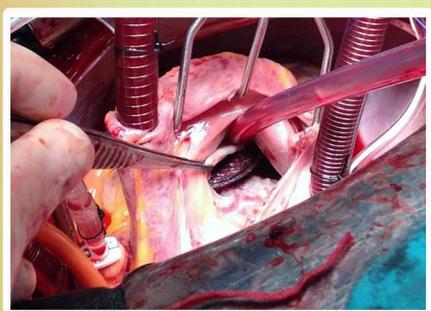




# The European Research Journal



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## Tissue eosinophilia: a histopathological marker associated with stromal invasion but not histopathological grade in cutaneous squamous neoplasia

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### ABSTRACT

**Objectives.** The literature does not include any comparative study on the eosinophil count in premalignant and malignant cutaneous squamous neoplasias. Our aim was to compare the tissue eosinophilic count in actinic keratosis (AK) and cutaneous squamous cell carcinoma (SCC). **Methods.** The study included 20 AK and 20 invasive SCC patients. Age, gender, and lesion location were retrospectively evaluated as clinical parameters. Histopathological parameters included density of inflammation score, lesion grade, and the lesion-associated eosinophil count per 10 high-power (40×) microscopic fields, all of which were compared between groups. **Results.** In all, 65% of the AK group had lesions with moderate inflammation, whereas 85% of the SCC group had lesions with dense inflammation ( $p=0.001$ ). The mean eosinophil count in the SCC group was significantly higher than that in the AK group, independent of the density of inflammation ( $p=0.000$ ). In addition, lesion grade was not associated with the eosinophil count in either group (AK group:  $p=0.601$ ; SCC group:  $p=0.416$ ). **Conclusions.** Cutaneous SCC lesions had higher eosinophil counts than AK lesions, indicating the role of the eosinophil count as a histopathological marker of stromal invasion.

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**Keywords:** Eosinophilia; actinic keratosis; squamous cell carcinoma; invasion

### Introduction

Tumor-associated tissue eosinophilia was first described in 1896 in cervical carcinoma and is defined as eosinophilic infiltration in a tumor that is not associated with necrosis or ulceration. Its functional role remains unclear [1]. Eosinophilic infiltration has

been reported in carcinomas located in the oral cavity, larynx, pharynx, gastrointestinal tract, lungs, cervix, and external genitalia; however, the literature includes limited data on eosinophilic infiltration in cutaneous squamous cell carcinoma (SCC) [1, 2].

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Currently, it is thought that cutaneous SCC manifests as a spectrum, ranging from precursor actinic keratosis (AK) to SCC in situ (SCCIS), invasive SCC, and metastatic SCC [3]. Very few studies have evaluated the role of eosinophils in such premalignancies as oral leukoplakia, and laryngeal, vulvar, and cervical carcinoma in situ, and it has been suggested that an elevated tissue eosinophilia count is a histopathological marker of stromal invasion; however, to the best of our knowledge no study has compared the eosinophil count in AK and invasive cutaneous SCC [1]. As such, the present study aimed to evaluate the eosinophil count in different grades of AK and SCC, and to elucidate the role of the eosinophil count as a histopathological marker of lesion grade and/or stromal invasion in cutaneous squamous neoplasias.

## Methods

The study included 20 histopathologically proven AK patients and 20 histopathologically proven invasive cutaneous SCC patients that were diagnosed between January 2013 and March 2014. Clinical data were obtained from pathology reports and included age, gender, and lesion location. Lesion locations were grouped as follows: scalp, forehead, periorbital region, malar region, ear, nose, and other regions (neck, trunk, and extremity). Histopathological parameters were determined via hematoxylin and eosin (H&E) stained sections that were microscopically re-examined. Diagnosis, lesion-associated inflammation, and lesion grade were evaluated as histopathological parameters, and the number of eosinophils was enumerated. As lesion-associated inflammation, in SCC; perilesional stromal inflammation and in AK; dermal inflammation underlying the lesion was evaluated.

The density of inflammation was scored, as follows:

- 0: no inflammation;
- 1: mild inflammation; scattered clusters of inflammatory infiltrate involving < 25% of the lesion;
- 2: moderate inflammation; inflammatory infiltrate involving 25%-75% of the lesion;
- 3: dense inflammation; thick clusters or sheets of inflammatory infiltrate involving > 75% of the lesion.

To minimize interobserver variability standard grading systems were used and lesion grading was based on the agreement of 2 of 3 observers. For dysplasia grading of AK lesions a 3-tiered classification scheme proposed by Cockerell et al. was used, and the lesions were subgrouped as AK-I, AK-II, and AK-III [4]. AK-I was defined as cellular atypia of basal and suprabasal keratinocytes confined to the lower 1/3 of the epidermis. AK-II was defined as atypia involving the lower 2/3 of the epidermis, and AK-III represented carcinoma in situ with full thickness atypia involving the epidermis.

Broder's classification was used to grade SCC and lesions were graded on the basis of the degree of differentiation and keratinization [5]. SCCs were graded, as follows:

- Grade I: Well-differentiated lesion; 75%-100% of cells are differentiated.
- Grade II: Moderately differentiated lesion; 50%-75% of cells are differentiated.
- Grade III: Poorly differentiated lesion; 25%-50% of cells are differentiated.
- Grade IV: Anaplastic lesion; 0%-25% of cells are differentiated.

Eosinophils were enumerated under high-power (40×) microscopic fields in regions with lesion-associated inflammation. A high-power field (HPF) with the maximum number of eosinophils was identified first, and then eosinophils in that field and in 9 adjacent contiguous HPFs were enumerated and recorded as eosinophils/10 HPFs-1. Areas of necrosis or ulceration were not included. Only intact nucleated cells with intense red granules in cytoplasm were accepted as eosinophils-eosinophils in lymphovascular spaces were not included. In addition, the eosinophil counts in the AK and SCC groups were compared, and the effect of density of inflammation on differences in the count was determined. Furthermore, the association between lesion grade and the eosinophil count was evaluated in both groups. The study has been carried out in accordance with Declaration of Helsinki and research protocol was approved by Institutional Review Board.

### Statistical Analysis

Statistical analysis was performed using SPSS v.18.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean  $\pm$  SD, and categorical variables as frequency and percentage. The chi-square test was used to determine associations between categorical variables. The normality of the distribution of numeric variables was evaluated using the Kolmogorov-Smirnov test. For normally distributed variables between-group differences were determined using the independent samples t-test, and the Mann-Whitney U test was used for variables not distributed normally. Eosinophil counts were categorized as  $< 10$  eosinophils 10 HPFs<sup>-1</sup> and  $> 10$  eosinophils 10 HPFs<sup>-1</sup>. To compare eosinophil counts

according to lesion grade AK lesions were grouped as AK-I and AK-II + AK-III, and SCC lesions were grouped as SCC-I and SCC-II + SCC-III due to the small number of samples. In addition, the eosinophil counts in AK-II/III lesions and SCC grade I-IV lesions were compared. The association between the eosinophil count and the density of inflammation in each group was evaluated using Spearman's correlation coefficient. Linear regression was performed to identify the effect of the density of inflammation on the difference in the eosinophil count between the AK and SCC groups. The level of statistical significance was set at  $p=0.05$ .

**Table 1.** Comparison of the clinical and histopathological features in the AK and SCC groups.

Feature	AK (n=20)	SCC (n=20)	<i>p</i>
Mean $\pm$ SD age (years)	59.5 $\pm$ 15.3	68.4 $\pm$ 10.5	<b>0.038</b>
Gender (female/male) (%)	10/10 (50/50)	2/18 (10/90)	<b>0.014</b>
<b>Lesion Location (%)</b>			
Malar	4 (20)	5 (25)	
Periorbital	3 (15)	3 (15)	
Ear	3 (15)	4 (20)	
Nose	2 (10)	5 (25)	0.756
Forehead	3 (10)	1 (5)	
Scalp	2 (10)	1 (5)	
The other	3 (15)	1 (5)	
<b>Density of Inflammation (%)</b>			
Mild	0 (0)	1 (5)	
Moderate	13 (65)	2 (10)	<b>0.001</b>
Dense	7 (35)	17 (85)	
Mean $\pm$ SD Eosinophil Count	2 $\pm$ 1.6	45 $\pm$ 26.3	<b>&lt;0.001</b>
<b>Eosinophils 10 HPFs<sup>-1</sup> (%)</b>			
<b>&lt; 10 eosinophils 10 HPFs<sup>-1</sup></b>	20 (100)	0 (0)	<b>&lt;0.001</b>
<b><math>\leq 10</math> eosinophils 10 HPFs<sup>-1</sup></b>	0 (0)	20 (100)	

Bold *p* value denotes significant difference ( $p<0.05$ ).

**Table 2.** Comparison of the eosinophil count, according to group and histological grade.

Group (n)	Mean±SD Eosinophil Count	<i>p</i>
AK (n=20) SCC (n=20)	2±1.6 45±26.3	<0.001
AK-II/III (n=11) SCC (n=20)	2.18±1.8 45±26.3	<0.001
AK-I (n=9) AK-II/III (n=11)	1.78±1.48 2.18±1.8	0.601
SCC-I (n=8) SCC-II/III (n=12)	39±27.5 49.1±25.9	0.416

Bold *p* values denote significant difference ( $p < 0.05$ ).

## Results

The study included 20 AK patients and 20 invasive cutaneous SCC patients. In the AK group the female-male ratio was 10:10, whereas in the SCC group, 18 (90%) of the patients were male ( $p = 0.014$ ). Mean age in the AK group was  $59.5 \pm 15.3$  years, versus  $68.4 \pm 10.5$  years in SCC group ( $p = 0.038$ ).

Lesions in the AK group were located, as follows: malar region (n=4, 20%), periorbital region (n=3, 15%), forehead (n=3, 15%), ear (n=3, 15%), nose (n=2, 10%), scalp (n=2, 10%), and other regions (n=3, 15%). Lesions in the SCC group were located, as follows: malar region (n=5, 25%), nose (n=5, 25%), ear (n=4, 20%), periorbital region (n=3, 15%), forehead (n=1, 5%), scalp (n=1, 5%), and other regions (n=1, 5%). The distribution of lesion location did not differ significantly between the 2 groups ( $p = 0.756$ ).

In 13 (65%) of the AK group lesions exhibited moderate inflammation, whereas in 17 (85%) of the SCC group lesions exhibited dense inflammation ( $p = 0.001$ ). The eosinophil count in all the lesions in the AK group was  $< 10$  eosinophils/10 HPFs-1, versus  $\geq 10$  eosinophils/10 HPFs-1 in the SCC group ( $p < 0.001$ ). Furthermore, the mean eosinophil count/10 HPFs-1 was  $2 \pm 1.6$  in the AK group, versus  $45 \pm 26.3$  in the SCC group, and the difference was significant ( $p < 0.001$ ); when the effect of the density of inflammation was adjusted for, the difference

remained significant ( $p < 0.001$ ). In the AK group the density of inflammation and the eosinophil count were not correlated, whereas in the SCC group there was a moderate positive correlation between the density of inflammation and the eosinophil count (Spearman's correlation coefficient: 0.58;  $p = 0.007$ ). In the AK group histopathological grade of the lesions was, as follows: AK-I in 9 (45%); AK-II in 10 (50%); AK-III/SSCI in 1 (5%) lesions. In the SCC group histopathological grade of the lesions was, as follows: well differentiated/grade I in 8 (40%); moderately differentiated/grade II in 11 (55%); poorly differentiated/grade III in 1 (5%) lesions.

The mean eosinophil count/10 HPFs-1 in AK-I, II and III lesions was  $1.78 \pm 1.48$ ,  $1.8 \pm 1.4$ , and 6, respectively. The mean eosinophil count/10 HPFs-1 in AK-I and AK-II/AK-III lesions did not differ significantly ( $1.78 \pm 1.48$  vs.  $2.18 \pm 1.8$ ,  $p = 0.601$ ). The mean eosinophil count/10 HPFs-1 in SCC-I, II and III lesions was  $39 \pm 27.5$ ,  $42.8 \pm 14.8$ , and 118, respectively. The mean eosinophil count/10 HPFs-1 in SCC-I and SCC-II/III lesions did not differ significantly ( $39 \pm 27.5$  vs.  $49.1 \pm 25.9$ ,  $p = 0.416$ ). Additionally, the mean eosinophil count/10 HPFs-1 in AK-II/AK-III and SCC lesions differed significantly ( $2.18 \pm 1.8$  vs.  $45 \pm 26.3$ ,  $p < 0.001$ ).

A detailed comparison between the AK and SCC groups is shown in Table 1, and a comparison of the eosinophil count between the various lesion grades and the 2 groups is shown in Table 2.

## Discussion

The literature includes limited data on eosinophilic infiltration in cutaneous SCC. In 1984, Lowe *et al.* published a study on tissue eosinophilia in keratoacanthoma (benign category), and early and late stage cutaneous SCC [6]. They suggested that lesions are more likely to be malignant when there is tissue eosinophilia, and recommended that eosinophilic infiltration be added to the criteria for differentiating the 2 types of lesions.

The role of eosinophils in premalignancies has been examined in a few studies; however, none included cutaneous pre-invasive neoplasias. In 2002 Spiegel *et al.* reported that eosinophils may be used as a marker of invasion in cervical squamous neoplasias and recommended that  $\geq 5$  eosinophils HPF-1 and/or  $\geq 10$  eosinophils 10 HPFs-1 in biopsy specimens should prompt a search for focal invasion in patients with high-grade intraepithelial neoplasia [7]. Agarwal *et al.* [8] reported findings similar to those of Spiegel *et al.* and suggested that the presence of stromal eosinophils should result in a search for invasion in deeper sections in lesions of cervical intraepithelial neoplasia II and III Alrawi *et al.* [2] reported higher eosinophilic counts in laryngeal SCC lesions than in SCCIS, concluding that tissue eosinophilia might be a pathological feature associated with stromal invasion. Similarly, Said *et al.* [9] reported that an elevated eosinophil count in squamous neoplasia of the larynx is associated with stromal invasion, and recommended a thorough search for invasion when the number of infiltrating eosinophils is  $> 10$  eosinophils HPF-1 and/or 20 eosinophils 10 HPFs-1. More recently, Jain *et al.* [1] observed higher eosinophil counts in oral SCC than those in oral dysplasia, suggesting they play a role in stromal invasion. In addition, they recommended that determination of the eosinophil count should be included in the routine histopathological evaluation of oral precancer and SCC.

As previously reported, in the present study the eosinophil count was higher in patients with invasive cutaneous SCC than in those with AK. Furthermore, the difference in the eosinophil count remained significant when it was compared between the SCC group and AKII/III lesions. In all the patients in the AK group-including 1 with SCCIS-the eosinophil count in all the lesions was  $< 10$  eosinophils 10 HPFs-1, whereas in the SCC group the eosinophil count was  $> 10$  eosinophils 10 HPFs-1 in all the lesions. As such, we recommend-as did Spiegel *et al.*-that an eosinophil count  $> 10$  eosinophils 10 HPFs-1 should prompt a search for invasion, especially in patients in which differentiating between pre-invasive neoplasia and invasive SCC is difficult [7].

In the present study, an evaluation of the relationship between the eosinophil count and AK lesion grade showed that they weren't strongly correlated. To the best of our knowledge, there is only one study that examined the relationship between dysplasia grade and the eosinophil count in patients with premalignancies [1]. In the present study there were not any significant differences in the eosinophil count according to dysplasia grade confirming that study.

The present study also evaluated the relationship between SCC grade and the eosinophil count, but the eosinophil count did not differ significantly according to SCC grade. The relation between SCC grade and the eosinophil count remains contentious; in some earlier studies an elevated eosinophil count was associated with non-keratinizing carcinomas [10, 11], whereas in others there wasn't a significant difference between keratinizing and non-keratinizing carcinomas [7]. In a more recent study Joshi *et al.* [12] reported that there was not a correlation between different grades of oral SCC and eosinophilic infiltration, which is in agreement with the present findings.

Eosinophil counts might have been higher in the present study's SCC group because the density of inflammation was higher; most of the AK lesions had moderate inflammation, whereas inflammation was dense in most of the SCC lesions. In the AK group there wasn't a correlation between the density of inflammation and the eosinophil count, whereas in the SCC group there was a moderate positive correlation; however, when the effect of the density

of inflammation on the eosinophil count was adjusted for via regression analysis the difference in the eosinophil count between the AK and SCC groups remained significant. In most of the earlier published studies the effect of the density of inflammation on the eosinophil count was not analyzed. Joshi *et al.* [12] suggested that there isn't an association between overall inflammatory response and the eosinophil count in their study on oral SCC, as all their patients had dense inflammation; however, they did not score the density of inflammation as in the present study, making a comparison of the findings difficult.

The mechanisms underlying eosinophilic accumulation in invasive SCC are not fully known [9]. It was suggested that lesion-derived eosinophil chemotactic factors induce eosinophilic infiltration.

Furthermore, lesion-associated eosinophils release eotaxin, which induces further eosinophil chemotaxis to the lesion. Similarly, mast cells in lesional infiltration release histamine and eosinophil chemoattractant factor, causing further eosinophil accumulation [1].

The functional role of eosinophils in stromal invasion is not known. Eosinophils produce several angiogenic factors and may promote lesion angiogenesis [1, 13]. Furthermore, they can break down basement membrane and extracellular matrix via the release of several matrix metalloproteinases and their inhibitors [1]. The exact mechanisms by which eosinophils induce stromal invasion need to be elucidated via additional research.

The limitations of the present study are its retrospective design and the small number patients included.

In conclusion, the eosinophil count was higher in the patients with invasive cutaneous SCC than in those with AK. Additionally, lesion histological grade and the eosinophil count in the AK group and SCC group were not correlated. The present findings show that an elevated eosinophil count (especially  $\geq 10$  eosinophils 10 HPF-1) might be indicative of stromal invasion in cutaneous squamous neoplasias. As such, we think that quantitative evaluation of eosinophils should be included in routine histopathological examination of such lesions, and that additional sections should be obtained and examined thoroughly for focal invasion in pre-invasive cases with high eosinophilic infiltration.

### Conflict of interest

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

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## Training to prevent healthcare associated infections

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### ABSTRACT

**Objectives.** Aim of this study was to investigate pre-education information level, efficiency of training, persistence of acquired information, and factors affecting information level of recently employed nurses about healthcare associated infections. **Methods.** One hundred and thirty-two nurses who have just started work were trained about “healthcare associated infections and infection control measures”. Tests were performed pre, post training and one year after training. Factors affecting test success were investigated. **Results.** Nurses who continued education after high school were more successful ( $p=0.002$ ). Duration of work-hours, unit where they work and presence of previous training didn't affect test success ( $p=0.705$ ,  $p=0.040$ ,  $p=0.105$ ; respectively). Test results were assessed over 100 points. Mean score before the training was  $67.95\pm 10.5$  and it increased to  $85.06\pm 7.6$  after the training ( $p=0.000$ ). Mean test score at test repeated one year later was  $80.04\pm 8.77$ . Unit where they have worked during previous year, application of isolation in their unit and presence of training didn't affect general success in the test ( $p=0.344$ ,  $p=0.316$ ,  $p=0.259$ ; respectively). **Conclusions.** Training programs using individualized, regularly repeated and approved training methods should be conducted in accordance with needs determined by these studies. Next target after knowledge increase will be reflection of this increase to daily practice and behaviour change.

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**Keywords:** Healthcare associated infections; education; nurse

### Introduction

Hospital infections which are commonly referred to as "Healthcare associated infections (HCAI)" recently are the most frequent complications in hospitalized patients [1]. HCAI is an important indicator of the quality in healthcare services and patient safety [2].

HCAI which increases length of hospitalisation, cost, morbidity and mortality is still observed amid improved healthcare [3-6]. At least one infection occurs in 5 to 10% of hospitalized patients [1-7]. Some of HCAs occur due to transmission of pathogens by healthcare staff [3]. At least 20% of

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HCAIs may be prevented by complying with infection control measures during daily activities in hospitals [8]. Therefore appropriate infection control measures should be applied to decrease HCAIs [3-9].

Training of healthcare staff about infection control measures are among basic preventions that should be used to decrease HCAI [10-12]. Lack of information about HCAI and infection control measures negatively affect the compliance with infection control measures [3, 4, 9, 13]. Inadequate placement of appropriate measures results in increased incidence of hospital infections [3]. Well-informed and skilled staff is required. To achieve this training is important. Training will also increase motivation of the employees and help them to work more efficiently [4]. Application of regular training programs and preparation of guidelines decrease HCAI incidence and healthcare costs [6, 10, 15-20].

Aim of this study was to investigate pre-education information level, efficiency of training, persistence of acquired information and factors affecting information level of recently employed nurses about HCAI.

## Methods

In 2010 a training program was organized to 132 recently employed nurses about "HCAI and Infection Control Measures" under the scope of orientation to hospital. A questionnaire including demographic data, education level of participants, unit where they work and duration of workhours and whether they were trained about nosocomial infections was applied to participants (Appendix 1). A preliminary test including 30 questions about definition and prevention of HCAI, hand hygiene, use of gloves, blood borne diseases, hospital cleaning, disinfection and waste management was performed (Appendix 2). Knowledge level of participants about HCAI was evaluated. Efficiency of the training was also evaluated by performing a final test with same questionnaire applied after the training. One year after, same questionnaire was applied to 91 nurses who continued to work in our hospital and unit in which they have worked during

previous year, whether patient isolation was applied in their unit and whether they were trained about HCAI were noted (Appendix 3). By applying same questionnaire after a year, persistence of acquired information was investigated. Test success was assessed over 100 points.

Effects of education level, unit where participants have worked, length of their workhours and training of participants about nosocomial infections to success from the first test were determined. One year later, effect of education level, the unit where participants have worked during this period, whether patient isolation is applied in the unit of the participants, and whether they were trained during this period to the success of the test were investigated.

### *Statistical analysis*

Data was computerized and preanalysis controls and groupings were performed. Wilcoxon Signed Ranks Test was used for repetitive measurements. Comparison of samples involving more than two groups was performed with Kruskal-Wallis analysis of variance. Significant parameters were also compared using Mann Whitney U test with Bonferroni correction. Comparison of two groups was performed with Mann Whitney U test. Significance level was accepted as  $p < 0.05$

## Results

Totally 132 nurses including 37 males and 95 females with a mean age of 27.12 (19-42 years) were involved in training program. Among nurses who participated in training, 47 (35.6%) of them were high-school graduates, 85 (64.4%) of them had associate's graduate, bachelor or master's degree. Sixty-six (50%) nurses were working in patient follow-up clinics, 27 (29.5%) were working in ICU and 39 (20.5%) were working in other units. Professional experience of 132 nurses who participated in this study was as follows; 70 (53.0%) 1 to 5 years, 40 (30.3%) less than 1 year and 22 (16.7%) more than 5 years. Sixty-three (47.7%) nurses reported that they were previously trained about nosocomial infections.

**Table 1.** Test results before the training

	Score	General information	Hand hygiene	Gloves	Blood borne infection	Isolation measures	Invasive device	Cleaning	Waste management
<b>General average</b>	67.95	90.15	66.67	68.94	70.15	79.36	62.88	58.48	83.84
<b>Education</b>									
<b>High school (n=47)</b>	63.69	82.98	61.70	61.70	67.23	76.06	57.45	56.60	79.43
<b>Other*(n=85)</b>	70.31	94.12	69.41	72.94	71.76	81.18	65.88	59.53	86.27
<b>p value</b>	0.002	0.000	0.059	0.081	0.287	0.353	0.036	0.255	0.214
<b>Experience</b>									
<b>Clinic (n=66)</b>	67.68	91.41	65.53	66.67	71.82	79.17	62.12	57.88	82.32
<b>ICU (n=27)</b>	69.74	88.03	71.15	76.92	66.15	83.97	70.51	57.95	85.47
<b>Other (n=39)</b>	66.05	90.12	62.96	62.96	71.85	75.00	53.70	60.74	85.19
<b>p value</b>	0.401	0.702	0.302	0.089	0.635	0.277	0.005	0.532	0.756
<b>Period</b>									
<b>&lt; 1 year (n=40)</b>	67.67	92.50	61.87	76.25	68.50	80.63	60.63	59.50	82.50
<b>1-5 years (n=70)</b>	68.48	88.10	70.71	68.57	71.43	79.29	63.57	57.71	84.29
<b>&gt;5 years (n=22)</b>	66.82	92.42	62.50	56.82	69.09	77.27	64.77	59.09	84.85
<b>p value</b>	0.705	0.455	0.059	0.092	0.802	0.910	0.669	0.861	0.660
<b>Previous Training</b>									
<b>Yes (n=63)</b>	69.10	91.53	71.03	73.02	72.70	78.97	64.29	55.87	84.13
<b>No (n=69)</b>	66.91	88.89	62.68	65.22	67.83	79.71	61.59	60.87	83.57
<b>p value</b>	0.105	0.168	0.208	0.312	0.227	0.191	0.210	0.170	0.207

\* Associate's graduate, bachelor or master's degree

Mean score in pre-training test was  $67.95 \pm 10.5$ . Effects of previous training and education level, the unit where participants work, length of their workhours and whether they were previously trained about nosocomial infections to the test success were summarized in Table 1. Mean score in post-training test increased to  $85.06 \pm 7.6$ .

