of blood sugar but also increased level of triglycerides in blood is a risk factor for development of diabetic complications (32). There is a consensus that lipid peroxidation is important in this relationship. There is evidence that lipid peroxidation increases in various tissues in DM. Lipid peroxidation may emerge enzymatically via lipooxygenase pathway from prostaglandins or nonenzymatically via effect of free radicals from lipids found in membranes of endothelial and phagocytic cells.

In addition, increase in low-density lipoprotein cholesterol (LDL) oxidation due to hyperglicemia has been shown in patients with DM with vascular complications. In addition, protein oxidation has been shown, especially in myelin, elastin and collagen which may result in diabetic complications such as atherosclerosis, cataract, angiopathy and nephropathy (33).

**Diabetes Mellitus and Endothelial Dysfunction**

Cardiovascular disease is the most important cause of morbidity and mortality in diabetic patients. These changes in the vessels due to DM are called micro or macrojaniopathy, according to the size of the vessel involved. The involvement of kidney vessels is called renal microangiopathy and it plays an important role in diabetic nephropathy. In the same way retinal microangiopathy causes diabetic retinopathy and microangiopathy of vaso nervorum causes diabetic neuropathy. Macroangiopathy is a

severe form of atherosclerosis in diabetic patients which affects coronary, carotid and peripheral arteries and increases the risk of myocardial infarction and leads to the development of stroke and diabetic foot (34).

The most important factor in the development of microvascular angiopathies in DM is high blood sugar (35). In addition, factors such as obesity, high blood pressure, smoking, hypercholesterolemia and dyslipidemia can cause microangiopathy. In macroangiopathy, other risk factors that may cause microangiopathy come to the fore rather than high blood sugar. These risk factors lead to inflammation and endothelial dysfunction and, as a result, progressive damage to the vessel wall. Studies after the determination of the importance of endothelial dysfunction in micro and macroangiopathy formation have focused on this subject (36).

Endothelium is simply the inner layer of the vessel. Endothelial function is a key factor in regulation of vascular functions. Dysfunction of endothelium due to any damage is called endothelial dysfunction (37). Factors such as hypercholesterolemia, dyslipidemia, smoking and DM are among the risk factors that may lead to endothelial dysfunction. The development of retinopathy, nephropathy and atherosclerosis in diabetic patients is associated with endothelial dysfunction.

HFD can cause hypercholesterolemia and storage of cholesterol on artery walls. Atherosclerosis occurs as a result of the association of fatty degeneration (atherosis) and narrowing of the arteries (sclerosis). Atherosclerosis has been shown to impair endothelial vasodilation in experimental animal models (38) and in humans (39), and may lead to vasoconstriction and vascular spasm. Many studies have shown that the vascular relaxation response is caused by the relaxation factor (EDRF) originating from the endothelium (40). Later, EDRF was reported to be the same substance with NO (41).

Pathophysiology of endothelial dysfunction is complex and it can develop through various mechanisms. The most important of these mechanisms is reduction in the release of NO from endothelium. NO is the most important vasodilator substance released from endothelium. Besides vasodilatation, it inhibits the growth of smooth muscle cells and inflammation and also has antiaggregant effects. Many studies have reported that reduction in NO levels is associated with endothelial dysfunction. This may be due to a decrease in the activity of endothelial NO synthetase (eNOS) or a decrease in the biological activity of NO. It is known that FORs react with NO and cause formation of peroxynitrite and this cytotoxic oxidant disrupts the function of cellular proteins via the nitration of proteins and leads to endothelial dysfunction. Peroxynitrite plays a proatherogenic role leading to oxidation of LDL. It also reduces eNOS activity by interacting with tetrahydrobiopterin, a cofactor of eNOS. Increase in oxidative stress causes more production of FORs by activating the reductase function of eNOS enzyme. FORs also initiate proinflammatory events on the vessel wall. FORs increase adhesion (vascular cell adhesion molecule and intersellular adhesion molecule) and production of chemotactic molecules (macrophage chemotactic peptide) increase. The onset of inflammation decreases the activity of NO. C-reactive protein has been shown to reduce eNOS activity (42).

Oxidative stress reduces NO levels and leads to deterioration of endothelium-dependent vasodilation. In patients with chronic renal failure, oxidative stress markers have been shown to increase with deterioration of endothelial functions. FORs are also thought to induce endothelial damage by causing apoptosis (42).

Another mechanism leading to NO reduction is increase in asymmetric dimethyl arginine (ADMA) level which is endogenous compensatory inhibitory of eNOS enzyme. ADMA is a product that is produced during protein catabolism and is eliminated via kidneys or via metabolizing to citrulline. It has been shown that eNOS inhibition is associated with increased plasma ADMA levels in patients with chronic renal failure. A negative correlation was found between the increase in ADMA levels and endothelium-associated vasodilation in hypercholesterolemic individuals, and the infusion of L-arginine, which is the substrat of eNOS enzyme and competative inhibitor of ADMA, has been shown to improve endothelial functions (42).

Endothelial dysfunction in DM manifests itself with imbalance between vasoconstriction and vasodilation. In large arteries, NO plays a major role in endothelium-dependent relaxation. The abnormal production or response of NO contributes to vascular and endothelial dysfunction seen in DM.

NO is produced as a result of oxidation of guanido nitrogen of L-arginine amino acid by NO synthase (NOS). It is an unstable substance and is reduced to nitrite and nitrate. Synthesis of nicotinamide adenine dinucleotide phosphate, calmodulin, oxygen and as cofactors; hem, flavin, mononucleotide, flavin adenine dinucleotide and tetrahydrobiopterin are required. The NOS enzyme, which is a tool for NO synthesis, has three different isoforms: neuronal, endothelial and immunological. Neuronal and endothelial isoforms are named as structural NOS (43).

Hyperglycemia affects NO formation and function; it also increases the formation of superoxide. It is thought that the imbalance between the production of superoxide and NO leads to endothelial dysfunction in DM (44). The superoxide inactivates NO by converting it into peroxynitrite, thereby reducing NO formation and bioavailability. In the treatment of vascular complications of DM, the goal should be to increase NO formation and bioactivity and reduce the formation of reactive oxygen radicals.

In coronary arteries of diabetic rats, the decrease in acetylcoline-induced vascular relaxation was associated with a decrease in plasma NO levels and expression of eNOS protein (45). A similar result was obtained in thoracic aorta of rats which were made diabetic with STZ (20). Endothelial NOS synthesizes NO in endothelium. Endothelial NO synthesis and vasodilation were significantly impaired in diabetic rats with insulin resistance. Expression of eNOS in diabetic rats was shown to decrease.

## Conclusion

Endothelial dysfunction is responsible for the development of vascular complications of DM. The development of endothelial dysfunction is the result of oxidative stress and a pathological process associated with it. Reducing oxidative stress sources and antioxidant treatments can help reduce and prevent serious complications by preventing the development of endothelial dysfunction in DM. It is important to know the pathophysiological process in order to create new treatment alternatives and there is much need for both experimental and epidemiological studies.

### Ethics

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Review

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# Patent Foramen Ovale and Diving

Şefika KÖRPINAR

Çanakkale Onsekiz Mart University Faculty of Medicine, Undersea and Hyperbaric Medicine, Çanakkale, Turkey

**ABSTRACT**

Although patent foramen ovale (PFO) was anatomically depicted in 1513 by Leonardo da Vinci and described as a thromboembolism route in 1877, it has been ignored for a long time as a potential way to produce pathological conditions. The unifying hypothesis associated with multiple clinical issues, such as cryptogenic stroke, migraine and decompression sickness is that a particle, inert gas bubbles or chemical substance in the venous circulation bypasses the lungs and enters to the systemic circulation via PFO. In this review, current data on the status of PFO in diving medicine are discussed.

**Keywords:** Patent foramen ovale, diving, decompression sickness

## Introduction

Foramen ovale is an interatrial connection that enables rapid transiting of umbilical blood to the brain and vital organs without any further oxygen loss during intrauterine period. After birth, the foramen ovale flap (septum primum) is closed on the septum secundum, physiologically when pulmonary vascular resistance and right atrium pressure drop. Fusion, which begins with contact, is completed irreversibly, in the first two years of life. Foramen ovale remains patent in 25% of the population (1,2). The patent foramen ovale (PFO) was drawn and depicted by Leonardo Da Vinci in the form of a "channel" centuries after the physiological closure was defined by Galen. Use of the term "channel" is unique in that century in terms of predicting the complex structure of PFO pathophysiology and pointing out that it is more than just a simple hole (3).

While individuals with PFO are generally identified incidentally in autopsies, antemortem diagnosis is often made during the etiological investigations of clinical pictures associated with PFO. In an autopsy study consisting of 965 people, PFO sizes were measured between 1-19 mm (4.9 mm on average) and the mean size was 3.4 mm in the first decade and was 5.8 mm in the tenth decade. This is interpreted as the fact that small-size PFOs are closed over time and that large-sized ones remain open (4). The combining hypothesis for the association of PFO with numerous clinical conditions such as cryptogenic stroke, migraine, sleep apnea, pulmonary edema due to high altitude, platypnea-orthodeoxia, decompression sickness (DCS), is based on the passage of a particulate, gas bubble, or chemical substance in venous circulation to systemic circulation without being exposed to the lungs through a right-to-left shunt. The left atrium pressure is higher than the right atrium, which prevents passage by holding down the septum primum flap to septum secundum. Even if the flap is partially open, the blood flow will be from left to right. However, daily activities such as lifting, coughing, vomiting, and pushing which increase intrathoracic (ITP) and intraabdominal pressure may reverse the interatrial pressure gradient, creating a temporary right-to-left shunt. One of the most effective methods is an extended and forced Valsalva maneuver (VM) (1,2,5). The maneuver, originally described in 1704 by Mario Antonio Valsalva in detail in his work "De Aure Humana Tractatus" (Treatise on the Human Ear), is simply an effort of forced expiration against a closed airway. In order to prevent middle ear barotrauma, the VM is frequently used during diving and hyperbaric oxygen treatment.

