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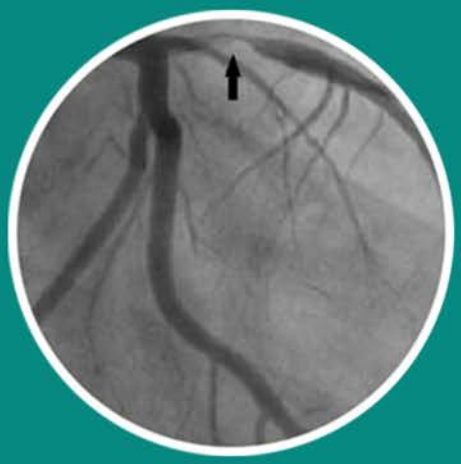

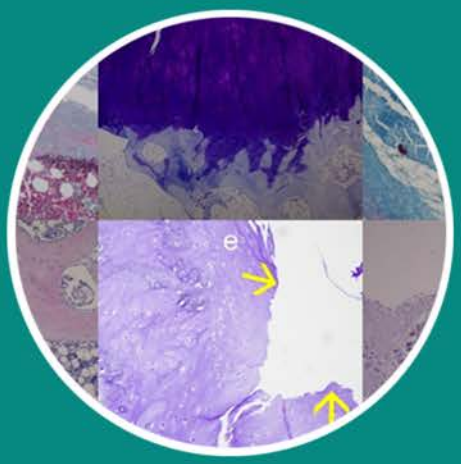

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The European Research Journal 2019;5(2):236-243 ORIGINAL ARTICLE

Management of constipation in preventing urinary tract infections in children: a concise review

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ABSTRACT

Objectives: Constipation is a common problem in children. Chronic functional constipation (CFC) has been a claimed conditions that may increase the risk for urinary tract infections (UTIs). Dysfunctional voiding (DV) and lower urinary tract dysfunctions (LUTD) with chronic constipation are referred to dysfunctional elimination syndromes (DES). The aim of the present review is to look at the management of constipation in children with CFC or DES in reducing the risk of recurrent UTIs.

Methods: We performed a literature search on electronic databases (Pubmed and Scopus) for relevant clinical trials investigating the results of one or more treatments for children's constipation in the term of UTIs recurrence.

Results: The search strategy identified 20 valuable clinical trials. The studies are not homogenous but showed an improvement in UTIs occurrences in children managed for bowel dysfunction.

Conclusion: In conclusion, children referred to a pediatric nephrologist for UTIs should include an inquiry bowel habits and those with a positive assessment for bowel dysfunction needs the collaboration with a pediatric gastroenterologist with a multidisciplinary approach.

Keywords: Children, constipation, dysfunctional elimination syndromes, dysfunctional voiding, urinary tract infection

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Urinary tract infections (UTIs) are frequent in children. By seven years of age, 8% of girls and 2% of boys will have had at least one episode of UTI [1]. Prospective studies using 99mTc-labelled dimercaptosuccinic acid (DMSA) scintigraphy have shown that, after a febrile UTI, 30-40% of children will have renal scarring [2]. Follow-up data has established that long-term complications of UTIs with renal scarring include hypertension, proteinuria, pregnancy-related complications and even end-stage kidney failure [3]. Many predisposing factors to UTIs recurrence (vesicoureteral reflux [VUR], bladder and bowel dysfunction [BBD], and genetic factors) have described in childhood [4, 5]. Both BBD and VUR are at high risk of developing recurrent UTIs than children with isolated VUR or children with isolated BBD [6]. There is still controversy about the role of chronic functional constipation (CFC) in predisposing children to UTIs [7].

Constipation is a common problem in children with a prevalence from 0.7% to 29.6% [8]. According to the Paris Consensus on Childhood Constipation Terminology (PACCT) Group, CFC as having at least two symptoms during the last eight weeks that include

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defecation frequency of less than three times, a fecal incontinence, frequency more than once, passage of large stools that clog the toilet, a palpable abdominal or rectal fecal mass, stool withholding and painful defecation [9]. CFC is chronic constipation without evidence of pathological conditions [10] and, at present, the most accepted definitions for CFC are the Rome III criteria [11]. In particular, sensation of anorectal blockage, straining during defecation and infrequent bowel movements are of great accuracy for the diagnosis of CFC [12]. Constipation may play a role in function and dysfunction of the urinary tract [13].

Dysfunctional voiding (DV), that refers to an intermittent and/or fluctuating uroflow rate due to involuntary intermittent contractions of the striated muscle of the external urethral sphincter or pelvic floor during voiding in normal individuals [14], and lower urinary tract dysfunctions (LUTD), that refers to patients with problems of bladder function [14], as dysfunctional elimination syndromes (DES) [15] with CFC [16]. DES and CFC increased the risk of UTIs in children [15, 17]. In agreement, it has observed recurrent UTIs in 25% of boys and 66% of girls among 180 patients with CFC [19], and in 62% of girls among 80 patients with DES [18].

Children with UTIs have more symptoms of constipation than without [20]. Wan et al. [21] suggested that up to 90% of children with UTI could have dysfunctional voiding or constipation habits.
Although the degree of fecal loading, as seen on a plain abdominal radiograph, is not synonymous of constipation, there is a significant association between the degree of fecal loading and UTIs [22]. Decreased bladder filling, impression of the bladder wall provoking overactivity, and pelvic floor dis-coordination caused by withdrawal manoeuvres as a response to painful defecation can have an important clinical meaning [23]. Another hypothesis is that constipation can figure bacterial stasis with huge proliferation and translocation of the same bacteria into genitourinary apparatus. In fact, it has reported a correlation between intestinal bacterial stasis, methanogenic intestinal flora and UTIs [24].

The general approach to the child with functional constipation comprises dietary interventions (high fibre diet, hydration changes), behavioural change, regular toilet habits and laxatives to assure that bowel movements occur at normal intervals with good evacuation [11].
The aim of the present look at to check if management of constipation in children with CFC or DES reduce the risk of UTIs recurrence.

METHODS

We performed a systematic literature search on electronic databases (Pubmed and Scopus) for relevant clinical trials published from January 1985 to June 2018, investigating the results of one or more treatments for children's constipation in the term of the resolution or amelioration of UTIs recurrence.
To find relevant articles in these electronic databases, we used the keywords constipation OR dysfunctional elimination syndrome OR dysfunctional voiding AND urinary tract infection AND children.

Studies were qualified for inclusion if they were clinical trials (excluding observational studies, letters, case reports, conference abstracts, studies on animals and comments), searching for the role of one or more treatments for constipation in the term of the resolution or amelioration of UTIs recurrence.

First, we screened the list of titles and abstracts (total number identifies: 321); then we selected clinical trials and the articles of interest in their entirety. The strategy identified 20 clinical trials. We extracted the first author and year of publication, the number of cases, characteristics of constipation and treatment, and time of follow-up. We extracted information on the prevalence of constipation and UTI before and after the treatment.

RESULTS

Clinical trials

Twenty clinical trials (Table 1) involving patients with CFC or DES reported different treatment regimens for constipation (laxatives, enemas, high-fibre diet, biofeedback therapy, pelvic floor muscle exercises, sacral neuromodulation, regular voiding, pharmacotherapy etc.) [23, 25-43].