Same test was applied for the third time to 91 nurses who continued to work in our hospital (132 nurses answered first test). Mean score from this test was  $80.04 \pm 8.77$ . Among nurses who were tested for third time, 34 (37.4%) were high-school graduates, 57 (62.6%) had associate's graduate, bachelor or master's degree. During previous year 51 (56.0%) nurses worked in in-patient clinics, 26 (28.6%) worked

in ICU and 14 (15.4%) worked in other units; patient isolation was applied in units of 63 (69.2%) nurses and 64 (70.3%) were trained about nosocomial infections during surveillance efforts. Contact isolation was applied to all isolated patients and additionally 3 of them were subject to droplet isolation.

Effects of patient isolation, HCAI training and education level to success from the third test were summarized in Table 2.

Mean scores in 3 tests are shown in Figure 1. Comparison of pre-training test result with post training test result and 1st year test result with pre and post training test results are summarized in Table 3.

**Table 2.** Results of the third test

	Score	General information	Hand hygiene	Gloves	Blood borne infection	Isolation measures	Invasive device	Cleaning	Waste management
<b>General average</b>	80.04	94.51	77.75	76.37	79.56	84.89	75.27	64.84	97.07
<b>Education</b>									
<b>High school (n=34)</b>	75.78	89.22	69.12	70.59	77.65	79.41	74.26	58.24	98.04
<b>Other* (n=57)</b>	82.57	97.66	82.89	79.82	80.70	88.16	75.88	68.77	96.49
<b>p value</b>	0.001	0.002	0.010	0.152	0.598	0.026	0.885	0.003	0.210
<b>Experience</b>									
<b>Clinic (n=51)</b>	78.63	92.81	78.43	77.45	78.04	82.35	72.06	63.53	95.42
<b>ICU (n=26)</b>	82.31	96.15	74.04	86.54	82.31	88.46	81.73	63.85	100.00
<b>Other (n=14)</b>	80.95	97.62	82.14	53.57	80.00	87.50	75.00	71.43	97.62
<b>p value</b>	0.344	0.320	0.526	0.001	0.642	0.356	0.202	0.267	0.188
<b>Isolated patient (follow-up)</b>									
<b>Yes (n=63)</b>	68.73	93.65	77.38	81.75	80.32	85.32	76.19	63.49	96.83
<b>No (n=28)</b>	70.12	89.29	78.57	64.29	77.86	83.93	73.21	67.86	97.62
<b>p value</b>	0.316	0.325	0.809	0.003	0.731	0.448	0.685	0.297	0.882
<b>Training</b>									
<b>Yes (n=64)</b>	81.09	94.79	77.73	79.69	80.94	87.50	76.17	65.00	97.92
<b>No (n=27)</b>	77.53	93.83	77.78	68.52	76.30	78.70	73.15	64.44	95.06
<b>p value</b>	0.259	0.735	0.803	0.110	0.423	0.022	0.741	0.869	0.408

\* Associate's graduate, bachelor or master's degree

**Table 3.** Statistical comparison of the tests performed before, after and 1 year after the training.

	Score	General information	Hand hygiene	Gloves	Blood borne infection	Isolation measures	Invasive device	Cleaning	Waste management
<b>1.-2. test p value</b>	0.000	0.067	0.000	0.000	0.000	0.038	0.000	0.000	0.000
<b>1.-3. test p value</b>	0.000	0.157	0.002	0.035	0.002	0.115	0.000	0.063	0.000
<b>2.-3. test p value</b>	0.000	0.670	0.004	0.003	0.000	0.730	0.000	0.080	0.796

## Discussion

Infection control trainings are difficult and time consuming. Therefore every opportunity should be used to get the highest efficiency from trainings. Training programs should be individualized according to the group of healthcare staff [12]. Participation of all healthcare staff and hospital companions in infection control measures should be provided [2, 9, 21]. Nurses who have the closest contact with the patient play an important role in application of infection control measures. Therefore it is important to increase knowledge level of nurses about HCAs and improve their attitudes and behaviours. This will be possible with in-house trainings [9-11, 22, 23]. Most of the nurses reported in questionnaires that they want to improve their knowledge level and trainings have increased their interest to work [14, 22]. Nurses request that training programs should be organized to complete their knowledge deficiencies, should include professional developments, and training topics should be determined taking into account opinions of participants [14]. We organized our training program, chose topics and test questions considering knowledge and practice deficiencies

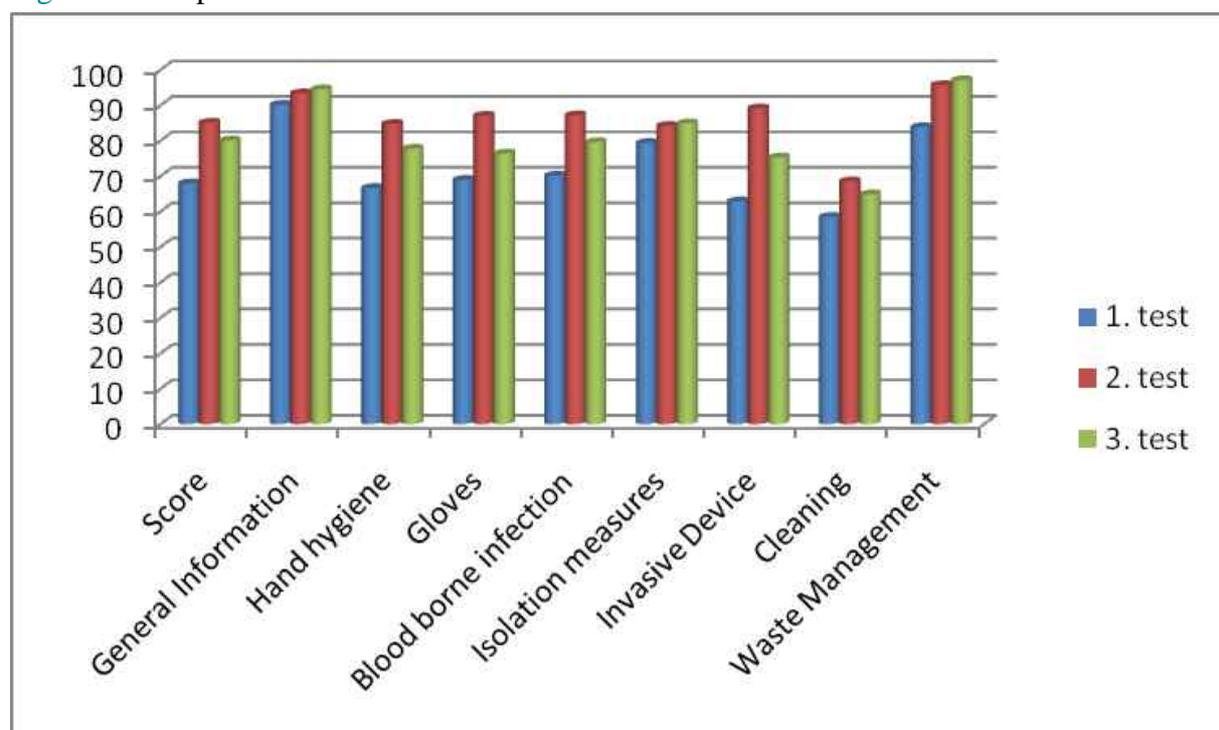
detected during surveillance studies. Our purpose was to convey information about determined topics in the light of up to date and scientific data.

It is difficult to determine the most efficient training model to prevent HCAs [10]. Video images, oral presentations, brochures, infection control bulletins, user guides and electronic media are among tools that may be used during training studies [2, 9, 13, 24]. Our training program involved seminars in which visual materials were also used.

Mean age of the nurses participated in our training program was 27.12 (19-42 years) and professional experience of 83.3% (n=110) were less than 5 years.

We can say that we had a young nurse group. Some studies investigating relation between professional experience and knowledge, attitude, and behavioural compliance of nurses detected a positive correlation [2, 3, 9]. Yamazhan *et al.* [21] in their studies where they have measured knowledge levels of cleaning personnel, has not detected any correlation between professional experience and knowledge level. In our study there wasn't a significant difference between professional experience and success in pre-post training tests and 1st year test. No statistically

Figure 1. Comparison of test scores



significant difference was observed between professional experience and success from the test ( $p=0.401$ ). Our nurses were recently employed and they had achieved professional experience in different organizations and working conditions. Therefore they didn't have same knowledge background. In previous studies a significant relation between education level of the nurses and their knowledge level about infection control measures was observed [2-22]. From our nurses who participated in the training 47 (35.6%) were high school graduates, 85 (64.4%) had associate degree, bachelor degree or master degree after the high school. Among nurses who were tested third time, 34 (37.4%) were high-school graduates, 57 (62.6%) had associate's graduate, bachelor or master's degree. Nurses who continued education after high school were more successful on all 3 tests performed before the training, after the training and at 1st year ( $p=0.002$ ,  $p=0.001$ ,  $p=0.001$ ; respectively).

In studies using questionnaires, nurses who were trained about HCAs were better in awareness of nosocomial infections and compliance with nosocomial infection control measures [2, 4, 9, 25]. In Indonesia, McDermott *et al.* [26] investigated effect of previous training of midwives in their practices related with delivery. Success of midwives were 71% in those who have taken in-service training, 62% in those who have taken an internship program and 51% in those who were not trained at all. Studies suggest giving occupational information to the employees through intensive training programs [2, 4, 9, 25]. However, Yamazhan *et al.* [21] found no effect of previous training on knowledge level of cleaning personnel. They suggested that inadequacy or discontinuity of training might be the cause. Sixty three (47.7%) nurses who participated in our training reported that they were previously trained about nosocomial infections. Although test success of the group previously trained was higher, this difference was not statistically significant ( $p=0.105$ ) (Table 4). Our nurses came to our hospital after working in different institutions. We didn't have sufficient information about content and form of their previous trainings other than their personal accounts. Parameters we have measured might not include topics they have trained before.

In literature, target group in most training studies

performed to prevent HCAs were intensive care unit staff [6, 10, 14-16, 25]. However considerable part of HCAs appear in general hospital units and units where long term care is provided. There are only a few studies which determine effect of trainings to the employees who work in these units [10]. We planned to train nurses working in all units. Among nurses who participated in training, 66 (50%) were working in in-patient clinics, 27 (29.5%) were working in ICU and 39 (20.5%) were working in other units. No statistically significant difference was observed on general success from the test between ICU staff, in-patient clinic staff and other units' staff ( $p=0.401$ ). Nurses having ICU experience were more successful on questions about invasive devices and waste management than nurses who do not have ICU experience in the first test ( $p=0.005$ ). Nurses with ICU experience were more successful in questions related with waste management in the second test than those who work in other units. Although general success was similar, observing a difference in more specific practices show that working areas affect knowledge level.

In Taiwan, Lin *et al.* [2] trained patient companions and non-relative caregivers about HCAI. Awareness of participants about infection control measures showed a statistically significant increase after training. Suchitra *et al.* [3] Detected a significant difference in correct answer rates in questionnaires applied before and after the training. Aytac *et al.* [25] detected mean 13.45 correct answers in their 20 item questionnaire. They recommended continued training efforts on topics which participants were lacking information. Results of the test which included 30 questions applied before and after our training program were assessed over 100 points. Mean score before the training was  $67.95 \pm 10.5$ , and after the training was  $85.06 \pm 7.6$ . There was a statistically significant difference between two test results ( $p=0.000$ ). Although these results suggest that our training program has been efficient, as the target score of 100 has not been achieved, this warrants continuing training programs.

Training program, when applied once, causes short-term changes in knowledge level healthcare staff. Persistence of knowledge can't be achieved by such a program. Similarly, effect of written training

applied once is not clear [13]. To improve the quality of practice long term, regularly repeated, well defined, multi-dimensional training programs should be applied [13, 21, 23]. Angelillo *et al.* [27] investigated knowledge, attitudes and behaviours of nurses working in operating theater about sterilization and disinfection. They suggested that participation to continuous trainings about nosocomial infections improves compliance with infection control measures and barrier methods. Suchitra *et al.* [3] applied questionnaires in two consecutive years and they noted a decrease in success in second test. They also reported that annual training programs would increase knowledge about nosocomial infections and their prevention and help to improve compliance on attitudes and behaviours for nosocomial infection prevention. To determine permanence of information we repeated questionnaire which we had applied previous year and mean score was  $80.04 \pm 8.77$ . Although this score was lower than the score after the training ( $80.04 \pm 8.77$  vs  $85.06 \pm 7.680$ ,  $p=0.000$ ), it was still higher than score in questionnaire performed before the training ( $80.04 \pm 8.77$  vs  $67.95 \pm 10.5$ ,  $p=0.000$ ). Investigation of subscales showed that success from the test on hand hygiene, use of gloves, blood borne diseases and invasive tool related infections has decreased significantly ( $p=0.004$ ,  $p=0.003$ ,  $p=0.000$ ,  $p=0.000$ ; respectively). Score on hospital cleaning has also decreased (from 68.55 to 64.84), but this was not statistically significant ( $p=0.080$ ). Scores on isolation measures remained same. Scores on definition and prevention of HCAI and waste management have increased, however this increase was not statistically significant ( $p=0.796$ ).

Factors, affecting the success of the test performed one year later were determined. From 91 nurses who continued to work in our hospital 26 (28.6%) have worked in ICU, 63 (69.2%) stated that patient isolation measures (contact isolation in all and contact and droplet isolation in 3 of them) were applied in their units and 64 (70.3%) were shortly trained for nosocomial infections during surveillance studies and got long term education about medical waste separation. Unit where participants have worked for previous year, application of isolation measures and training didn't affect general success from the test

( $p=0.344$ ,  $p=0.316$ ,  $p=0.259$ ; respectively). However success levels differed regarding subtopics. Nurses who work in ICU and in clinics where patient follow-up is performed were more successful on questions related with use of gloves; those who were trained were more successful on questions related with isolation methods ( $p=0.001$ ). We conclude that regular training programs should be performed hospital-wide on all topics to increase permanency of information.

Nurses lacking knowledge about preventing HCAI's are known to comply with control measures less [2, 4, 9, 25]. However it is also observed that improved knowledge level achieved via trainings is not always reflected to clinical practice [3, 13]. Tvedt *et al.* [13] applied a training program to healthcare staff involving monthly infection control bulletins and slide shows. Although 92.9% of the nurses who followed the bulletins stated that their knowledge is updated only 72.1% noted changes their behaviours. Therefore next step of training programs should be to encourage behavioural improvement.

## Conclusion

Knowledge level of healthcare staff about HCAI and infection control measures should be detected. Training programs including individualized, regularly repeated, approved training methods should be applied through needs which are determined taking into account service areas of healthcare staff. Next target should be to encourage reflection of such improved knowledge levels to behaviours and to establish behaviour change. More studies are required to develop the most efficient model for healthcare staff training, to provide change in practices and to search effects of these improvements on nosocomial infection rate.

### Conflict of interest

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

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## Questionnaire form

### Appendix 1. Demographic data of the nurses who has participated into the training

---

1. Name, Surname:

2. Age- Gender:

3. Education Level:

High School       Undergraduate       Graduate       Master

3. Describe your professional experience:

The institution and the department that you have worked:

Working period:

- 1. ....
- 2. ....
- 3. ....

4. Have you taken any education about nosocomial infections in institutions where you have worked before?

Yes       No

5. In which department do you work now? .....

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## Appendix 2. Preliminary tests

### QUESTIONS

1. Which of the following definitions is correct about nosocomial infections?
  - a) Nosocomial infections only cause death in newborns and elders.
  - b) Nosocomial infections appear within the first 48 hours after the birth.
  - c) Hand washing does not prevent nosocomial infections.
  - d) Nosocomial infections are infections which develops after patients apply to the hospital, are not in the incubation period at the time of application and appears after 48-72 hours after the hospitalization.
  - e) The patient meets the microorganism before the hospitalization and infection symptoms and findings appear at the hospital.
2. Which of the following definitions is correct for nosocomial infections?
  - a) Nosocomial infections are a medical defect which is possible to prevent.
  - b) They are infections which appear within the first 48-72 hours after hospitalization.
  - c) Nosocomial infections may appear after discharge.
  - d) Healthcare staff and contaminated tools cause nosocomial infections.
  - e) Nosocomial infections only cause epidemics.
3. Which of the following is not among applications to prevent nosocomial infections?
  - a) To comply with instructions determined by Infection Control Team.
  - b) To prevent epidemics by discharging infected patients.
  - c) To comply with hand hygiene.
    - d) To use right antibiotic medication.
    - e) To use clean tools and materials.
4. Which of the following application related with alcohol based hand disinfectant is wrong?
  - a) We should rub our hands to provide them wet with a hand disinfectant for 30 seconds.
  - b) We should immediately use a hand disinfectant when blood is contacted to our hand.
  - c) Gloves should be worn after using hand disinfectant.
  - d) We should absolutely wait our hand to dry after using the hand disinfectant.
  - e) Hand disinfectant removes microorganisms rapidly and efficiently.
5. Which of the following is wrong about gloves usage?
  - a) We should take off the gloves after contacting to the patient.
  - b) We should use hand antiseptics before and after wearing gloves.
  - c) We should change the gloves when providing care between patients.
  - d) To use hand antiseptic over gloves decreases transmission rate of microorganisms.
  - e) The gloves should be changed for different interventions on the same patient.
6. Which of the following applications a non-sterile clean gloves may be worn?
  - a) In urinary catheter interventions
  - b) Before surgical procedures
  - c) In peripheral venous catheter applications
  - d) In aspiration of respiratory secretions
  - e) During central venous catheter placement
7. Which of the following diseases is not transmitted via blood?
  - a) Hepatitis D
  - b) Hepatitis C
  - c) Hepatitis B
  - d) Hepatitis A
  - e) HIV
8. Which if the following statement is wrong related with blood borne infections?
  - a) We should accept all patients' bloods infected.
  - b) There is a vaccine for Hepatitis B.
  - c) We should not hang diagnosis of the patients who were infected with Hepatitis B, C and HIV on their bed heads.
  - d) Blood of a patient who is anti HCV positive may be used in blood transfusion.
  - e) Hepatitis B virus may stay alive on inorganic surfaces.
9. Which of the following is not one of the preventions that we will take in hazardous injuries?
  - a) The injury area should be washed with water and soap.
  - b) If mucosa contact is present, it should be washed with water.
  - c) The injury area should be pressed and made bleed, thus the infected blood should be discharged.
  - d) The injury area may be swabbed by antiseptic solutions.
  - e) If the source is not known, it should be screened for Hepatitis markers.
10. Which of the following is wrong?
  - a) We should throw needle tips to sharp object box without covering.
  - b) We should apply contact isolation to patients who were infected with MRSA and VRE or were colonized.
  - c) Different isolation preventions are applied to a patient with HIV and a patient with tuberculosis.
  - d) We should separate patients infected with Hepatitis virus B and Hepatitis virus C from other patients.
  - e) We should use gloves, mask and apron when providing care to isolated patients.
11. Which of the following is not one of standard methods used to prevent nosocomial infections?
  - a) Disposable materials should be immediately thrown after using.
  - b) Gloves should be worn before touching objects contaminated with blood, body fluids, secretions and excreta and disintegrated skin.
  - c) Patient thermometers should be disinfected via alcohol after every use.
  - d) If there is not a visual contamination on gloves used, it is not necessary to change them.
  - e) Non-sterile clean apron is worn during procedures which have possibility to splash body fluids, secretions, excreta and blood.
12. Which of the following is not one of the preventions that we will take in a patient whom contact isolation is applied?
  - a) The patients should be taken into a single room, if possible.
  - b) We should wear gloves before contacting the patient and surfaces in her/his room.
  - c) In cases that more contact with the patient or surfaces in her/his room is expected, the patient has urinary or fecal incontinence, ileostomy, colostomy or open drainage, a non-sterile clean apron should be worn addition to the gloves when entering into the room.
  - d) We should take off gloves and the apron and provide hand hygiene before leaving the room.
  - e) Object and medical material transfer may be done between rooms or patients.

## Appendix 2. Preliminary tests (continued.)

13. Which of the following is not one of the preventions that we will take in a patient whom airway isolation is applied?
  - a) Special ventilation conditions are not necessary.
  - b) The door of the room should be kept closed.
  - c) If the patient is required to get out of the room, surgical mask should be worn.
  - d) N95 respiratory mask should be placed on patients with tuberculosis.
  - e) Pregnant women should not enter into the patient room.
14. Which of the following is wrong?
  - a) Sterile material should be used in urinary catheter applications.
  - b) Hand hygiene should be provided before every contact with the urinary catheter.
  - c) Regular catheter change should be applied to prevent urinary system infections.
  - d) The urinary catheter should be fixed on the leg for patients on lying position.
  - e) Urinary catheter bags should be held under bladder level and hang on the bed without contacting the ground.
15. Which of the following statements is wrong about bleach using?
  - a) The bleach should be prepared in appropriate concentrations according to the purpose.
  - b) Bleach is a highly efficient disinfectant.
  - c) The bleach prepared should be poured on the surface contaminated with blood and body fluids.
  - d) 1/10 bleach is used when blood and body fluid contamination is present.
  - e) After disinfection procedure with the bleach, it is flushed.
16. Which of the following is wrong?
  - a) Service corridors are areas with low risk, therefore cleaning with water and detergents is sufficient.
  - b) The cleaning solution which was prepared for areas cleaned with water and detergent is not required to be changed until the cleaning is terminated.
  - c) Unless contamination with blood and body fluids occurs, the cleaning should be performed with water and detergent.
  - d) No liquid soap should be added on fluid soap dispensers including detergent.
  - e) The cleaning always should be performed from the clean area to the contaminated area.
17. Which of the following statements related with medical waste separation is wrong?
  - a) Red litter bags should be used for medical wastes.
  - b) Blue litter bags should be used for recyclable wastes.
  - c) Black litter bags should be used for domestic wastes.
  - d) Broken vials should be thrown into the blue litter bag.
  - e) If a medical waste is seen in a blue or black litter bag, this bag should be put into a red litter bag and removed as a medical waste.
18. Which of the following is wrong?
  - a) Used intravenous fluid sets should be thrown into the red litter bag.
  - b) Medical waste collecting personnel should be separate.
  - c) Used serous fluid bottles should be thrown into the blue litter bag if they are not contacted with the patient.
  - d) Infected needle tips used should be thrown into the red waste bag.
  - e) We should not carry medical wastes and domestic wastes together in the same carrier.
19. Which of the following is wrong?
  - a) Humidifier containers should be changed periodically.
  - b) Sterile distilled water should be used in humidifier containers.
  - c) When humidifier containers are not used, they should be kept ready by putting water into them.
  - d) Humidifier containers should be used by disinfecting.
  - e) Humidifier containers should not be used commonly by the patients.
20. Which of the following statements is wrong about preventing intravenous catheter infections?
  - a) The person who placed the catheter should record the catheterization date.
  - b) Sterile gloves are not required when placing the peripheral venous catheter.
  - c) Peripheral venous catheters should be changed daily.
  - d) When temperature increase and erythema develops in catheter entrance area or it is detected that the catheter does not operate properly, peripheral catheter should be changed immediately.
  - e) Catheter entrance areas should be observed every day and dirty covers should be changed.
21. Surfaces such as patient bed, cabinets, dining tables should be cleaned via bleach in clinics without high risk.
  - a- Correct
  - b-False
22. Hand washing does not prevent nosocomial infections.
  - a- Correct
  - b-False
23. Hands should be disinfected by an alcohol based hand disinfectant after washing the hands with water and soap.
  - a- Correct
  - b-False
24. Hand hygiene should be provided before and after every intervention related with urinary and venous catheters.
  - a- Correct
  - b-False
25. Antibiotic pomade should be used during placement or maintenance of urinary and central venous catheters.
  - a- Correct
  - b-False
26. Hepatitis B virus dies instantly on surfaces at room temperature.
  - a- Correct
  - b-False
27. There is not any efficiency proven vaccine and immunoglobulin for hepatitis C.
  - a- Correct
  - b-False
28. Medical waste bags and sharp object boxes should be immediately changed with new ones when 3/4 of them are filled.
  - a- Correct
  - b-False
29. Surfaces where blood and body fluids poured should be disinfected with 10% (1/10) diluted bleach.
  - a- Correct
  - b-False
30. Patient rooms should be cleaned daily, when contaminated and the patient was discharged.
  - a- Correct
  - b-False

**Appendix 3.** The questionnaire applied before the third test

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Name, Surname:

- 1- In which units have you worked for the last 1 year?
  - 2- Have you ever performed isolated patient follow-up in your unit?
  - 3- If it is done, which isolation method was applied?
  - 4- Have you taken any information or training related with infection preventions told after the training program 1 year ago (including notifications done by infection control committee during your work)?  
In which subjects?
-

## Relationship between fibroblast growth factor and arrhythmogenesis in normotensive patients with polycystic kidney disease

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### ABSTRACT

**Objectives.** Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening genetic disease. Recent prospective studies showed a powerful and dose dependent association between increasing FGF-23 levels and greater risk of mortality among chronic kidney disease patients. In this study, our aim is to evaluate electrocardiogram derived arrhythmogenesis markers such as Tp-e, Tp-e/QT and Tp-e/QTc ratio ADPKD. **Methods.** Data of 31 patients with ADPKD and age-sex matched 26 healthy were gained for study. Electrocardiogram and echocardiogram measurements, various serum markers were compared between groups. **Results.** FGF-23 was significantly higher, and eGFR was significantly lower in the ADPKD patients. Myocardial thickness was also higher in ADPKD group. Corrected QT dispersion, Tp-e, Tp-e/QT and Tp-e/QTc were also compared between groups. All indicators were significantly worse in ADPKD group. In the correlation analyzes, FGF-23 was significantly correlated with Tp-e, Tp-e/QT and Tp-e/QTc ( $r=0.388$ ,  $p=0.003$ ;  $r=0.472$ ,  $p<0.0001$ ;  $r=0.442$ ,  $p=0.001$ , respectively). **Conclusions.** In this occasion, we suggest that FGF-23, which probably accumulates ventricular electrical remodeling, may be helpful for risk stratification in patients with ADPKD when used with other indicators. Myocardial cell de-arrangement and electrical remodelling due to fibrosis are suggested mechanisms for this effect.