**Address for Correspondence:** Şefika KÖRPINAR, Çanakkale Onsekiz Mart University Faculty of Medicine, Undersea and Hyperbaric Medicine, Çanakkale, Turkey
**E-mail:** s_korpinar@yahoo.com **ORCID ID:** orcid.org/0000-0002-8155-3867

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The response to the maneuver is related to the duration of the maneuver, the level of strain, the position of the body and the respiratory pattern (5). Astonishingly, while gentle VMs during diving do not increase the ITP at all, much larger increases are observed if maneuver is performed during challenging and crouching (6).

Another issue about PFO-mediated transition that has recently been discussed is the blood flow dynamics in the right atrium and its relationship with fossa ovalis. At the right atrium, the currents from the caval veins do not collide head to head, they turn forward and contribute to the rotation of the blood in the clockwise. This filling pattern associated with directing the atrial volume towards the tricuspid valve entry is extremely important in maintaining the continuous activity of the heart with minimal energy. This vortex formed at the right atrium entrance is thought to remove the blood out of PFO which carries the majority of thrombus material, bubble, vasoactive chemicals and which is coming with the inferior caval current directed at almost to the fossa ovalis at the beginning which (7,8).

The PFO-mediated shunt can be determined by different echocardiographic techniques, including transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and transcranial Doppler (TCD). Having superior image resolution, having ability to distinguish shunt localization, having ability to define morphology, presence of accompanying defects, number and size of these defects, completeness of septum apart from defect and the presence of anatomic structures that will affect the placement of the device and visualizing the three-dimensional appearance of PFO in mind make TEE the gold standard in the diagnosis of PFO (1,2,9,10). However, it comes after TTE or TCD in the evaluation hierarchy because it is a semi-invasive procedure with well defined staff training criteria, it has life-threatening complications such as esophagus hemorrhage, perforation and it is contraindicated in patients with severe bleeding risk. TTE is the most frequently used initial screening test because of its low cost, non-invasive nature and easy accessibility (9,10).

The most common contrast used in echocardiography routine is saline which is agitated by mixing with air. Air bubbles are cleared as they pass through the lungs, and those who can pass are dissolved in the blood. Because tissues are not supersaturated with nitrogen, DCS symptoms are not observed even if there is a high bubble passage (11). However, during echocardiographic studies with contrast agents, for safety reasons, oxygen should be available and the diver should not have dived within the last 24 hours (6). It has been shown that TCD has similar sensitivity to shunt detection, but it fails to differentiate cardiac and pulmonary localizations (2,9,10).

Provocative maneuvers that increase the ITP, also significantly increase the sensitivity of TTE and TEE. Because conscious sedation is applied during TEE, the effect to be achieved with a challenging VM is tried to be performed by abdominal compression. The timing of the bubbles in the left heart is very important in the separation of intracardiac and transpulmonary shunts. In the presence of a shunt at the cardiac level, the bubbles are expected to be seen in the left heart in three cardiac cycles. In the presence of a large pulmonary shunt, it should be noted that contrast in the left heart can be seen in three cardiac cycles, and a more detailed imaging of the shunt to clarify localization should be performed with TEE. The systems used in grading are subjective and are usually based on semi-quantitative factors that focus on the number of bubbles seen in the left atrium. Therefore, there is no widely accepted schema (9,10). Another important point is the localization of contrast injection. Femoral injections have been shown to be more effective than conventional brachial injections. This effect is related to the blood flow dynamics in the right atrium and its relation with PFO, which is described above, and to the rapid bolus and shorter venous transit time provided by a larger diameter femoral catheter, and thus to the reduction of the dissolved bubbles (9,12).

**Diving and Patent Foramen Ovale**

During diving, the environmental pressure increases by 1 atmosphere (760 mmHg) at every ten meters of depth. Increasing pressure does not affect the liquid and solid parts of the body, but forces gas-filled cavities and organs of the body to squeeze into smaller volumes. For this reason, divers inhale high pressure air (or mixture gas) to prevent the lungs from being collapsed with the aid of equipment (SCUBA) that allows the environmental pressure to be balanced with ambient pressure. During the dive, inert gas (nitrogen, helium) in the inhaled gas mixture is dissolved in the tissues, depending on the depth and duration. If the inert gas pressure in the lungs or gas mixture does not decrease, the dissolution may continue until equilibrium is reached between the breathing gas known as saturation and the tissues. The decrease in inert gas pressure in the lungs is possible with decrease in ambient pressure (decompression). When divers begin to rise to the surface, inert gas is transported from tissues to the blood and lungs and expelled from the alveoli. During decompression, the inert gas in the tissues can be effectively removed by slowing down the ambient pressure or waiting at certain depths (decompression stops). There are detailed decompression algorithms designed to control this process and ensure that the diver returns safely to the surface. In an inadequate decompression, supersaturation (over saturation) develops and a tendency to produce bubbles occurs (11,13-15).

Gas bubbles that occur after supersaturation and do not cause any symptoms are called “silent bubbles” and can be detected by Doppler imaging in venous circulation (13,16,17). Bubbles, depending on their numbers and sizes, can cause clinical signs and symptoms of DCS by causing mild or severe damage in any part of the body. DCS is a systemic disease with complex pathogenesis including the development of mechanical distortion, ischemia, hypoxia, vascular occlusion, increased capillary permeability with endothelial damage, plasma extravasation, hemoconcentration, platelet activation and aggregation, leukocyte-endothelial adhesion, ischemia reperfusion damage due to mechanical, embolic and biochemical effects of bubbles (13,14,17). It is seen in pilots, astronauts, compressed-air (caisson) workers and known as “bends” colloquially. The traditional classification of

DCS based on the severity of clinical findings in the form of type 1/2 is based on the experience gained from caisson workers in the construction of the Dartford Tunnel in London (18).

Silent bubbles can also be seen after dives made according to the rules. In the presence of DCS, bubbles are usually found in high amounts (13,16,17). In a study conducted by the Divers Alert Network (DAN), venous gas bubbles were found with Doppler in 91% of divers after repeated dives at different depths, however DCS was not seen in any diver (19). The current data suggest that the risk of DCS development is 13%, even in the presence of a high amounts of bubbles (17). Under normal conditions, these gas bubbles go to the right heart, then to the lungs through venous circulation. The gas in the bubbles is eliminated by diffusion from pulmonary capillaries to alveoli. The size of the bubbles is 19-700 μm and the diameter of the capillaries in the gas exchange area is 6-15 μm, which explains the working mechanism of the pulmonary filter. A more rare and dangerous condition is that the transition of bubbles to arterial circulation through a right-to-left shunt at cardiac or pulmonary level (13,14,16,17,20).

Initial publications suggesting that venous gas bubbles may cause paradoxical embolism through a defect in the interatrial septum have begun to enter the literature from the late eighties (21). Although PFO has been known for a long time as a route of thromboembolism, it has begun to attract the attention of cardiology and neurology since the late eighties (22-25). The presence of a PFO to provide arterialization of silent bubbles has been considered to be a part of an incomplete "undeserved DCS" puzzle following a safe dive profile or arterial gas embolism without pulmonary barotrauma. However, it has paved the way for new discussions. The most important objection concerns the numbers. It is clear that only 0.005-0.08% of all recreational dives result in DCS; PFO is found in 25% of divers as in the normal population and we know that bubbles that can cause DCS are formed in 91% of divers. So, this ratio is much lower than expected. The second objection is that clinical observations made so far, correlate PFO with neurological damage, but this group constitutes only one third of all DCS cases. Although the majority of DCS cases occurring in recreational dives are presented with pain and sensory disturbances, the association with PFO has not been established (26). Recent publications suggest that the risk of developing DCS is associated with the diameter of the atrial defect rather than with the presence of PFO, and that stroke and DCS prevalence are higher than normal population in patients with migraine with aura and that migraine with aura may be regarded as an indicator of the presence of a large scale PFO (25,27,28).

Short-term increases in the ITP may be insufficient for passing of large amounts of bubbles. However, in professional and military diving, depending on the nature of the job, physical activities that form a significant increase in ITP are made in decompression period and in first 30-60 minutes after rising to the surface which are the periods with the highest level of bubble formation. In addition to professional activities such as lifting anchor, rope pulling, transferring people that are expelled from water to boat, there are activities that increase the individual workload such as swimming to the boat from the exit point from the surface, climbing to the boat with heavy equipment such as diving cylinder. Unconscious VM is also frequently performed during this period. The activities during this period elicit the opening of intrapulmonary arteriovenous anastomoses, especially for those whose shunts open at a relatively low percentage of their maximal oxygen consumption ($VO_{2max}$) (20,28). Undersea and Hyperbaric Medical Society (UHMS) Best Practice Guidelines recommend avoiding aerobic (running), anaerobic (lifting weight) exercises for four hours unless there is no operational requirement (29).

On the other hand, although the bubbles are called "silent", their acute, asymptomatic but repeated presence in circulation plays a role in the formation of cardiovascular, osteonecrotic and cerebral lesions in the long-term period (16). In particular, concerns about decreased neuropsychological performance, the question of whether "silent" bubbles cause "silent" cerebral damage, and the role of PFO in this damage, due to its contribution in arterial migration of bubbles, have been subject to numerous studies (30-33). With increased use of magnetic resonance imaging (MRI), white matter hyperintensities (WMHs) as an incidental finding in T2-weighted images were significantly much more seen in healthy divers with no DCS history than in non-diving controls, which has brought new questions that need to be answered. Cerebral WMHs are neuronal axon defects where the myelin is replaced by the central nervous system fluid. They are known as hyperintense lesions in T2-weighted, FLAIR and proton density images without showing significant hypointensity in T1-weighted images in MRI. Histologically, represent demyelination, axonal loss and astrocytic gliosis. Long-term results of WMHs associated with diving are not known for today. However, it is well known that WMHs increase dramatically over the age of 55 and increase the risk of stroke, dementia, and death (31,33,34). The relationship between increased WMHs and subclinical disturbances in neurocognitive functions has been shown in studies performed in U-2 pilots (35). This situation seems to be compatible with subtle cognitive disorders seen in healthy individuals with punctate WMHs (31,34,35). The acute and chronic consequences of gas bubbles passing through the venous circulation to the systemic circulation via PFO are still under investigation.