Studies that showed a significant reduction of UTIs related to DV [26-28, 40] or DES [29, 30, 32] or LUTD [42]. Other studies did not report if the results

Table 1. Characteristics and analysis of the included clinical trials

Clinical trials	n. (M/F)	Mean age (range)	Main pathology	Treatment	Follow-up	n. of patients with constipation before/after	n. of patients with UTI before/after
Chrzan 2008 [23]	50 (6/44)	9.6 (6.5-12) yrs	CFC, recurrent UTIs	Colonic washout enemas	6 mos	50/33 p = n.a.	50/20 p = n.a.
Kibar 2007 [25]	78 (8/70)	7.20 ± 2.04 (5-14) yrs	DV, vesico-ureteral reflux	Biofeedback, timed voiding	6 mos	9/2 p = n.a.	41/8 p = n.a
Vesna 2010 [26]	86 (35/51) Group A 43 (15/28) Group B 32 (9/23)	7.1 ±2.5 (3-13) yrs	DV	Group A) Standard urotherapy, pelvic floor exercises Group B) conservative treatment Laxatives; antibiotic prophylaxis if UTIs recurred in both groups	1 yr	Group A 15/0 p < 0.001 Group B 10/4 p < 0.05	Group A 19/6 p < 0.0001 Group B 15/9 p < 0.05
Vesna 2011 [27]	86 (35/51) Group A 43 (15/28) Group B 32 (9/23)	Group A 7.5±2.5 yrs Group B 6.7±2.5 yrs	DV	Group A) diaphragmatic breathing, pelvic floor muscles retraining plus group B treatment, Group B) regular voiding, hydration, posture, laxatives; antibiotic prophylaxis if UTIs recurred	1 yr	Group A 15/0 p < 0.0001 Group B 10/4 p < 0.05	Group A 19/6 p < 0.001 Group B 15/9 p < 0.05
Zivkovic 2012 [28]	43 (15/28)	7.5±2.5 (5-13) yrs	DV	Pharmacotherapy (11 anticholinergics, 11 desmopressin, 15 antibiotic prophylaxis); constipation treatment (education and laxatives); diaphragmatic breathing exercises; pelvic floor muscle exercises	1 yr	15/0 p < 0.0001	19/6 p < 0.0001
Kajbafzadeh 2011 [29]	80 (18/62) Group A 40 (8/32) Group B 40 (10/30)	Group A 8.5±2.7 yrs Group B 9±2.3 yrs	DES	Group A) animated biofeedback therapy and behavioral modification Group B) conservative therapy (only behavioral modification)	6 and 12 mos	Group A 25/8/8 Group B 20/12/12 6 mos: p = 0.01 12 mos: p = 0.009	Group A 14/2/4 Group B 22/5/10 6 mos: p = 0.02 12 mos: p= 0.3
Humphreys 2006 [30]	23 (8/15)	(6-15) yrs	Severe DES	Sacral neuromodulation, medical therapy	(4-37 mos) mean 13.3 mos	15/3 p = 0.001	18/6 p < 0.0001
De Paepe 2000 [31]	20 (2/18)	M 4.5 yrs F 4.44 yrs	DV	Training program, biofeedback, antibiotic prophylaxis if UTIs recurred, drugs to relieve the impaction of encopresis	6-12 mos	8/3 p = n.a	8/0 p = n.a.

Table 1 continued. Characteristics and analysis of the included clinical trials

Clinical trials	n. (M/F)	Mean age (range)	Main pathology	Treatment	Follow-up	n. of patients with constipation before/after	n. of patients with UTI before/after
Vasconcelos 2006 [32]	56 (18/62) Group 1 26 (9/17) Group 2 30 (10/20)	Group 1 10.8 ± 1.9 yrs Group 2 10.3 ± 2.6 yrs	DES	Group 1) 24 training sessions over a 3-month period Group 2) 16 training sessions over 2-month period	12 mos	Group 1 11/7 p = n.s Group 2 11/9 p = n.s	Group 1 8/1 p = 0.023 Group 2 13/3 p = 0.004
Yagci 2005 [33]	168 (16/152)	7.44 ± 2.24 (5-14) yrs	DV	Biofeedback, timed voiding, high-fiber diets, laxatives	6 mos and 2 yrs	26/7/9 p = 0.5	102/17/13 p = 0.125
McKenna 1999 [34]	41 (8/33)	7.2 (5-11) yrs	DV	Pelvic floor muscle retraining using interactive computer games, timed voiding, high-fiber diet	(3-15 mos) mean 7 mos	6 Improved: 66% Cured: 34% p = n.a.	22/3 p = n.a.
Barroso 2006 [35]	36 (n.a.)	7 (3-14) yrs	LUTD	Electrical stimulation and/or biofeedback training, behavioral training, antibiotic prophylaxis	(4-24 mos) mean 13.8 mos	12/3 p = n.a.	25/4 p = n.a.
Petronijevic 2007 [26]	9 (girls)	6.1 (3-11) yrs	DV	Botulin Toxin type A, standard urotherapy, education, regular toilet visits, dietary and hydration changes, laxatives	6 mos	2/1 p = n.a.	8/2 p = n.a.
O'Regan 1985 [37]	47 (girls)	8.2 ± 2.53 yrs	Recurrent UTIs, constipation	Enema regimen	12±2 mos	47/2 Encopresis 21/1 p = n.a.	47/3 p = n.a.
Loening-Baucke 1997 [38]	234 (176/58)	9 ± 3 (5-18) yrs	CFC, encopresis	Disimpaction (hypertonic phosphate enemas OR hyperosmolar milk-of-molasses enemas), fiber-rich foods, laxatives, education, prophylaxis if UTIs recurred	12 months (mean, 15 months)	234/112 p = n.a.	25/0 p =n.a.
Loening-Baucke 1989 [39]	97 (69/28)	9.0 (5-14.5) yrs	CFC, overflow incontinence	Laxatives, high fiber diet, bowel training	12 mos	97/43 (F>M)	n.a. (UTI in recovered 3/43, UTI in non-recovered 11/54; p = n.s.
Khen-Dunlop 2006 [41]	60 (12/48)	8 (5-14) yrs	DV	Pelvic floor training, regular voiding	21 mos	25/n.a.	37/6
Amira 2013 [42]	72 (girls)	8 (7-10) yrs	LUTD	Standard and computer game assisted pelvic floor muscle retraining	(6-17 weeks) mean 11 weeks	36/n.a. p < 0.002	70/n.a. p < 0.001
Tugtepe 2015 [40]	45 (38 female)	8.5 ± 2.2 years	DV, refractory overactive bladder	Biofeedback therapy	3 months	8/1 p < 0.05	20/4 p < 0.001

Table 1 continued. Characteristics and analysis of the included clinical trials

Clinical trials	n. (M/F)	Mean age (range)	Main pathology	Treatment	Follow-up	n. of patients with constipation before/after	n. of patients with UTI before/after
Sarvari 2017 [43]	105 CFC (23.8% males) 104 controls (26% males)	CFC 4.38 ± 2.38 yrs Controls 4.43 ± 2.44 yrs	CFC	Lifestyle changes, child's family life style modification, increased physical activity, and pharmacotherapy	3 months	CFC 105/68	-3.8%

CFC = chronic functional constipation, DES = dysfunctional elimination syndrome, DV = dysfunctional voiding (urinary incontinence, hesitancy, straining, intermittency, weak stream), LUTD = lower urinary tract dysfunctions, n.a. = not available, n.s. = not significant

were different [23, 25, 31, 34-38, 43].

Few studies applied a randomization [26, 27, 29, 32]. In two studies by Vesna *et al*. [26, 27] divided the patients into two groups to compare different treatment regimens for DV; both groups had significant positive results in terms of amelioration of UTI recurrence and constipation. In another study, Kajbafzadeh *et al*. [29] randomized patients into 2 groups (biofeedback and conservative treatment) reporting a significant improvement of both constipation and UTI recurrence. Vasconcelos *et al*. [32], who compared two different treatments for DES, reported in both groups a significant improvement only in UTIs recurrences, because the prevalence of constipation had not decreased at follow-up compared to baseline.

Published studies involved a variable number of patients, from small cohorts of patients to a wide number (mean 71.4 patients, range 9-234), and often were only partial [41, 42].

A study of Loening-Baucke [38] is the one with the largest number of patients. The author observed that in 234 children with known CFC and encopresis which treatment of constipation could prevent UTIs in 10% of patients with recurrent UTIs. In a study by the same author [39], treatment of constipation resulted in amelioration of the CFC but reported no results in terms of UTI incidence. Khen-Dunlop *et al*. [41] reported the outcome only to resolve UTI recurrences and not for constipation. A recent study involving 209 children, CFC treatment did not show a significant (not stated) amelioration of UTIs recurrences [43]. In particular, this case-control study (105 CFC children versus 104 controls) showed that the prevalence of UTI in case and control groups was 13.3% and 6.7% ($p = 0.17$), showing a large link between constipation and UTIs, but the prevalence of UTIs in case group decreased only to 3.8% after treatment of constipation [43].

A bias in the clinical trials [26-28, 31, 35, 38] was the association between antibiotic prophylaxis, used if UTIs recurred, and constipation treatment.

DISCUSSION

UTIs recurrence prevention in children is again a challenge question whether antimicrobial prophylaxis is still a matter of debate. It has conducted investigtions to find optimal approaches to the assessment and management of UTIs and later interventions [44, 45].

Studies suggested a link between constipation and UTI recurrences in children. Guidelines for children with UTIs considered for investigate and managing of the bowel dysfunctions. The studies conducted so far reported a large reduction in UTIs occurrences in children managed for DES, DV or CFC [26, 28-30, 32, 33, 40].