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**Keywords:** Polycystic kidney disease; fibroblast growth factor; arrhythmogenesis; Tp-e interval; Tp-e/QT ratio

### Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening genetic disease [1]. Cardiovascular disease is the leading cause of morbidity and mortality in patients with

ADPKD, with over 80% of deaths attributable to coronary artery disease [2,3]. Left ventricular hypertrophy (LVH) is common in these patients, even in the absence of hypertension [4,5]. LVH is also

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associated with poor renal outcomes in these patients [6]. Although some studies indicate that increased stimulation of the renin-angiotensin system (RAS) may be responsible from increased LVH in ADPKD, other studies did not support this suggestion [7]. Fibroblast growth factor 23 (FGF-23) is secreted by osteoblasts and osteocytes and increases in response to increase in serum phosphorus and calcitriol levels in patients with chronic renal failure (CRF). Markedly elevated circulating FGF-23 levels are also found in patients with ADPKD when compared with other causes of chronic kidney disease independent of renal function and hormones that regulate phosphate metabolism [8]. It was clearly shown in different stages of CRF that there was a correlation between FGF-23 levels and LVH [9].

For a long time, noninvasive indices of sudden cardiac death derived from surface electrocardiogram (ECG) have been utilized in patients who are at risk of sudden death. These indices mainly depend on the QT interval [10,11] Prolongation of QT interval, dispersion of QT interval; which is calculated by extracting minimum measured QT interval from maximum measured QT interval, were widely utilized in many studies and were shown to be related with increased sudden death risk in HD patients [12-14].

Recent studies indicate that prolongation of the T wave peak to T wave and interval (Tp-e) on the 12-lead ECG is a marker of ventricular arrhythmogenesis [15-17]. Prolongation of this interval represents a period of potential vulnerability to re-entrant ventricular arrhythmias. Prolonged Tp-e has been associated with increased risk of mortality in the congenital and acquired long QT syndromes, hypertrophic cardiomyopathy and also in patients undergoing primary PCI for myocardial infarction [18-20].

In this study, our aim is to evaluate electrocardiogram derived arrhythmogenesis markers such as Tp-e, Tp-e/QT and Tp-e/QTc ratio, QT interval and QT dispersion in normotensive polycystic kidney disease patients and put forward if there is a relationship between ventricular depolarization heterogeneity and serum FGF-23 levels, which plays role in left ventricular hypertrophy.

## Methods

### *Patients*

Data of thirty one patients (male and female) with diagnosis of ADPKD were collected. Data of age-sex matched 26 healthy subjects with similar demographics (13 male and 13 female) were gained for control group. The study was approved by the Institutional Ethics Committee, and written consent was obtained from all patients.

The diagnosis of ADPKD was reached by the ultrasonographic criteria described by Ravine et al [21]. All of the patients had family history of ADPKD. Estimated glomerular filtration rate (eGFR) was determined using the 4-variable Modification of Diet in Renal Disease (MDRD) equation. The most commonly used formula is the "4-variable MDRD," which estimates GFR using four variables: serum creatinine, age, race, and gender [22]. All patients had an eGFR >60 mL/min/1.73 m<sup>2</sup>.

Patients with diabetes mellitus, renal failure (eGFR <60 mL/min/1.73 m<sup>2</sup>), hepatic failure, major cardiac diseases (heart failure, coronary artery disease, arrhythmia, cardiac valvular disease), were excluded from the study. During the baseline examination, fasted weight and height were measured by one examiner using the ambulatory standard measurement devices as the patient was standing.

Body mass index (BMI) was calculated using the formula "weight (kg)/height (m<sup>2</sup>)". Clinical blood pressure measurements were performed using a mercury sphygmomanometer following 10 minutes rest in the sitting position. Three consecutive readings were obtained using 2-minutes interval settings and the mean of these readings were considered as clinical BP. Patients with systolic BP of >140 mmHg and/or diastolic BP of >80 mmHg or who were already receiving treatment for hypertension were considered to be hypertensive and excluded from the study.

### *Blood analyses*

Fasting glucose, creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride levels were measured by routine techniques. The level of PTH was measured by chemiluminescence method

on an IMMULITE 2000® analyzer (Diagnostic Products Corporation, Los Angeles, USA). Plasma FGF-23 concentrations were measured with the human FGF-23(C-Term) ELISA kit (Immutopics Inc., San Clemente, CA, USA) according to the manufacturer's instructions.

#### *Measurement of Tp-e, QT and QRS Intervals from the 12-Lead ECG*

All ECGs were scanned. The Tp-e interval was defined as the interval from the peak of T wave to the end of T wave. Measurements of Tp-e interval were performed from precordial leads as it was described [23]. T wave peak to end interval, QT and RR intervals were measured by an engineer with a computer program. By using a ruler, vernier caliper or any other manual measuring tool; getting measurements off from ECG papers could be either inaccurate or slow. Therefore ECG papers were scanned and this made gathering measurements possible in digital environment. These measurements are done by a program which is generated with MATLAB (MathWorks, Natick, Massachusetts, U.S.A.) codes that written by an engineer. These codes are based on image manipulation principles. Image manipulation method could be divided into three subdivisions image processing, image analysis and image understanding. Image analysis is the technique that should be used to gather measurement data from ECG. Running the written code imports the image file first and then, by choice, allows user to pick points that need to be picked to get measurements or generates a matrix that consists of a dedicated numeric value of each pixel's color. Creating a matrix gives user the flexibility of using functions which predefined by program. In spite of this, hand picking is easier and has a simple interface especially for beginner level users. Algorithms are developed and used to get excellent measurements in order to tolerate differences such as tilting during scanning process, different scanning resolutions and using different ECG.

The QT interval was defined as extending from the beginning of the QRS complex to where T waves descend onto the isoelectric baseline. When a U wave interrupted the T wave before returning to baseline, the QT interval was measured to the nadir of the curve between the T and U waves. The

QTc interval was calculated using the Bazett formula:  $QTc \text{ (ms)} = QT \text{ measured} / RR \text{ (sec)}$ . All measurements (Tp-e and other surface ECG related ones) were mean value of three calculations. All measurements were double checked by a blinded engineer.

#### *Echocardiography*

Whole echocardiographic approach, all measurements and definitions were done according to related clinical guideline [24]. Each echocardiogram was evaluated by 2 experienced cardiologists. Echocardiograms that were difficult to evaluate due to technical defects, and the cases in which the cardiologists could not agree, were excluded from the study.

#### *Statistical analysis*

Statistical analysis was performed using SPSS 13.0 for Windows. Normal distribution of the data was checked using the Kolmogorov-Smirnov test. Continuous variables are presented as means  $\pm$  standard deviations whereas categorical variables are presented as percentages. The differences between the groups for categorical varieties were compared by the Chi-square test. According to the distribution, the differences between the groups for numeric parameters were compared by Student's t-test or the Mann-Whitney U test. The correlations among the study variables were examined by Pearson or Spearman correlation tests according to normality of distribution. The significance level was assumed as  $p < 0.05$ .

## **Results**

The baseline clinical and laboratory characteristics of the patients and controls are summarized in Table 1. There was no statistically significant difference between the two groups with respect to age, gender, systolic blood pressure, diastolic blood pressure, weight, height and body mass index. The biochemical characteristics of the patients did not differ in creatinine, serum phosphate, calcium, uric acid, 25- OH vitamin D, PTH and lipid levels except

**Table 1.** Comparison of biochemical and echocardiographic variables of in ADPKD patients and controls

	<b>ADPKD group (n=31)</b>	<b>Control group (n=20)</b>	<b>p value</b>
<b>Age (years)</b>	32.30±11.10	35.54±6.40	NS
<b>Gender (male/female)</b>	10/21	13/13	NS
<b>Systolic blood pressure</b>	126±13	123±11.40	NS
<b>Diastolic blood pressure</b>	73±12.10	70±8	NS
<b>BMI(kg/m<sup>2</sup>)</b>	24.20±4.40	26.50±4.10	NS
<b>Smoking (%) (n)</b>	40 (9)	50 (13)	NS
<b>Glucose (mg/dl)</b>	85.60±9.90	84.30±6.80	NS
<b>Urea (mg/dL)</b>	28.50±8.90	26.10±7.60	NS
<b>Creatinine (mg/dL)</b>	0.70±0.16	0.60±0.08	NS
<b>Calcium (mg/dL)</b>	9.53±0.40	9.45±0.20	NS
<b>Phosphorus (mg/dL)</b>	3.44±0.47	3.25±0.42	NS
<b>eGFR (mL/dk)</b>	104±16.70	116±12.80	0.03
<b>PTH (pg/mL)</b>	58.30±33	76±42.50	NS
<b>FGF-23 (RU/ml)</b>	536.70±506	42.70±23.10	0.0001
<b>TC (mg/dl)</b>	191±33	188±28.60	NS
<b>HDL-C (mg/dl)</b>	52±12.80	48±13.20	NS
<b>LDL-C (mg/dl)</b>	115±26.70	118±23	NS
<b>TG (mg/dl)</b>	125±90.90	117±96.20	NS
<b>LVEDD (mm)</b>	47.80±3.20	45.60±5.4	NS
<b>LVESD (mm)</b>	28.30±5.60	26.5±6.20	NS
<b>IVSD (mm)</b>	1.06±0.10	0.95±0.13	0.01
<b>LVPW (mm)</b>	1.02±0.09	0.90±0.001	0.01

ADPKD=autosomal dominant polycystic kidney disease, BMI=body mass index, PTH=parathyroid hormone, TG=triglycerides, TC=total cholesterol, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, eGFR=estimated glomerular filtration rate, FGF-23=fibroblast growth factor 23, LVEDD=left ventricular end diastolic diameter, LVESD=left ventricular end systolic diameter, IVSD=interventricular septum diameter, LVPD= left ventricular posterior wall diameter, EF=ejection fraction. Data are presented as means±SD, NS=non-significant

**Table 2.** Comparison of electrocardiographical features of ADPKD patients and controls

	<b>ADPKD group (n=31)</b>	<b>Control group (n=20)</b>	<b>p value</b>
<b>QTc dispersion (ms)</b>	36.60±12.70	19.50±8.30	0.001
<b>QTc (ms)</b>	418±24.60	427±44	NS
<b>Tp-e interval (ms)</b>	87.10±12.50	74±8.50	0.001
<b>Tp-e/QT ratio</b>	0.24±0.03	0.20±0.02	0.001
<b>Tp-e/QTc ratio</b>	0.20±0.02	0.17±0.02	0.001

ADPKD=autosomal dominant polycystic kidney disease, QTc=corrected QT, QTd=QT dispersion, Tp-e=T wave peak to T wave end interval. Data are presented as means±SD. NS=non-significant

for FGF-23 were significantly higher and eGFR was significantly lower in the ADPKD patients. Electrocardiogram derived risk indicators corrected QT dispersion (cQTd), Tp-e, Tp-e/QT and Tp-e/QTc were also compared between groups. All indicators were significantly worse in ADPKD group (Table 2).

In the correlation analyzes; FGF23 was significantly correlated with Tp-e (Figure 1) and Tp-e/QTc (Figure 2) ( $r=0.388$   $p=0.003$ ;  $r=0.442$   $p=0.001$ , respectively).

## Discussion

Cardiovascular disease is the leading cause of premature mortality in patients with ADPKD [25]. A wide range of factors that end up with structural myocardial disease are responsible for this adverse outcome. A variety of subclinical organ damage markers such as LVH, increased carotid intima-media thickness, endothelial dysfunction, microalbuminuria, decreased coronary flow velocity reserve and low-grade systemic inflammation, and chronic oxidative stress have been reported in several studies of patients with ADPKD with well-preserved renal function [26, 27]. Functional data supporting a role of FGF-23 in vascular biology is derived from Klotho null mice, which carry no functional FGF-23 activity due to lack of co-receptors [28]. Recent prospective studies showed a powerful and dose dependent association between

increasing FGF-23 levels and greater risk of mortality among CKD patient [29, 30]. The reason for increased cardiovascular mortality in CKD may be associated with LVH. Recent experimental studies have clearly demonstrated that FGF-23 can directly induce LVH [31]. The action of FGF-23 in the kidney and the parathyroid gland is different from that in the heart. In renal and parathyroid tissue, FGF-23 acts via the classical pathway, by stimulating FGF receptor and Klotho, the obligatory co-receptor, to inhibit both renal phosphorous reabsorption and 1,25-OH vitamin D synthesis through ras/mitogen-activated protein (MAP)-kinase pathway. In contrast, at the level of cardiomyocytes, FGF-23 acts through the phospholipase C gamma/calcineurin pathway, independent of Klotho. A recent trial in ADPKD patients at different stages of CKD showed markedly elevated levels of FGF-23 compared with other CKD etiologies. Because of the absence of Klotho in cardiomyocytes, increased FGF-23 levels may explain increased rates of LVH in normotensive ADPKD patients with normal renal functions. In our study, ADPKD subjects had higher levels of FGF-23 but normal calcium and phosphate levels when compared to controls.

Marked fibrosis or de-arrangement of uniformity of ventricular myocardium may lead to heterogeneous scattering of electrical wavelet through cardiomyocytes. In fact it is the most frequent cause of ventricular arrhythmogenic substrate development which leads to sudden cardiac

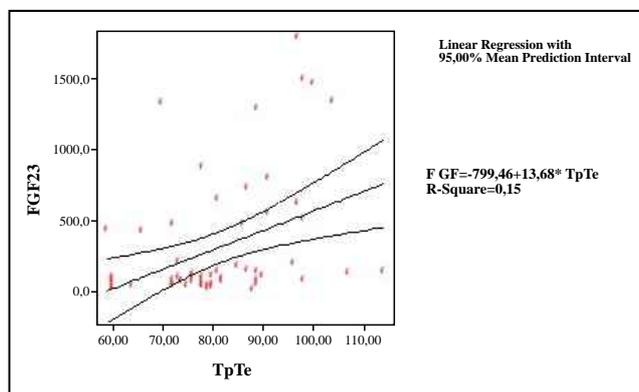


Figure 1. Correlation between FGF23 and Tp-e

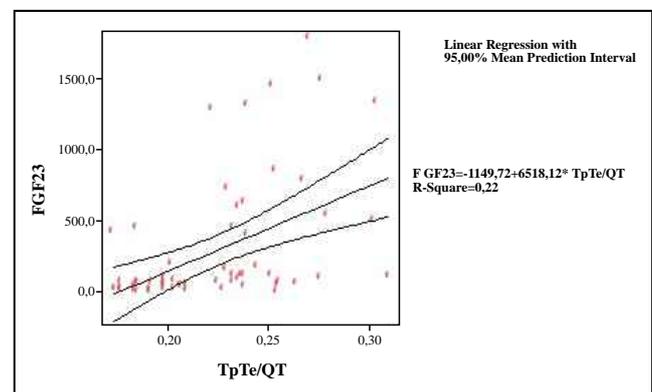


Figure 2. Correlation between FGF23 and Tp-e/QTc

death in heart failure [32]. There is a high variety of comorbidities in renal disease patient population. Burden of multiple factors that increase myocardial fibrosis preceding repolarization heterogeneity, electrolyte imbalance that causes myocardium cell depolarization defects, neuro-humoral instability with increased automaticity end up with a substrate for sudden cardiac death [33, 34]. Prolongation of QT interval and increased QT dispersion in renal disease are subjects of interest for a long time. Previously published articles mainly point out similar findings these indices of sudden death on the surface ECG are significantly higher in patients with CKD [12, 35]. Because of increased risk of cardiac mortality in this large patient group, risk stratification becomes more and more important to save lives. Newly introduced surface ECG indices may contribute in risk prediction. T wave peak to end interval is a measure of transmural dispersion of repolarization in the left ventricle and accepted as a surrogate for increased ventricular arrhythmogenesis risk. Tp-e/QT and Tp-e/QTc are relatively new markers which also indicate repolarization defects. Published studies clearly suggest the applicability of Tp-e/QT ratio as a potentially important index of arrhythmogenesis, both under the conditions of short, normal and long QT interval, as well as in congenital and acquired channelopathies. In various high-risk populations, such as, patients with long QT syndrome [36], inducible ventricular tachycardia [37, 18], repaired tetralogy of Fallot [38] or Brugada syndrome [39]. T wave peak to end interval had been found to be more prolonged than control patients. In our study, we exhibited that there was a strong positive correlation between serum FGF-23 levels and ECG derived arrhythmia indicators, Tp-e, Tp-e/QT and Tp-e/QTcd but not QT and QTd. Prolonged QT and increased QTd are established indicators of SCD, however these relatively newer indicators are more specific and sensitive [25] and do not get affected from heart rate [40]. Our study corresponds with previous studies that show significant relationship between FGF-23 and cardiac mortality, yet, this is the first study which evaluates FGF-23 by using surface ECG parameters including Tp-e and Tp-e/QT. Also, this is the first study that introduces Tp-e and derived indicators in polycystic

renal disease.

The limitations of our study are retrospective method, absence of a hypertensive control group and the small sample size.

In this occasion, we suggest that FGF-23, which probably accumulates ventricular electrical remodeling, may be helpful for risk stratification in patients with ADPKD when used with other indicators.

#### *Conflict of interest*

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

#### *Financing*

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## Evaluation of healthcare providers' approach towards pandemic influenza and their vaccination ratio

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### ABSTRACT

**Objectives.** Pandemic influenza is a contagious disease caused by the new pandemic influenza A H1N1 virus, originated from the genetic combination of human, pig and avian influenza viruses. Our research aimed to determine the level of pandemic influenza vaccination in healthcare providers and the factors influencing this level. **Methods.** Doctors, midwives and nurses working in primary, secondary and tertiary health institutions in Denizli established the universe of the research. Four nurses visited these health institutions on five work-days between the 4th and 8th of April 2011, informed the healthcare providers that participation to the research was voluntary and handed over data collection forms in the institutions visited. Then, these data collection forms were collected by the same nurses. Research data were analyzed with SPSS package program. Frequency, percentage, chi-square and logistic regression analyses were used in the evaluation. **Results.** 44.7% of the healthcare providers participating in the study stated that they had been vaccinated with pandemic influenza vaccine. When factors effecting the vaccination decision with pandemic influenza vaccine of the individuals participating the study was evaluated; statistically significant difference between vaccination and occupation ( $p=0.001$ ), sex ( $p=0.001$ ), and age ( $p=0.026$ ) was detected. The proportion of doctors, males and individuals older than 40 years was higher among the vaccinated professionals. **Conclusions.** It is important to make announcements about vaccination with determination and by taking support from media and non-governmental organizations. Statements and explanations should be released with this in mind and media, and non-governmental organizations should also take responsibility regarding this matter.

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**Keywords:** Pandemic influenza; vaccination; healthcare providers

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## Introduction

Pandemic influenza is a contagious disease caused by the new pandemic influenza A H1N1 virus, originated from the genetic combination of human, pig and avian influenza viruses. In infections like influenza that transmit easily and rapidly, healthcare providers may also form an important focus in respect to transmitting the disease to the high risk group. Healthcare providers are recommended to be vaccinated with seasonal influenza vaccine every year. Although many methods reducing the risk of transmission of influenza exists, the most effective method today is still vaccination [1].

Influenza affects approximately 5-10% of the community and may result in admission to the hospital and therefore results in a significant social cost in the government budget [2]. Vaccination of the healthcare providers with influenza vaccine is recommended by CDC (Center for Disease Control and Prevention) since 1981, and by WHO (World Health Organization) since 2002 [3-5]. Vaccination of healthcare providers with influenza vaccine reduces the occurrence of diseases like influenza, absence rates and also reduces the infection risk by preventing nosocomial transmission to the patients [6-9].

During the influenza pandemic experienced in our country, 43 million doses of vaccine was provided by the Ministry of Health and applied to the healthcare providers starting from November 2, 2009.

Our research aimed to determine the level of pandemic influenza vaccination of healthcare providers and the factors influencing this level.

## Methods

Eight-hundreds and forty-six doctors and 1542 midwives/nurses working in primary, secondary and tertiary health units in Denizli established the universe of the research. No samples were selected in the research and it was aimed to reach the whole population. For this purpose, related health units were visited by four nurses between the 4th and 8th of April, 2011 on five workdays. Doctors and midwives/nurses were informed that participation to the research was voluntary and data collection forms were left to the healthcare units. Then, these data

collection forms were collected by the same nurses. A total of 360 individuals filled the forms; 86 of them were from primary health institutions, 102 from secondary and 171 from tertiary health institutions. 174 of the participants were doctors and 186 were midwives/nurses. Before the collection of data, approval of the health directorate, management of the Faculty of Medicine and the local ethics board were obtained. Data collection form consisted of questions covering socio-demographic characteristics, research activities and factors influencing the vaccination status of the participated individuals.

Research data were analyzed with SPSS package program. Frequency, percentage, chi-square and logistic regression analyses were used in the evaluation. For statistical comparisons  $p < 0.05$  was set as statistical significance.

## Results

Of the individuals participating to the study 29.4% was below and 70.6% was above the age of 40. When the working life duration of the participants was evaluated it was determined that 34.2% was working for 5 years or less, 13.3% was for 6-10 years, 17.5% was for 11-15 years, and 35.0% was for 16 years or more. Their ratio of vaccination with seasonal influenza vaccine was found to be 32.4%, 45.3% and 18.6% in the years 2008-2009, 2009-2010 and 2010-2011, respectively (not provided in the Table). 44.7% of the healthcare providers participating in the study stated that they have been vaccinated with the pandemic influenza vaccine (Table 1).

When factors influencing the vaccination of participants with pandemic influenza vaccine were evaluated; statistically significant difference between vaccination and occupation ( $p=0.001$ ), sex ( $p=0.001$ ), and age ( $p=0.026$ ) was detected. Doctors, males and individuals older than 40 years were more among the vaccinated ones (Table 1).

When the effects of research activities of the participants on the vaccination ratios with pandemic influenza vaccine was evaluated no statistically significant difference between the institution he/she

**Table 1.** Distribution of socio-demographic characteristics of the healthcare providers regarding the vaccination status

Variables	Vaccination status		Total Number (%)**	X <sup>2</sup>	p
	Vaccinated Number (%)*	Not vaccinated Number (%)*			
<b>Age</b>					
<b>40 years and below</b>	104 (40.9)	150 (59.1)	254 (70.6)	4.979	<b>0.026</b>
<b>Over 40 years</b>	57 (53.8)	49 (46.2)	106 (29.4)		
<b>Sex</b>					
<b>Male</b>	67 (57.3)	50 (42.7)	117 (32.5)	11.030	<b>0.001</b>
<b>Female</b>	94 (38.7)	149 (61.3)	243 (67.5)		
<b>Occupation</b>					
<b>Doctor</b>	98 (56.3)	76 (43.7)	174 (48.3)	18.330	<b>&lt;0.001</b>
<b>Nurse</b>	63 (33.9)	123 (66.1)	186 (51.7)		
<b>Total</b>	161 (44.7)	199 (55.3)	360 (100.0)		

\*Row percentage, \*\* Column percentage

**Table 2.** Distribution of research activity characteristics of the healthcare providers regarding the vaccination status

Variables	Vaccination status		Total Number (%)**	X <sup>2</sup>	p
	Vaccinated Number (%)*	Not vaccinated Number (%)*			
<b>Institution</b>					
<b>Primary Care</b>	44 (51.2)	42 (48.8)	86 (23.8)	1.984	<b>0.384</b>
<b>Secondary Care</b>	43 (42.2)	59 (57.8)	102 (28.3)		
<b>Tertiary Care</b>	74 (43.0)	98 (57.0)	172 (47.9)		
<b>Number of patients examined in a day</b>					
<b>25 and below</b>	59 (39.6)	90 (60.4)	149 (41.4)	2.701	<b>0.100</b>
<b>26 and above</b>	102 (48.3)	109 (51.7)	211 (58.9)		
<b>Department</b>					
<b>Polyclinic</b>	88 (49.2)	91 (50.8)	179 (49.7)	2.839	<b>0.092</b>
<b>Service</b>	73 (40.3)	108 (50.7)	181 (51.3)		
<b>Total</b>	161 (44.7)	199 (55.3)	360 (100.0)		

\*Row percentage, \*\* Column percentage

is working in ( $p=0.384$ ), department he/she is working in ( $p=0.092$ ) and the number of patients examined in a day ( $p=0.100$ ) was found (Table 2).

When an assessment was conducted regarding whether the announcements made by official authorities had an effect on vaccination with pandemic influenza vaccine; a statistically significant difference between vaccination and information provided by Ministry of Health ( $p=0.001$ ) and information level ( $p=0.006$ ) was found, while no statistically significant differences were detected between the announcements of the official authority (Ministry of Health) ( $p=0.233$ ) and vaccination.

Vaccination level is higher in the individuals influenced by the announcements of the Ministry

of Health on vaccination and in individuals who think that they have sufficient information on the vaccine (Table 3).

Independent risk factors found to be statistically significant in Logistic regression analysis. According to this, vaccination with pandemic influenza vaccine was 2.9 times higher in those who were influenced by the announcements of the Ministry compared to those who were not influenced (OR: 1.9- 4.6); was 2.3 times higher in physicians compared to the other healthcare providers (OR: 1.5- 3.7); was 3.4 times higher in those who had received an influenza vaccination in the year preceding the pandemic compared to those who had not received vaccination (OR: 2.1- 5.6) (Table 4).