**Closure of PFO: Results From Cardiology and Neurology Experience**

PFO, defined in the autopsy studies of Julius Cohnheim in 1877 as an unusual route for thromboembolism (22) was considered to be a rare condition until two observational studies in 1988 (23,24) in which the prevalence of PFO was found to be higher in patients with cryptogenic stroke at a young age (40-50% vs 10-15%, $p<0.001$). A retrospective analysis of the PICSS (PFO in Cryptogenic Stroke Study) which was a subgroup survey of the WARRS (Warfarin Aspirin Recurrent Stroke Study) that was a randomized trial, consisting of 2206 patients, showed that recurrent stroke risk in patients aged over 65 years with a history of cryptogenic stroke was 37.9% in patients with PFO and 14.5%

in patients without PFO at two years follow-up (36). In patients with atrial septal aneurysm (ASA) concomitantly, there is an increase in the risk of initial and recurrent stroke events (1,24). Although this relationship was originally thought to be related to the formation of thrombus caused by aneurysmal tissue, it was not confirmed. The current theory is that the presence of ASA increases the risk by causing more interatrial flow (1).

A meta-analysis of forty-eight observational studies including 10327 patients with cryptogenic stroke/transient ischemic attack (TIA) with PFO showed that the rate of recurrent events was 0.8 events/100 person-years in patients with PFO closure, whereas it was 5.0 in patients with medical treatment (37). However, large-scale, randomized controlled trials (RCTs) planned with the hypothesis that the closure of PFO in the prevention of cryptogenic stroke would be superior to medical treatment did not meet the proposed hypothesis. The first was CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale). The study included 909 patients aged 18-60 years with a history of cryptogenic stroke or TIA, whose PFO was confirmed by TEE. Patients were randomized into two groups; antiplatelet therapy (clopidogrel for 6 months followed by aspirin) after percutaneous closure of PFO and only medical treatment (warfarin, aspirin or both, according to the researcher's decision). The PFO closure attempt failed in 14% of patients. At the end of the two-year follow-up, 5.5% in the group with PFO closure and 6.8% in the group receiving medical treatment had stroke or TIA (confidence interval: 0.45-1.35; p=0.37). Although it was a well-designed study with the high number of participants, it had the power of only determining a 30% difference between the two groups (38).

The discrepancies between the results of observational studies and the CLOSURE I study were mainly attributed to the device used for the closure (2). The advantageous safety features of the Amplatzer PFO Occluder have enabled it to be preferred in other two RCTs: the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) and the PC (Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale (PFO) Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism) (39,40). Although the studies resolved the problems related to the device, they did not eliminate the uncertainty about whether PFO is causative or incidental finding in cryptogenic stroke (2).

The relationship between PFO and migraine, as well as PFO-cryptogenic stroke relationship began to draw attention at the end of the nineties. The first studies which indicated that lungs act as a filter in removing the triggering agents acting in migraine pathogenesis from the venous circulation rather than releasing them, included divers who underwent transcatheter closure before return to diving after neurological DCS. In addition to the relief of migraine symptoms as a secondary gain after closure, it is also important to note that migraine with aura-PFO- DCS relationship was revealed by this study (25). Observational studies and meta-analyses were followed by three consecutive RCTs, as in stroke cases. The first one was the MIST (Migraine Intervention With STARFlex Technology) study. It showed that the prevalence of shunt in patients with migraine with aura (60%) was much higher than in the general population, however there was no difference between closure and sham (imitation, skin incision in the groin) groups on primary and secondary endpoints. Hence, has created a disappointment (41). The much more remarkable feature of the MIST study was the sensational debate about the evaluation of device and residual shunts in the sixth month follow-up (42). PRIMA (Percutaneous Closure of PFO in Migraine with Aura) was a study with the use of the Amplatzer PFO Occluder that started in 2006 and ended prematurely due to slow participation in 2012. The primary endpoint was the number of days with migraine headache per month, and it was concluded that the closure of PFO in refractory migraine cases did not reduce the monthly migraine days (43). The PREMIUM (Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the Amplatzer PFO occluder Compared to Medical Management) study was initiated in the same year with the PRIMA study and used the same device. It was a sham-controlled study with larger number of participants, but it was not published yet (NCT00355056).

All of these data show that cardiology and neurology have shown much more progression than diving medicine in terms of PFO. PFO closure is a less risky procedure in patients with stroke and migraine than the disease itself, which is a factor in the progress. With the contribution of the studies, the number of procedures increased fifty times over the last decade which has brought important developments in technics and device (1). However, due to the fact that the results are not as spectacular as expected, it can be said that the current experiences do not add much to the relationship between diving and PFO. The risk-benefit ratio of closure also remains controversial for diseases other than diving.

**PFO Screening in Medical Examinations to Fitness to Dive**

The purpose of medical examinations for professional divers, instructors, guides and divemasters is to determine whether there is a temporary or permanent impediment to diving or require further specialist assessment. It should also assess the functional capacity of the diver to undertake their work safely. Standards developed in the light of scientific evidence, expert opinions and experiences obtained from suitability examinations for diving determine the way to be followed in diving examinations. Standards are based on scientific evidence, expert opinions and experiences obtained from examinations of fitness to dive and help achieve these aims and promote a consistent approach to fitness assessments. In our country, medical examination and assessment of professional divers or diving instructors are carried out in accordance with the principles determined by the Professional Divers Regulation and the Turkish Underwater Sports Federation (TSSF) Equipped Diving Instruction. Legislation gives responsibility to the undersea and hyperbaric

medicine specialists in examination, assessment of suitability for diving and preparing health reports (44,45).

There is a general consensus that the PFO screening does not need to be routinely performed in all divers, but it is unclear when and who should be scanned. Despite the enrichment observed in the literature, deciding which diver should be referred to for closure is still a commonly asked clinical question and the answer is not clearly revealed. The ideal is to establish consistent and evidence based principles in the light of available data and to implement them in evaluations (28). A review of the current guidelines gives the following results: According to the DAN: "Although medical data suggest that there is a relationship between severe neurological DCS and the presence of PFO, the cause-effect relationship is not conclusively proven and associating a common finding (PFO) with a rare disease (DCS) is a commonly made mistake" (26). According to the United Kingdom Sports Diving Medical Committee (UKSDMC), for sport diving: "Testing is recommended to exclude the possibility of a shunt in case of neurological DCS in sport divers after a theoretically safe dive profile. Paradoxal embolism risk is greater in those with a large shunt. It therefore seems reasonable that sport divers known to have intra-cardiac shunts should be allowed to dive shallower than 15 m, provided no other cardiac contra indications exists" (28). Health and Safety Executive for professional divers: "Examination for the presence of an intracardiac shunt is not a requirement of either the initial or annual examinations. However, PFO screening should be performed in patients with neurological, cutaneous or cardio-respiratory DCS, especially in divers with history of migraine with aura, or in divers developing DCS after a dive profile which can be considered as safe; because PFO screening may contribute to the overall risk assessment when deciding to start diving and continue diving. The presence of a positive finding is not sufficient reason to decide whether the diver is unsuitable for diving. However, any diver who has suffered these should be assessed by a cardiologist with a special interest in diving medicine" (46). According to the National Institute of Clinical Excellence: "It is important to include a cardiologist with knowledge of diving medicine in the evaluation. If the assessment of PFO presence and size is inadequate, inappropriate advice may pose a risk in the future" (47). According to the UHMS Best Practise Guidelines: "PFO screening for divers with clinically severe or recurrent neurological DCS can help advise divers on changing dive profiles" (29). According to the Carl Edmonds's Diving Medicine for SCUBA Divers: "The risk from a PFO is not great enough for it to be appropriate to test all divers for it, and repair of the hole is probably more dangerous than diving with it" (48). The situation is similar in our regulations. There is no opinion on the obligation to scan for PFO in the Professional Divers Regulation and the TSSF Equipped Diving Instruction (44,45). According to "the TSSF Equipped Diving Instruction, Sixth Section, Health Conditions, Item 20b": "Unless evaluated as hemodynamically insignificant by a cardiologist; organic heart diseases such as cardiomyopathy, ischemic heart disease, valvular heart disease, cyanotic heart disease and right-to-left shunts are impediments to diving" (45).

The report produced from the consultation with UKSDMC members after the workshop held at the 43th Annual Scientific Meeting of the South Pacific Underwater Medicine Society is extremely important in terms of its content and setting out the need for this issue. According to this consensus statement: "Routine screening for PFO at the time of dive medical fitness assessment (either initial or periodic) is not indicated. An investigation for PFO should be considered in the history of cerebral, spinal, vestibulocochlear or cutaneous DCS, cryptogenic stroke, PFO or atrial septal defect in first degree relatives and current or past history of migraine with aura. If screening for PFO is performed, it should be done by centres well practiced in the technique. The screening must include bubble contrast, ideally combined with TTE because this best facilitates cooperation with provocation maneuvers. A spontaneous shunt without provocation or a large, provoked shunt is recognized as an unequivocal risk factor for cerebral, spinal, vestibulocochlear and cutaneous DCS. There is a lower but poorly defined risk in smaller shunts. Following diagnosis of a PFO, the diver may consider stop diving, adopting more conservative diving profiles or PFO closure options in consultation with a diving physician. Following closure of a PFO and before returning to diving, the diver requires a repeat bubble contrast echocardiogram demonstrating shunt closure, a minimum of three months after the closure. Diving should not be resumed until satisfactory closure of the PFO is confirmed, and the diver has ceased potent antiplatelet medication" (49).