American Academy of Pediatrics (AAP) published guidelines for the diagnosis and management of UTIs in febrile infants and young children younger than 2 years. No mention concerns evaluation and treatment of the associated constipation [46]. In the same way, the Italian Society of Pediatric Nephrology reports the recommendations for diagnosis and treatment of UTIs

in children younger than 3 years, but did not mention evaluation and treatment of constipation in affected ones [47]. The American Urological Association (AUA) guidelines recommended a continuous antimicrobial prophylaxis as management of a child >1-year-old with VUR, recurrent febrile UTIs, bladder and bowel dysfunction, or renal cortical anomalies. No mention regards the constipation in affected children [48]. The European Urological Association reported that if symptomsm are suggestive of LUTD (urgency, incontinence, constipation, or holding manoeuvres), should do an extensive history and examination. No mention regarded constipation management in these children [49].

Only NICE clinical guideline (https://www.nice.org.uk/guidance/qs36) reported that constipation and DV are risk factors for UTIs and should as part of history and examination on confirmed UTI. A systematic review of 27 studies (1 RCT and 26 case studies) on the role of biofeedback in DES in paediatric patients showed a rate of improvement from 18% to 100% for constipation and of 83% in cases of UTI [50]. In children with severe constipation, a structured bowel management program decreases unplanned visits to the emergency department, hospital admissions, and costs for constipation-related health care for constipation-related morbidities (abdominal pain 39%, fecal impaction 17%, urinary retention 2.2%, urinary tract infections 14%) [51].

Limitations

Further studies are necessary to show the effectiveness of constipation treatment regimens in preventing recurrent UTIs in children. In fact, most clinical trials, investigating the results of one or more treatments for constipation in the term of the resolution or amelioration of UTI recurrence, lacking in randomization and controlled groups. The published study results often involved small cohorts of patients or were only partial.

CONCLUSION

In conclusion, constipation seems to be a predisposing factor for UTIs recurrence in children. Studies were not homogenous but showed an improvement in UTIs occurrences in children managed for CFC or DES. Children referred to a paediatric nephrologist for UTIs should include an inquiry on bowel habits and those with a positive assessment for bowel dysfunction should by a paediatric gastroenterologist as a multidisciplinary approach.

Abbreviations

CFC = chronic functional constipation
DES = dysfunctional elimination syndromes
DV = dysfunctional voiding
LUTD = lower urinary tract dysfunctions
UTI = urinary tract infection
VUR = vesicoureteral reflux

Conflict of interest

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

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The European Research Journal 2019;5(2):244-249 ORIGINAL ARTICLE

Quitting smoking before surgical interventions and its relationship to health literacy

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ABSTRACT

Objectives: The aim of our study was to evaluate the effect of health literacy (HL) level and smoking dependence of patients on their compliance with advice given by the physicians in anesthesia polyclinics on giving up smoking.

Methods: This prospective study included 165 smokers. HL was evaluated by The European Health Literacy (HLS-EU). Nicotine dependence was measured by Fagerstrom test for nicotine dependence (FTND). Patients were advised not to smoke and their carbon monoxide levels in expired air were measured before on the operation day.

Results: The number of patients smoking on the day of surgery was significantly higher among females (p = 0.001). While the HL was lower, the FTND scores (p = 0.006), daily cigarette consumption (p < 0.001) and years of cigarette smoking (p = 0.002) were found to be significantly higher. Fewer number of days between the polyclinic interview and the surgery date were positively correlated with compliance with the advice to give up smoking (p = 0.011).

Conclusion: Since the number of patients continuing to smoke cigarettes was high, it was concluded that verbal advice on giving up smoking is not enough and that other more effective measures are needed to ensure patient compliance. The reminder of 'quit smoking' on the day very close to the surgery may help more patients to stop smoking on that day.

Keywords: Health literacy, anesthesiologist, smoking, verbal advice, Fagerstrom test for nicotine dependence

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Cigarette smoking, one of the most serious health-threatening problems, is responsible for the increasing incidence of chronic disorders of the respiratory and circulatory systems [1, 2]. It has been reported that the probabilities of small airway narrowing and increased bronchial reactivity should be considered during administration of anesthesia to patients who smoke cigarettes [3].It may lead to various complications ranging from intraoperative hypoxia to bronchospasm, delayed recovery, postoperative pneumonia, delayed wound healing and extended hospital stay [4, 5]. Therefore, it is of great importance to advise smoking cessation and to motivate patients to quit smoking within the scope of

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preoperative evaluation [4, 6, 7]. In preoperative patients, determining the general condition of the patient, reducing anxiety, making the patient aware of the risk factors, and making recommendations to reduce these risk factors are among the responsibilities of anesthesiologists [7].

Health literacy (HL) is the degree to which people have the ability to understand and access basic health services information, prevent disease, and make and implement decisions during treatment in the process of acquiring health information [2, 8-11]. Low levels of HL indicate that health information is difficult to understand and that the instructions given are difficult and lead to adverse health outcomes [8, 12, 13]. The World Health Organization considers health literacy as a key factor in promoting health [2]. In addition, HL has great importance in the efficiency of health recommendations and consultations [14].

HL is becoming increasingly accepted as a critical factor affecting patient-physician communication and health outcomes [15]. It is also reported that lower HL is strongly associated with smoking [16, 17]. HL is also considered to be an important factor because it affects the response of smokers to different types of smoking risk messages [16, 18].

The aim of our study was to evaluate the effect of HL level and smoking dependence of patients on their compliance with advice given by physicians on smoking cessation in anesthesiology polyclinics.

METHODS

This prospective, observational study included smokers who came to the preoperative anesthesiology polyclinic of a university hospital for their scheduled surgery. Demographic information about the level of education and previous anesthesia experience was obtained. Patients who were between 18-80 years old, had regular use of tobacco products on a daily basis, agreed to fill out the HL scale, had no communication problems and who were scheduled for elective surgery were included in the study. Patients who had communication problems, psychiatric disorders, vision problems and those who declined to complete the survey were excluded from the study.

The HL scale was applied after the patient was recommended not to smoke until the day of surgery, as we routinely do in the anesthesiology polyclinic (the nature of the scale requires an interview method where a health care professional asks questions and the patient gives answers). The scale contains 12 sub-dimensions, which are operationalized with 47 items. Each item is assessed using a 4-point self-report scale: 1 = very difficult, 2 = difficult, 3 = easy, 4 = very easy. We used code "5" to indicate the "don't know" answers. Additionally, demographic data and smoking habits of all patients were queried and recorded along with the age when they started smoking and the duration of the habit. We also recorded the cigarettes smoked per day, whether patients consumed tobacco or not till the day of operation, and if yes, the amount of cigarettes consumed. Nicotine dependency was assessed by means of the Fagerstrom Test for Nicotine Dependence (FTND) [19] in the anesthesiology polyclinic. To verify the use/non-use of tobacco, the eBCO (Exhaled Breath Carbon Monoxide) levels were estimated using the piCO+ Smokerlyzer® (piCO+ smokerlyzer®Bedfont Micro Breathalyzer, Kent, United Kingdom) in the operation room on the day of surgery.

Statistical Analysis

Statistical analyses were conducted using the SPSS 21 package program. The Kolmogorov-Smirnov test was used to investigate the distribution of variables. Non-normally distributed variables are given as median (minimum – maximum). Categorical data was recorded in percentages. Whereas the Mann Whitney U test was employed to compare averages, the Spearman Chi-square test and the Fisher's exact test were used for the comparison of rates, and correlations were analyzed with the Spearman correlation test. $p < 0.05$ was considered statistically significant.