**Table 3.** The effect of being influenced or not by the statements of official authorities about vaccination on the vaccination status

Variables	Vaccination status		Total Number (%)**	X <sup>2</sup>	p
	Vaccinated Number (%)*	Not vaccinated Number (%)*			
<b>Information provided by the ministry has influenced my decision on vaccination</b>					
Yes	80 (60.6)	52 (39.4)	132 (36.7)	<b>16.248</b>	<b>&lt;0.001</b>
No	80(35.2)	147 (64.8)	227 (63.3)		
<b>Official authority statements have influenced my decision on vaccination</b>					
Yes	38 (50.7)	37 (49.3)	75 (20.8)	2.915	0.233
No	123 (43.2)	162 (56.8)	285 (79.2)		
<b>I have sufficient information on pandemic influenza</b>					
Yes	93 (52.0)	86 (48.0)	179 (49.7)	<b>7.534</b>	<b>0.006</b>
No	68 (37.6)	113 (62.4)	181 (50.3)		
<b>Total</b>	161 (44.7)	199 (55.3)	360 (100.0)		

\*Row percentage, \*\* Column percentage

**Table 4.** The results of logistic regression analysis covering the factors that influence SDPE

Independent variables		Odds Ratio	95% Confidence Interval
<b>Information provided by the ministry has influenced my decision on vaccination</b>	Yes	<b>2.9</b>	<b>1.9-4.6</b>
	No	Reference	
<b>Occupation</b>	Physician	<b>2.3</b>	<b>1.5-3.7</b>
	Healthcare providers other than physician	Reference	
<b>Vaccination with seasonal influenza vaccine a year before the pandemic</b>	Yes	<b>3.4</b>	<b>2.1-5.6</b>
	No	Reference	

## Discussion

The case of pandemic influenza was first detected in our country in May 15, 2009 and the number of cases did not increase during summer. However the number of cases started to increase rapidly in the fall of 2009-2010 due to reasons such as opening of the school year and preferring indoor places more frequently due to weather conditions [10]. Fatal pandemic fear arose throughout the world and because the number of pandemic influenza vaccines manufactured was limited, it was decided that the risk groups should be vaccinated first.

According to the results of our study, the ratio of being vaccinated with pandemic influenza vaccine was found to be 44.7%, and different results were obtained in the studies performed in our country. In a study by Ormen *et al.*, which was performed in 2012 among healthcare providers the ratios of getting vaccinated with pandemic influenza vaccine was found to be 40%; in a study performed by Ertek *et al.*, it was found to be 9.3% in 1164 participants from Ankara and 3.7% in 804 participants from Diyarbakir [11, 12]. In a survey on pandemic influenza vaccination performed among healthcare providers in Greece in 2009, vaccination rate was found to increase with advanced age, being male, being doctor and having a seasonal influenza vaccination history [13]. In another study, age was found to be an important factor in the preference of being vaccinated [14]. It was found that individuals who consider vaccination were older, and who do not consider

vaccination were younger [14].

In a study performed in US, the ratio of those who accepted to be vaccinated with pandemic influenza vaccination was 81%, and it was thought that this high ratio might have occurred as a result of various methods used by CDC to increase vaccination [15]. CDC recommended vaccinations to be administered free of charge and seminars related to the risks of the disease and probable side effects of the vaccine to be arranged for healthcare providers in order to increase vaccination ratios [16, 17].

In studies conducted in our country it was found that the most frequent reasons for not getting a vaccination with pandemic influenza vaccine were the fear of the side effects of the vaccine and the lack of adequate studies on the vaccine [18]. Again in a study performed in Greece, though 97% of healthcare providers accept the importance of vaccination, only 17% were reported to have a vaccination with pandemic influenza vaccine [19]. In another study about the vaccine (28%) and thinking that he/she does not have the risk of contracting the disease (11%) were found to be the most important reasons in rejecting vaccination [20]. In our study, rationale of those who have rejected vaccination was the doubts about the protectiveness of the vaccine in 24.9% and fear of the side effects in 1.9%. Our results were similar to the other studies performed in our country and also in the world.

In the studies performed, the most important reasons for accepting vaccination with 2009 pandemic influenza vaccine were protecting himself/herself and the patients from the disease, fear of transmitting the disease to the people close to them and following the recommendations of the health authorities [21, 22]. However in our study, most frequent reasons to accept vaccination were being in the high risk group and the presence of a pandemic.

## Conclusions

It is important to make announcements about vaccination with determination and by taking support from media and non-governmental organizations. Statements and explanations should be released with this in mind and media and non-governmental organizations should also take responsibility regarding this matter.

### *Conflict of interest*

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

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## Diabetic foot infections: effective microorganisms and factors affecting the frequency of osteomyelitis and amputation

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### ABSTRACT

**Objectives.** Diabetic foot infections are common reason for hospitalization and are associated with high morbidity and mortality. We aimed to evaluate the clinic features and predisposed causes of osteomyelitis and amputation of patients with diabetic foot infections. **Methods.** Patients with diabetic foot infections who admitted and hospitalized at Infection Diseases and Clinical Microbiology department between January 2012 and July 2014 were included. Osteomyelitis was evaluated using magnetic resonance imaging (MRI) or bone scintigraphy. Microbiological examinations (Gram staining and culture) of the debridement materials and pus aspiration materials of the lesions were performed. **Results.** Of the seventy-three diabetic foot infected patients, 37 (50.7%) were female, and 36 (49.3%) were male. The mean age of patients was  $57 \pm 9.8$  years. The mean duration of diabetes and HbA1c level were  $13.3 \pm 5.3$  years and  $8.17 \pm 1.83\%$ ; respectively. Soft tissue infection without osteomyelitis was present in only 34 out of 73 (46.5%) patients. A total of 89 pathogens were identified in 52 patients whereas any microorganism was not identified in 28.7%. Polymicrobial infections were detected in 30 (41%) patients. The most common isolated microorganism was *Pseudomonas aeruginosa* (36.9%), followed by *Staphylococcus aureus* (31.5%) and *Enterococcus* spp. (13.6%). Of the 37 (50.7%) patients had a history of diabetic foot infection previously, osteomyelitis progression was higher (89.2%) and statistically significant in these patients. Twelve (16.4%) patients underwent amputation. **Conclusions.** Advanced age and presence of osteomyelitis were found as risk factors for amputation. In the presence of osteomyelitis, treatment of diabetic foot infections is difficult and amputation rate is higher. For this reason, diabetic foot infections should be promptly treated before the development of osteomyelitis, and multidisciplinary approach is needed.

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**Keywords:** Diabetic foot infection; osteomyelitis; amputation

### Introduction

Diabetic foot infection is one of the complications of diabetes; it has high mortality and morbidity and is also one of the most common causes of hospitalization in diabetes [1, 2]. Diabetic foot

infections generally start as a soft tissue infection secondary to a minor trauma, may advance to osteomyelitis, and eventually become a risk factor for amputation [3, 4]. Approximately one-fourth of

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patients with diabetes mellitus (DM) have a diabetic foot infection in their lifetime and 15-20% of those cases result in amputation [3-6].

The development of diabetic foot infections can be primarily prevented by education of the patient and a good glycemic control; however, a multidisciplinary approach with various targets, such as appropriate antibiotic treatment, good glycemic control, appropriate surgical debridement, and education of the patient is needed once an infection has developed [1, 6, 7]. Some classification systems have been used to define the types, severity of infections and the outcomes of the cases. The most commonly used and easiest to use is the Meggit-Wagner classification [4-6].

The isolation of the effective microorganism, in addition to the wound classification, is needed for appropriate treatment in these infections. The most frequently isolated agents are gram positive cocci such as *Staphylococcus aureus* in superficial infections of mild to moderate severity in acute phases; Polymicrobial infections, in which gram negative bacilli and anaerobic bacteria are effective concomitantly, in addition to gram positive cocci in advanced stages and in the presence of severe infection [1, 3, 7, 8]. The most reliable method to detect the causative agent is obtaining a culture; however, when this is not possible, culturing the aspiration material from the pus provides more reliable results compared to swab samples [9, 10].

The aim of this study was to retrospectively evaluate various aspects of patients with diabetic foot infections who were followed-up during a two and a half year period.

## Methods

Patients with diabetic foot infection that were followed-up at the Infection Diseases and Clinical Microbiology Clinic of Ankara Training and Research Hospital between January 2012 and July 2014 were included in the study retrospectively. The age and gender of the patients, duration and treatment of diabetes, use of oral antidiabetic agent (OAD) or insulin, past medical history including microvascular complications such as presence of

neuropathy, nephropathy, and retinopathy, past episodes of diabetic foot infections, HbA1c (glycosylated hemoglobin) values at the time of diagnosis, and the opinion of an endocrinology consultant were recorded. The lesions of the patients were classified according to the Wagner classification (Table 1) [4]. According to this classification, patients with pressure in the foot due to shoes (callus formation) (Stage 0) were excluded from the study.

Osteomyelitis was evaluated using magnetic resonance imaging (MRI) or bone scintigraphy besides the direct roentgenograms according to the stage of the patient. The bilateral lower extremity arterial Doppler ultrasonography report of each patient was analyzed in order to detect peripheral vascular disease and the joint decision of the orthopedic, cardiovascular surgery, and plastic surgery clinics was recorded.

Microbiological examinations (Gram staining and culture) of the debridement materials and pus aspiration materials of the lesions were performed. Aerobic cultures were performed in all samples, while anaerobic cultures could not be done in most patients due to technical impossibilities. Clinical samples were routinely cultured in blood agar and EMB (Eosin methylene blue) agar plaques for both aerobic and anaerobic identification. The samples were incubated for 24 hours at 35°C under aerobic conditions to identify the aerobic microorganisms. For anaerobic cultures, the samples arriving the laboratory in a capped syringe with no air inside were cultured into anaerobic blood agar, which was prepared adding 5% sheep blood and vitamin K1 (1 •g/mL). The cultured anaerobic agars were placed into anaerobic jars and an environment without oxygen is provided with a dry system gas package (AnaeroGen-Oxoid, Basingstoke, UK). An anaerobic indicator (Oxoid, Basingstoke, UK) was used as an indicator to control the anaerobic environment. To grow the anaerobic bacteria, the agars were incubated for 48 hours at 35-37°C in an anaerobic environment. The definition of microorganisms and the antibiotic sensitivities were performed using the VITEK II automated system (Biomèrieux, France) according to the CLSI (Clinical and Laboratory Standards Institute) [11] guidelines.

**Table 1.** Wagner classification in diabetic foot ulcers

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<b>Stage 0:</b> Formation of bone protrusion with healthy skin and/or callus formation (risk of ulceration)
<b>Stage 1:</b> Superficial ulcer with no involvement of deep tissues
<b>Stage 2:</b> Deep ulcer involving tendon, bone, ligament of joint
<b>Stage 3:</b> Deep ulcer including abscess and/or osteomyelitis
<b>Stage 4:</b> Gangrene involving the toes and/or metatarsal region
<b>Stage 5:</b> Gangrene involving the heel and/or the whole foot at an unrecoverable level that necessitates amputation

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### Statistical analysis

Statistical analysis of the data obtained was performed using SPSS for Windows 15.0 package program. The descriptive analysis was performed and the data was expressed as number, percentage, and mean±standard deviation. The normal distribution of continuous variables was tested using the Shapiro-Wilk test. The t-test and Mann-Whitney U-test were used to compare two independent groups in case of normal distribution and non-normal distribution, respectively. The chi-square test was used to analyze the categorical variables. The level of statistical significance was determined as  $p<0.05$ .

## Results

Thirty-seven of the patients were females (50.7%) and 36 were males (49.3%) among the total 73 patients included in the study. The mean age of the patients was  $57\pm 9.8$  years (range: 34-77 years) and mean duration of diabetes was  $13.4\pm 5.3$  years. The mean HbA1C level of the patients was  $8.17\pm 1.83\%$ .

Thirty-six patients (49.3%) were on insulin treatment, 23 (31.5%) were on insulin in addition to oral antidiabetic drugs (OAD), and 14 patients (19.1%) were on OAD alone. Diabetic foot infections of fifteen patients (20.5 %) were classified as Stage 1, 19 of (26%) were Stage 2, seven (9.6%) were Stage 3, 20 (27.4%) were Stage 4, and 12 (16.4%) were Stage 5. Clinical and demographic characteristics of the patients are summarized in Table 2. Thirty-nine patients (53.4%) of patients had osteomyelitis in addition to soft tissue infection, while 34 (46.5%) had only soft tissue

infection. The mean age of the patients whose disease advanced and did not advance to osteomyelitis was  $63.25\pm 5.7$  years and  $49.88\pm 8.5$  years, respectively, and the difference between the two groups was statistically significant ( $p<0.001$ ). The mean duration of diabetes and HbA1c levels in patients with osteomyelitis was 15 years and 8.9%, respectively, and these were significantly higher than those of without osteomyelitis ( $p=0.042$  and  $p<0.001$ , respectively). Past medical history revealed prior diabetic foot infections in 37 patients (50.7%); the rate of advancement to osteomyelitis (89.2%) was statistically significantly higher in these patients than those of without infection history ( $p<0.001$ ). Clinical and laboratory findings of the patients with osteomyelitis and comparison with the patients without osteomyelitis as shown in Table 3. The rate of all antidiabetic drug use was markedly higher in patients with osteomyelitis. Amputation not performed in any of the patients who had soft tissue infection alone; however, amputations at specific levels were performed in 12 patients ((30.8%) out of 39 patients who had concomitant osteomyelitis ( $p<0.001$ ). All of the patients who had osteomyelitis and underwent amputation were Stage 5 according to the Wagner classification ( $p<0.001$ ). The age and the rate of presence of osteomyelitis were higher in patients who underwent amputation. Clinical and laboratory findings of patients who did and did not undergo amputation are summarized in Table 4. Anaerobic cultures were performed in 16 patients (20.8%), although aerobic cultures were performed in all patients. However, no anaerobic agent was isolated. According to the culture results, a total of

**Table 2.** Clinical and Demographic characteristics of the patients

Properties	Number of patients (%)
Male/Female	36 (49.3)/ 37 (50.7)
Mean age (years, range)	57±9.81 (34-77)
Mean duration of diabetes	13.4±5.33
Mean HbA1c* (%)	8.17±1.83
OAD** use	14 (19.1)
Insulin use	36 (46.3)
OAD**+insulin use	23 (31.5)
Past history of infection	37 (50.7)
Wagner classification	
Stage 1	15 (20.5)
Stage 2	19 (26)
Stage 3	7 (9.6)
Stage 4	20 (27.4)
Stage 5	12 (% 16.4)

\*HbA1c=Glycosylated hemoglobin, \*\*OAD=Oral antidiabetic drug

**Table 3.** Clinical and laboratory findings in patients with and without osteomyelitis

	Osteomyelitis (n=39)	No Osteomyelitis (n=34)	p value
Wagner stage ≤3	7 (17.1%)	34 (82.9%)	<0.001
Wagner stage >3	32 (100%)	-	<0.001
Age (mean±SD)	63.25±5.7	49.88±8.5	<0.001
Duration of diabetes (year) (median)	15	9.5	<0.001
Past history of diabetic foot infection	33(89.2%)	4 (10.8%)	
OAD* use	13 (38.2%)	1 (2.6%)	<0.001
OAD*+insulin use	18 (52.9%)	5 (12.8%)	
Insulin use	33(84.6%)	3 (8.8%)	0.044
HbA1c** (%) (median)	8.9	8.3	

\*OAD=Oral antidiabetic drug, \*\*HbA1c=Glycosylated hemoglobin

89 pathogenic agents were identified in 52 patients (71.2%), while no agent was identified in other patients (28.7%). More than one agent was isolated in 30 patients (41%). The most commonly isolated bacteria in order of frequency were *Pseudomonas aeruginosa* (n: 27, 36.9%), *Staphylococcus aureus* (n: 23, 31.5%), and *enterococcus* spp. (n: 10, 13.6%).

Among the isolated *S. aureus* species, 19 (21.1%) were methicillin sensitive and four (3.9%) were methicillin resistant. Methicillin resistance rate was 17% among the *S. aureus* species. Isolated microorganisms are summarized in Table 5. When the antibiotherapies administered to the patients were analyzed, monotherapy was applied

**Table 4.** Clinical and laboratory findings in patients with and without amputation

	<b>Amputation (n=12)</b>	<b>No Amputation (n=61)</b>	<b>p value</b>
<b>Wagner stage <math>\leq 3</math></b>	-	41 (67.3%)	
<b>Wagner stage <math>&gt; 3</math></b>	12 (100%)	20 (32.7%)	<0.001
<b>Age (mean<math>\pm</math>SD)</b>	64.75 $\pm$ 6.0	55.5 $\pm$ 9.7	<0.001
<b>Duration of Diabetes (year) (median)</b>	11	16	0.042
<b>Presence of osteomyelitis</b>	12 (100%)	27 (44.3%)	<0.001
<b>Past history of DFI*</b>	8 (66.6%)	29 (47.5%)	0.345
<b>HbA1c **(%)(median)</b>	8.65	8.6	0.644

\*DFI=Diabetic foot infection, \*\*HbA1c=Glycosylated hemoglobin

to 27 patients (36.9%), while 46 patients (63%) were received combined antibiotherapy. Piperacillin-tazobactam was used in 18 (66.6%) of the patients who received monotherapy. Other antibiotics used in monotherapy were imipenem, meropenem, ampicillin-sulbactam, and glycopeptides. The most frequently used combination among the patients who received combined antibiotherapy was vancomycin-meropenem combination (41.3%). Other antibiotics used in combined antibiotherapy were ampicillin-sulbactam+ciprofloxacin, vancomycin+piperacillin-tazobactam, and glycopeptide+ rifampin.

## Discussion

The development of DFI and advancement to osteomyelitis and amputation in diabetic patients are closely related with advanced age, presence of microvascular complications (retinopathy, nephropathy, and neuropathy), duration of diabetes, and blood glucose level [12-14]. Diabetic foot infections were found to occur after 40 years of age, the frequency of the infections and amputations were found to increase with age, and they were found to occur in higher rates in men compared to women [12, 13, 15]. The mean age was also found to be high in the present study; however, the male/female ratio was found to be equal (49.3% / 50.7%). Compatible with other studies, the age of the patients was significantly higher in patients who

underwent amputation compared to the ones who had no amputation ( $p < 0.001$ ) [14, 16].

Effective wound care, appropriate antimicrobial treatment, and good glycemic control are of utmost importance in the multidisciplinary approach to diabetic foot infections. Chronic hyperglycemia, which develops as a result of poor glycemic control, is known to cause impairment in neutrophil functions and to provide a basis for infections [15, 16]. High levels of HbA1c were suggested in two different studies to pave the way for the recurrence of diabetic foot infections and the development of neuropathy, and as a result, become a risk factor for amputation [17, 18]. Mean HbA1c levels in the present study at the beginning were 8.17% and high values were detected in patients with a prior history of diabetic foot infection. We suggest that providing glycemic control with conversion to insulin treatment or dose adjustment in patients with initial high levels of HbA1c will be effective in controlling infections.

In western societies, diabetic foot infections are generally seen 18 or more years after the diagnosis [14, 19]. This time period was reported to be 14.4 years and 16.6 years in the studies performed by Savas *et al.* and Demirci *et al.*, respectively, in Turkey [20, 21]. The same measure was a mean 13.4 years in the current study. The reason of the earlier onset of diabetic foot infections in Turkey might be due to differences in the educational and socioeconomical level of the patients.

The first step in the diagnosis and treatment planning of diabetic foot infection is to define the extension

**Table 5.** Isolated microorganisms

<b>Microorganism</b>	<b>Number of patients (%)</b>
<b>Agent not specified</b>	21 (28.7)
<b>Single microorganism</b>	22 (30.1)
<b>P. aeruginosa</b>	7 (31.8)
<b>MSSA*</b>	4 (18.1)
<b>Enterobacter cloacae</b>	3 (13.6)
<b>MRSA**</b>	2 (9.1)
<b>Coagulase negative staphylococcus</b>	2 (9.1)
<b>Morganella morganii</b>	1 (4.5)
<b>Escherichia coli</b>	1 (4.5)
<b>Klebsiella spp.</b>	1 (4.5)
<b>Proteus mirabilis</b>	1 (4.5)
<b>More than one microorganism</b>	30(41.1)
<b>P. aeruginosa</b>	20 (66.6)
<b>MSSA*</b>	15 (50)
<b>Enterococcus spp.</b>	10 (33.3)
<b>Coagulase negative staphylococcus</b>	5 (16.6)
<b>Morganella morganii</b>	5 (16.6)
<b>Escherichia coli</b>	4 (13.3)
<b>Enterobacter cloacae</b>	3 (10)
<b>MRSA**</b>	2 (6.6)
<b>Proteus mirabilis</b>	2 (6.6)
<b>Klebsiella spp.</b>	1 (3.3)

\*MSSA=Methicillin sensitive *S. aureus*, \*\*MRSA=Methicillin resistant *S. aureus*

of tissue damage and the isolation of the causative agent. The commonly used Wagner classification was preferred in this present study due to its easier application compared to other classifications [22]. Most of infections in our patients were Wagner 4 stage. This may be explained by the level of our hospital (tertiary hospital). Advanced age, duration of diabetes and past history of diabetic foot infection were all found the main factors effecting development of osteomyelitis in this study. A prior history of diabetic foot infection and the presence of osteomyelitis play major roles in treatment failure and advancement of the condition necessitating amputation [6, 7, 12]. An association between the

presence of osteomyelitis and frequency of amputation, similar to the current study, has been reported in many previous studies [1, 4, 12, 15]. The rate of amputation in the present study was identified as 16.4%. The high rate of amputation might be due to the fact that our hospital is a tertiary hospital and thus particularly complicated cases are generally referred to this hospital. The presence of a prior diabetic foot infection and a statistically significantly high rate of osteomyelitis and amputation, especially in this group of patients, support the findings of the previous studies performed [1, 7].

Obtaining a sample by aspiration following careful

cleansing with serum saline without using any antiseptic solutions in cases when deep tissue and biopsy samples could not be obtained for various reasons has been reported to be more reliable compared to superficial swab samples in the isolation of causative agents in these infections [1, 3, 4]. In the present study, debridement materials and pus aspiration materials obtained from the lesions were evaluated. Anaerobic cultures can be performed in only 16 patients with no isolation of any causative agents, while aerobic cultures were performed in each sample. The reason for the inadequate detection of anaerobic agents may be due to the fact that they could not be performed in an adequate number of patients. Anaerobic bacteria frequently are involved in generally severe infections; however, isolation rates of anaerobic agents is low due to various factors such as the difficulties in obtaining and transport of these anaerobic culture samples and technical insufficiencies.

The most commonly seen microorganism in diabetic foot infection is *S. aureus*, while other gram positive microorganisms, gram negative aerobic bacilli, and anaerobic microorganisms may also be the causative agent. Although the agent is a single one in mild to moderate or acute infections (most commonly *S. aureus*), the most frequently seen agents in severe or chronic infections are gram negatives and anaerobes and polymicrobials, in general [1, 3, 7, 22]. A total of 89 causative pathogens were identified in 52 patients (71.2%) and no agent could be identified in the rest of the patients (28.7%). The number of causative agents identified was more than one in 30 patients (41%). The most frequently isolated bacteria were, *P. aeruginosa* (30%), *S. aureus* (25.5%), and enterococcus spp. Some studies have found *P. aeruginosa* as the most frequently seen causative agent, similar to the current study [1, 9]. The isolation of *P. aeruginosa* as the most commonly seen agent in the current study may be due to the fact that 53.4% of our patients were Wagner stage  $\geq 3$ . The agents in severe infections with a high risk of amputation due to advancement of the lesion into the deep tissues and accompanying osteomyelitis are most commonly polymicrobial in contrast to low risk infections.

Empirical antibiotic treatment should be started

early in these patients due to the risk of fast dissemination of infection to the deep tissues. The application of surgical debridement in addition to possible empirical antibiotic treatment decreases morbidity and mortality [1, 3, 23]. There is no gold standard antimicrobial treatment regimen in the management of diabetic foot infections [3, 23]. The severity of the infection, probability of the presence of resistant microorganisms, accompanying microvascular complications, the presence of osteomyelitis, and a prior history of infection episodes should all be taken into account. Since the most commonly encountered agents in mild to moderate superficial infections are gram positive bacteria and mainly staphylococci, targeting gram positive cocci in empirical therapy is reported to be adequate and monotherapy is generally stated to be effective in this group of patients. For the initial treatment of this type of infections, oral amoxicillin-clavulanate or parenteral beta-lactam + beta-lactamase inhibitors such as ampicillin /sulbactam, piperacillin/tazobactam, ticarcillin /clavulanic acid are among the recommended drugs. The most important advantages of beta-lactam + beta-lactamase inhibitors are the possibility of the application of monotherapy, the presence of oral forms, and the avoidance of disadvantages of multiple drug use [1, 3, 24-26]. Monotherapy was administered to 27 out of 73 patients (36.9%), while combined antibiotherapy was administered to 46 patients (63%). However, 44.4% of those patients had superficial soft tissue infection, while 54.6% had osteomyelitis. Piperacillin-tazobactam was the most common (66%) used agent as monotherapy. An analysis of isolated bacteria revealed that gram negative bacteria such as *P. aeruginosa* and gram positive bacteria such as *S. aureus* ranked first. This finding is compatible with the opinion that suggests the use of a beta-lactam+beta-lactamase inhibitor such as piperacillin-tazobactam in empirical treatment which has gram negative, antipseudomonal, and anti-anaerobe efficacy, in addition to gram positive efficacy.