The ultimate goal of practicing diving medicine is to protect the health of divers both during and after the dive. The diving-PFO relationship requires close cooperation with the cardiologist who will perform the procedure during screening, diagnosis, closure and follow-up. In addition, the use of experience of cardiology and neurology which have studies with high number of patients and resources should be considered in the design and methodology of future research. It should be emphasized that the most important factor in DCS development is the diving profile, that even the most successful closure procedure can not prevent DCS formation in the presence of an aggressive dive profile, and that the risk is only returning to normal and can never be reset.

**Ethics**

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Case Report

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# Coexistence of Occupational Asthma and Desquamative Interstitial Pneumonia: A Case Report

Hüseyin ARPAĞ[1], Muhammet SAYAN[2], Nurhan ATİLLA[1], Abdülkadir Yasir BAHAR[3], Fulsen BOZKUŞ[1], Hasan KAHRAMAN[1], Mahmut TOKUR[2]

[1]Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Chest Diseases, Kahramanmaraş, Turkey
[2]Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Chest Surgery, Kahramanmaraş, Turkey
[3]Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Pathology, Kahramanmaraş, Turkey

## ABSTRACT

Desquamative interstitial pneumonia (DIP) is an interstitial pneumonia whichis characterised by diffuse intra alveolar accumulation of macrophages. Restrictive type of respiratory failure occurs in this entity. Although DIP is an idiopathic disorder, smoking is a major risk factor in etiology. In addition, occupational exposure can cause this pathology. The cornerstone of treatment of DIP is removing the state of exposure such as smoking or occupational exposure. Herein, we presented a case of coexistence of occupational asthma and DIP.

**Keywords:** Asthma, desquamative interstitial pneumonia, occupational exposure

## Introduction

Desquamative interstitial pneumonia (DIP) was first described by Liebow et al. in 1965 (1). The etiology of DIP is unknown. While DIP is an idiopathic disorder it is thought to be associated with smoking habit. Pneumoconiosis, some rheumatologic disorders, viral infections and drug reaction can be accepted as etiologic factors in non-smoker individuals (2-4). DIP is generally seen in the age range of 40-60 years and it is seen more frequently in male patients (1-6). The diagnosis of DIP is not easy and usually lung resection is required. Histopathologically pigmented macrophages and sometimes giant cells collection are detected in distal airway (3).

## Case Report

Thirty one-year-old welder, non-smoker, male patient admitted to us with dyspnea, cough and chest tightness complaints. His medical history included occupational asthma and use of inhaled bronchodilator therapy for 10 years. He was diagnosed as having occupational asthma due to his respiratory symptoms and positivity of reversibility test on pulmonary function tests occurred in 2 years after he started his welding job. Rhonchi and prolonged expirium were detected at the bilaterally lower zones on thorax auscultation. Despite using of inhaled bronchodilator therapy regularly his respiratory symptoms were not healed. Hyperinflation and linear density increase at right middle zone on chest X-ray. Thorax computed tomography revealed the nonhomogeneous infiltrates which featured ground glass densities distributed patchy peripheral (Figure 1). There was no restriction in pulmonary function tests. The diffusing capacity for carbon monoxide was 80%. There was neither hypoxia nor hypercapnia on arterial blood gas analysis. His laboratory tests including hemogram, biochemical tests, collagen tissue diseases markers and urine tests were normal. Informed consent form included intervention and publishability of his medical records were obtained from the patient then fiberoptic bronchoscopy

**Address for Correspondence:** Muhammet SAYAN, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Chest Surgery, Kahramanmaraş, Turkey
**E-mail:** drsayann@gmail.com **ORCID ID:** orcid.org/0000-0002-5402-9031

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and transbronchial biopsy were performed but it was not for diagnostic purpose. Lung wedge resection was performed via video assisted thoracic surgery. Histopathologically; interstitial fibrosis and thickening, lymphocytic and plasmacytic infiltrates and accumulation of macrophages and giant cells were detected in alveolar lumen (Figure 2). Final pathology was reported as DIP based on that histopathologic signs. We administered methylprednisolone treatment (1 mg/kg) to patient with diagnosis of occupational asthma with DIP. After 6 months from steroid therapy, clinical and radiological improvement were achieved in patient and corticosteroid treatment was discontinued. The patient was followed without treatment. Here, we presented this rare association.

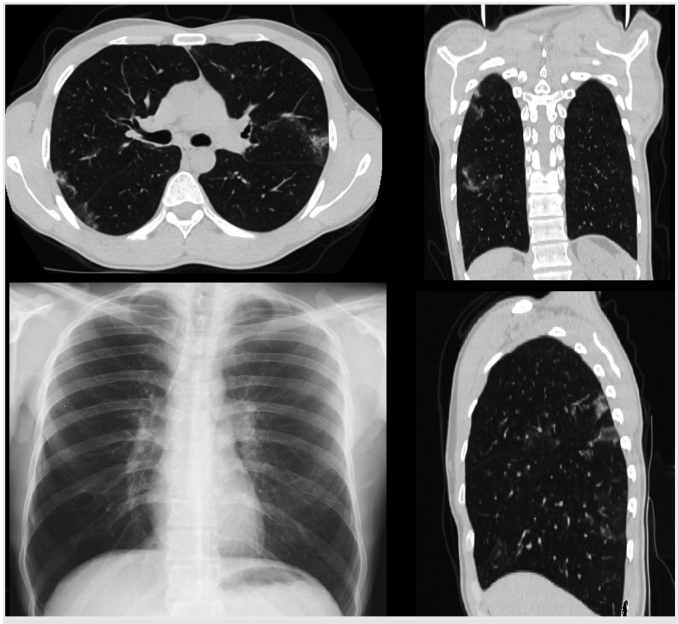

**Figure 1.** Radiologically; increase of pleuroparenchymal density, patchy ground glass located peripheral regions and increase of reticular density are seen in the bilateral lung fields

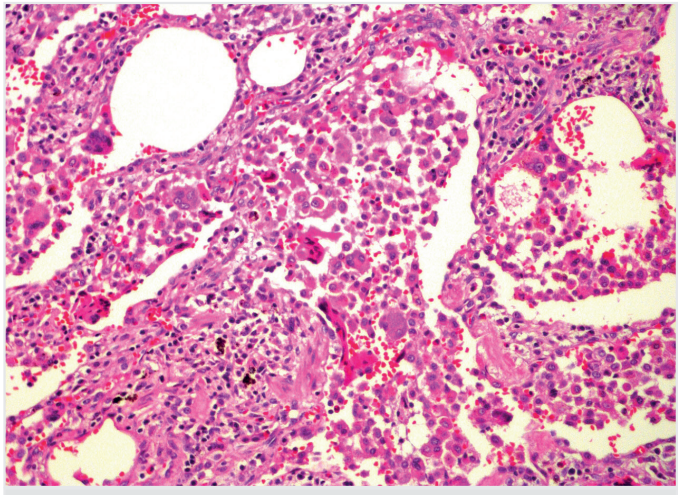

**Figure 2.** Large eosinophilic cytoplasmic alveolar macrophages and giant cells filling the alveoli are seen (hematoxylin and eosin, 200x magnification)

## Discussion

DIP is a rare type of interstitial lung disease. DIP was first described by Liebow et al. (7) in 1965. DIP is a restrictive disorder. Radiologically it is characterised by diffuse infiltration. Histopathologically, intraalveolar diffuse macrophage accumulation is seen (7). Although etiology of DIP is unknown, usually it is detected in smoker individuals. Other accused factors in etiology of DIP are; environmental-occupational exposure, drug related reactions, viral infections, rheumatologic and autoimmune diseases, solder fumes, copper dust, fire extinguisher powder, diesel fumes, inhalation of nylon fibers and marijuana habit (2,3,6). Our patient was non-smoker but he had been a welder for 10 years so we linked the cause of DIP of him to this condition. Usually DIP is seen in the middle age and male population (1). The age and gender of our patient (31-year-old and male) were also consistent with the literature.

Common symptoms of DIP are cough and shortness of breath. Our patient's complaints were cough, dyspnea and chest tightness. Inspiratory velcro rales and clubbing can be detected on physical examination in the cases of DIP (8). But end-inspiratory rhonchi and prolonged expiration and no rales and no clubbing were found in our patient. We thought the cause of rhonchi was coexisting asthma. Radiologically, chest X-ray may be normal or increased reticular traces, ground glass patchy opacities may be detected on thorax computed tomography (CT) or high-resolution CT (9). Findings of thorax CT of our case was coherent with literature.

DIP can lead to restrictive type deterioration in pulmonary function tests (2,7,10). But, pulmonary function tests of our patient showed obstructive pattern and there was no restriction. We linked this condition to the accompanying asthma.

Histopathologically, intra alveolar accumulation of pigmented macrophages and mild interstitial fibrosis are seen in DIP (6). Similarly interstitial fibrosis and thickening, lymphocytic and plasmacytic infiltrates and accumulation of intra alveolar macrophage and giant cells were detected in histopathologic examination of our patient. Removing the etiological factors such as smoking, occupational or environmental exposure, drug reaction etc. is the main factor of treatment of DIP. Additionally corticosteroid and even immunosuppressive treatments may be needed in some patients (5,7,10). We recommended to him change his welding job and started to corticosteroid treatment. Almost complete clinical and radiological recovery was achieved in our patient for 6 months.

Consequently, we reported here that DIP due to occupational exposure may occur in non-smoker individuals and occupational asthma may accompany to this entity.