RESULTS

Of 700 patients that came to the preoperative anesthesiology polyclinic during the three months, only 288 patients agreed to participate in the study. After the exclusion of patients that were unobserved in the operating room, did not give consent to measurement of the eBCO level and those filling out invalid forms, a total of 165 patients' data was

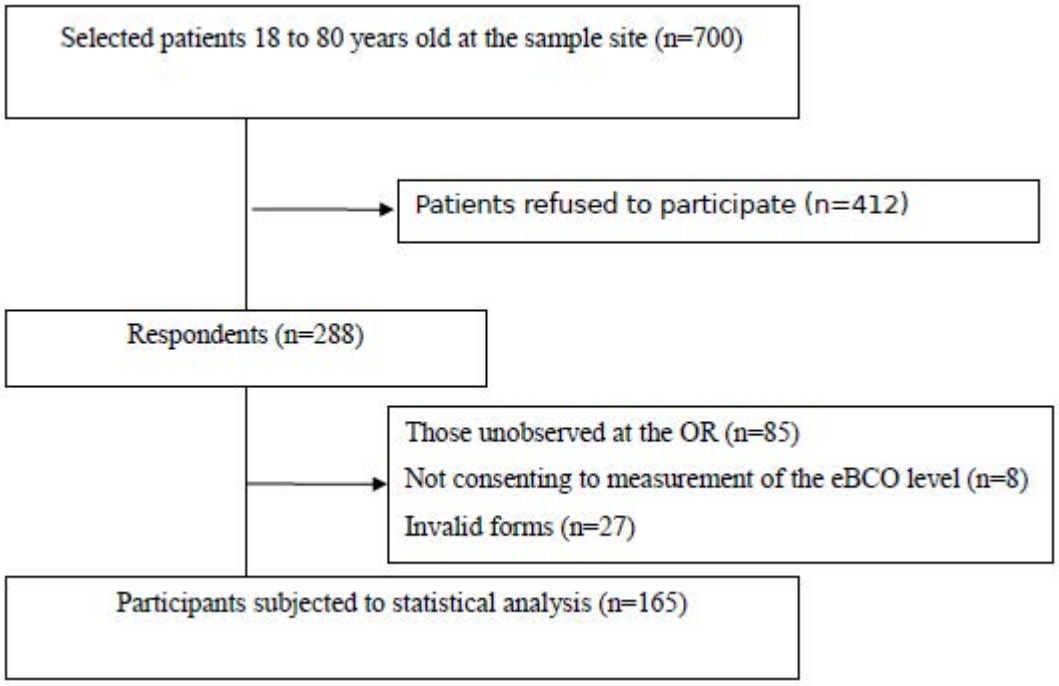

Figure 1. Participants flow chart of procedures

subjected to statistical analysis (Figure 1). The patients' demographic data is shown in Table 1. Table 1 also shows the smoking status till the day of operation, the HL level and the details of the cigarette smoking habit. In this study, the mean FTND score was consistent with a low level of nicotine dependence. The FTND score was used to estimate the dimension and profile of nicotine dependence [3]. The

Table 1. General characteristics of the patients (n = 165)

Characteristics		Data
Age, median (min-max), years		39 (22-73)
Male gender, n (%)		125 (75.8)
BMI, median (min-max)		25.2 (16.6-20.6)
Starting age of smoking (years)		18 (7-43)
Cigarettes smoked per day, n (%)		18 (5-40)
Duration of smoking, median (min-max), years		18 (1-65)
COppm		12 (1-88)
FTND		3 (0-10)
Smoking on morning of operation		56 (33.9)
Smoking on previous day		156 (94.5)
Health Literacy Category, n (%)	Inadequate	31 (18.8)
	Limited	63 (38.2)
	Adequate	40 (24.2)
	Excellent	31 (18.8)

Data are shown as median (maximum-minimum) or number (%). FTND = The Fagerstrom Test for Nicotine Dependence

Table 2. Health literacy and variables related to smoking

Spearman Correlation Test	Health Literacy Score		Health Literacy Category	
	p value	Correlation Coefficient	*p* value	Correlation Coefficient
Age	**0.007**	-0.210	**0.027**	-0.172
Cigarettes smoked per day	**< 0.001**	-0.279	**0.001**	-0.263
Duration of smoking	**0.002**	-0.241	**0.01**	-0.199
FTND	**0.006**	-0.211	**0.008**	-0.205

FTND = The Fagerstrom Test for Nicotine Dependence, $p < 0.05$ statistically significant

mean total HLS-EU (European Health Literacy Survey – Turkish Adaption) score was 32.6 (range 7.4-50). The patients' HL levels were as follows: inadequate 18.8%; limited 38.2%; adequate 24.2% and excellent 18.8%. While the percentage of the patients who smoked on the day prior to surgery was 94.1%, the percentage of those who smoked on the day of surgery was 33.9%.

The eBCO levels were statistically higher in patients that smoked before or on the day of surgery as compared to those who did not smoke ($p = 0.001$ for both). The number of female patients that smoked on the day of operation was significantly higher than male patients ($p = 0.001$). However, there was no statistically significant difference between the patients that smoked and did not smoke on the day of surgery regarding health literacy ($p > 0.05$). When the patients that smoked cigarette(s) one day before surgery were compared with those who did not smoke, a statistically significant difference was detected regarding the duration from the day of preoperative polyclinic examination till the day of surgery ($p = 0.011$).

The lower the HL level was, the higher the FTND level, cigarettes smoked per day and the duration of smoking habit ($p = 0.006$, $p < 0.001$ and $p = 0.002$, respectively). Furthermore, the HL level was found to be significantly lower among older patients ($p = 0.007$) (Table 2).

DISCUSSION

In this study, we aimed to investigate the effect of HL level and smoking dependence of patients on their compliance with advice given by the physicians in anesthesiology polyclinics. Whereas the HL level did not differ between the compliant and noncompliant patients, there was a relation between HL and nicotine dependence. Women's preoperative smoking prevalence was higher as compared to men. Additionally, the prevalence of smoking one day before surgery significantly increased as the time interval between preoperative anesthesiology examination at the polyclinic and surgery was extended.

There are a large variety of studies investigating the relationship of HL with self-efficacy, management of chronic diseases, depression, eating habits, endocrinological diseases, and the capacity to understand and use the information and treatment given by a physician [11-13, 17, 18, 20]. Inou *et al*. [11] indicated in their observational study that communicative and critical HL was positively associated with diabetic care and self-efficacy. Carrara and Schulz [13] found different results in their review related to the role of HL in adherence to the diet advice of doctors.

In our literature review, we came across only one study investigating anesthesiology polyclinics and HL within the same context. In the study conducted on a total of 502 patients, Garcia-Marcinkiewicz *et al*. [21] investigated the knowledge of patients with adequate or high health literacy levels on the responsibilities of anesthesiologists related to intensive care, blood transfusion and pain, and their knowledge level was found to be low on these topics. An educational booklet was the preferred method to provide this information [21]. Also, the HL levels were heterogeneous among the patients.

Although there are studies addressing the relation

of HL to quitting smoking [16, 17], we could not find studies investigating the association of HL and smoking cessation in the setting of anesthesiology polyclinics. There was only one study evaluating the knowledge of patients on the role of anesthesiologists [21]. For this reason, we think that this is the first study evaluating the influence of HL on compliance with the advice not to smoke. Low health literacy is associated with unhealthy behaviors including smoking [16, 18]. Steward *et al*. [18] reported in their study that low HL negatively affected the results of smoking cessation. Those with low health literacy reported that they were less informed and had lower perceptions about the health risks of smoking. It was also suggested that nicotine dependency is the most significant indicator in giving up smoking and is associated with lower smoking cessation rates. Similarly, in the present study, HL was found to be associated with daily cigarette consumption, the duration of smoking habit and the level of nicotine dependency. However, we could not find a relation between the adherence to advice to give up smoking and HL level.

Health literacy is becoming more important in doctor and patient communications [12, 15, 18]. Williams *et al*. [15] demonstrated in their retrospective study that low HL influences health-related outcomes by complicating the communication between patients and physicians. Additionally, patients with low health literacy often have difficulties in understanding the information provided to them due to lack of knowledge, which consequently may result in bad temper and anxiety [12]. These patients have less information about their medical condition and treatment, and may have increased hospitalization rates. [12, 15]. In this context, Chu and Tseng [12] stated that using different approaches like empathic communication was more beneficial and helped patients with low HL better understand physicians' advice. Furthermore, Hoover *et al*. [16] suggested that besides HL, emotionality also impacts the overall effect and credibility of the messages on the risks of smoking that are intended to help facilitate smoking cessation. A person's HL is important when considering the factual or emotional content of communication in determination of risks associated with smoking cigarettes [16]. Steward *et al*. [17] suggested the use of methods that involve less text and more images to facilitate the understanding of people regardless of HL in studies on smoking cessation. Johnson *et al*. [22] mentioned the need for increasing the awareness of pharmacists on limited health literacy of patients and providing education to them with the support of health systems for an effective communication with patients.