Anti-anaerobic agents should be included in the treatment regimen in the presence of predisposing factors for amputation due to the high rate of involvement of anaerobic

bacteria in diabetic foot infections. Therefore, initially, monotherapy or combined antibiotherapy including wide spectrum antibiotics should be selected that will cover gram positive, gram negative, and anaerobic bacteria in empirical treatment. Parenteral monotherapy with beta-lactam+beta-lactamase inhibitors such as ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin-clavulanic acid, carbapenems, ciprofloxacin+clindamycin combination, or third/fourth generation cephalosporines +clindamycin/metronidazole combinations can be preferred in this group of patients [1, 3, 24-26]. Combined antibiotherapy was applied in 46 patients (63%) in this study. A deep soft tissue infection was present in 47.8% of our patients, while 52.2% had osteomyelitis. Eleven (91.7%) out of 12 patients who underwent amputation had received combined antibiotherapy. The most commonly used combination was vancomycin+meropenem (41.3%). Other antibiotics that were used in combined antibiotherapy were combinations of ampicillin-sulbactam+ciprofloxacin, vancomycin+piperacillin-tazobactam and glycopeptide+rifampin combinations. In other studies published in the literature, factors such as prior history of diabetic foot infection, presence of osteomyelitis, poor glycemic control, advanced age, accompanying microvascular complications, and Wagner stage ?3 were reported to negatively affect the treatment success and to be the predisposing factors for amputation; therefore, wide spectrum antibiotics have been recommended in this group of infections [1, 4, 12, 15]. The reason for the frequent use of carbapenem group of antibiotics and glycopeptides in the present study is the presence of recurrent cases, advanced age, and presence of life-threatening and severe infections. The frequency of amputation and presence of osteomyelitis was statistically significant. The reason for this was thought to be the failure of treatment due to the difficulties in penetration of the antibiotics to the bony tissues in osteomyelitis or delay in the diagnosis of osteomyelitis.

The multidisciplinary treatment approach involves surgical debridement, control of blood glucose levels, and some procedures such as bone resection in the presence of osteomyelitis in addition to

appropriate antimicrobial treatment.

## Conclusions

Diabetic foot infection is a major health problem, since it causes loss of labor, psychosocial damage, and economic loss due to high treatment costs. Appropriate foot cares and good glycemic control decrease the rate of development of infections and amputations by 50% [22]. Therefore, the primary approach to diabetic foot infection should be education of the patient regarding the complications of diabetes. In addition, a multidisciplinary approach and follow-up at all stages is necessary.

### *Conflict of interest*

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## Relationship between internet addiction, psychopathology and self-esteem among university students

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### ABSTRACT

**Objectives.** Internet addiction is closely associated with general psychopathology and interpersonal relationships. The aim of our study is to investigate the relationship between internet addiction, psychopathology and self-esteem among university students. **Methods.** One hundred and eighty-five volunteer university students were involved in this study. The participants are evaluated with socio-demographic data form, Internet Addiction Scale (IAS), Symptom Check List (SCL-90), Rosenberg Self-Esteem Scale (RSES). **Results.** In order to evaluate the internet addiction, the participants were divided into three internet addiction (IA) groups as "none", "low" and "moderate/high" according to their addiction status. The addiction status was assessed as risk of low level in 59 (31.89 %) participants, high level in 27 (14.59 %) participants and none in 99 (53.51%) participants. A high positive correlation was found between IAS and SCL-90 subscales and RSES ( $p<0.001$ ). In three different IA groups it was found out that all SCL-90 subscale averages increase ( $p<0.001$ ), and RSES subscale averages decrease ( $p=0.001$ ) as internet addiction severity increases. According to regression analysis it is seen that, all SCL-90 subscale scores explain 19.4% of IAS scores and, all SCL-90 subscales and RSES subscale scores explain 25% of IAS scores. **Conclusions.** Significant relationship was found between internet addiction and general psychopathology and self-esteem. This result shows that psychopathology and self-esteem must be taken into consideration as important parameters in approach to internet addiction.

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**Keywords:** Internet addiction; psychopathology; self-esteem

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## Introduction

Despite the simplicity it brings to our daily lives, one of the most important problems that we face with internet is the internet addiction (IA) that is associated with loose of control of the user on internet usage [1, 2]. It is thought that among reasons of IA there may be psychological, neurobiological and cultural factors [3]. In studies about IA; it was found out that addiction scores are positively correlated with depression and anxiety scores, and individuals with IA are more affected by depression and anxiety. At the same time, it was observed that there are depressive symptoms in more than half of the ones who seek for IA treatment, and depressive symptoms diminish in treated individuals with IA [4-8].

It is evaluated that, personality traits of the young people with IA are different, in addition to depression and anxiety symptoms, introversion, neurotic personality traits, hyperactivity and impulsivity signs are much more in people with IA; second axis clinical diagnosis of the young people with IA may be borderline personality disorder, obsessive compulsive personality disorder [9-12]. It is seen that, paranoid ideation, hostility, anxiety, depression, interpersonal sensitivity, obsessive compulsive average scores are higher in individuals with high IA scores than the ones without IA [13, 14]. It is reported that in the individuals with IA, attention deficit hyperactivity disorder (ADHD) incidence and ADHD scores are higher, and obsessive compulsive symptoms, attention and motor impulsivity may raise internet addiction [15-17]. Beside this, it is shown that overuse of internet may cause deprivation as in the substance usage disorder, and internet addicted people have difficulty in inhibition of inappropriate behavior [18, 19].

Another important topic in IA is self-esteem. Especially, it is evaluated that there is a significant relationship between low self-esteem and IA; and self-esteem of people with IA increases significantly after treatment [20-22]. It is assessed that self-esteem mediates positive parental behavior which is important for IA [23]. It is reported that, self-esteem explains 38% of IA with life satisfaction and isolation, and it may explain time management problems, interpersonal relationships and health problems in IA [24]. In another study, it is considered that, self-esteem may be an important factor in relationship between childhood abuse and internet addiction, and self-esteem may predict internet addiction in these individuals and it may be a factor to be considered

in treatment process of these individuals [25]. It is reported that there is a significant relationship between severity of IA and depressive symptoms, somatic symptoms and low self-esteem, and it is suggested that anxiety, depression and self-esteem must be taken into consideration in IA prevention and intervention programs for adolescents with attention deficit and hyperactivity diagnosis [26].

The severity of internet addiction and several psychopathological features and self-esteem may be closely related to each other. Beside this, self-esteem may have an important role as well as psychopathological features in prediction of IA. The aim of this study: is to analyze the relationship between internet addiction, psychopathology and self-esteem among university students.

## Methods

In this study, students of Bursa Orhangazi University were evaluated in April 2014. We have obtained permission from the university administration and the students were informed about the study before participation.

Participation was determined on a voluntary basis and participation approval permission was taken from each student. 200 students were evaluated in our study who declares to use internet. Exclusivity criteria of the study were determined as incorrect or incomplete measurement and 15 students' data were excluded from the study as they were incorrect or incomplete. In our study exclusion criterias are schizophrenia, manic phase of bipolar disorder and psychosis are determined. But with these exclusion criteria of the subjects it did not appear to be any person.

The students were evaluated as groups in a quiet classroom. Following the briefing the participants were assessed with socio-demographical data form and scales of paper and pencil tests.

### *Internet Addiction Scale (IAS)*

Validity of the Internet Addiction Scale (IAS) [27] which was developed by Nicolas and Nichi in 2004 in order to evaluate the internet addiction(IA) was made by Kayri and Gunuc (2009) in Turkey on

university students [28]. The Crombach  $\alpha$  value of the scale was found as 0.93 in this study. Scale is composed of 31 articles and there is no reverse scored article. The attitudes in likert form are scored as; "1-never, 2-rarely, 3-sometimes, 4-frequently and 5-always" and the scores of the scale ranges between 31 and 155. In the validity study made by Kayri and Gunuc (2009) addiction scores are evaluated in 5 groups as 30-60, 61-70, 71-80, 81-89 and 90-over. However, in the study of Dalbudak and friends on the university students in our country, it is seen that cut-off point of the scale in terms of addiction is 81, and IA is assessed in three groups in IAS as 30-60 (no addiction), 61-80 (light addiction) and 81 and over (risk in terms of addiction/addicted) [9]. Therefore we also evaluated the severity of total IAS scores of the participants in 3 groups as determined by Dalbudak and friends.

*Symptom Check List (SCL-90)*

Symptom Check List is an evaluation tool which was developed by Derogatis (1983) and that evaluates psychiatric symptoms composed of 90 articles and 9 subscales [29]. Validity and reliability of the scale was made by Dag (1991) and its reliability co-efficient according to subscales were as follows; Somatization (SOM) 0.82; Obsessive-Compulsive (O-C) 0.84; Interpersonal Sensitivity (INT) 0.79; Depression (DEP) 0.78; Anxiety (ANX) 0.73; Anger-Hostility (HOS) 0.79; Phobic Anxiety (PA) 0.78; Paranoid Ideation (PAR) 0.63; Psychoticism (PSY) 0.73; Additional Scale (AS) 0.77 [30].

*Rosenberg Self Esteem Scale (RSES)*

The inventory developed by Rosenberg is used for the purpose of self-esteem evaluation of the individuals [31]. The validity of the inventory was made by Cuhadaroglu in our country and the test retest reliability of the inventory was found as 0.89 [32]. The sub dimensions of the inventory composed of 63 multiple choice articles are as follows: Self-esteem, Continuity of self-concept, Relying on people, Sensitivity to criticism, Depressive mood, Visionary, Psychosomatic symptoms, Feeling threatened in interpersonal relationships, Degree of participating in discussions, Interest of parents, Relationship with father, Psychic isolation. Increase of scores obtained from these subscales (except relationship with father) is evaluated as a negative situation in terms of self-esteem. Increase of the score obtained from Relationship with father subscale shows that relation with father increases. All subscales of the inventory are used in our study.

*Statistical Analysis*

In this study, the data has evaluated with SPSS 22.0 program. For all analyzes, a level of significance  $\alpha=0.05$  was determined. We have used the independent groupst test to evaluate socio-demographic data; Kruskal Wallis analysis to compare psychopathology and self-esteem in three different internet addiction (IA) groups (without IA, mild IA, moderate/high IA); and Pearson correlation coefficient and hierarchical linear regression analysis to analyze the relationship between internet addiction and self-esteem.

**Table 1.** Correlations between the scale scores.

	1	2	3	4	5	6	7	8	9	10	11	12	13
<b>1-IAS</b>	-												
<b>2-SE</b>	0.25*	-											
<b>3-S</b>	0.34*	0.34*	-										
<b>4-O-C</b>	0.40*	0.40*	0.68*	-									
<b>5-INT</b>	0.41*	0.38*	0.56*	0.67*	-								
<b>6-DEP</b>	0.42*	0.48*	0.71*	0.75*	0.79*	-							
<b>7-ANX</b>	0.45*	0.42*	0.79*	0.77*	0.73*	0.84*	-						
<b>8-HOS</b>	0.37*	0.33*	0.57*	0.62*	0.59*	0.65*	0.77*	-					
<b>9-PA</b>	0.35*	0.36*	0.63*	0.60*	0.69*	0.74*	0.77*	0.62*	-				
<b>10-PI</b>	0.33*	0.35*	0.61*	0.63*	0.74*	0.70*	0.76*	0.69*	0.68*	-			
<b>11-PSY</b>	0.41*	0.38*	0.63*	0.70*	0.72*	0.73*	0.80*	0.61*	0.76*	0.71*	-		
<b>12-AS</b>	0.32*	0.33*	0.60*	0.60*	0.62*	0.72*	0.71*	0.58*	0.66*	0.66*	0.69*	-	
<b>13-GP</b>	0.45*	0.45*	0.81*	0.84*	0.84*	0.91*	0.94*	0.78*	0.83*	0.83*	0.86*	0.79*	-

IAS=Internet Addiction Scale, SE=Self Esteem S=Somatization, O-C=Obsessive-Compulsive, INT=Interpersonal Sensitivity, DEP=Depression ANX=Anxiety, HOS=Anger-Hostility, PA= Phobic Anxiety, PI=Paranoid Ideation, PSY=Psychoticism, AS= Additional Scale GP= General Psychopathology, \* $p<0.001$ .

**Table 2.** Comparing subscale scores according to severity of internet addiction (IA)

	without IA n=99		mild IA n=59		moderate/high IA n=27		Chi-Square	p
	mean	SD	mean	SD	mean	SD		
<b>Somatization<sup>b</sup></b>	0.48	0.46	0.66	0.44	1.02	0.71	17.70	<0.001
<b>Obsessive-Compulsive<sup>b</sup></b>	0.98	0.61	1.32	0.73	1.64	0.84	16.20	<0.001
<b>Interpersonal Sensitivity<sup>a</sup></b>	0.71	0.64	1.06	0.63	1.46	0.96	21.83	<0.001
<b>Depression<sup>b</sup></b>	0.65	0.60	0.85	0.57	1.46	0.96	20.40	<0.001
<b>Anxiety<sup>a</sup></b>	0.58	0.60	0.91	0.69	1.50	1.02	26.10	<0.001
<b>Anger-Hostility<sup>b</sup></b>	0.64	0.73	0.88	0.75	1.41	0.97	18.64	<0.001
<b>Phobic Anxiety<sup>b</sup></b>	0.31	0.46	0.41	0.51	0.84	0.88	11.40	0.003
<b>Paranoid Ideation<sup>b</sup></b>	0.78	0.66	1.02	0.61	1.24	0.75	13.23	0.001
<b>Psychoticism<sup>a</sup></b>	0.37	0.42	0.59	0.49	0.90	0.76	19.00	<0.001
<b>Additional Scale<sup>b</sup></b>	0.71	0.60	0.91	0.53	1.17	0.91	10.04	0.007
<b>General Psychopathology<sup>b</sup></b>	0.62	0.47	0.86	0.48	1.29	0.81	22.06	<0.001
<b>Continuity of self-concept<sup>c</sup></b>	3.17	1.30	3.66	1.16	3.85	1.26	10.23	0.006
<b>Relying on people<sup>d</sup></b>	2.56	1.12	3.00	0.98	2.74	1.12	6.64	0.036
<b>Sensitivity to criticism<sup>e</sup></b>	1.49	1.06	1.89	1.09	1.88	1.05	6.20	0.045
<b>Depressive mood<sup>e</sup></b>	1.52	1.14	1.69	1.00	2.07	1.07	4.63	0.099
<b>Visionary<sup>a</sup></b>	1.13	1.20	1.67	1.41	2.51	1.34	18.08	<0.001
<b>Psychosomatic symptoms<sup>b</sup></b>	2.26	2.16	2.88	2.48	4.66	2.61	16.36	<0.001
<b>Feeling threatened in interpersonal relationships<sup>d</sup></b>	0.81	0.92	1.05	0.91	1.29	0.91	7.69	0.021
<b>Degree of participating in discussions<sup>e</sup></b>	1.08	0.88	0.81	0.86	0.92	0.91	3.92	0.141
<b>Interest of parents<sup>e</sup></b>	1.18	1.38	1.20	1.04	1.51	1.76	0.90	0.630
<b>Relationship with father<sup>b</sup></b>	1.19	1.11	1.22	1.13	2.14	1.76	9.78	0.007
<b>Psychic isolation<sup>e</sup></b>	0.66	0.76	0.79	0.86	1.03	0.89	3.72	0.156
<b>Self-esteem<sup>c</sup></b>	0.81	0.60	0.90	0.61	1.25	0.89	7.41	0.025

<sup>a</sup>Moderate/high>mild>no. <sup>b</sup>Moderate/high>mild, no. <sup>c</sup>Moderate/high>no. <sup>d</sup>Moderate/high, mild>no. <sup>e</sup>Moderate/high, mild, no.

## Results

The participants of our study were composed of 81 men (43.78%), and 104 women (56.21%). The internet addiction scores obtained show that, 99 of the individuals with an age average of 19.51±1.04 (53.51%) have no addiction, 59 of them (31.89%) have light addiction and 27 of them (14.59%) have high risk of addiction/addicted. As we assess the socio-demographic properties, we have not found significant variety in IAS score averages in terms of independent groups t-test results that is applied according to sex ( $p=0.471$ ,  $F=0.487$ ,  $t=-0.723$ ), usage of tablet ( $p=0.502$ ,  $F=0.02$ ,  $t=-0.672$ ), android

telephone ( $p=0.644$ ,  $F=1.219$ ,  $t=0.463$ ), loss of education year ( $p=0.655$ ,  $F=0.704$ ,  $t=-0.448$ ), smoking situation ( $p=0.122$ ,  $F=0.097$ ,  $t=1.556$ ). We have found out a high level of positive correlation ( $p<0.001$ ) among IAS scores and self-esteem subscale scores and SCL-90 total and some subscale scores (Table 1).

When we compare the SCL-90 subscale grades of IAS scores of three groups with no addiction, light and high internet addiction levels with Kruskal Wallis analysis, we found out that somatization, obsession, interpersonal sensitivity, depression,

**Table 3.** Linear regression analysis model when IAS score was taken as a dependent variable.

	Unstandardized coefficients		t	p
	B	Standard error		
(Constant)	40.964	5.248	7.806	<0,001
Somatization	0.084	3.718	0.023	0.982
Obsession	2.093	2.712	0.772	0.441
Interpersonal Sensitivity	1.413	3.114	0.454	0.651
Anger-Hostility	4.441	2.304	1.927	0.056
Phobic Anxiety	-1.199	3.605	-0.332	0.740
Paranoid Ideation	-1.837	3.012	-0.610	0.543
Psychoticism	4.787	4.253	1.126	0.262
Additional Scale	-1.913	2.778	-0.689	0.492
Depression	-2.007	3.971	-0.505	0.614
Anxiety	3.216	4.281	0.751	0.454
Continuity of self-concept	2.028	0.965	2.101	0.037
Relying on people	-0.042	1.106	-0.038	0.970
Sensitivity to criticism	-0.395	1.206	-0.327	0.744
Depressive mood	-0.194	1.242	-0.156	0.876
Visionary	2.256	0.955	2.361	0.019
Psychosomatic symptoms	-0.291	0.662	-0.439	0.661
Feeling threatened in interpersonal	1.901	1.378	1.380	0.170
Degree of participating in discussions	-1.296	1.419	-0.914	0.362
Interest of parents	0.990	0.892	1.110	0.269
Relationship with father	2.216	0.979	2.264	0.025
Psychic isolation	1.435	1.591	0.902	0.369
Self-esteem	-0.315	1.991	-0.158	0.874

IAS= Internet Addiction Scale, Variables entered SCL-90 subscales and Rosenberg Self-Esteem Inventory Subscales; F= 3.724,  $p<0.001$  adjusted R2 =0.250 R2 change =0.103.

anxiety, anger-hostility, additional, psychoticism SCL-90 subscales and SCL-90 total score averages vary in a level of  $p<0.001$ , whereas SCL-90's paranoid ideation and phobic-anxiety subscale score averages vary in a level of  $p<0.003$ . We also found out that, Rosenberg self-esteem inventory subscales such as depressive mood, ability to participate in discussions and psychic isolation subscale score averages in 3 different internet addiction groups do not vary as a result of Kruskal Wallis analysis, visionary and psychosomatic symptoms sub scales vary in a level of  $p<0.001$ , self-esteem vary in a level of  $p<0.05$  and other scale averages vary in a level of  $p<0.05$  (Table 2).

In the linear regression analysis; it is reported that all SCL-90 subscales explain 19.4% (F=5.329,  $p<0.001$ , adjusted R2=0.194 R2 change=0.239) of

IAS scores. It is determined that, all SCL-90 subscales and all Rosenberg Self-Esteem Inventory subscale scores explain 25% ( $p<0.001$ ) of IAS scores (Table 3).

## Discussion

In our study, the rate of the individuals carrying risk in terms of IA and with a risk of high internet addiction was determined as 14.59%. When the other studies made on university students are evaluated, it is assessed that the ratio that we obtain in terms of addiction is lower 19.9 % [9], 17.9% [33] than some studies, 6,4% [34], 7,2% [35], 12,2% [36], 14,4% [37] while higher than some other.

We stated a high positive correlation ( $p < 0.001$ ) between IAS scores and SCL-90 all subscale scores (somatization, obsession, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation, psychoticism, additional scales). It is reported in the literature that IA and anxiety and depression are highly positively associated, the designs about psychopathologic features in internet addicts vary and SCL-90 subscale scores are highly positively ( $p < 0.001$ ) associated with IA scores [13, 14]. It is shown in many studies that SCL-90 subscale averages increase significantly as severity of IA group increases. [9, 13, 14, 38-40]. We also evaluated in our study that, average of general psychopathologic features in three internet addiction groups differentiate, and general psychopathologic features averages increase as internet addiction severity increases. In the clinical assessments on internet addicts, it is found out that several additional psychiatric disorders accompany internet addiction in these people [7, 9, 12].

We stated in our study that IAS scores have the highest correlation with anxiety and depression subscales. Beside this, it is found out in results of Kruskal Wallis analysis that anxiety and depression scores increase as IAS scores increase. In many studies in the literature it is declared that; depression and anxiety assessed among leading psychopathologic features in internet addiction not only frequently accompany internet addiction in the clinical picture, but also presents high positive correlation with internet addiction in correlative studies [4-8]. High presence of isolation, depressive mood and impulsivity in the groups assessed as internet addicts and unusual sympathy of these people towards strangers and their rather vulnerable situation in interpersonal relationships may explain these psychopathologic processes in IA addiction [41].

It is found out that self-esteem in the internet addicts is lower than healthy individuals, and self-esteem of internet addicts increases after treatment [42, 22]. Similarly, we determined in our study that there is a decrease in self-esteem as IAS scores increase. It is also stated in the literature that self-esteem is associated with IA severity, it acts as intermediary for psychological factors that may be associated with IA and it is an important factor that explains the time management problems, interpersonal relationships and health problems in internet addicts [23-25]. Nonetheless, it is also put forward that, not only self-

esteem of the person himself but also his self-esteem regarding social and family concept is effective in explaining IA scores and self-esteem may decrease with decreasing control regarding addiction in addicted adolescents [43].

In our study we concluded that, visionary and psychosomatic symptom subscale score averages increase significantly as IA severity increases; and that depressive mood, ability to participate in discussions and psychic isolation subscale averages do not differentiate significantly. Differentiation of psychosomatic symptoms subscale averages associated with psychopathologic features in IA groups supports the results that we obtain from SCL-90 subscales. However, it may be assumed that the same situation is not valid for depressive symptoms subscale averages. At the same time, it is determined that relationship with the father increases and interest of parents subscale averages do not change as internet addiction severity increases. The fact that the interest of parents subscale score averages do not change and the increase of relationship with father as IA severity increases is not compatible with the results of other studies in the literature. It is put forward that, self-esteem is associated with mother and father education status, mother's job, family's level of income and direct interest of the family and parental attitudes, family communication and family atmosphere are important factors in internet addiction. [44-48]. Despite this, it is discussed in the literature that overprotective family attitudes, especially overprotective behavior of the fathers may be associated with internet addiction [23].

It is evaluated that IA is associated with social inhibition and social maladjustment [42, 49]. In our study, differentiation of averages of continuity of self-concept, sensitivity to criticism, relying on people and feeling threatened in interpersonal relationships subscales in three IA groups may be related to socialization problems of internet addicts. A suggestion of a family based protective approach may be profitable in internet addiction treatment which is similar to the risk factors of substance addiction [50]. According to linear regression analysis results, psychopathologic features explain 19.3% of IA scores, psychopathologic features and self-esteem explain 25% of IA scores in our study. In the study made by Khoshakhlagh and Faramarzi, SCL-90 subscales are proved to explain 49% of internet addiction [51]. In

the study of Bahrainian and Khazae depression and self-esteem explain 11% of internet addiction [52]. In another study, it is seen that temperament and character properties, alexithymia, depression and anxiety explain 21% of IA scores [36]. In a study made by Dalbudak and Evren it is found out that neuroticism, psychoticism, extraversion, lie sub-personality features and hyperactivity/impulsivity, anxiety and depression explain 35.2% of IA scores [9]. At this point when we evaluate the results we have obtained, we may assume that primarily psychopathologic features and self-esteem are important while explaining IA scores.

Some limitations of our study are; small number of subjects, lack of clinical examination, and our results are only generalizable to university students. As a result; realization by the clinicians of family dissatisfaction of the internet addicted adolescents, increasing self-esteem in internet addiction, explanation of psychopathologic elements involved in addiction and preparation of a systematic treatment plan in which addicted individual and the family are included is suggested [53-54]. With the results we obtained we similarly observe that, general psychopathologic features and self-esteem and self-esteem related factors (continuity of self-concept, relying on people, sensitivity to criticism, depressive mood, visionary, psychosomatic symptoms, feeling threatened in interpersonal relationships, ability to participate in discussions, interest of parents, relationship with father, psychic isolation) present risk in university students in terms of internet addiction. That's why, in the conclusion of our study, we may suggest considering all psychopathologic features, self-esteem and self-esteem related factors as well as anxiety and depression in internet addiction treatment and in internet abuse prevention programs.