### Ethics

**Informed Consent:** It was obtained.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: H.A., M.S., M.T., Concept: M.S., M.T., A.Y.B., Design: H.A., M.S., N.A., A.Y.B., Data Collection Or Processing: H.A., M.S., N.A., A.Y.B., M.T., Analysis Or Interpretation: H.A., M.S., N.A., A.Y.B., F.B., H.K., M.T., Literature Search: H.A., M.S., N.A., A.Y.B., F.B., H.K., M.T., Writing: H.A., M.S.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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Case Report

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# Ectopic Liver Tissue on the Gallbladder

Cemil YÜKSEL[1], Yunus DÖNDER[1], Nihal Deniz BULUT YÜKSEL[2], Uğur İZOL[3]

[1]Kilis State Hospital, Clinic of General Surgery, Kilis, Turkey
[2]Kilis State Hospital, Clinic of Anesthesiology and Reanimation, Kilis, Turkey
[3]Kilis State Hospital, Pathology Laboratory, Kilis, Turkey

## ABSTRACT

Ectopic liver tissue is a rare developmental abnormality and is thought to be caused by aberrant migration in the embryological development of the liver. A 34-year-old female patient underwent laparoscopic cholecystectomy and ectopic liver tissue was found on the gallbaldder. Ectopic liver tissue was removed during cholecystectomy. Pathology was reported as normal liver tissue with the gallbladder tissue. Ectopic liver tissue is incidentally detected with no preoperative diagnosis. Ectopic liver tissue should be removed due to malignancy potential.

**Keywords:** Laparoscopy, gallbladder, ectopic liver tissue

## Introduction

Ectopic liver is a rare developmental abnormality and its incidence is 0.24%-0.48% (1). The first case was published in 1922. Ectopic liver is thought to develop due to aberrant migration occurred during embryological development (2). Although there are many different locations such as hepatic ligaments, falciform, omentum, diaphragm where it can locate; most oftenly it is located on the gallbladder (3). It can not be diagnosed by radiological imaging methodsand is usually seen during the operation. Although we have much knowledge about the ectopic liver the associated pathologies, treatment approaches, and complications should be known. Ectopic liver has been shown to have potential for hepatocellular cancer development (4). For this reason, removal of the ectopic liver is necessary. We present a patient in whom an ectopic liver on the gallbladder was detected during laparoscopic cholecystectomy performed due to cholelithiasis.

## Case Report

A 34-year-old female patient had abdominal pain that was intermittent for about 1 year. It was associated with meals and sometimes was accompanied by nausea and vomiting. The patient had no comorbidities and physical examination showed minimal sensitivity on the right upper side and there was no defense or rebound. The patient did not use any drug. There was no significant feature in family history. In the preoperative laboratory tests; alanine aminotransferase: 49 U/L, aspartate aminotransferase: 27 U/L, alkaline phosphatase: 134 U/L, total bilirubin: 1 mg/dL, direct bilirubin: 0.5 mg/dL, white blood cells: $9.58*10^3$, hemoglobin: 12.7. There was no pathology in the chest X-ray. Preoperative hepatobiliary ultrasonography showed millimetric stones in the gallbladder and the wall thickness of the gallbladder was shown to be increased. The patient was evaluated as ASA1 by the anesthetistand the patient was operated. During laparoscopic cholecystectomy, on the medial side of the free face of the gallbladder fundus, a liver-like brown tissue was observed that was not associated with the liver. It was totally removed with the gallbladder (Figure 1). The patient was discharged on the first postoperative day without any complications. The patient did not have any complaints at follow ups. Chronic cholecystitis, cholelithiasis and ectopic liver tissue of 1.7 cm in diameter adhered to the gallbladder and microscopically; ectopic liver tissue with normal liver histology with bile ducts were reported in the pathology report (Figures 2 and 3). Written informed consent was obtained from patient.

**Address for Correspondence:** Yunus DÖNDER, Kilis State Hospital, Clinic of General Surgery, Kilis, Turkey
**E-mail:** ydonder@hotmail.com **ORCID ID:** orcid.org/0000-0002-0560-1708

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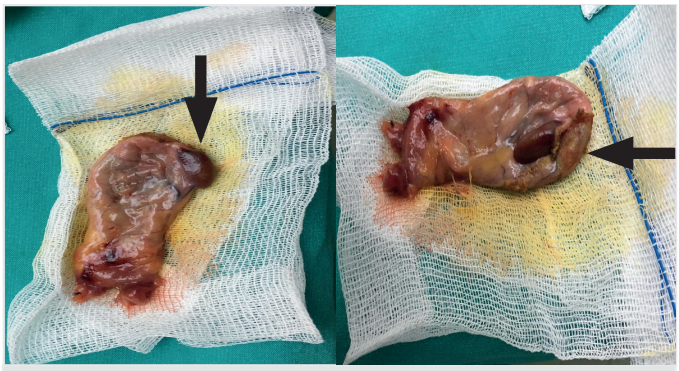

**Figure 1.** Macroscopic view of ectopic liver tissue of 1.7 cm in diameter marked with arrow on the gallbladder

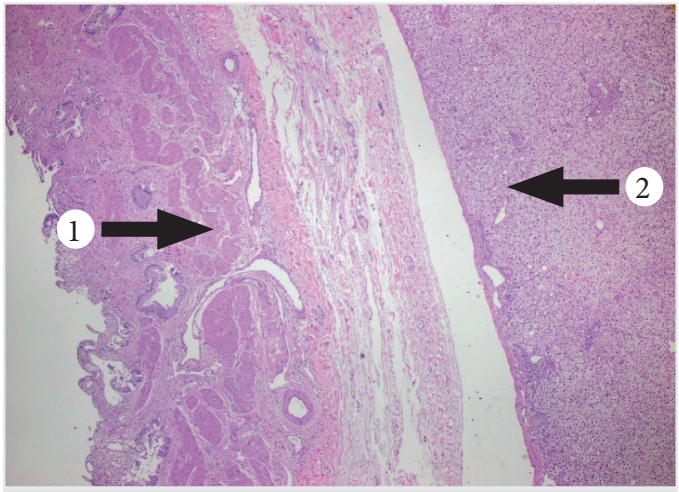


**Figure 2.** Microscopic view of the gallbladder and ectopic liver tissues (gallbladder tissue is shown by arrow 1, normal ectopic liver tissue is shown by arrow 2)

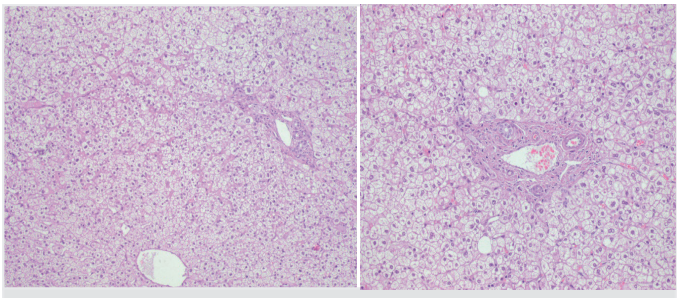

**Figure 3.** Histopathologic view of ectopic liver tissue

## Discussion

The ectopic liver can be found in the abdomen or in the thorax, but most commonly on the gallbladder. The incidence is between 0.24% and 0.48% (1). Hepatobiliary system originates from foregut at the 4th week of embryological development. Development of ectopic liver is thought to be caused by aberrant migration during the embryological development of the liver (2). Ectopic liver is frequently encountered incidentally during surgery (5). Patients often do not have symptoms. Symptoms may be due to torsion, necrosis, compression, or malignant transformation. However, it may cause cholelithiasis and cholecystitis (6). Ectopic liver may rarely be associated with some abnormalities. Ectopic liver can be seen rarely with cardiac abnormalities, biliary atresia, omphalocele and biliary duct cysts (7).

Ectopic liver tissue is generally not diagnosed, preoperatively. By ultrasound imaging, ectopic liver on the gallbladder can be seen and can be diagnosed with biopsy but biopsy should notbe done due to risk of bleeding and malignant spread.

In general, the pathology is reported as normal liver histology. Sometimes bile or portal vascular system may not develop. Although not fully proven, several publications have shown that ectopic liver increases the risk of hepatocellular cancer. This is thought to be caused by insufficient bile drainage and low arterial feeding (8).

Ectopic liver tissue should be removed because of the risk of malignancy. Ectopic liver tissue on the gallbladder should be resected together with the gallbladder. The vascular component of ectopic liver tissue is not seen, oftenly. If the liver has a vascular component, it is necessary to dissect the vascular component before separating the gallbladder from the liver bed. In this way, unwanted bleeding can be avoided.

As a result, ectopic liver is very rare and it is incidentally seen during surgery. It is most commonly found on the gallbladder. Ectopic liver is removed when it is seen because of risk of hemorrhage, pressure, rupture, necrosis and hepatic cancer.

### Ethics

**Informed Consent:** Written informed consent was obtained from patient.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: C.Y., Y.D., Concept: N.D.B.Y., U.İ., Design: N.D.B.Y., C.Y., Data Collection or Processing: Y.D., U.İ., Analysis or Interpretation: U.İ., Literature Search: C.Y., Writing: Y.D.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Case Report

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# Asymmetric Blepharospasm Treated with Botulinum Toxin-A: Case Report

Gözde BARAN[1], Çiğdem DENİZ[2], Azize Esra GÜRSOY[2], Gülsen BABACAN YILDIZ[2]

[1]Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Neurology, İstanbul, Turkey
[2]Bezmialem Vakıf University Faculty of Medicine, Department of Neurology, İstanbul, Turkey

## ABSTRACT

Benign essential blepharospasm (BEB) is a focal dystonia that causes involuntary occlusion of the eyelids as result of bilateral contraction of orbicularis oculi muscle. A 51-year-old female patient evaluated at the outpatient clinic with complaints of contraction and closure of the left eye for about 11 years and the same complaints of right eye for 10 years. Cranial magnetic resonance imaging was normal and blepharospasm was diagnosed based on the clinical and neurological evaluation. The patient underwent a botulinum toxin-A injection and was called for control 2 weeks later. BEB is a disease that seriously affects the quality of life of the patient, sometimes it can cause functional blindness. The time between diagnosis and treatment may be delayed in atypical cases. For this reason; differential diagnoses of atypical cases should be done well.