It is also among the responsibilities of an anesthesiologist to determine the general condition of the patient, reduce anxiety, raise the awareness of the patient about the risk factors, and make recommendations to reduce identified risk factors. In our study, we could not find any association between HL and compliance to our verbal advice, and the rate of preoperative smoking was very high. It may be beneficial to use supporting techniques like empathy and emotionality while approaching these patients. Additionally, using visual materials to promote the influence of verbal warnings/advice and including surgeons and other allied health personnel in the preoperative evaluation process at anesthesiology polyclinics, which are generally intensely busy, may positively affect the outcome.

Limitations

The heterogeneity of smoking habits among the patients, the single-centered nature of the study and the smoking cessation advice being given by various doctors with different levels of experience in the polyclinic were the limitations of this study. It may change the outcome if smoking cessation advice is given by a surgeon, and therefore, this should be investigated in further studies.

CONCLUSION

No correlation was observed between verbal advice for giving up smoking in anesthesiology polyclinics and the patients' HL scores. Since the number of patients continuing with smoking was high, it was concluded that verbal advice on quitting smoking is not enough, and thus, other more effective measures are needed to ensure patient compliance. Regardless of the HL score, the shorter the interval between the advice to quit smoking and the day of operation, the greater the adherence to the advice becomes.

Conflict of interest

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The European Research Journal 2019;5(2):250-257 ORIGINAL ARTICLE

Significance of thiol/disulphide homeostasis and ischemia modified albumin levels in chronic obstructive pulmonary disease

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ABSTRACT

Objectives: The severity of inflammation occurring during chronic obstructive pulmonary disease (COPD) is closely associated with oxidative stress. The aim of this study was to investigate the diagnostic value of Thiol/disulphide homeostasis (TDH) and ischemia modified albumin (IMA) levels in evaluating oxidative stress in COPD patients.

Methods: This prospective study was performed with COPD patients presenting to the Kırıkkale University Hospital and with healthy volunteers. Subjects' demographic data (age, sex, body mass index, and smoking status), native thiol (NT), total thiol (TT), disulphide (Ds), IMA levels and Ds/NT, Ds/TT and NT/TT ratios were recorded. Statistical analysis was performed with SPSS 21.0 software.

Results: One hundred ninety subjects were enrolled in the study, 141 COPD patients and 49 healthy volunteers. No difference was determined between the patient and control groups in terms of age, sex or body mass index. The antioxidant markers; NT and TT levels and NT/TT ratio were significantly lower in the patient group compared to the control group ($p < 0.001$, $p < 0.001$, and $p < 0.003$, respectively). The oxidant markers; IMA levels and Ds/NT and Ds/TT ratios were significantly higher in the patient group ($p = 0.006$, $p = 0.003$, and $p = 0.003$, respectively). Significant negative correlation was determined between antioxidant and oxidant parameters. Sensitivity values were NT: 87.2%, TT: 83.3%, Ds/NT ratio: 68.1%, Ds/TT ratio: 68.1%, and IMA: 77.8%.

Conclusions: TDH was impaired in favor oxidants in COPD patients. TDH parameters and IMA can be used to monitor oxidative stress emerging in COPD.

Keywords: Chronic obstructive pulmonary disease, oxidative stress, thiol/disulphide homeostasis, ischemia modified albumin

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Chronic obstructive pulmonary disease (COPD) is a condition with high morbidity and mortality resulting from exposure to several harmful gasses or particles, and particularly smoking [1, 2]. Inflammation occurring during the course of COPD is closely related to the clinical course of the disease. The severity of inflammation also depends various infectious, genetic and environmental factors, and particularly oxidative stress [1]. Various cells, such as monocytes, macrophages, CD8 T-lymphocytes, neutrophils and eosinophils, and inflammatory mediators including interleukin-1, -6, and -8 and tumor necrosis factor-alpha are responsible for the development of inflammation [1, 3]. The damage caused by inflammatory products in COPD is essentially responsible for the emergence of pathological findings; reactive oxygen species (ROS) overproduction in cells makes damage in the pulmonary parenchyma resulting from oxidative stress and proteinase activity irreversible [4]. ROS are highly reactive molecules emerging as the result of enzymatic and non-enzymatic reactions. They are implicated in the pathogenesis of numerous diseases, and particularly cancers [5, 6]. ROS are eliminated from the body by antioxidant substances. These include substances with enzymatic structures such as superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase, or molecules such as glutathione, ascorbic acid, tocopherols and carotenoids [7].

Thiols are organic compounds with a sulphydryl group exhibiting antioxidant effects [8]. These compounds form disulphide (Ds) bonds by reacting with ROS in the body. The emerging Ds bonds are reversible, and can be reduced back to thiols, depending on the oxidant-antioxidant status in the organism [8, 9]. The antioxidant effect of thiol/disulphide homeostasis (TDH) plays a critical role in signal transmission, enzymatic reactions, transcription, detoxification, and apoptosis mechanisms [8, 9]. Under normal conditions, TDH has a dynamic structure, but it can be adversely affected by pathologies involving increased oxidative stress. Studies have shown that oxidative stress, the effect of which are exacerbated by impairments in TDH, is involved in the pathophysiology of many diseases, including diabetes mellitus, cardiovascular diseases, cancer, kidney failure, rheumatoid arthritis, Parkinson's disease, Alzheimer's disease, Friedreich's ataxia, multiple sclerosis, and amyotrophic lateral sclerosis [8-13]. Demonstrating the destructive effects of oxidative stress can elicit valuable information in terms of understanding the biochemical process involved in many diseases [14-16]. The TDH measurement method newly developed by Erel *et al*. [8, 15, 17-22] has been shown to a reliable indicator in showing oxidative stress.

Albumin is the most abundant protein in the body, and has several functions, including playing a role in the elimination of ROS [23]. In case of ischemia, changes occur in the amino acid sequence, the albumin N-terminal, and the resulting new protein is known as ischemia-modified albumin (IMA). IMA has a low binding capacity to heavy metals such as cobalt, nickel and copper, and this is closely associated with an increase in ROS, ischemia or the hypoxic process [23]. Studies have shown that IMA levels rise in several conditions, including muscle ischemia, aortic pathologies and diabetic retinopathy [24-28].

The aim of this study was to investigate changes occurring in the oxidant-antioxidant system, TDH parameters and IMA measurements in COPD.

METHODS

Study Population

Following receipt of local ethical committee approval (No.2016-08/10), this study was performed prospectively with patients with previous definite diagnosis of COPD presenting to the Kırıkkale University School of Medicine, Emergency Medicine and Chest Diseases departments and with healthy volunteers agreeing to take part of their own volition. Signed inform consent forms were received from the participants, and the study was carried out in strict accordance with the Declaration of Helsinki and Good Clinical Practice Directive.

Age, sex, body mass index (BMI), smoking status, laboratory results (complete blood count, AST, ALT, urea, creatinine, albumin and serum electrolytes), TDH parameters and IMA levels were recorded for all subjects. Spirometry measurement results were also recorded for the COPD patients.

Patients with cancer, diabetes mellitus, coronary artery disease, cerebrovascular disease, heart, liver or

kidney failure, pregnant and lactating women, patients aged under 18 and subjects refusing to take part were excluded from the study.

Specimen Collection and Analysis

We first collected 10 cc blood samples from all subjects in the patient and control groups. These were placed into biochemistry tubes (GranierBio-one, North America, Inc., North Carolina, USA) and centrifged for 6 min at 5000 rpm for serum separation. These serum specimens were subsequently placed into Eppendorf tubes and frozen at-800C until biochemical analysis. When the target participant number was reached, the specimens were transferred under appropriate conditions in iced boxes to the Kırıkkale University School of Medicine Biochemistry laboratory. All specimens were thawed at the same time, and NT, TT, Ds, and IMA levels were measured. TDH parameters levels were analyzed using the automatic measurement method newly developed by Erel and Neselioglu [8], and the results were expressed as'µmol/L'. IMA levels were analyzed using the rapid, colorimetric method developed by Bar-Or *et al*. [29], and the results were expressed as absorbance units (ABSU).

Statistical Analysis

Data analysis was performed on SPSS 21.0 (IBM SPSS Statistics 21.0, IBM Corporation, Armonk, NY, USA) software. Compatibility with normal distribution was investigated using the Kolmogorov-Smirnov test. Descriptive statistics were expressed as constant and discrete numeric variables and shown as mean±standard deviation (SD) or median and interquartile range (IQR). Categoric variables were expressed as number (n) and percentage (%). Parametric data were compared using Student's t test and non-parametric data using the Mann-Whitney U test, while Pearson's Chi-square test was used to analyze categorical variables, and Spearman's rho correlation test to compare numerical variables. ROC analysis was used to determined sensitivity, specificity and cut-off values. A $p < 0.05$ was regarded as statistically significant.