#### *Conflict of interest*

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

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## Evaluation of headache in children: a retrospective study

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### ABSTRACT

**Objectives.** Headache is a very common symptom that can be seen in the children. It can be seen due to primary or secondary causes. Migraine and tension-type headache are the most commonly seen primary headache types in children. In this study, we retrospectively evaluate etiologic and clinical features of the 228 patients. **Methods.** In this study, clinical features and neuro-imaging characteristics of the patients, who admitted Eskisehir Osmangazi University pediatric neurology department between 2007 and 2011 were evaluated retrospectively. Headache classification was made according to "International Headache Society" criteria. **Results.** The ages of the patients ranged from 4 to 18 years (average 12.9±3.1). There were 136 (59.6 %) girls, and 92 (40.4%) boys. The most frequent causes of the headache were migraine (37.3%) and tension type headache (25%). There were other associating diseases at 54 (23.7%) patients. Allergic rhinitis and asthma bronchilitis were the most commonly associated diseases. Abnormalities were encountered in 3 (6.8%) of the 44 (19.3%) patients taken computerized brain tomography, 18 (20.2%) of the 89 (39%) patients taken magnetic resonance imaging and 8 (3.5%) of the 77 (33.8%) patients taken electroencephalography. No serious problem is established in patients undergoing neuro-imaging. **Conclusions.** In this study, it was seen that migraine and tension-type headache are the most frequently seen causes of the headache in the children. It is concluded that unnecessary neuroimaging examination should be avoided by detailed anamnesis and neurologic examination of children that admitted hospital with headache complaint.

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**Keywords:** Headache; child; migraine; tension type headache; neuroimaging

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## Introduction

As in adults, headache is the frequent complaint of children and adolescences that admitted to clinics and emergency rooms and also to neurology clinics. Whereas families think headache is rarely seen at children, so they especially concern brain tumor [1]. Headache frequency increases with aging. Headache frequency is determined as 46.2% in Isyk *et al.*'s epidemiologic study made with 2669 children aged between 5-13 years [2].

Headache can be seen due to primary and secondary causes. Headaches can be due to a simple infection as well, though rarely due to intracerebral hemorrhage or meningitis or a brain tumor. Migraine and tension type headache are the most frequently seen primary headache types at children. Since the age of the child will affect the headache statement of child; frequency, diagnosis and treatment of headache may be different in each age group. The patient admitting with headache must be evaluated detailed. Medical history plays important role to rule out secondary causes. Taking good anamnéza, detailed physical and neurological examination and headache diary are the important and critical steps for diagnosis and treatment [3,4].

In this study 228 patients aged 4-18 years of age are evaluated retrospectively with the etiologic, clinical and neuroimaging findings between 2007-2011.

## Methods

Two hundreds and twenty-eight patients aged 4-18 years of age are evaluated retrospectively with the etiologic, clinical and neuroimaging findings between 2007-2011 that admitted Eskisehir Osmangazi University Medical Faculty pediatric neurology department for headache complaint. Frequency, duration, location, lateralization of headache, presence of triggering factor, associated symptoms, presence of treatment for sinusitis, transmission of any other diseases, family history of headache/migraine, neurologic examination findings are recorded. Neuroimaging findings are evaluated. Headache classification is made according to "International Headache Society" criteria [5].

## Results

Patients aged between 4-18 (median  $12.9 \pm 3.1$ ), 136 (59.6%) of them are female, 92 (40.4%) of them are male, 228 patients in total are retrospectively evaluated. Female to male ratio was 1.48. In about three-quarters of patients with headache it was ongoing for more than 6 months. Headache duration, frequency, localization, attack duration, causes of headache and classification are shown at Table 1.

Headache in 133 patients (58.3%) passed with painkillers, 95 (41.7%) had no response. 89 patients (39%) had a history of getting sinusitis treatment due to headache. Blood pressure values of all other patients except one patient were normal. Neurological examination findings for all patients except for patients having meningitis diagnosis and neurodevelopmental delay was natural. 3 patients having Pseudotumor cerebri diagnosis had papilledema. In 4 patients having Meningitis and pseudotumor diagnosis, lumbar puncture was performed.

The most frequent cause of the headache is migraine (37.3%) and tension type headache (25%). 39 (68.4%) of 57 patients having tension type headache diagnosis were female. Headache was bilateral at 51 (89.5%) of the patients. There was family history at 18 (31.5%) of patients that had tension type headache. 44 (51.8%) of 85 patients with migraine were female, 41 (48.2%) were male, female to male ratio was 1.07. Headache was bilateral at 64 (75.3%) of the patients while 21 (24.7%) of the patients was unilateral. 81 (95.3%) of the patients had migraine without aura, the rest 4 (4.7%) had migraine with aura, 3 of them with visual findings, one of them had parestesias. Noise and stress were the most seen triggering factors at 41 (48.2%) of the patients. The other triggering factors were fatigue, sleeplessness, odor, menstruation, reading a book, taking bath, coffee, computer, and watching television. In 62 patients (72.9%), most commonly nausea, vomiting, and photophobia as visual finding and paresthesia, vertigo, wetting of the eyes and phonophobia as associating symptoms of migraine were seen. 52

(61.2%) patients had a family headache history, including migraine in 35 (41,2%) patients.

Fourteen (6.1%) of 24(10.5%) patients that their headache was evaluated as psychological has major depression and common anxiety disorder diagnosis at child psychiatry clinics. There was an associated disease at 41(18%) of the patients. Most commonly associated diseases are allergic rhinitis and asthma

bronchitis whereas the other ones are obesity, goitre and attention deficit hyperactivity disorder.

Neuroimaging was done in 133 (58.3%) patients. In 112 (84.2%) out of 133 patients, no abnormal finding was reported. There were abnormal findings in three (6.8%) of 44 patients with CT imaging and 18 (20.2%) of 89 patients performed MRI. Neuroimaging findings are seen in Table 2.

**Table 1.** Features, causes and classification of the headache

	Patients (n=228)	%
<b>Duration of the headache</b>		
<7 days	10	4.4
<8 days- 1 month	28	12.3
1-5 month	28	12.3
6-12 month	100	43.9
1-3 years	34	14.9
3-6 years	13	5.7
?6 years	15	6.6
<b>Headache frequency</b>		
Every day	75	32.9
More than once per week	91	39.9
More than once per month	52	22.8
Every two-three months	10	4.4
<b>Duration of headache attack</b>		
<30 minutes	32	14
30-60 minutes	26	11.4
1-4 hours	114	50
4-24 hours	48	21.1
?24 hours	8	3.5
<b>Lateralization of headache</b>		
Bilateral	188	82.5
One sided	39	17.1
Variable	1	0.4
<b>Location of the headache</b>		
All over head	87	38.2
Forehead	64	28
Temple	48	21.1
Nape ache	17	7.5
Eye	7	3
Vertex	5	2.2
<b>Causes</b>		
<b>Primary headache</b>		
Migraine	85	37.3
Tension type headache	57	25
<b>Secondary headache</b>		
Sinusitis	31	13.6
Pshchologic	24	10.6
Visual abnormality	10	4.4
Trauma	6	2.6
Structural disorder of the neck and eye	6	2.6
Pseudotumor cerebri	3	1.3
Upper airway infection	2	0.9
Otitis	2	0.9
Menengitis	1	0.4
Hypertension	1	0.4

**Table 2.** Neuroimaging findings of the patient

Neuroimaging findings	Patients	%
<b>Brain CT</b>		
Retention cyst at maxillary sinus	2	0.9
Arachnoid cyst	1	0.4
<b>Brain MRI</b>		
Nonspecific hyperintensities	6	2.6
Arachnoid cyst	5	2.2
Periventricular leucomalacia	3	1.3
Retention cyst at maxillary sinus	3	1.3
Arnold Chiari Type I	1	0.4

## Discussion

Headache is one of the frequent symptom seen at childhood. The incidence has been increasing in recent years. In Finland while the frequency of headache at 7 years old children was 14 % in 1974, it was reported as 52 % in 1992. Migraine frequency increased from 1.9 % to 5.7 % [6]. A study made at Turkey between the years 1993-1998 showed that 4.33 % of the patients admitted to clinics with headache complaint [7]. The incidence of the headache has peak value at ages of 12-14 years and headache is seen more frequently at girls [8]. In this study the average ages of the patients were  $12.9 \pm 3.1$  and female to male ratio was 1.47. The most frequent causes of the headache was migraine (37.3%) and tension type headache (25%). Alehan's study revealed that migraine (44.2%) and tension type headache (31.5%) were the most common causes of headache [9]. Migraine is the important cause of headache that negatively influences the life quality of the child. While it is more frequent at males in prepubertal period, at females it is frequently seen in adolescence. Migraine frequency increases with age and it is reported as 3.9% at ages 7-15 [10]. Tension type headache is the second most frequent cause of headache other than migraine [9].

Most common form of migraine at children and adolescences is migraine without aura (60-85%).

Doing homework, fatigue, stress, hunger, bright lights, infections, some food (cheese, chocolate, drinks with caffeine) may trigger headache attacks. Autonomic findings (nausea, vomiting, photophobia, phonophobia) may associate to the pain. Visual symptoms (brighth light, scotoma, blurred vision), auditory and odor hallucinations, motor symptoms (speech disorder, hemiplegia) and autonomic disturbances may be seen at migraine with aura [11]. In this study 95.3% of the patients with migraine without aura whereas 4.7% of them had migraine with aura. Nausea-vomitting, photophobia were the most commonly seen associated symptoms. There was triggering factors where most common ones are stress and noise at almost 50% of the patients. There was family history of headache at 61.2% of the patients with migraine and at 31.5% of the patients with tension type headache. In the study that Alp et al. had made on children that migraine was seen more frequently in females than males (1.45), where 34.4 % had aura and visual and auditory aura were the most frequent ones. Also in this study 84.8% of the patients with migraine and 69.7% of the patients with tension type headache had family history of headache [12].

Headache may associate the underlying disease at children. At France, in a study made with children, it was reported that 43.2% of patients had other

diseases such as psychologic disturbances, gastrointestinal diseases, hyperactivity, epilepsy, endocrine, dermatologic, hematologic diseases including most common allergy and asthma [4]. In this study there was associated diseases at 23.7% of the patients. The other associated diseases were obesity, epilepsy, goitre, deficit attention and hyperactivity including most common allergic rhinitis and asthma. Fouteen patients diagnosed as major depression and common anxiety disorder. Neuroimaging is not necessary at the patients with normal neurologic examination and long lasting repeating headache. If the patient has abnormal neurologic examination or has convulsions or newly started severe headache, cranial MRI that is more sensitive in showing structural defects should be preferred [10]. In this study 58.3 % of the patients had underwent neuroimaging. Neuroimaging findings were normal at 86.4% of the patients. Non spesific hyperintensities, arachnoid cysts, periventricular leukomalacia, Arnold Chiari type 1 malformation, maxillary sinus retention cyst were abnormal neuroimaging findings seen at 15.8% of the patients. Serious neuroimaging findings like brain tumor are rarely detected at childhood headaches, 20% of the patients are reported to have sinusitis, Chiari type 1 malformation, nonspesific white matter hyperintensities, venous angiomas, arachnoid cysts, pineal cysts, cerebral malformations like mega sisterna [13,14].

## Conclusions

In this study, migraine and tension type headache are found to be the most frequent causes for headaches seen in children. In patients where neuroimaging was done, no serious underlying reason was found. It is concluded that unnecessary neuroimaging examination should be avoided by detailed anamnesis and neurologic examination of children that admit hospital with headache complaint.

## Conflict of interest

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

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## Nora's disease: a series of six cases

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### ABSTRACT

**Objectives.** Nora's disease is a mesenchymal bone tumor with controversial diagnosis and treatment due to the benign but locally aggressive course and high recurrence rates. **Methods.** A retrospective analysis was made of patients diagnosed with Nora's Disease at Ankara University Orthopedics and Traumatology Clinic. The evaluation was made of the age of the patient, gender, symptoms, lesion location, trauma history, treatment choice and recurrence rates during follow-up. **Results.** Excision was applied to 6 patients diagnosed with Nora's disease, and in 1 patient an additional autograft and internal fixation were required. Recurrence was observed in 3 patients, 2 of whom underwent revision surgery and one who did not as there no patient complaints. **Conclusions.** Nora's disease is problematic for orthopedic surgeons as there are difficulties in diagnosis, there is no absolute treatment algorithm, recurrence potential is high, and there are limited additional treatment choices. Therefore, treatment and follow-up at clinical center's dealing with orthopedic tumor surgery can be considered appropriate.

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**Keywords:** Nora's disease; excision; recurrence

### Introduction

Nora's disease, first described by Nora et al in 1983, is also known as bizarre parosteal osteochondromatous proliferation (BPOP) and is a mesenchymal formation with bone, fibrous tissue and cartilage components, often located in the hands, feet and long bones, which has a benign but locally aggressive course [1]. It is typically observed in the proximal and mid phalanges, the metacarpals and metatarsals. There is no gender

dominance and although it can be seen at any age, it is generally observed in young patients [1, 2].

Although the radiological appearance of Nora's disease is confusing, wide-based calcified lesions not continuing with the medulla can be evidently differentiated from the bone cortex and may often be confused with osteochondroma [3, 4]. Histologically, without seeming atypical cellular, they are formed

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from a bone, cartilage and fibrous stroma. The cartilage caps are hyper-cellular and contain large double nucleus chondrocytes. Osteoblastic activity is high in the bone structure and suggests reactive activity.

Due to rapid growth, and radiological and histological difficulties in diagnosis, periosteum rooted malignant and benign lesions can be confused in the differential diagnosis. Absolute diagnosis cannot be made radiologically and clinically and sometimes because of the aggressive course histological confirmation is necessary.

In this paper, we wanted to present our clinical experience related to Nora's disease and review the literature with the challenges for orthopedists due to difficulties in diagnosis and treatment.

## Methods

A retrospective analysis was made of 6 patients diagnosed histologically with Nora's Disease

between 1990 and 2014 at Ankara University, Orthopedics and Traumatology Clinic Oncology Department. Patients were evaluated by age, gender, symptoms, lesion location, trauma history, treatment and recurrence (Table 1).

## Results

The patients comprised 4 females and 2 males with a mean age of 39 years (range, 17- 62 years). The lesions were localized in the metacarpal in 2 cases, in the metatarsal in 2 cases and in the medial distal femur in 2 cases. Physical examination revealed localized swelling in all patients and in 4 patients, the lesion was painful. Apart from 2 patients, there was no history of trauma. The mean follow-up period was 72 months (range, 36-132 months).

Using direct radiographs, CT and MRI, radiological evaluation was made of lesion location,

**Table 1.** Data of patients with bizarre parosteal osteochondromatous proliferation.

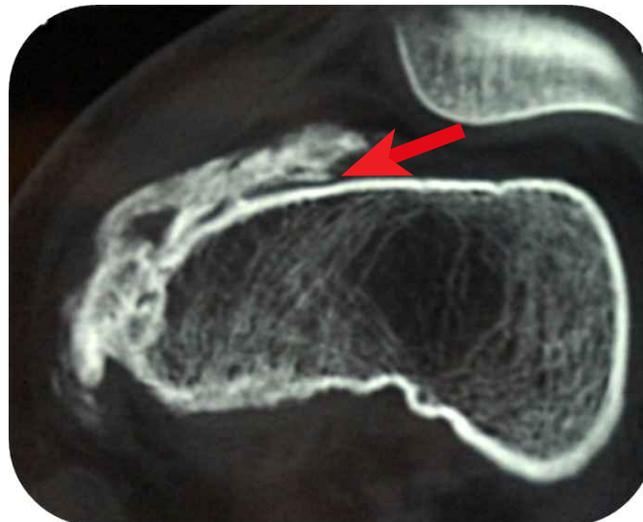
Age / Gender	Location	Size (cm)	Complaint	Treatment	Follow-up / Recurrence
48/F	5 <sup>th</sup> Metacarpal - dorsal	2x3	Painless mass - 2 yrs No Trauma	Excision	11 yrs -No recurrence
58/F	5 <sup>th</sup> Metatarsal - plantar	1x1,5	Painful mass - 1 yrs Trauma +	Excision	6 months- recurrence 5 yrs
17/M	Distal femur - medial	3x2	Painless mass - 1.5 yrs No Trauma	Excision	8 yrs-No recurrence
21/M	5 <sup>th</sup> Metatarsal - lateral	2x1,5	Painful mass - 2.5 yrs No Trauma	Excision Autograft Fixation	4 yrs - No recurrence
28/F	Distal femur - medial	2x2	Painful mass - 1 yr Trauma +	Excision	1 yr -recurrence 5 yrs -No recurrence
62/F	2 <sup>nd</sup> Metacarpal - proximal	1x1	Painful mass - 1 yr No Trauma	Excision	8 months - recurrence 3yrs -No recurrence

periosteal reaction, continuation with the medullar canal, calcifications and soft tissue. Histological examination was made in all cases for an absolute diagnosis.

On direct radiographs, in all lesions, calcified masses adjacent to the bone cortex were seen and damage to the cortex over which they were located. There was no continuity with the medullar canal on CT (Figure 1). On MRI slices, no abnormalities apart from edema were determined in the soft tissue. In the pathological evaluation, the lesion surface was hyper-cellular, fibrous and covered with cartilage tissue, the stroma spindle was of cartilage cells and in the inner part increased osteoblastic activity was observed in the form of bone trabeculae. Following histological confirmation of the diagnosis, the patients were treated surgically.

In 1 patient with metatarsal location, excision, autograft and fixation was applied and in all the other patients only excision was applied (Figure 2 a-d).

Recurrence was observed in a total of 3 patients. In 2 of these patients, revision surgery was applied by extending the excision and recurrence was not observed again in the follow-up. In the other patient with recurrence during follow ups (left foot, proximal 5th metatarsal), as the patient had no complaints, no operation was planned and kept on following for any complaint (Table 1).



**Figure 1.** Axial CT image of lesion with distal femur location. There is no continuity of the lesion to the medullar canal.

### Discussion

Bizarre parosteal osteochondromatous proliferation is an uncommon reactive mineralizing mesenchymal lesion that typically affects the surfaces of bones in the hands and feet, usually the proximal and middle phalanges, and the metacarpal and metatarsal bones [5]. There are two theories related to the formation of Nora's disease. The first



**Figure 2.** Radiographies of lesion with 5th metatarsal location (a,b), image after excision, autograft and fixation (c,d).

is that the lesion forms with a periosteal reaction following trauma [6]. According to the second theory, it is a tumoral process characterized by t(1;17) translocation without any trauma [7]. As there was a history of trauma in 2 of the current cases, the trauma could have been a predisposing factor, and when taking the patient history, the etiology should be kept in mind.

Although Nora's disease has a characteristic clinical and histological appearance, it may be confused with other benign and malignant lesions. The parosteal location distinguishes Nora's disease from parosteal osteosarcoma, which is rarely found in the hands and feet. The absence of cellular atypia helps to distinguish this lesion from osteosarcoma [8]. Again due to location, it can be confused with periostitis ossificans, but it often shows location in the hand and other skeletal systems are not involved.

With osteochondromatous composition, osteochondroma, myositis ossificans and subungual exocytosis may be considered in the differential diagnosis [3]. However, although osteochondroma is the most commonly seen benign bone tumor, it rarely shows involvement close to the physis in the long tubular bones, hand and foot location is rare and the lesion forms continuity with the medullar canal [9, 10]. However, in myositis ossificans cartilage caps are not seen. Anatomic locations of subungual exocytosis is typical and they do not contain classic cartilage tissue [11]. However, much heterotrophic ossification may resemble Nora's disease radiologically, there is generally a history of head trauma.

As confusion is created radiologically and clinically in the absolute diagnosis and because there is sometimes an aggressive course, there are reports recommending excision even if the patient has no complaints [12]. Thus, it is possible to make a histological diagnosis of the lesion.

According to some authors, wide excisions made to the depth of the periosteum together with the mass, reduce the frequency of recurrence. However, due to increased surgical morbidity, there are also authors who do not recommend wide excision as the first treatment option. When there is distal extremity location, wide excision may require amputation. If there is no suspicion of malignancy, marginal excision can be selected as the first stage [13, 14]. Although it is predicted that intralesionary excision increases the possibility of recurrence, the rates of recurrence in the en bloc excision with negative surgical limits used in the cases of the current series were seen to be no different to those of other series. The 50% recurrence rate was similar to the 51% rate of Nora *et al.*, thereby showing again how high the actual recurrence rate is in Nora's disease.

Before evaluating the surgical treatment choice for patients with recurrence, observational follow-up may be firstly considered, taking the patient's complaints into account.

As Nora's disease is rarely seen and the diagnosis and treatment algorithm has not been fully defined, this series of 6 cases can be considered to contribute to literature together with the 35-case series of Nora, the 65-case series of Menses *et al.*, the 24-case series of Dhondt *et al.*, and the 13-case series of Jibu *et al.* [1, 3, 15, 16].

As this study was retrospective, there was a reliance on those who had taken the patient records and as the number of patients was low, statistical analysis could not be applied.

Nora's disease is problematic for orthopedic surgeons as there are difficulties in diagnosis, there is no absolute treatment algorithm, having recurrence potential and there are limited additional treatment choices. Therefore, according to our opinion treatment and follow-up at clinical center's dealing with orthopedic tumor surgery can be considered appropriate.

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## Surgical removal of an embolized amplatzer septal occluder device from the right ventricle

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### ABSTRACT

Atrial septal defect is one of the most common congenital heart defects encountered in adults. Currently, transcatheter atrial septal defect closure techniques have increasingly gained wide popularity as an alternative to surgery in many centers. However, they are associated with severe procedural complications requiring immediate surgical intervention. Here, we report a 29-year-old male patient with device embolization due to the migration of Amplatzer septal occluder device to the right ventricle at an early stage following percutaneous intervention. He underwent an emergency operation because of hemodynamic deterioration. The device was successfully removed with surgery and atrial septal defect was closed with a pericardial patch. The postoperative course was uneventful, and he was discharged from hospital on postoperative day 5.

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**Keywords:** Atrial septal defect; transcatheter closure technique; Amplatzer septal occluder; device embolization; cardiac surgery

### Introduction

A secundum atrial septal defect (ASD) is one of the most common congenital cardiac abnormalities encountered in adults, accounting for 10% to 17% of congenital heart disease [1-3]. In recent years, transcatheter closure of ASD by means of the percutaneous deployment of a variety of occluder devices has increasingly gained wide popularity as an alternative to surgery in many centers [3-7].

As seen in all invasive procedures, complications are encountered from time to time with increasing interventional number. These complications are associated with increased morbidity and mortality rates compared to surgical closure. A major complication of ASD device closure using percutaneous techniques is device embolization or malposition [3-8]. In complicated circumstances,

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if a transcatheter removal of the embolized device is not possible, a surgical therapy is the most reasonable option to remove these devices.

In this paper, we present a patient who was operated on due to device embolism in the early postprocedural stage after ASD device closure.

## Case Presentation

A 29-year-old male patient with complaints of fatigue, palpitations and shortness of breath was admitted to the Cardiology Clinic of our hospital. Physical examination revealed a 3/6 systolic murmur at the pulmonary area. Echocardiographic examination showed an ASD of 28 mm in diameter with left to right shunt ratio ( $Q_p/Q_s$ ) of 3.5. The posteroinferior rim tissue around the defect was 11 mm and also anterior rim of 12 mm, aortic rim of 22 mm, and total interatrial septum of 46 mm.  $Q_p/Q_s$  was 3.5. His left ventricular ejection fraction was 60%. Pulmonary artery was mildly dilated and 2+ tricuspid regurgitation were detected. He was planned for percutaneous transcatheter closure of ASD.

A 40 mm Amplatzer septal occluder device (St. Jude Medical, Inc. Cardiovascular and Ablation Technologies, Plymouth, MN, USA) was successfully deployed via right femoral vein under fluoroscopic and echocardiographic guidance. After the device smoothly and properly was placed, the patient was taken to the ICU control. However, thirty minutes after the percutaneous intervention, the patient had a sudden deterioration in the general condition. Sinusal tachycardia (heart rate of 115/min), bigeminal ventricular extra-systole attacks and hypotension (blood pressure of 80/55 mmHg) were observed on the monitor. Bedside control echocardiographic study demonstrated embolization of the device into the right ventricle. It was not possible to retrieve the embolized device via catheterization procedures. Thereupon, he was immediately taken to the operation under general anesthesia. The patient was heparinized for systemic anticoagulation. A standard median sternotomy was performed and cardiopulmonary bypass under moderate hypothermia was immediately instituted

with an aortic and bicaval cannulation. After cardioplegic cardiac arrest, right atriotomy was performed and the atrial septal occluder device was seen in the right ventricle (Figure 1). The embolized device was removed from the right ventricle using a forceps introduced through the tricuspid valve (Figure 2). There also was no thrombi on the surface of the device. Secundum type ASD was present, the defect width was approximately 4x3 cm in size. Posteroinferior rim was insufficient. The ASD was closed with a pericardial patch (Figure 3). He was uneventfully weaned off cardiopulmonary bypass. Heart worked spontaneously. Cross clamp time was 18 min, total perfusion time was 23 min. Patient was in sinus rhythm.



Figure 1. Operative appearance of the Amplatzer device in the right ventricle.



Figure 2. Removed Amplatzer septal occluder device.

Postoperative course was uneventful and he was discharged from the hospital on postoperative day 5 with a daily dose of 300 mg of acetylsalicylic acid. He was free of cardiac symptom and there was no residual defect in his one-year follow-up echocardiography.