**Keywords:** Asymmetric, blepharospasm, focal, dystonia, botulinum toxin-A

## Introduction

Benign essential blepharospasm (BEB) is the second most common focal dystonia after cervical dystonia which is caused by involuntary contraction of orbicularis oculi, procerus and neighbouring corrugator muscles (1,2). The excessive activity of these muscles causes the eye to open and close too frequently or too vigorous to increase the blink frequency or cause functional blindness (2). Pathogenesis of the disease, as of all dystonias, is unknown; although it is thought to develop as a result of dysfunction in cortico-striato-thalamo-cortical circuits (3). Rarely, it may start unilaterally or asymmetrically, but almost always involves involuntary closure of both eyes (1). In patients who do not have typical onset or course, the diagnosis and treatment process may be delayed due to misdiagnosis. In this article; a patient with BEB who started unilaterally and still went on asimetrically for long years was reported with literature review.

## Case Report

A 51-year-old female was admitted to the neurology outpatient clinic for contraction and closure of eyelids which started in the left side 11 years ago and spread to the right side 1 year later. The patient stated that especially in bright areas, the contraction and closure of eyelids increased significantly, and that from time to time the left eye was completely closed and therefore she had to open left eye with her hands, frequently. In neurologic examination, left eyelid was nearly completely closed and right eyelid was minimally closed. There was no contraction at the edges of the mouth. Especially while speaking, it was observed that the eyelids of the patient could remain open. The patient was trying to keep her eyelids open with her eyebrows raised. There was no history of illness, medication use or operation in her medical history. She had no history of disease in her family history. Routine blood tests (hemogram, biochemical tests, thyroid funtion tests) were normal. Cranial magnetic resonance

**Address for Correspondence:** Gözde BARAN, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Neurology, İstanbul, Turkey
**Phone:** +90 212 375 50 00 **E-mail:** drgozdebaran@gmail.com **ORCID ID:** orcid.org/0000-0002-6369-7218

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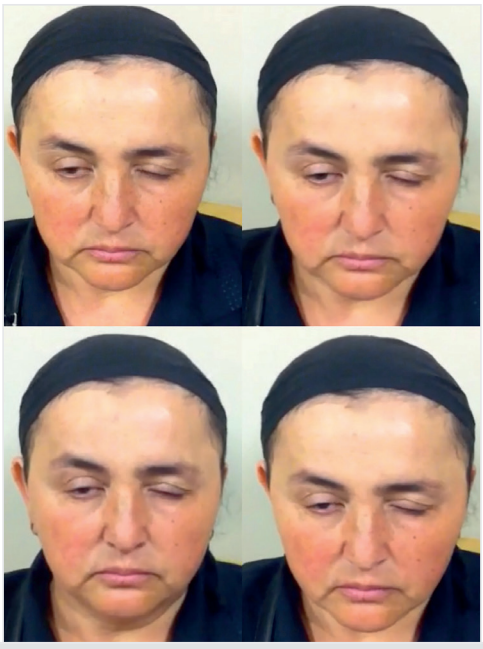

**Figure 1.** Before botulinum toxin-A injection

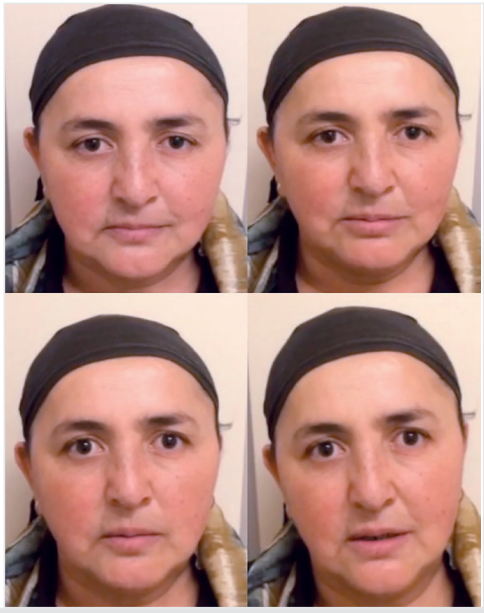

**Figure 2.** After botulinum toxin-A injection

and cranial magnetic resonance angiography imagings were normal. Diagnosis of blepharospasm was considered based on the anamnesis and neurologic examination findings and botulinum toxin-A injection was planned (Figure 1). Botulinum toxin (Botox®) was diluted with 2 mL 0,9% sodium chloride and subcutaneously injected as 5 units into 5 different points in the pretarsal section of the orbicularis oculi muscle. Also 5 units were injected into the corrugator muscle. At 2 weeks follow-up, complaints of the patient improved almost completely (Figure 2).

Informed consent for using the patient's pictures was taken from the patient.

## Discussion

BEB is a focal dystonia that causes the eyelids to involuntarily close as a result of two-sided contraction of the orbicularis oculi muscle (2). The main symptoms of BEB are involuntary contractions of eyelids and increased blink reflex resulting in chronic involuntary contractions that ultimately affect both eyes. BEB usually begins with the increase in the frequency of eye blinking. Spasm follows the increase in the frequency of eye blinking over time. Some patients develop functional blindness as a result of these spasms. A sensory trick in the form of stretching eyebrows and eyelids is often seen. Spasm starts bilateral in approximately 88% of cases (4,5). Oftenly, diagnosis and pre-treatment processes can be prolonged. According to Jankovic and Orman (4), symptoms start 4-10 years before diagnosis in 50% of the patients and more than 10 years in 20% of the patients. We found out that our patient was followed up from an ophthalmology outpatient clinic for a while after the onset of the complaints and then from a neurology outpatient clinic with the diagnosis of hemifasial spasm because of the spasms being very asymmetrical. In about 78% of the patients with BEB, which is a progressive disease, dystonia can be seen in the lower face or neck region (Meige syndrome, orofacial dystonia or oromandibular dystonia) or in other parts out of the facial nerve region (6). The complaints of our patient started unilaterally, and in a short period of time spread to the other side as reported in the literature, but the patient had always distinctly asymmetric course. Several oral medications were used to treat BEB. These include anticholinergics (trihexyphenidyl, benztropine), GABAergic drugs (clonazepam, baclofen), antidopaminergics (tetrabenazine) and mexiteline. Because of side effects and low efficacy in evidence-based studies, oral agents are often not preferred in clinical practice. Aproclonidine, an alpha-2-adrenergic agonist, produces a lid elevation by sympathetic stimulation of the Muller muscle, but its therapeutic use is limited due to tachyphylaxis (7-12). Chemodenervation with botulinum toxin injection is an effective first step treatment in BEB. There are two main serotypes of botulinum toxin commercially available: Botulinum toxin-A and Botulinum toxin-B. Botulinum toxin-A is more commonly used and contains onabotulinum toxin-A (ONA), abobotulinum toxin-A (ABO) and incobotulinum toxin-A (INC) (13). In the 2016 update, "Report of the therapeutical and Technology Assessment Subcommittee of the American Academy of Neurology", ONA and INC was considered as evidence level B, ABO was considered as evidence level C as treatment options (14). More than 90% of motor symptoms have been observed to improve after botulinum toxin treatment in BEB (15). Therefore, we preferred to use onabotulinum toxin (Botox®) in our patient. Spontaneous remission rates in BEB were reported in a wide range of 1.2-11.4% (16,17). In the first or second degree relatives of approximately one third of the patients, the presence of at least one of the disorders including BEB, Meige syndrome, Parkinson's disease, or essential tremor suggests that some patients have a genetic predisposition (5). However, most patients with BEB are sporadic and the causing gene has not been identified. A history of a movement disorder was not found in the first and second degree relatives of our patient.

Some disorders should be considered in differential diagnosis of BEB. If contraction affects one side of the face, hemifacial spasm should be considered as diagnosis but it should be noted that BEB rarely presents unilateral initially. Hemifacial spasm remains unilateral in its course, but BEB always becomes bilateral although it can present unilateral initially (6). If spasm affects one group of fibers in the orbicularis oculi muscle, the diagnosis is probably ocular myokymia. If bilateral eyelid spasms are associated with twitching or spasms in one part of the face, the most accurate diagnosis is Meige syndrome or idiopathic cranial-cervical dystonia. Antidepressants, antihistaminics, sympathomimetics, dopamine blocking or stimulating drugs and decongestants should be investigated as possible triggers of BEB (6). Other diseases that need to be considered in differential diagnosis are apraxia of eyelid opening which is characterized by difficulty in voluntary opening of eyelid without spasm in the orbicularis oculi muscle, reflex blepharospasm and blepharitis (6,18).

BEB is a disease that disrupts the quality of life of patients by even causing functional blindness. The time between diagnosis and initiation of treatment can be delayed, especially in patients with atypical onset course. Presenting with unilateral twitching of eyelids and continuing its course as significantly asymmetric, lack of symptoms in other parts of the face except eyelids, stretching eyebrows as a sensory trick and good response to botulinum toxin-A injection suggest a diagnosis of BEB. Therefore, it is important to note that in patients who do not have a typical onset or course, it may interfere with other diseases in the differential diagnosis.