RESULTS

One hundred ninety subjects were included in the study; 141 patients with previous definite diagnosis of

Table 1. The groups' demographic and laboratory characteristics

	Group COPD (n = 141)	**Group Control (n = 49)**	***p* value**
Gender	**n (%)**	**n (%)**	
male	108 (76.6)	39 (79.6)	0.843*
F emale	33 (23.4)	10 (20.4)	
	mean ± SD	**mean ± SD**	
Age (year)	63.8 ± 10.9	61.1 ± 7.6	0.106†
NT (µmol/L)	274.2 ± 88.3	427.2 ± 74.1	**< 0.001**†
TT (µmol/L)	315.4 ± 86.5	468.7 ± 80.3	**< 0.001**†
	median (IQR)	**median (IQR)**	
BMI (kg/m^2)	25.7 (5.5)	24.6 (2.6)	0.275‡
Ds (µmol/L)	20.4 (13.4)	20.8 (10.3)	0.153‡
Ds / NT	6.7 (8.2)	4.8 (2.4)	**0.003**‡
Ds / TT	5.9 (6.3)	4.4 (2.0)	**0.003**‡
NT / TT	88.3 (12.6)	91.3 (4.0)	**0.003**‡
IMA (ABSU)	72.5 (5.0)	72.1 (4.8)	**0.006**‡

BMI = body mass index, Ds = disulphide, NT = native thiol, TT = total thiol, IMA = ischemia modified albumin, IQR = interquartile range, SD = standard deviation, *Chi-square test, †Student-t test, ‡Mann-Whitney U test

Table 2. Correlation between TDH parameters and IMA

Parameters		NT	TT	NT/TT	Ds	Ds/NT	Ds/TT	IMA
NT	r	1.000	0.958†	–.537†	–.049	–.537†	–.537†	–.291†
TT	r		1.000	.325†	.184*	–.325†	–.326	–.265
NT/TT	r			1.000	–.811†	-1.000†	-1.000†	–.165*
Ds	r				1.000	.811†	.811†	.064
Ds/NT	r					1.000	1.000†	.166*
Ds/TT	r						1.000	.166*
IMA	r							1.000

NT = native thiol, TT = total thiol, Ds = disulphide, IMA = ischemia-modified albumin, r = Spearman rho correlation coefficient, *$p < 0.05$, †$p < 0.01$

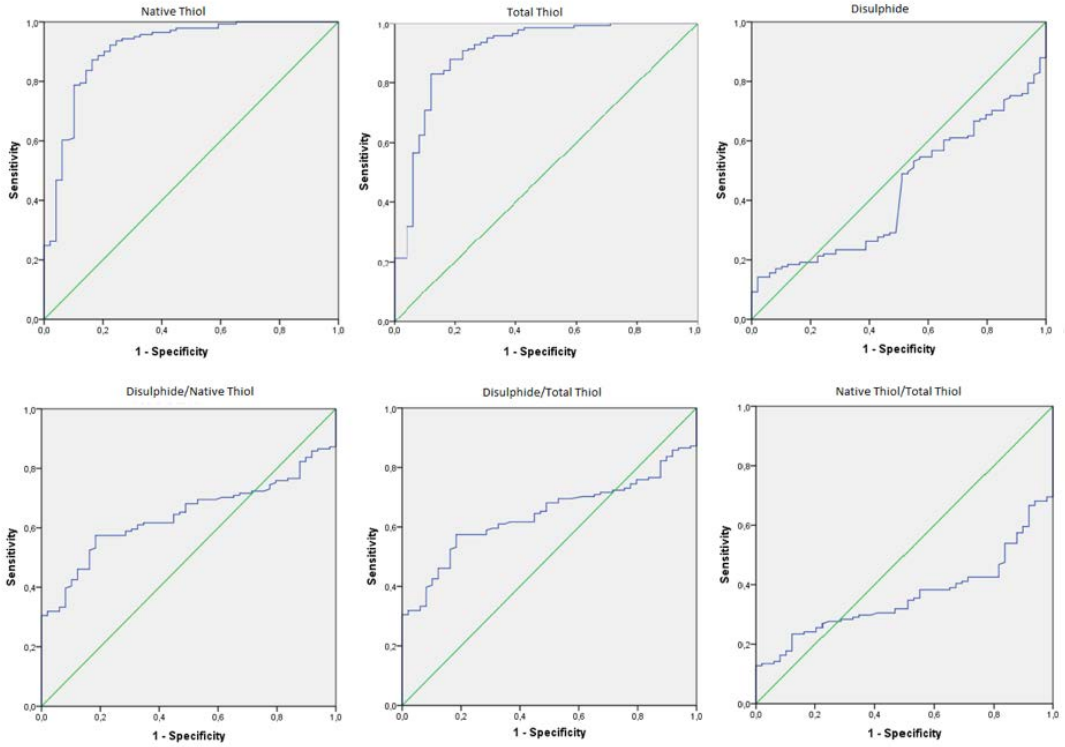

Figure 1. ROC curve analysis of thiol/disulphide homeostasis parameters

Table 3. ROC curve analysis of TDH parameters and IMA levels

Parameters	Area	Cut-off	Sensitivity (%)	Specificity (%)
NT (µmol/L)	0.910	368	87.2	83.7
TT (µmol/L)	0.902	368	83.3	87.8
Ds (µmol/L)	0.431	20.6	48.9	49.0
Ds/NT (µmol/L)	0.641	4.8	68.1	51.0
Ds/TT (µmol/L)	0.641	4.4	68.1	51.0
NT/TT (µmol/L)	0.641	90.5	38.3	44.9
IMA (ABSU)	0.633	71.3	77.8	62.0

NT = native thiol, TT = total thiol, Ds = disulphide, IMA = ischemia-modified albumin

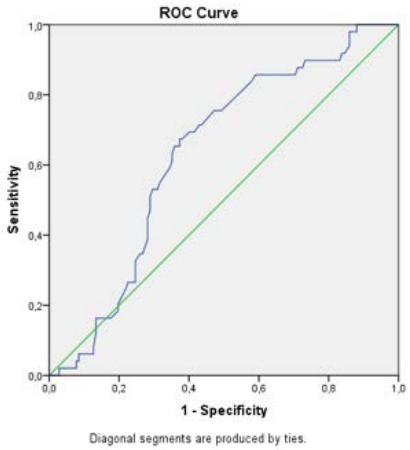

Figure 2. ROC curve analysis of ischemia-modified albumin.

COPD constituted the patient group. The control group consisted of 49 healthy volunteers similar to the patient group in terms of age, sex, and BMI. The mean age of the patient group was 63.8 ± 10.9 years, 76.6% were men, and the median BMI value was 25.7 kg/m2. The mean age of the control group was 61.1 ± 7.6 years, 79.6% were men, and the median BMI value was 24.6 kg/m2. No significant difference was determined between the two groups in terms of age, sex or BMI (p = 0.106, p = 0.843, and p = 0.275, respectively) (Table 1).

Mean native thiol (NT) levels were 274.2 ± 88.3 µmol/L in the patient group and 427.2 ± 74.1 µmol/L in the control group ($p < 0.001$). Mean total thiol (TT) levels were 315.4 ± 86.5 µmol/L in the patient group and 468.7 ± 80.3 µmol/L in the control group ($p < 0.001$). Mean NT/TT ratio values were 88.3% in the patient group and 91.3% in the control group (p = 0.003) (Table 1).

Median Ds values were 20.4 µmol/L, in the patient group and 20.8 µmol/L in the control group (p = 0.275). Median IMA levels were 72.5 ABSU in the patient group and 72.1 ABSU in the control group (p = 0.006). The median Ds/NT ratio was 6.7% in the patient group and 4.8% in the control group (p = 0.003), while the median Ds/TT ratio was 5.9% in the patient group and 4.4% in the control group (p = 0.003) (Table 1).

Antioxidant parameters (NT and TT) and oxidant parameters (Ds, Ds/NT, Ds/TT and IMA) both exhibited positive correlation among themselves, while negative correlation was determined between antioxidant and oxidant parameters (Table 2). Sensitivity values in showing COPD were NT: 87.2%, TT: 83.3%, Ds/NT ratio: 68.1%, Ds/TT ratio: 68.1%, and IMA: 77.8% (Table 3) (Figures 1 and 2).