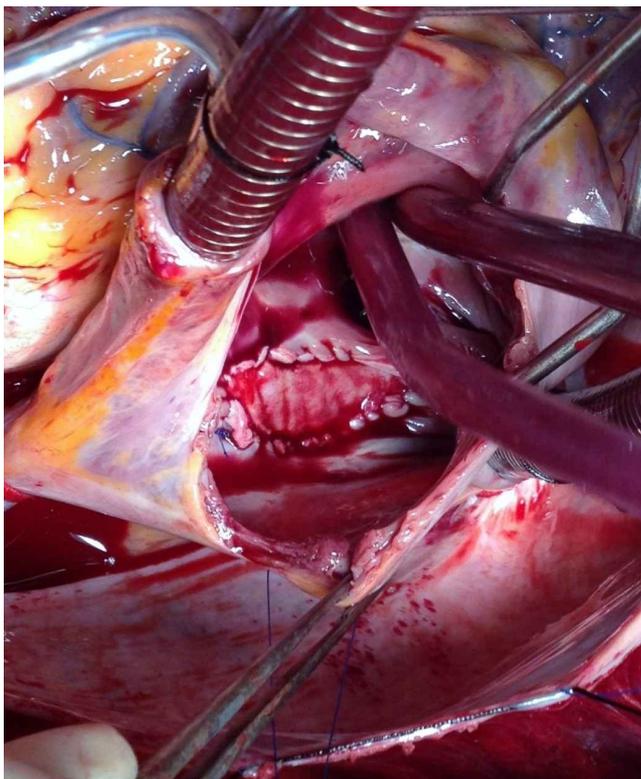


Figure 3. Repaired ASD with a pericardial patch.

## Discussion

Surgical closure of ASD has been performed for over 50 years and appears to be a safe and effective operation with excellent long-term results [2, 9]. Today, depending on the development of catheter-based technology, percutaneous transcatheter closure of congenital anomalies such as mainly ASD, ventricular septal defect, and patent ductus arteriosus, is performed with success in many centers [3,10]. Percutaneous closure of ASD, was firstly reported in 1976 by King *et al.* [11].

Transcatheter procedures in the treatment of the secundum ASD have been increasingly applied more frequently and are relatively safe and viable options, but complications are possible. These

procedures have the advantages of including a less invasive approach, which saves the patient from open heart surgery and cardiopulmonary bypass, a better cosmetic result, a shorter hospital stay, a faster rehabilitation, and an earlier return to work [3, 7, 9].

Transcatheter septal occluder device closure of the ASD may lead to serious complications despite its all advantages over surgical closure. The device-based complications may occur both at early and late stages after device implantation regardless of the size or type of used devices. These procedure-related complications include device embolization or malposition, residual shunts, thrombus formation on the device, thrombus embolization, air embolism, vascular trauma, access site hematoma, sciatic nerve compression due to retroperitoneal hematoma, peripheral embolization of thrombus/device, deep venous thrombosis, arteriovenous fistula formation, septal tearing, pulmonary vein dissection, atrial wall erosion, erosion of the device into the ascending aorta with associated aortic-to-right atrial fistula formation, ventricular outflow tract obstruction, atrioventricular valve regurgitation due to device impingement or catheter injury, atrial or ventricular arrhythmias requiring treatment, infectious endocarditis, septal aneurysm formation, systemic allergic reaction to nickel, cardiac perforations presenting as cardiogenic shock, and sudden death [1, 3, 4, 6-9, 12-13]. Correcting these complications mostly require surgical intervention. The case presented was early stage device embolization.

The size, location and competence of the rim area of the ASD, anatomical structures surrounding the defect and patient preferences are indicators of ASD devices applicability [14]. Risk factors for the device embolization include inadequate experience, a large defect presence, improper size of the device used, inadequate atrial septal rims holded the device, oblong shape of the defect, inaccurate deployment, and tearing of the interatrial septum due to the manipulation of catheter or device [6, 13, 14]. Unsuitable choice of patient and device is the most important cause of acute failure in this procedures. The device might embolize to the right or left atrium, right or left ventricle, main pulmonary artery, or anywhere in systemic circulation [6].

In our case, embolized device was found in the right ventricle and there was no device-related thrombus formation. This complication probably occurred due to insufficient posteroinferior rim of the defect.

The most frequent complication requiring surgical intervention during closure of ASD with Amplatzer septal occluder is device embolization or malposition [7]. The embolization rate of the device has been ranged from 4% to 20% in different devices and series in the past, and nowadays it was dramatically decreased to 0.5% with new generation devices [7, 13].

In a study by Wu *et al.* [7], device embolization was the most common indication for surgery, occurring in 4 (0.8%) of 508 patients with secundum ASD closure using an Amplatzer septal occluder. In another study, Ueda *et al.* [15] reported that 208 patients with a significant secundum ASD underwent percutaneous transcatheter closure using an Amplatzer septal occluder. They found that 1 (0.5%) case within 1 h of device implantation had device embolization. The device was surgically retrieved.

In a retrospective study, Berdat *et al.* [8] reported early and late outcome of 10 (8%) of 124 patients, who underwent percutaneous closure of ASD or PFO and, who subsequently required surgical treatment of either cardiac or vascular complications related to the device insertion. In these 10 patients, 8 had a significant shunt caused by malposition or dislocation of the device requiring surgical closure of the defect and 2 patients had the femoral artery injury at the puncture site required surgical repair. In this series, one patient died of left ventricular perforation after dislocation of the device [8].

Sarris *et al.* [4] retrospectively reviewed the records of 56 patients, who underwent early or late surgical repair for complications of transcatheter ASD closure in 19 participating European Congenital Heart Surgeons Association institutions over a 10-year period (1997-2007). They reported that possible serious life-threatening complications had been treated successfully with surgical intervention in the majority of patients. When a complication requiring surgery occurred, the management of this complication is associated with significant mortality rate, which is higher than that in the primary surgery of ASD. The most

encountered complication was device embolization (n=29) and hospital mortality was 5.4%. In the same time period, mortality for all 4453 primary surgical ASD closures reported in the European Association of Cardio-thoracic Surgery Congenital Database was 0.36% (p = 0.001). This comparison shows that salvage surgery for complication is associated with significantly more risk than observed in standard primary ASD closure [4].

Chessa *et al.* [6] reported on a large series of 417 patients, who had catheter closure of secundum ASD. They determined that the overall incidence of complications, including those due to the learning curve for each device, was 8.6% (n=36). They also reported that complications were classified into major (need for surgical intervention, life-threatening hemodynamic deterioration requiring emergency treatment, serious permanent functional or anatomic, and death) or minor (transient or resolved events with specific treatment) [6].

The septal occluder device can easily be retrieved or repositioned before leaving from delivery system. However, after deployment, embolized or malpositioned devices require a percutaneous catheter or surgical intervention. If transcatheter retrieval is not possible or successful for embolized device, surgical intervention is necessary [6, 9, 13, 14].

Emergency surgery is usually necessary in complicated situations including device embolization or erosion resulting in catastrophic complications, such as aorta-to-right atrial fistula, the left or right ventricular outflow tract obstruction, cardiac rupture or cardiac tamponade. Surgical removal is usually performed with the cardiopulmonary bypass and through a full sternotomy. Surgery is a quite safe and effective option, but operative mortality might rise when surgery is performed for complications in a delayed manner [5, 7]. Cresce *et al.* [5] reported a case of a late device embolization into the pulmonary trunk 10 months after device implantation and the successful surgical removal through a minimally invasive video-guided port-access approach.

In a recent study, Kotowycz *et al.* [2] retrospectively assessed the comparative effectiveness and long-term safety of transcatheter versus surgical closure of secundum ASD in 718

adult patients. They reported that transcatheter ASD closure is associated with a higher long-term reintervention rate (7.9% vs. 0.3% at 5 years,  $p=0.0038$ ) and long-term mortality (5.3% vs. 6.3% at 5 years,  $p=1.00$ ) that is not inferior to surgery. In this study, the majority of these reinterventions occurred in the first year and secondary outcomes were similar in the both surgery and transcatheter groups. This results support the current practice of choosing transcatheter closure whenever possible.

## Conclusions

Device embolization is still a major complication in transcatheter closure of the secundum ASD. If percutaneous catheter retrieval attempts fail, emergency surgical intervention is the only remedy to remove the embolized devices. Therefore, close monitoring and surgical backup should be available for all patients to deal with potentially lethal acute complications.

In our case with device embolisation, the device embolization was diagnosed soon after its occurrence within 30 minutes, the ASD were closed surgically and the device was retrieved without any further complication in a very short time. Our experience shows that surgical intervention to treat complication of device placement for ASD closure is still safe and effective modality.

### *Informed Consent*

Written informed consent was obtained from the patient for the publication of this case report.

### *Competing interests*

The authors declare that they have no competing interests with respect to the authorship and/or publication of this article.

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## Cervical conglutination: a rare disorder of uterine cervix

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### ABSTRACT

Cervical conglutination is quite rare complication of labor that can be misinterpreted as fully dilated totally effaced intact amniotic membrane, and in inexperienced hands trying to open the membrane results in the catastrophic outcome. Only a few articles present in literature and most of them are very old articles. Sharing this rare disorder as an experience may increase the attention of obstetricians and midwives to be careful about such condition in prolonged labor cases.

*Eur Res J 2015;1(3):151-153*

**Keywords:** Uterine cervix; conglutination; labor

### Introduction

Cervical conglutination is one of the rarest disorders of uterine cervix in labor due possibly to inappropriate dilatation-effacement relationship. A very rare disorder that can easily be misinterpreted as fully effaced cervix with a strong unruptured amniotic membrane. Careless evaluation and trying to open the amniotic membrane in such cases may result in a deep uterine tear that may proceed up to corpus with the strong uterine contractions [1].

Obstetricians should be careful in evaluating patients with strong contractions and full effacement with intact amniotic membrane which gives an abnormal amniotic membrane feeling in cervical examination. Thorough evaluation of amniotic membrane reveals a pin point opening and a small tuberosity (nipple like structure) on the membrane and experienced physicians could interpret this as cervical

conglutination and emergency cesarean section should be organized as soon as possible with a careful control and suturing of the laxated dilated cervico-istmic region of uterus for preventing abnormal bleeding. Any obstetrician suspected from conglutination must share this experience with the other colleagues and residents to have an idea about how conglutination happens and how cervical examination findings are.

### Case Presentation

Here we present a case of cervical conglutination in a 27-year-old term primigravida woman admitted to delivery room for fully effaced cervix with intact amniotic membrane and emergency delivery was arranged. As we experienced in our teaching hospital

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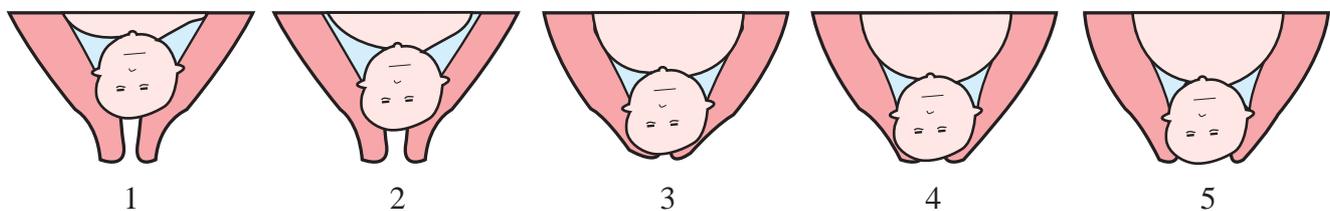
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practice in residency in two cases, the evaluation of the patient gave us the same sensation that something is wrong with the full dilatation. Careful cervical evaluation revealed a small tuberosity on the surface and a very tiny opening was observed on the paper-thin membrane and we diagnosed this as cervical conglutination and all team including midwives examined the patient with permission. The rarity and the possible risks were explained to both patient and her relatives and cesarean section was carried out with the delivery of a healthy 3210 grams male baby with 8-10 APGAR score. At the cesarean section fluctuating cervico-isthmus region was carefully sutured

and evaluated for any bleeding taking place or not. No parametrial tearing was observed per op and cervix was dilated through the abdominal route by a ring forceps in order to prevent blood collection in the uterine cavity that may complicate the postoperative course.

Patient was followed two days after operation and no any postoperative complications were observed and she was discharged from hospital and called for control one week later and the physical evaluation was normal. Later follow up revealed no any problems related to this rare problem.



**Figure 1.** Illustration of effacement and dilatation of the cervix. During the labor, the cervix opens (dilates) and thins out (effaces). The cervix is closed (1), the cervix is partly effaced (2), the cervix is fully effaced (3). A partial dilatation is 2-4 cm (4), and dilatation is upto 8-10 cm (5).

## Discussion

Cervical conglutination or conglutinatio cervicis uteri orifici externi is one of the rarest obstetrics complications that misdiagnosis may result in detrimental effects. This clinical situation is quite rare that you cannot find any reports in literature. PubMed search revealed two reports published in 1957 by Lope Garcia *et al* [2]. and in 1951 by Morgan and Price in journal of obstetric gynecol Br emp [3]. We found a small paragraph in the oldest book of Kazim Arisan one of the greatest physicians in obstetrics in Turkey [1]. Our main reference was previous two case experiences.

There is no sonographic or other diagnostic method to be used for this rare disorder and no photography can be presented here and the only diagnostic tool is the physician's experience or in other words sense of clinic. This condition can be predicted in cases with controlled labor but most of the time these cases directed to cesarean section due to prolonged labor. All cases we faced are emergency cases with full effacement and intact amniotic membrane thus it becomes more important to know that cervical

conglutination should be kept in mind in such obstetrical emergency situations.

The incidence may be higher than expected but there is no data about how often this complication happens. Also the number of elective cesarean sections is so high in Turkey that may be many of the problematic complications were bypassed by this approach. However all obstetricians and also midwives must be alert about such a rare but deteriorating complication with very good cervical examination at labor.

The dilatation and effacement are the two main components of cervical ripening during labor that takes place mostly synchronously with the contractile power of the uterus and the mechanical support of fetal head (Figure 1). Any changes in the synchrony of ripening process will result in distocia that may trouble the normal delivery or may push the team for cesarean section. The uterine contractions are strong and painful.

Incoordinate dilatation and effacement can be managed by pain relieving medications and or

iatrogenic amniotic membrane rupture or by induction but long delay in labor process should lead obstetricians to cesarean section [4].

Generally the fetal head is one of the main power for cervical opening and ripening but fetal head can be found mobile and not launched while dilatation and effacement is going on.

Pathological mechanism of conglutination is not known and there is not enough knowledge or literature supporting this rare disorder. James O. Waterman in his publication described conglutination of cervix as achalasia of cervix where cervical canal is effaced or obliterated but external os remains closed at times difficult to locate. In that paper Carter (1941) was evaluated literature from 1859 and found 28 articles most of which were case reports [5]. None of the papers distinguished primary achalasia of cervix from secondary forms from inflammation surgery or injuries. Pathological mechanism is believed to be due to non-relaxation of the circular fibers around the os and is similar to the conditions which occur in the esophagus and colon producing achalasia of the cardia and Hirschprung's disease respectively. The symptomatology is similar to normal labor but labor is prolonged in cervical conglutination. The cervix is usually thin soft and more or less obliterated or it may be soft and oedematous. The external os after a varying interval of time may dilate and patient deliver herself spontaneously [5]. A small description is written in Varney's midwifery book as catastrophic complication of labor that is rarely seen and needs urgent obstetrician support. All literatures here are very old publications and it was not easy to find them and this paper will be a reminder after a long time of such a rare disorder of cervix .

The ministry of health of Turkey has been trying to lead the obstetricians to more spontaneous deliveries than cesarean section which brings more obstetrical complications together. Thus any obstetrical rarity should be kept in mind and our aim is to remind a forgotten obstetrical emergency to our colleagues they may onetime confront in the delivery room.

## Conclusion

Cervical conglutination is quite rare complication of labor that can be misinterpreted as fully dilated totally effaced intact amniotic membrane and in inexperienced hands trying to open the membrane results in catastrophic outcome. Only a few articles present in literature and most of them are very old articles. Sharing this rare disorder as an experience may increase the attention of obstetricians and midwives to be careful about such condition in prolonged labor cases.

### *Informed Consent*

Written informed consent was obtained from the patient for the publication of this case report.

### *Competing interests*

The author declares that he have no competing interests with respect to the authorship and/or publication of this article.

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## West syndrome and autism: a case report

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### ABSTRACT

West syndrome is an epileptic encephalopathy accounting for one-fourth of epilepsies occurring in the first year of life and is highly associated with cognitive impairment. Autism spectrum disorders refer to a group of developmental disorders that are characterized by a wide range of impairments in social and communicative abilities, stereo-typed behaviors, and restricted range of interests with an onset of initial symptoms present before three years of age. In children with West syndrome, autism symptoms arise frequently. The present case, who is a 7-year-old boy followed with the diagnosis of West syndrome and autism, is presented to emphasize this association.

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**Keywords:** West syndrome; autistic disorder; epilepsy

### Introduction

West syndrome (WS) is an epileptic encephalopathy which accounts for 4-10% of childhood epilepsies and 25% of epilepsies occurring in the first year of life. Three main features of WS are as follows: 1. Infantile spasms, 2. Cessation and regression of psychomotor development, 3. The finding of hypsarrhythmia in EEG [1,2].

West syndrome is classified into symptomatic, cryptogenic and idiopathic depending upon the cause. Approximately 75% of the patients are in symptomatic WS group in which convulsions develop due to cortical malformations, prenatal events, neurocutaneous syndromes (tuberous sclerosis, Sturge-Weber), chromosomal impairment and metabolic diseases. In cryptogenic group, the underlying cause

can not be clarified, while in idiopathic WS, the psychomotor development of the patients prior to convulsion attacks is normal [3].

Course primarily rests on etiology. Cryptogenic/idiopathic etiology, late onset and rapid response to treatment is associated with good prognosis. In 50% of all cases, spasms disappear before the age of two. In 70%, severe mental retardation, autism, conduct disorder, develop and in 25-50% Lennox-Gastaut syndrome is seen. Only 5-10% of the cases may show normal or near normal mental development [4].

Autism spectrum disorders represent a group of neurodevelopmental disorders characterized by marked impairment in social and communicative

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skills, restricted interest and stereotypical behavior in which first symptoms arise before the age of three [5]. The term autism spectrum disorders is used to include children with Autistic disorder, Asperger disorder and with those Pervasive Developmental Disorder-not-otherwise-specified [6]. Despite decades of recognition autism spectrum disorders commonly co-occurs with epilepsy, the relation between epilepsy and autism still remains unclear [7]. Based on a meta-analysis of Amiet et al, the prevalence of epilepsy in people with autism spectrum disorder was found to be 8% and 20% respectively in the absence and presence of intellectual disability [8]. In a prospective study, it was reported that of children diagnosed with onset of epilepsy in the first year of life, autism spectrum disorder developed in 14% while it developed in 46% of children diagnosed with West syndrome [9]. In another community-based study, autism spectrum disorder was detected in 5% of newly diagnosed epilepsy cases. In the same study, West syndrome and mental retardation were found to be independently associated with autism spectrum disorders [10].

The comorbidity of epileptic syndromes and autism still remains to be unclarified. The present case describes a child with west syndrome and has severe autism symptoms.

The comorbidity of epileptic syndromes and autism still remains to be unclarified. The present case describes a child with west syndrome and has severe autism symptoms.

## Case Presentation

The case, a 7-year-old boy, referred to our clinic due to health council report. He has received special education and physical therapy for last six years. There was severe impairment in language development and social-emotional reciprocity, and repetitive behaviours in his psychiatric evaluation. He had no verbal expression and limited non-verbal communication with poor eye contact and his response to instructions was inconsistent. He had no pretend play, and he had an unusual preoccupation with holding saliva in his mouth and playing with it. He was not able to join his peers or interact with them. He was born at term after a normal pregnancy by an

unremarkable delivery. He developed normally until he was five months old and after five months spasms and convulsions started and his neuro-motor development was stopped. He was diagnosed with west syndrome and valproic acid and topiramate were instituted. He is still on valproic acid. Following a period with convulsions for about 6 months, no new convulsion has occurred, but valproic acid was continued as epileptiform anomaly continued to be seen in frontal and parieto-temporal regions in EEG. When he was at the age of 2-3, it was established that he had no eye contact with people, did not look when his name was called, was not interested in people and rocked forward and backward in sitting position and lived in his own world. He was diagnosed with WS+ Autistic disorder and special education was initiated. He started to walk at the age of five, never became continent and language was not developed. There was no evidence of autistic spectrum disorders in his family history.

His weight and height were below the 3rd percentile, and his head circumference was in the 3rd percentile. Blood chemistry analysis yielded normal values. His hearing and eyesight were found to be normal in previous tests and there was no pathology in cranial MR.

His total score in the Childhood Autism Rating Scale (CARS) [11] was 52 / 60, indicating severe autism and total score on the Autism Behavior Checklist (ABC) [12] was 91 / 158 points. He was diagnosed with AD according to DSM-IV criteria [13].

## Discussion

Although the course of disease depends on the underlying cause in West syndrome, intellectual disability at various levels occurs in 80% of the patients. Prognosis is better in children in idiopathic group [11]. Considering the developmental process of the present case, it was determined that he was in idiopathic/cryptogenic group, convulsions were controlled with drug treatment within 5-6 months after onset, but retardation in psychomotor development continued and autism symptoms emerged in later years. His score in childhood autism rating scale was 52, "extremely autistic" and

his score in autism behavior checklist was 91. Although there is no specific finding, 17-60% of autistic children display various EEG abnormalities. Findings are usually observed in frontal, temporal, parieto-temporal, and centro-temporal regions. In a study comparing video-EEG recordings and ages of WS patients with or without autism, it was thought that the continuation of hypsarrhythmia in later ages and the presence of dominant spike and wave findings in frontal regions were associated with the development of autism and it was concluded that hypsarrhythmia led to permanent damage in cognitive functions and behavioral skills [14]. In the present case, although convulsions did not continue, epileptic discharges continued to be seen in frontal and parieto-temporal regions, and in parallel he had severe autism symptoms, which is consistent with the literature. However, as his history was evaluated retrospectively, and some of his medical records could not be reached, it was not known how long hypsarrhythmia in his EEG lasted and to what degree it contributed to his autism.

In a study in which children diagnosed with WS were screened with autistic behavior checklist and children with high probability of being autistic were compared with those with low probability, it was established that in those with WS+high probability autism, cryptogenic and symptomatic groups constituted 5.9% and 94.1% of the cases. In the symptomatic group, congenital causes were the leading ones [15]. In a study of Saemundsen, 83% of the cases with autistic WS displayed in symptomatic group [9]. The present case was a patient with WS belonging to cryptogenic/idiopathic group with severe autism symptoms.

Mental retardation is present in 75% of autistic cases [8]. In another study, psychomotor retardation was detected in 86% of WS group while in 100% of WS and high probability autism group [15]. Consistent with the findings in the literature, our case had severe autism symptoms and marked psychomotor retardation.

WS is frequently associated with autism. Autism is a chronic disorder lasting lifelong and the most important treatment modality is education. As early onset of education is of critical importance, care should be taken in order not to overlook these cases and to refer them to treatment.

### *Informed Consent*

Written informed consent was obtained from the patient for the publication of this case report.

### *Competing interests*

The authors declare that they have no competing interests with respect to the authorship and/or publication of this article.

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## Spontaneous ejaculation; caused by venlafaxine, reverted by mirtazapine

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### ABSTRACT

Spontaneous ejaculation is a rare side effect of antidepressants. SSRIs, SNRIs, and reboxetine are reported to cause spontaneous ejaculation. Previous reports suggest to stop or change medication in the presence of this side effect, and less is known how to manage patients who want to continue the medication with this side effect. Mirtazapine is a noradrenergic and specific serotonergic antidepressant, mostly used for the treatment of depression. It is recommended as an add-on pharmacotherapy to relieve sexual side effects. Here, we demonstrate a case of spontaneous ejaculation, caused by venlafaxine, and reverted by mirtazapine.

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**Keywords:** Spontaneous ejaculation; management; venlafaxine; mirtazapine

### Introduction

Venlafaxine is a dual reuptake inhibitor of serotonin and noradrenaline. It is widely used to treat depressive and anxiety disorders [1]. The frequency of sexual side effects with antidepressants are reported to be about 58-73% [2] and 36% of psychiatrists prefer to change medication when sexual side effects occur [3]. Spontaneous ejaculation is a rare sexual side effect of antidepressants, mostly reported by serotonergic and noradrenergic reuptake inhibitors [4, 5]. According to previous reports antidepressant switch is suggested to manage spontaneous ejaculation

[6]. We have limited information about pharmacological management of spontaneous ejaculation.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant, mostly used for treatment of depression. As far as we know, mirtazapine cause fewer sexual side effects and recommended as an add on treatment for antidepressant induced sexual side effects [7-9]. Here, we present a case report of spontaneous ejaculation, caused by venlafaxine and reverted by mirtazapine.

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## Case Presentation

A 29-year-old male patient, admitted to our clinic to prescribe his drugs. During the psychiatric interview, he stated he was on venlafaxine 75 mg/d treatment for 1 year, his symptoms were headache and neck ache, spasm in shoulders, feeling anxious and being worried about all fields of life at the beginning of his illness. Patient said that he was feeling well with venlafaxine, his symptoms were mostly gone, but he was experiencing loss of sexual desire and spontaneous ejaculation following micturition and defecation 3 weeks after initiation of venlafaxine. Urological consultation and total urine examination didn't explain this condition. We offered patient to stop medication, because we thought it was related to venlafaxine. Patient refused to stop venlafaxine because of its' beneficial effects on his symptoms, so we started mirtazapine 30 mg/d. Because to the best of our knowledge, mirtazapine is beneficial for management of loss of sexual desire caused by antidepressants and also has fewer sexual side effects. At the visit 2 weeks after starting mirtazapine, patient stated frequency of spontaneous ejaculation decreased apparently. At the visit after 6 weeks, spontaneous ejaculations ended up and loss of sexual desire relieved. At the visit after 3 months patient was still stable and free of spontaneous ejaculation.