**Ethics**

**Informed Consent:** Informed consent for using the patient's pictures was taken from the patient.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: G.B.Y., Concept: G.B.Y., A.E.B.G., Design: G.B.Y., A.E.B.G., Data Collection or Processing: G.B., Analysis or Interpretation: G.B., Ç.D., Literature Search: G.B., Ç.D., Writing: G.B.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Case Report

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# Dental Treatment of Two Children with Niemann Pick Disease Type B Under General Anesthesia: Case Reports

Mustafa Sarp KAYA[1], Meltem BAKKAL[1], Serdar YEŞİLTAŞ[2]

[1]Bezmialem Vakıf University Faculty of Dentistry, Department of Pedodontics, İstanbul, Turkey
[2]Bezmialem Vakıf University Faculty of Medicine, Department of Anaesthesiology and Reanimation, İstanbul, Turkey

## ABSTRACT

Niemann-Pick disease (NPD) is an autosomal recessive lysosomal lipid storage disorder with accompanying symptoms including hepatosplenomegaly and thrombocytopenia. Delayed or extensive dental treatment may need to be delivered under general anesthesia and the management of such treatments in these children may require advanced medical support including intensive care (IC). Two children with NPD type B who underwent dental treatment with general anesthesia and their post-operative follow-ups requiring in IC are were presented. Patients with NPD may present with fragile blood clots in extracted tooth socket and should be subjected to strict bleeding control standards; especially the ones that may require further respiratory assistance since oral intubation is an invasive application to the oral surgical site.

**Keywords:** Niemann-Pick disease, general anesthesia, hemostasis

## Introduction

Niemann-Pick disease (NPD) is an autosomal recessive disorder caused by pathogenic mutations in *SMPD1* gene. It is characterized by lysosomal acid sphingomyelinase (ASM) deficiency causing accumulation of cholesterol and sphingomyelin in various organs, intercellular space, central nervous system and especially in reticuloendothelial system cells (1). Type A and B exhibit defective ASM activity in 0-1% and 1-10% of the healthy individuals, respectively. Patients with type C cannot metabolize cholesterol and other lipids properly which cause accumulation in tissues (2). Patients with NPD may present with cerebellar ataxia, dysphagia, dysarthria, progressive neurodegeneration, dementia, mental retardation, seizures, impaired motor development, hepatosplenomegaly, thrombocytopenia, interstitial pulmonary disease and cardiac symptoms which are of significance in anesthesia procedures (1). Diagnosis is based on tissue biopsy showing characteristic foamy histiocytes or ASM enzyme analysis in leucocytes (2). Thrombocytopenia secondary to hypersplenism is a significant factor that leads to difficulties in dental management in these patients (3). We, hereby presented two children with NPD type B who underwent dental treatment with general anesthesia (GA) and their post-operative follow-ups in pediatric intensive care unit (PICU).

## Case Reports

### Case 1

A four-year-old boy was referred for dental treatment due to numerous caries by the ear nose throat specialist who was planning adenoidectomy for obstructive sleep apnea and adenoid hypertrophy. Offspring of a consanguineous marriage, the child was diagnosed with NPD type B and had undergone a bone marrow transplant at the age of two. Intraoral exam that was performed with the assistance of father due to child's limited ability to hold the head erect and keep the mouth open revealed chronic odontogenic abscesses and deep dentinal caries. Dental radiographs could not be taken because diagnostically valid images could not be obtained. Restorations and extractions were planned

**Address for Correspondence:** Mustafa Sarp KAYA, Bezmialem Vakıf University Faculty of Dentistry, Department of Pedodontics, İstanbul, Turkey
**E-mail:** mkaya3@bezmialem.edu.tr **ORCID ID:** orcid.org/0000-0003-4482-9040

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under GA in the same session with and before adenoidectomy (Table 1). Pre-operative blood panel was shown in Table 2; consulting hematologist recommended regular hemostatic precautions and observation in PICU. Written parental informed consent was taken before the operation.

In GA procedure, an intravenous midazolam premedication (0.5 mg/kg) was administered 15 minutes before taken to operating room. Non-invasive blood pressure, echocardiogram and peripheral pulse oximetry were used for standard anesthesia monitorization. Intravenous line using 24 gauge catheter was placed and saline infusion was administered. After 5 minutes of stabilization, patient's heart rate, systolic/diastolic arterial pressure and average arterial pressure were recorded as basal vitals. Before the induction, 6 L/min 100% oxygen insufflation was achieved. Following preoxygenation, 1 mcg/kg of fentanyl and 3.5 mg/kg of propofol doses were administered intravenous. Following the disappearance of eyelash reflex patient was ventilated with airway mask breathing unit and 0.5 mg/kg recuronium bromide was administered. Patient was intubated orally using (spiral) endotracheal tube. For the maintenance of anesthesia, 50% nitrous oxide/oxygen and sevofluorane (2%) were used.

Antisepsis of the oral cavity was performed with 0.12% chlorhexidine swabbing. Ferric sulfate pulpotomy and composite restorations were performed in all second primary molars, maxillary and mandibular canines were also restored with composite. All primary first molars and maxillary incisors were extracted with local anesthesia (articaine and epinephrine) injection (Table 1). Hemostasis was achieved with gauze pressure and suturing was not necessary in these minor wound sites with closed extractions of roots.

Following dental treatment, adenoidectomy was performed using curette and nasopharynx was packed with gauze for three minutes until bleeding was controlled. Excised tissue was sent for biopsy and foamy histiocyte appearance was detected. Operation site was irrigated with sterile saline nasally and orally and hemostasis was observed. At the end of the operation patient was extubated and transferred to PICU as planned preoperatively.

Patient's oxygen saturation declined four hours after the operation and was decided to be reintubated. Oral intubation preparations dislodged the blood clots leading to hemorrhage from anterior extraction site which had to be sutured after hemostatic agent (Gelfoam, Pfizer, USA) was packed into the sockets before the intubation. Patient received intravenous tranexaminic acid (10 mg/kg/day) for four days and post-operative bleeding from extraction sites was stopped in 72 hours. Patient was kept intubated for two days, monitored in PICU for further respiratory distress and discharged on day 11 following surgery.

## Case 2

A nine-year-old boy was admitted for dental treatments before bone marrow transplant to eliminate any possible oral infection focus. Offspring of a consanguineous marriage, child was diagnosed with NPD type B. Intraoral exam revealed multiple carious and infected deciduous and permanent teeth (Figure 1). Restorations and extractions were planned under GA due to child's poor rapport (Table 1). Before the dental operation, an anesthesiologist examined the child with pre-operative blood panel that was shown in Table 2. Consulting hematologist suggested regular hemostatic precautions. Written parental informed consent was taken before the operation and the same GA procedure was followed as in case 1 described above. Indirect pulp capping with mineral trioxide aggregate in two maxillary first permanent molars were performed and restored with composite. Two mandibular first permanent molars and both primary canines were restored with composite. Ten primary teeth were extracted after local anesthesia. Hemostasis was achieved with gauze pressure and suturing was not necessary in these minor wound sites with closed extractions of roots. Patient was extubated and referred to PICU for overnight observation and discharged the next day uneventfully.

**Table 1.** Dental treatments of the cases

| | Teeth extractions | Restorations | Pulpal treatments |
|---|---|---|---|
| Case 1 | 51, 52, 61, 62, 64, 74, 84 | 53, 63, 73, 83 | 55, 65, 75, 85 |
| Case 2 | 51, 52, 53, 54, 55, 63, 64, 65, 74, 75 | 36, 46, 73, 83 | 16, 26 |

Teeth were numbered according to International Dental Federation Classification

**Table 2.** The preoperative blood panels of 2 cases

| | International normalizing ratio | Prothrombin time (second) | Activity (%) | Thrombocyte count ($10^3$ cells/mL) |
|---|---|---|---|---|
| Case 1 | 1.53 | 47.5 | 56.7 | 116 |
| Case 2 | 1.66 | 20.9 | 55.8 | 449 |

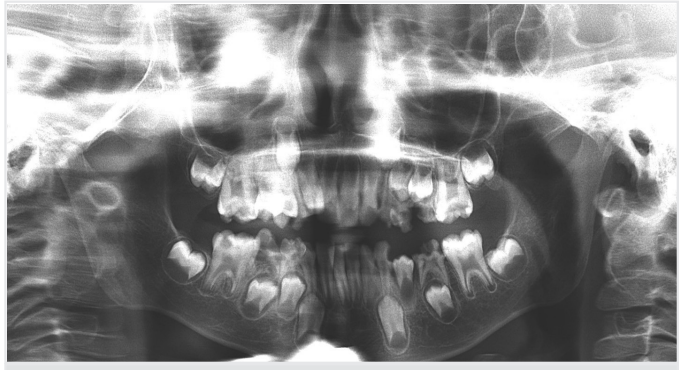

**Figure 1.** Preoperative radiography of case 2

## Discussion

Children with special health care needs often present high caries risk and high caries activity and oral cavity has frequently been documented as the leading source of sepsis in medically compromised patients (4,5). According to the American Academy of Pediatric Dentistry, GA is indicated in patients with cooperation problems due to physical/medical disability and

children in need of immediate, comprehensive oral/dental care among others (6). In patients with NPD without severe physical disability and mental retardation, treatment on an outpatient basis may be less costly and encourage the family to be involved in their child's oral health and motivate for follow-ups (2). Although that is not an ideal scenario, unachievable volume of work has been reported as a reason for dental treatment indication under GA (7). Both cases presented were in need of comprehensive dental treatment due to delayed oral care. Since elimination of both the present and possible odontogenic infections was intended in a single-session GA procedure, mostly extractions were preferred. But extractions in these patients may cause unstable blood clots over the course of healing and may cause post-op hemorrhage. Thrombocytopenia may present secondary to hypersplenism in patients with NPD as in case 1, although this has been reported as clinically insignificant in the literature (8,9). According to the American Academy of Pediatric Dentistry guideline, platelet count below 75000 cells/mlis recommended to be checked 24 hours before and after the surgery and hemorrhage control can be provided with application of local hemostatic agents, pressure packs (10). Our patient was above this level and local bleeding control and hemostasis were provided with gauze pressure as suggested by consulting hematologist. But respiratory distress requiring intervention to the oral wound site disorganized blood clots and necessitated impromptu hemostatic control need.