DISCUSSION

In this study of the relation between COPD and oxidative stress, levels of NT and TT, antioxidant markers of TDH were significantly low in the patient group, while oxidant markers Ds/NT and Ds/TT ratios increased significantly in the patient group compared to the control group. In addition, IMA levels, another oxidant parameter, were also significantly high in the patient group, and positive correlation was determined between other oxidant parameters. These findings show that TDH alters in favor of oxidants in COPD patients and that oxidative stress increases in these patients.

Although oxidative stress affects several organs, the organs most exposed to such stress are the lungs [30-32]. Oxidant substances accumulating in the airways reduce surfactant activity in addition to impairing cellular genetic structure, biological membranes, the ciliary matrix and ciliary functions, while increasing mucus and cytokine production [1, 31, 32]. Knowing the function of thiols involved in the antioxidant system is therefore becoming increasingly important in terms of understanding several diseases associated with oxidative stress, including COPD [19]. Studies investigating the relation between oxidative stress and TDH have shown that such homeostasis is impaired in oxidative terms in patients with acute

myocardial infarction, migraine, alopecia or chronic urticaria, in pregnant women with hyperemesis gravidarum (compared to normal gravidas), and in workers exposed to polycyclic aromatic hydrocarbons [14-16, 33-35]. Babaoglu *et al*. [36] assumed the presence of oxidative stress in COPD and investigated TDH in other subgroup diseases causing lower airway obstruction, such as asthma and asthma-COPD overlap syndrome (ACOS). However, in the absence of a control group for purposes of comparison, they were unable to clearly demonstrate changes in TDH [36]. Evaluated from that perspective, ours is the first study to compare TDH in patients with COPD and healthy controls.

Oxidative stress-related effects are known to be exacerbated in COPD patients for reasons such as inflammation, infection, smoking, increased hypoxia and a decreased antioxidant response [32, 37, 38]. Şahin *et al*. [39] determined an association between ROS accumulation and bronchial hyperactivity and reported that this was responsible for irreversible damage and narrowing in the airways. Rahman *et al*. [40] reported insufficient antioxidant response in COPD exacerbation and that this insufficiency persisted for 48 h. Demir *et al*. [41] reported higher than normal levels of glutathione, an antioxidant molecule, in cases of COPD, and that this elevation increased still further in the acute exacerbation period. Studies have shown that products of oxidative stress produce new radicals by removing protons from various molecules, such as thiols and also fatty acids [6, 16, 42]. A decrease in plasma thiol concentrations is therefore regarded as indicating oxidative stress and increased ROS production [16]. In our study, the Ds/NT andDs/TT ratios showing the presence of oxidative stress were significantly higher compared to in the control group, while a statistically insignificant decrease was observed in Ds levels. The antioxidant markers NT andTT levels and the NT/TT ratio were significantly lower than in the control group. At the same time, negative correlation was determined between oxidant parameters and antioxidant parameters. We interpreted these findings as indicating that the oxidant-antioxidant balance is impaired in favor of oxidants in patients with COPD, and that the organism consumes thiols in order to combat increasing oxidative stress.

Several parameters exhibiting oxidant or antioxidant characteristics have been investigated in terms of showing oxidative stress in patients with COPD. These include glutathione, glutathione peroxidase, superoxide dismutase, catalase, ferroxidase, and myeloperoxidase [43-46]. IMA is an oxidant marker resulting from the differentiation of albumin, with antioxidant properties, in situations involving increased oxidative stress [23]. Recent studies have again emphasized the relation between IMA and diseases involving increased oxidative stress. Ataş *et al*. [47] reported that IMA is superior to other biomarkers in showing oxidative stress in patients with vitiligo. In another study of the effectiveness of IMA in showing oxidative stress in COPD patients, Can *et al*. [48] determined significant elevation in IMA levels in COPD patients compared to controls and concluded that IMA may be a useful biomarker for assessing chronic inflammation and oxidative stress in COPD. IMA levels in our study were significantly higher in patients with COPD than in the control group. At the same time, IMA exhibited positive correlation with other oxidant parameters and inverse correlation with antioxidant parameters. IMA therefore shows that the increase in oxidant markers in TDH is not coincidental and may be considered as another biomarker for showing increased oxidative stress in COPD.

CONCLUSION

In conclusion, TDH is impaired in favor of oxidants in COPD, as shown by increasing Ds/NT, and Ds/TT ratios and decreasing NT and TT levels and NT/TTratios. In addition, the increase in levels of IMA, another oxidant marker, supports these findings. We therefore think that TDH parameters and IMA can be used to evaluate oxidative stress in COPD.

Authorship declaration

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

Conflict of interest

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

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The European Research Journal 2019;5(2):258-267 ORIGINAL ARTICLE

A cross-sectional study of female sexual dysfunction among Turkish pregnant and nonpregnant women: correlation with hormone profile

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ABSTRACT

Objectives: To determine the prevalence of female sexual dysfunction (FSD) and its correlation with the androgenic hormones among pregnant and nonpregnant Turkish women.

Methods: This was a cross-sectional study of 251 women, including 137 healthy pregnant and 114 healthy nonpregnant Turkish women. Assessment of female sexual function index (FSFI), sociodemographic characteristics, serum androgen levels, including the total testosterone, dehydroepiandrosterone sulfate (DHEAS), 1-4 delta androstenedione.

Results: There was a 65.7 % incidence of FSD in all of the participants, with an incidence of 58.8% in the pregnant and 41.2% in the nonpregnant women. There was no significant difference in the FSFI total scores between the pregnant and nonpregnant women ($p > 0.05$). Moreover, the androgen levels were not different between the women with sexual dysfunction and those without. The Spearman correlation test results were significant between the total testosterone level and the FSFI arousal domain ($r = 0.167$, $p < 0.05$), FSFI lubrication domain ($r = 0.264$, $p < 0.01$), and FSFI total score ($r = 0.212$, $p < 0.01$), as well as between the androstenedione level and FSFI lubrication domain ($r = 0.211$, $p < 0.01$), FSFI orgasm domain ($r = 0.156$, $p < 0.05$), and FSFI total score ($r = 0.174$, $p < 0.05$). In the logistic regression analysis for sexual dysfunction, an increase in the DHEAS level increased the sexual dysfunction by 0.996-fold. Women with one pregnancy had 3.312-fold greater sexual dysfunction than those with no pregnancies. Moreover, the women with more than eight years of education had 0.358 times more sexual dysfunction than those with eight years of education and less.

Conclusion: The FSFI total scores were not significantly different between the pregnant and nonpregnant women. However, there were significant correlations between the total testosterone and androstenedione levels and the FSFI total scores. Any increases in the DHEAS level and educational level in women decrease the chance of developing sexual dysfunction.

Keywords: Female sexual function index, androgens, pregnancy

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The female sexual response cycle is divided into four phases, including desire, arousal (excitement), orgasm, and resolution [1]. With regard to these phases, female sexual dysfunction takes different forms, including the absence of sexual desire, impaired arousal, an inability to achieve orgasm, and pain during sexual activity [1]. It is a multifactorial and underestimated problem with an overall prevalence of 20-50% [2]. One international survey, the Global Study of Sexual Attitudes and Behaviors (GSSAB), evaluated the sexual problems of 13,882 women from 29 different countries, aged 40 to 80 years old, who responded to a questionnaire in person or on the telephone [3]. The most commonly reported sexual problems were a lack of interest in sex (26-43%) and an inability to reach orgasm (18-41%). For all the different sexual problem types, the highest prevalences were seen in Southeast Asia (Indonesia, Malaysia, the Philippines, Singapore, and Thailand) and the lowest prevalences were seen in Northern Europe (Austria, Belgium, Germany, Sweden, and the United Kingdom) [3]. Cayan *et al.* [4] evaluated women between the ages of 18 and 65 years old, and they found that the sexual dysfunction prevalence in Turkish women was 46.9%; it was 43.4% in the study by Aslan et al. [5].