## Discussion

Spontaneous ejaculation is a rare side effect of antidepressants. There are several reports of spontaneous ejaculation with noradrenergic drugs. Three cases of spontaneous ejaculation due to noradrenergic drugs was reported by Oosterhuis *et al.* [10]. First case was a 40-year-old man taking atomoxetine, second one a 25-year-old man using methylphenidate and third case was a 60-year-old man whom was started venlafaxine. In addition, two cases were reported with a specific noradrenergic reuptake inhibitor reboxetine [4, 11]. nefazodone, milnacipran and zotepine are other noradrenergic drugs that caused spontaneous ejaculation [12-14]. In our case, although

venlafaxine is a dual reuptake inhibitor of serotonin and noradrenaline, thus we think potential mechanism related with spontaneous ejaculation is serotonergic mechanism, because patient was taking venlafaxine 75 mg per/day.

Belli *et al.* [6] reported spontaneous ejaculation and erectile dysfunction with escitalopram. They switched to fluvoxamine to manage this side effect. Virit and Savas [15] described a 27-year-old man who experienced spontaneous ejaculation after initiation of citalopram and they changed citalopram with paroxetine to stop spontaneous ejaculation. Although some SSRIs are reported to cause spontaneous ejaculation, however it is a fact that they are used effectively for treatment of premature ejaculation [6, 15, 16]. Taking into account both SSRIs cause spontaneous ejaculations rarely and ejaculation inhibition frequently, we interpret that spontaneous ejaculation is a unique and patient specific side effect due to antidepressants. Owing to diverse effects of SSRIs on ejaculation, it is not easy to explain exact mechanisms of ejaculation and spontaneous ejaculation.

Mechanisms of ejaculation depends on central and peripheral interaction of multiple systems. These systems could be sorted as parasympathic, sympathetic, dopaminergic and adrenergic systems. In the rat models, suppressor effects of serotonin have been demonstrated on ejaculation. However various serotonin receptors may effect ejaculation in different ways [17]. Somatodendritic 5HT<sub>1A</sub> stimulation shortens ejaculatory latency time, conversely postsynaptic 5HT<sub>2c</sub> stimulation causes ejaculation inhibition. selective alpha 1 receptor antagonists like tamsulosin and alfuzosin are responsible from decreased ejaculate volume [18].

Mirtazapine is a noradrenergic and specific serotonergic antidepressant. It has a unique receptor binding profile, differentiating from other antidepressants. Mirtazapine increases serotonergic and noradrenergic stimulation, regardless of reuptake inhibition. Alpha 2 auto receptor plays a crucial role in acting mechanism of mirtazapine and its' antagonism causes disinhibition of serotonergic and noradrenergic transmission. Likewise, mirtazapine blocks 5HT<sub>2c</sub> and 5HT<sub>3</sub> [19].

To date, in most cases changing or stopping medication recommended to manage spontaneous

ejaculations. To the best of our knowledge, almost all antidepressants are related with this side effect, also less is known about how to manage spontaneous ejaculation if patient refuses to change medication with this side effect. Our case is important in terms of demonstrating mirtazapine combination as an option to manage spontaneous ejaculation. Mirtazapine was chosen in this patient for two reasons. First, combination of mirtazapine with antidepressants is suggested by previous studies, to relieve sexual side effects and second mirtazapine itself has fewer sexual side effects [7]. Furthermore, alpha 2 agonistic and 5HT<sub>2c</sub> and 5HT<sub>3</sub> antagonistic properties of mirtazapine are believed to relieve diminished sexuality in depression and sexual side effects of antidepressants [9]. In this context, alpha 2 agonism and 5HT<sub>2c</sub> and 5HT<sub>3</sub> antagonism of mirtazapine could be the potential regulatory mechanisms that stopped spontaneous ejaculation in our case.

## Conclusion

Management of spontaneous ejaculation with mirtazapine hasn't been reported before. It is the first case report suggests combination of mirtazapine as a novel option to treat spontaneous ejaculation caused by antidepressants.

### Informed Consent

Written informed consent was obtained from the patient for the publication of this case report.

### Competing interests

The authors declare that they have no competing interests with respect to the authorship and/or publication of this article.

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## Fifteen-year treatment of metastatic thyroid medullary carcinoma: a case report

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### ABSTRACT

Although very rare, medullary thyroid carcinoma (MTC) is the most aggressive in differentiated thyroid malignancies. We report a 48-year-old male patient with the diagnosis of MTC, who was monitored for fifteen years and showed no serious adverse events due to long-term chemotherapy. Total thyroidectomy, neck dissection, retrosternal nodule excision and pericardiectomy were performed, and radiotherapy was applied to the neck area. Due to progressive metastatic disease cyclophosphamide, dacarbazine, and vincristine were administered. He tolerated chemotherapy well, and no severe systemic side effects were detected. He died due to multi-organ failure after fifteen years of diagnosis. The only curative treatment is surgery in MTC, however; radiotherapy, chemotherapy, and embolization may be used for patients for whom surgery cannot be performed. Although success rates of systemic chemotherapy are low, it is a treatment option in the progressive metastatic disease.

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**Keywords:** Medullary thyroid carcinoma; metastatic; chemotherapy; thyroid cancer

### Introduction

Medullary thyroid carcinoma (MTC) accounts for 5 to 10% of all thyroid malignancies and shows more aggressive progression than papillary and follicular carcinomas. Average age is approximately 50 years and it is reported that the disease is slightly more common in women. Although the most common initial complaint is painless swelling on

the neck, dysphagia, dysphonia and dyspnea may also be seen. It is reported that 75% of MTC cases are sporadic and 25% are familial (multiple endocrine neoplasia type 2A or 2B or isolated familial medullary thyroid cancer).

While Ret proto-oncogene mutation is detected in more than 95% of familial medullary cancers, Ret

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somatic mutation is detected in 40 to 70% of cases in sporadic medullar thyroid carcinoma [1-3]. Calcitonin, calcitonin gene-related peptide (CGRP), carcinoembryogenic antigen (CEA) and serotonin are released from tumor tissue. Calcitonin is the most specific circulating and immunohistochemical marker for MTC, widely employed for diagnostic purposes [2, 3]. Calcitonin is increased in all the cases of clinically palpable MTC; however, in smaller tumors and C-cells hyperplasia. Patients with MTC should be followed postoperatively with periodic measurement of serum markers such as calcitonin and CEA that indicate residual disease. If a patient has a persistently elevated serum calcitonin concentration after total thyroidectomy and regional node dissection, neck ultrasound, CT, MRI and/or PET should be done. Over all survival rates in MTC can be favorable, with a mean survival of 75 - 85% at 10 years [4]. MTC is most aggressive in patients with MEN 2 B, less aggressive in sporadic type, and least aggressive in MEN 2A and familial MTC. This disease usually follows an indolent course even at the stage of distant spread. Some patients with distant metastases may not survive years without systemic treatment. Although the primary treatment is surgery, other treatment options such as embolization, radiotherapy and chemotherapy are available for patients who have local relapse, distant metastasis, or those who cannot be operated. Systemic chemotherapy may be used in patients who have diffuse metastasis, progressive disease and those for whom there is no curative surgical option. Common chemotherapy protocols include single administration of doxorubicin, single administration of cisplatin, dacarbazine-5-fluorouracil in combination, doxorubicin-cisplatin combination, cyclophosphamide-vincristine-dacarbazine, and a combination of doxorubicin-5-fluorouracil-etoposide-cyclophosphamide. Toxicity rates of these treatments are low and response rates do not exceed 20% [1, 2].

## Case Presentation

A 48-year-old male patient presented to our clinic due to swelling on the neck, which first appeared in 1994. The patient had diarrhea and systemic examination revealed multiple nodules in the thyroid

gland. A fine needle aspiration (FNA) biopsy of the thyroid was malign; the patient was therefore referred to surgery. As the frozen section result indicated MTC, total thyroidectomy, neck dissection, retrosternal nodule excision were performed the patient. Microscopically, these tumors consist of sheets of cells separated by a pink-staining substance that stains with Congo red. Cervical exploration and sternotomy were performed, but a residual tumor was detected 3 months after the operation. There was no abnormal elevation of serum calcitonin level; 32 sessions, including cyclophosphamide, dacarbazine, and vincristine, were administered between 1995 and 1998. Local relapse was detected in 1998 and radiotherapy was applied to the neck area. No recurrence or relapse was observed in the patient Between 1998 and 2002. During this period, we didn't apply any treatment to the patient. Due to increased serum calcitonin levels in 2002, 6 more courses of chemotherapy were administered to the patient; pericardiectomy was performed due to pericardial MTC invasion in 2004. Cervical lymph node dissection in 2005 and cervical dissection in 2006 were performed due to local relapse. In 2006, multiple and different size of paratracheal, bilateral hilar, retrosternal, infraclavicular, right axillary lymph node metastases were detected and the patient was re-evaluated by chest surgery. The operation was found inappropriate and the patient was taken into the chemotherapy program again, but this was subsequently discontinued due to failure in general status and cachexia (Figure 1). After improvement in patient's condition we decided to continue with the chemotherapy and a total of 85 courses of same chemotherapy were administered until 2009. Thus, the 32 cycle of cyclophosphamide, dacarbazine, and vincristine, were administered between 1995 and 1998. In 2002, 6 cycle of chemotherapy were applied. Forty-seven cycle of chemotherapy were administered between 2006 and 2009. The patient tolerated chemotherapy well during this period and no severe systemic side effects were detected. Chemotherapy was terminated due to side effects such as medication resisted nausea-vomiting in 2009. The patient died due to multi-organ failure 8 months after discontinuation of the treatment.

## Discussion

Generally, the initial complaint prompting hospital visit is the existence of a thyroid nodule or cervical lymphadenopathy. However, dysphonia, dysphagia and dyspnea which are developed due to local invasion may be the reason for the first application; and far metastases are detected in 10 to 15 % of patients at the moment of diagnosis [3]. Cervical lymph node involvement is common, and it is reported that involvement of central and ipsilateral lymph nodes are more common compared to other lymph sites. It is also reported that lymph node involvement at the moment of diagnosis is approximately 50% in MTC. Contralateral and mediastinal lymph node involvement reach up to

50 to 60% in cases of local invasive disease [2, 5]. MTC distant metastases are frequently observed in mediastinum, lung, liver, abdominal lymph nodes and bone. Cervical and mediastinal lymph node metastasis were detected in our patient at the time diagnosis.

Primary treatment of MTC is surgical. The purpose in the initial surgery should be to remove all tumor tissues and lymph nodes due to increased risk of complication in subsequent surgeries. High calcitonin and CEA levels postoperatively may indicate metastasis and should be evaluated. If metastases are large and located in areas that are easy to remove, they should be removed surgically

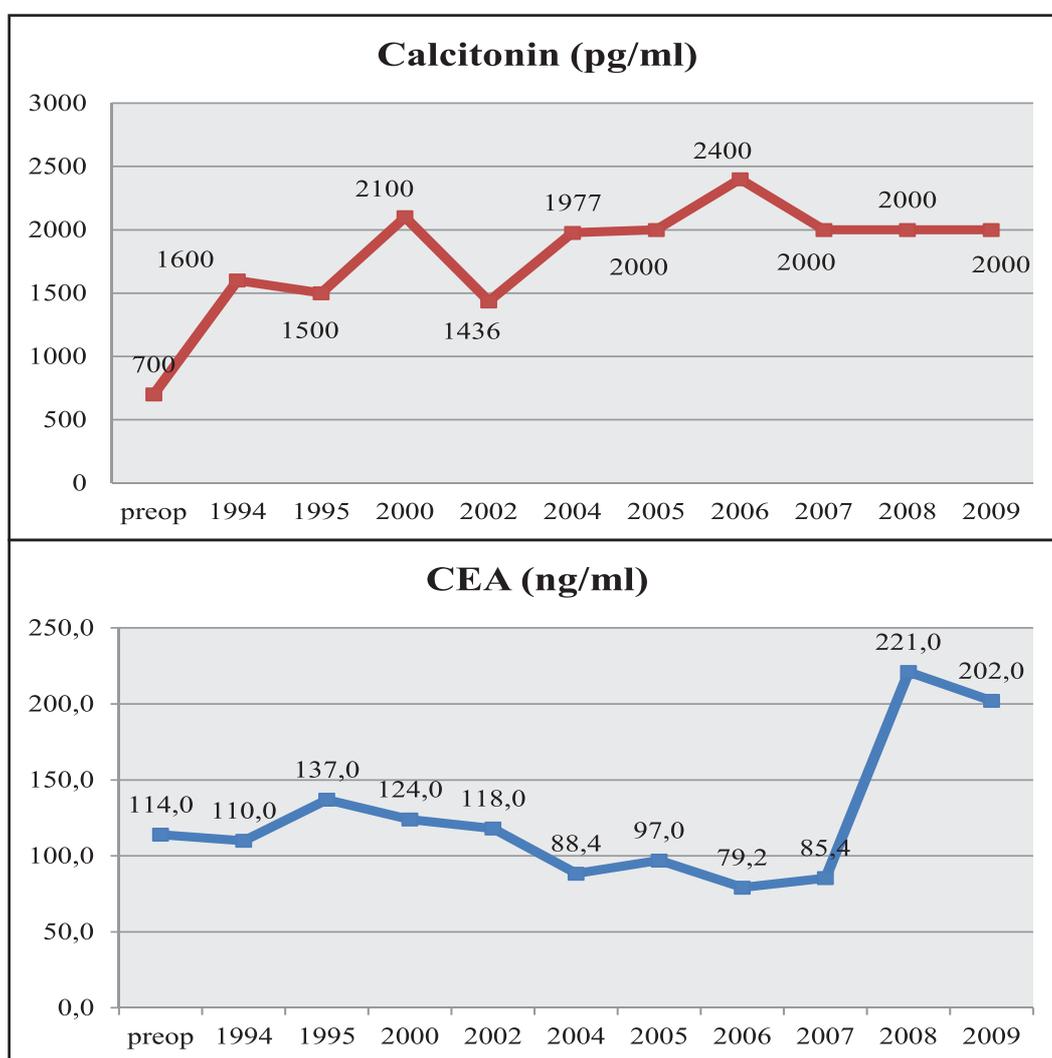


Figure 1. Calcitonin and CEA levels by year

[5, 6]. Other treatment options, such as radiation treatment, chemotherapy and embolization, are applied for patients for whom surgery is not an option [7, 8].

MTC generally progresses slowly and it is considered that the course of the disease is even slower with distant metastasis [8]. Typical survival rates are not known in metastatic MTC, due to insufficient number of studies and patients with MTC, and the non-homogenous distribution of the patients who were involved in those studies. Prognosis and treatment effectiveness are largely related to the tumour stage [9]. Early diagnosis is essential in patients with MTC, in order to obtain the best cure rate. Chemotherapy is recommended for a small proportion of the patients who have rapid, progressive metastatic disease and digress from natural progress of MTC [8]. Success rates of cytotoxic chemotherapy are quite low in metastatic MTC and rates varying between 2 and 25% are reported [8]. Doxorubicin has been the most frequently reported agent with a response rate probably not higher than 15-20%, all responses being partial and transient and with high toxicities [8]. Combination of doxorubicin with other drugs such as cisplatin [10], or streptozocin [11] did not increase the response rate. Many regimens have been tried in systemic chemotherapy, including a combination of cyclophosphamide, vincristine and dacarbazine; Wu *et al.* [12] reported on seven patients with progressive MTC who were treated by this combination. Calcitonin and CEA were measured regularly before the treatment and until detection of progression of the disease. That the study reported partial response in 2 patients who were followed-up for 14 and 29 months; partial biochemical response in 1 patient who was followed for 9 months, stable disease in 1 patient who was followed for 14 months and progressive disease in 3 patients throughout the study period. It was emphasized that chemotherapy was well tolerated in general, but efficacy was intermediate [12]. The amount of number of chemotherapy is not known in metastatic MTC, due to insufficient number of studies and patients with MTC. The alternating therapies using 5-fluorouracile-streptozosine and 5-fluorouracile-dacarbazine have been used. Select

tyrosine kinases inhibitors have been of interest for the treatments of advanced MTC, given the oncogenic role of mutations in the tyrosine kinase RET, as well as the contributory roles of tyrosine kinases in growth factor receptors such as VEGFR [13]. These drugs partially inhibit multiple kinases and often affect multiple signaling pathways. So availability of effective tyrosine kinases inhibitors (TKIs; vandetanib, cabozantinib, etc) is changing the standard approach in MTC, further limiting the role of cytotoxic agents [14]. Thus, there is a trend toward using traditional cytotoxic agents as a salvage therapy in MTC or reserved for patients who are unable to participate in clinical trials or have failed or cannot tolerate kinase inhibitors. TKIs as first line therapy but these drugs are only available after systemic cytotoxic treatment in Turkey with special permission. Because of our clinical experience is much more in the combination of cyclophosphamide, vincristine and dacarbazine, we treated our patient with this combination therapy.

Our case of metastatic disease showed stable progression and we did not observe any severe toxicity due to medication.

In another study, no response was seen with a single chemotherapeutic agent and alternating therapies using 5-fluorouracile-streptozosine and 5-fluorouracile-dacarbazine were administered to 20 metastatic patients every 3 weeks [15]. On average, 5-fluorouracile-streptozosine was applied 4 times and 5-fluorouracile-dacarbazine was applied 5 times. Partial response was observed in 3 patients, stable disease in 11 patients and progressive disease in 6 patients. Since severe medication side effects were not observed, emphasis was placed on preference for regimens including medications used in this treatment. We also applied combination therapy including dacarbazine with our patient. The disease showed stable progression with this treatment over a period of 15 years.

Toxicity and side effects are important factors which limit the long-term use of chemotherapeutic medications [14-16]. Cyclophosphamide is an alkylating agent, the most important side effect of which is cardiotoxicity (such as congestive heart failure, cardiac necrosis, and pericardial tamponade). Cardiotoxicity is especially observed in high dose

or long term treatments and the risk for cardiotoxicity increases when used with other alkylating agents. Additional side effects include nausea, vomiting, alopecia, hemorrhagic cystitis, bone marrow suppression, hepatotoxicity, flushing, inappropriate ADH syndrome, hyponatremia, and secondary malignancy. Vincristine is a vinca alkaloid, the most important side effect of which limits its use is peripheral neuropathy. Although this side effect is more common when it is used in patients over 40 years and in repetitive doses, it was also reported after a single dose. Dacarbazine is also an alkylating agent, of which the most important side effect is myelosuppression. We used combination treatment including cyclophosphamide (750 mg/m<sup>2</sup>), vincristine (1.4 mg/m<sup>2</sup>) and dacarbazine (600 mg/m<sup>2</sup>) every 3 weeks. Intermittently, 85 courses were administered to our patient and no severe side effects were observed except slight nausea, vomiting and mild myelosuppression. Cardiology consultation was requested for cardiotoxicity and physical examination, ECG and ECHO examination results of the patient were reported to be normal. The patient also evaluated for peripheral neuropathy and neurological examination and ENMG were found to be normal.

Metastatic thyroid medullar carcinoma is a type of malignancy for which current treatments are unsuccessful; therefore, new treatment options are being developed. The use of systemic chemotherapies is limited due to toxicities, side effects and limited success rates. However, chemotherapy may prolong survival for appropriate patients whose progressive disease cannot be controlled by surgical treatment.

#### *Informed Consent*

Written informed consent was obtained from the patient for the publication of this case report.

#### *Competing interests*

The authors declare that they have no competing interests with respect to the authorship and/or publication of this article.

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## Popliteal artery injury due to blunt trauma: delayed diagnosis and treatment

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### ABSTRACT

Despite the appropriate treatment, the rate of amputation in popliteal artery injuries is still high in current practice. Hence, early diagnosis and treatment are extremely important in cases with such vascular injuries to save extremities. We present a 30-year-old male patient with popliteal artery injury, who had diagnosed 20 hours after internal fixation of the femoral fracture. He successfully underwent arterial repair.

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**Keywords:** Blunt trauma; delayed diagnosis; popliteal artery injury; vascular surgery

### Introduction

The amputation rates due to popliteal artery injury in lower extremity traumas are quite high despite the appropriate treatment. The diagnosis of vascular injuries especially after blunt traumas of the extremities can be quite difficult in some cases, causing delayed treatment. Delayed diagnosis and treatment may cause neurological damage and loss of extremity [1, 2].

In this report, the successful delayed treatment of a popliteal artery injury due to blunt trauma following a traffic accident was presented. Neurological deficit related with delayed treatment and complications of

compartment syndrome were discussed with reviewing the literature.

### Case Presentation

A 30-year-old male patient admitted to the emergency department with complaints of pain, coldness and swelling of the left leg. In his history, he had a traffic accident the day before and internal fixation was performed due to left femur fracture at other hospital. The patient was transferred to our cardiovascular surgery clinic with complaints

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of swelling and pain in the left leg after the initial treatment. During the examination, on physical examination, his left leg was extremely swollen, tight and cold. Both femoral arteries were strongly palpable during pulse examination whereas left leg distal pulses were non-palpable below the left popliteal artery. Arterial pulses of the right leg were palpable. Sensorial loss and motor deficit was determined during the neurological examination of the left leg. A clear image could not be achieved by the Doppler examination due to widespread edema. Computerized tomographic angiography (CTA) study showed total occlusion of the popliteal artery at the upper knee region (Figure 1).

The patient was taken to the operating theatre for immediate surgery. Under general anesthesia the popliteal artery was explored via posterior popliteal incision. Hematoma of 600 ml was removed from the Hunter channel and the popliteal region. Popliteal artery was occluded. No injury was determined in the popliteal vein and nerve. After intravenous administration of 5000 IU unfractionated heparin, embolectomy was carried out on the distal and

proximal artery segments by Fogarty embolectomy catheter. The thrombus materials inside the distal and proximal artery segments were removed. Following embolectomy, retrograde blood flow from the distal segment and normal blood flow from the proximal artery was achieved. The damaged segment of the popliteal artery was excised. Popliteal artery was suitable for end-to-end primary repair. After mobilization of the proximal and distal arterial segments, the end to end anastomosis was done by 6/0 prolene suture. There was tension in the left leg compartments. Hence, multiple fasciotomies were performed in the same session (Figure 2). Distal pulses were palpable after the operation and motor deficit regressed. Leg edema reduced during the one month follow-up and fasciotomy incisions were closed 5 weeks after the first operation. The patient was discharged at the postoperative 45th day. Left leg pulses were palpable and the left lower extremity neurological examinations were normal at the time of discharge.



**Figure 1.** Imaging of computerized tomographic angiography of occluded popliteal artery at the upper knee region.



**Figure 2.** The appearance of postoperative fasciotomy.

## Discussion

Even though the ratio of popliteal artery injury is low, it causes a high rate of amputation due to complications. The amputation rate following popliteal artery injury is reported to be between 37%-65% [1, 3]. The reperfusion time is crucial in vascular injuries. Ischemia duration of over 7 hours and the development of compartment syndrome are significant factors that increase the risk of amputation [1]. Another factor that increases the amputation risk following vascular injuries is skeletal trauma. Wani *et.al.* [4] stated that the saved extremity ratio was 85% for patients with both vascular damage and skeletal trauma whereas this ratio was 100% for the patients with no accompanying skeletal trauma. Left leg femur fracture was present in this case following blunt trauma and the femur fracture was initially treated with internal fixation. However, the vascular injury was somehow overlooked. Appropriate treatment including revascularization was carried out even though the ischemia duration of 20 hours and distinct compartment syndrome.

The symptoms and findings known as "hard signs" and "soft signs" are determined for vascular injury diagnosis. Active bleeding or hematoma widening, feeling of thrill at the lesion site and ischemia are among the hard signs. Bone fracture / soft tissue damage as well as the existence of pathologies such as hematoma and knee dislocation are known as "Soft signs". These patients should be examined frequently by Doppler ultrasonography. CTA or conventional angiography are also useful for the diagnosis of these patients. Primary end-to-end repair is suggested as the treatment of choice in popliteal artery injuries. However reversed saphenous vein graft should be preferred in cases of which a graft interposition is required [5].

Compartment syndrome can be diagnosed with a clinical suspicion and the patients should be examined closely with the foresight that compartment syndrome might develop in patients following extremity ischemia of over 6 hours and the existence of popliteal vein ligation. Early prophylactic fasciotomy carried out prior to the

signs of tissue loss in patients is preferred instead of therapeutic fasciotomy. This ratio is stated to be 64% in some series [6]. Compartment syndrome in the left leg was detected in this case during vascular repair. The patient was diagnosed late and thus the leg was ischemic and fasciotomy was applied just after the revascularization. It is stated in literature that complete occlusion of popliteal artery following blunt trauma was treated successfully after a delay of 10 hours but that a neurological damage remained in the related extremity [2].

In this case, it was observed that the neurological deficit in the left lower extremity determined prior to the operation regressed afterwards. Collateral circulation can be effective in the regression of the neurological deficit despite a delay of 20 hours. The existence of retrograde blood flow following the embolectomy on the distal PA site during the operation supports this hypothesis.

## Conclusion

Early diagnosis and revascularization are crucial for preventing the possible amputation that might occur after vascular traumas. However, in cases such as this one where the diagnosis is delayed, extremity loss can be prevented by a proper surgical operation. It should not be forgotten that Doppler ultrasonography will not always be enough for diagnosis in patients with blunt trauma and that the vascular pathology should be verified via CTA or conventional angiography for suspicious cases.

### *Informed Consent*

Written informed consent was obtained from the patient for the publication of this case report.

### *Conflict of interests*

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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