Comprehensive dental treatment under GA in patients with NPD may carry risks due to unforeseeable complications. Dental caries may be prevented or treated earlier by referral to the dental team by their primary physicians as part of their medical management plan. This approach may avoid unnecessary advanced procedures or prevent delay to critical treatments.

Patients with NPD may present with unstable blood clots and should be subjected to strict bleeding control standards; especially the ones that may require further respiratory assistance since oral intubation is an invasive application to the oral surgical site.

### Ethics

**Informed Consent:** Written informed consent was obtained from the patients who participated in this study.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.S.K., M.B., Concept: M.S.K., Design: M.S.K., Data Collection or Processing: M.S.K., M.B., Analysis or Interpretation: M.S.K., M.B., S.Y., Literature Search: M.S.K., M.B., Writing: M.S.K., M.B.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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Case Report

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Bezmialem Science 2019;7(1):77-9

# Diffuse Retinal Thickening due to Epiretinal Membrane in a Patient with Idiopathic Parafoveal Telangiectasia

İgbal HAMZAYEV, Ahmet ELBAY, Cansu EKİNCİ, Hakan ÖZDEMİR

Bezmialem Vakıf University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey

**ABSTRACT**

Idiopathic parafoveal telangiectasia (IPT) is characterized by abnormal dilated or ectatic retinal capillaries with exudation. In many studies macular hole or pseudohole was demonstrated in patients with IPT. However, only one case with the coexistence of IPT and epiretinal membrane (ERM) formation was reported before. In this study, we presented the retinal alterations of a patient with IPT admitted to our clinic with complaint of blurred vision for two months. A hyperreflective band refers to ERM, diffuse thickening and increased reflectance of inner retinal layers and cystic spaces in the inner nuclear layer of the retina were detected in horizontal optic coherence tomography (OCT) images of left eye. Due to the thickening of the inner retinal layers, foveal depression was lost. There was no full-thickness or partial-thickness retinal tissue defect in any OCT scan.

**Keywords:** Idiopathic parafoveal telangiectasia, epiretinal membrane, optic coherence tomography

## Introduction

Idiopathic parafoveal telangiectasia (IPT) is characterized by abnormal dilated or ectatic retinal capillaries with exudation in one or both eyes. The term IPT was first used by Gass and Oyakawa (1) in 1982. The classification of the disease was established by Gass and Blodi (2) according to clinical and fundus fluorescein angiography findings. In following years, macular hole or pseudohole was demonstrated in patients with IPT in many studies (3,4). However, only one case with the coexistence of IPT and epiretinal membrane (ERM) formation was reported before (5). In this case report, we presented ERM formation and related retinal alterations in a patient with IPT.

## Case Report

A 82-year-old male was admitted with blurred vision of left eye for 2 months. He expressed that his right eye was blind due to a blunt trauma. The corrected best visual acuity in the examination of the patient who did not undergo any intraocular surgery was at the level of 6/10 in the left eye and he could only see hand movement in the right eye. Severe corneal leukoma and vascularization were observed in examination of the anterior segment in the patient who had no systemic disease except hypertension. Lens could not be visualized due to leukoma. Nucleocortical lens opacification was observed in the left eye. Intraocular pressure was measured as 12 mmHg in the right eye and 16 mmHg in the left eye. Fundus examination could not be performed in the right eye. In the left eye, telengiectasias and small retinal hemorrhages were observed in the white-grey region, which was about 1.5 disc diameter in temporal area of the fovea. It was observed that the retinal vessels in the macula and in the described white-grey region were slightly pulled due to ERM (Figure 1). A hyperreflective band refers to ERM, diffuse thickening and increased reflectance of inner retinal layers and cystic spaces in the inner nuclear layer of the retina were detected in horizontal optic coherence tomography [(OCT), Spectralis, Heidelberg Engineering)] images of left eye. Due to the thickening of the inner retinal layers, foveal depression was lost (Figure 2). There was no full-thickness or partial-thickness

**Address for Correspondence:** Cansu EKİNCİ, Bezmialem Vakıf University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
**E-mail:** cansuekinci@yahoo.com **ORCID ID:** orcid.org/0000-0002-7687-5853

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retinal tissue defect in any OCT scan. It was observed in fundus fluorescein angiography that telengiectasias appearing in temporal area of the fovea in the left eye in the early period caused leakage in the late period. No choroidal neovascularization was observed (Figure 3).

Written and oral informed consents were taken from the patient. Written consent could not be attached because it was lost.

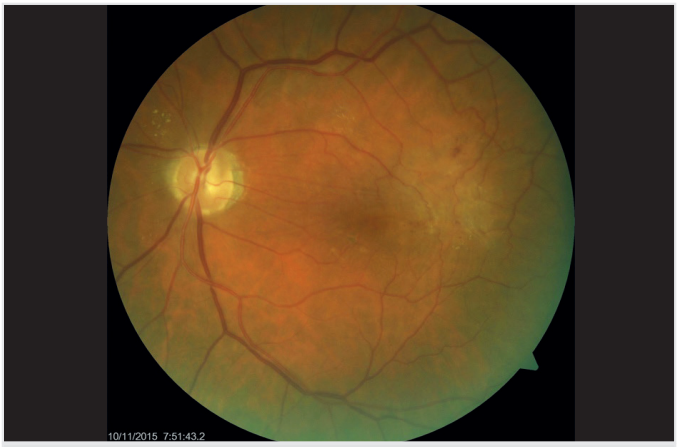


**Figure 1.** Colored fundus figure of the patient's left eye

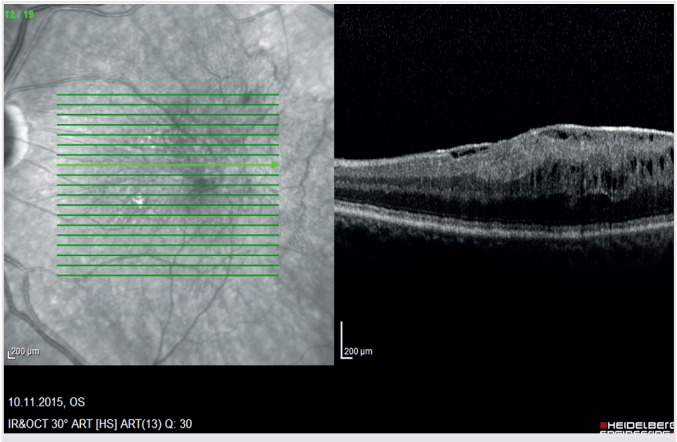


**Figure 2.** Horizontal optic coherence tomography image of the patient's left eye

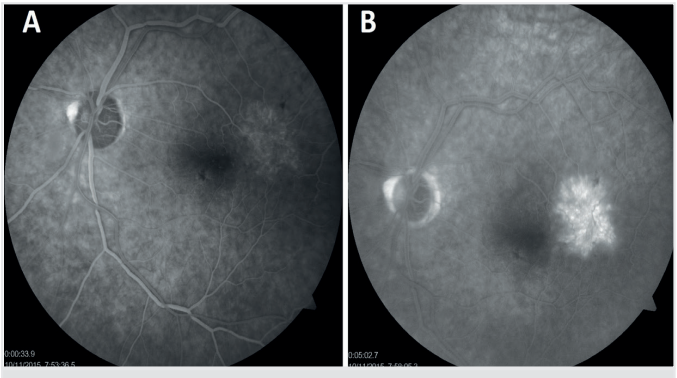


**Figure 3.** Fundus fluorescein angiography images of the patient's left eye in the early (A) and late (B) phases

## Discussion

The pathophysiology of IPT is not fully understood. In the early studies, it was thought that retinal capillaries were primarily responsible for the disease, and in the subsequent studies, it was suggested that chronic liquid leakage could lead to metabolic deterioration and cell death, especially in Muller cells and photoreceptors (6). It was also suggested that chronic retinal ischemia may play role in Muller cell destruction (6). Muller cells have an astrocyte-like function; supporting nerve cells in the retina capillary endothelium and surrounding nerve cells, and extend from the photoresporter cell layer to the inner limiting membrane. Destruction of Muller cells in IPT is known to lead to the development of macular hole or pseudohole. There are many studies in the literature showing development of full-thickness or partial-thickness retinal tissue defects as well as macular holes or pseudoholes in patients with IPT (3). It was reported that in some of those patients, ERM accompanied macular hole or pseudohole. Diffuse retinal thickening was described in primary ERM before and it was described in ERM due to IPT only in one patient. In the article by Gomes et al., (5) a 46-year-old female patient with IPT was reported to have ERM and diffuse retinal thickening in both eyes and it was emphasized that their patient was the first patient with diffuse retinal thickening and ERM due to IPT reported in the literature. In that patient, diffuse thickening of the inner layers of the retina due to ERM in both eyes and large hyporeflective cavitation in the outer layers of the retina which suggested serous macular detachment were observed. In our patient, ERM and diffuse retinal thickening without any retinal tissue defect were observed. However, unlike in the patient reported by Gomes et al., (5) cystic cavities were detected in the inner nuclear layer of the retina in our patient. This is not usual in primary ERM. Probably, leakage from telangiectasic vessels caused cystic formations. It should also be kept in mind that, due to the patient's age, epiretinal membrane might not be secondary. The presence of cystic cavities that are not seen in patients with primary ERM and the presence of ERM, especially in the region of telangiectasic vessels support the relationship between ERM and IPT. But, only one patient reported in this case report is a limitation. Similar case series or studies with larger number of patients will provide more information.

### Ethics

**Informed Consent:** Written and oral informed consents were taken from the patient. Written consent could not be attached because it was lost.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: H.Ö., İ.H., Concept: A.E., H.Ö., Design: H.Ö., A.E., Data Collection or Processing: İ.H., C.E., Analysis or Interpretation: İ.H., C.E., H.Ö., Literature Search: İ.H., C.E., Writing: İ.H., C.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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