In the literature, a significant decline in sexual activities was shown with increasing gestation [6-8]. The reasons suggested for this decline in the sexual activity during pregnancy was physical discomfort, fear of injury to baby, loss of interest, physical awkwardness, painful coitus and perceived lack of attractiveness [7-9]. Large and representative studies reported no overall association between birth complication (prenatal mortality, preterm birth, premature rupture of the membranes, low birth weight) and either coital activity or orgasmic frequency unless a sexually transmitted disease is acquired [10, 11]. Besides parental sexuality during pregnancy has positive effects on the long-term quality of the marital relationship, that is reported as being as better with regard to tenderness and communication at 4 months postpartum and, 3 years later, the relationship is more stable and less affected in the view of both partners [12].

Dehydroepiandrosterone (DHEA) is an androgenic hormone and one of the precursors in the biosynthetic pathway of steroid hormones 13]. It has been suggested that androgens play roles in female sexual function, but the magnitudes of these roles are uncertain [14]. Several randomized controlled trials (RCTs) evaluating the safety profile of DHEA with regard to sexual performance in postmenopausal women found that DHEA had a positive effect on sexual function [15, 16], while other RCTs did not [17, 18].

Female sexual dysfunction (FSD) is considered to be a public health problem, affecting the quality of life of couples. Pregnancy is a special time that includes physical, psychological, and hormonal changes affecting the sexual lives of women. However, the sexual changes during pregnancy and their relationships to the androgenic hormones require further research. Therefore, the aim of this study was to determine the prevalence of FSD and its correlations with the androgenic hormones among pregnant and nonpregnant Turkish women.

METHODS

Subjects

This study was conducted with a total of 251 women, including 137 healthy pregnant and 114 healthy nonpregnant women evaluated at the Derince Training and Research Hospital Obstetrics and Gynecology Clinics between February 2016 and April 2017. The research was carried out with participants aged 18-41 years old who were sexually active (those who were married and reported having sexual intercourse during the previous 4 weeks). The main exclusion criterion was the presence of a chronic systemic/endocrine illness, such as diabetes mellitus, hyperthyroidism, hypothyroidism, and psychiatric problems. Those pregnant women with abnormal ongoing pregnancies, including the risk of miscarriage, preterm labor, and hypertensive disorder, were not enrolled in this study. All of the pregnant patients were given information about sexuality in pregnancy at the pregnancy training outpatient clinic in the same hospital, and their questions were answered by a midwife. They were informed that sexual intercourse is safe during pregnancy, except in conditions of pain, cramping, unexplained vaginal bleeding, premature cervical dilatation, and premature membrane rupture. Those patients who wanted to participate were given a patient information sheet and self-reporting questionnaire. Sixteen of the women

who agreed to participate were not included in the study since they did not fill out their questionnaires completely.

Design

This was a cross-sectional observational research study in which the author gathered data over a 15-month time period. All of the patients provided blood samples between the hours of 10 am and 3 pm in order to minimize the diurnal variations in the hormone levels. They filled out self-reporting questionnaires, including the Female Sexual Function Index (FSFI) and questions related to their sociodemographic data. The questionnaire related to the sociodemographic data included the participant's educational status, occupational status, income, medical history, and obstetric history, including gravity, parity, abortus, vaginal births, and cesarean sections. The educational status was categorized as ≤ 8 years (elementary and secondary school) and > 8 years (high school and university). All of the participants were married.

Ethics

Ethical approval was provided by the Kocaeli University Ethical Committee, and written informed consent was obtained from all of the participants.

Main Outcome Measures

The sexual function was measured via the FSFI, which is a validated, self-administered, 19-item questionnaire evaluating sexual function during the previous four weeks with six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. Rosen *et al*. [19] constructed the self-reported questionnaire for the assesment of female sexual function. The Turkish validation of the FSFI has been performed previously [20]. Questions 1, 2, 15, and 16 are scored between 1 and 5, while all of the other questions are scored between 0 and 5. The sum score of each domain obtained from the related questions was multiplied in its coefficient factor (Table 1). The sum score of all of the domains ranged from 2 to 36. Those women having a total score below 25 were considered to have sexual dysfunction 21].

All of the patients gave blood samples for evaluating the hormonal androgen concentrations, including the total testosterone, dehydroepiandrosterone sulfate (DHEAS), and 1-4 delta androstenedione. All of the samples were run simultaneously in the biochemistry laboratory of the same hospital.

The total testosterone (TT) was measured via an Advia Centaur kit (Advia Centaur and Advia Centaur XP Systems, Siemens, USA), which is a competitive immunoassay using direct chemiluminescent technology. The test sensitivity and assay range was 10-1,500 ng/dL (0.35-52.1 nmol/L). The DHEAS was also measured using an Advia Centaur kit (Advia Centaur and Advia Centaur XP Systems, Siemens, USA), which is a quantitative competitive immunoassay that uses direct chemiluminescent technology. The test sensitivity and assay range was 3-1,500 µg/dL (0.08-40.75 µmol/L).The 1-4 delta androstenedione was measured via Agilent Technologies 6460 Triple Quad using LC-MS/MS method. The test sensivitiy was 0.009 ng/mL and the reportable range was 0.03-500 ng/mL.

Statistical Analysis

The statistical parameters were computed using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA). The continuous variables were expressed as the mean±standard deviation and median (minimum-maximum), and the

Table 1. Female sexual function index domain scores

Domain	Item number	Score range	Minimum score	Maximum score	Coefficient
Desire	1, 2	1-5	2	10	0.6
Arousal	3, 4, 5, 6	0-5	0	20	0.3
Lubrication	7, 8, 9, 10	0-5	0	20	0.3
Orgasm	11, 12, 13	0-5	0	15	0.4
Satisfaction	14, 15, 16	(0 or 1)-5 *	2	15	0.4
Pain	17, 18, 19	0-5	0	15	0.4

Range for item 14 = 0-5; range for items 15 and 16 = 1-5

categorical variables were expressed as the number and percentage. The Mann-Whitney U test was used in the comparison between the averages of two groups. The Kruskal-Wallis test was used to compare more than two continuous variables. The Spearman correlation test was used for evaluating the relationships between the continuous data, and statistical significance was defined as $p < 0.05$. The independent predictors of sexual dysfunction using the possible factors in the multivariate analysis were examined using a logistic regression analysis. Finally, the Hosmer-Lemeshow test was used for the model adaptation. Those cases with less than 5% type 1 error levels were interpreted as statistically significant.

The GPower 3.1 program Posthoc analysis was used for the power analysis retrospectively. When the effect was 0,50 and the total of 251 (114 + 137) cases were analyzed in two independent groups, the power was calculated as 0.97.

RESULTS

A total of 251 women (137 pregnant and 114 nonpregnant) with a mean age of 28.57 ± 6.15 years old constituted the study group. The obstetric history of the participating women is shown in Table 2. In total, 61.4% of the women had less than eight years of education, 38.6% had more than eight years of education, 90.4% of the women were housewives or unemployed, 9.6% were working, 78.4% had low incomes (under 570 US dollars), and 21.6% had middle incomes (over 570 US dollars) (Table 2).

The mean FSFI total score was 23.08 ± 5.18, while the number of women with sexual dysfunction based on an FSFI total score of less than 25 was 165 (65.7% of all the participants). Of those women exhibiting sexual dysfunction, 58.8% were pregnant and 41.2% were not. Of the pregnant women, 70.8% had sexual dysfunction and 29.2% did not (Table 2).

Table 2. Demographic ,obstetric characteristics ,FSFI total scores and sexual dysfunction rates of the patients.

		Total group	Pregnancy Present n = 137	Pregnancy Absent n = 114
Age (years)	Mean ± SD	28.57 ± 6.15	26.59 ± 5.1	30.94 ± 6.4
BMI	Mean ± SD	26.06 ± 4.99	26.1 ± 5.0	25.99 ± 4.99
Gravidity	0	23 (9.2)		23 (20.2)
n (%)	1	81 (32.3)	53 (38.7)	28 (24.6)
	≥ 2	147 (58.6)	84 (61.3)	63 (55.3)
Number of vaginal birth	0	153 (61)	86 (62.8)	67 (58.8)
n (%)	1	45 (17.9)	24 (17.5)	21 (18.4)
	≥ 2	53 (21.1)	27 (19.7)	26 (22.8)
Number of caesarean section	No	167 (66.5)	103 (75.2)	64 (56.1)
n (%)	≥ 1	84 (33.5)	34 (24.8)	50 (43.9)
Gestational week	1.trimester	42 (30.7)	42 (30.7)	
n (%)	2.trimester	35 (25.5)	35 (25.5)	
	3.trimester	60 (43.8)	60 (43.8)	
Educational attainment	≤ 8 years	154 (61.4)	81 (59.1)	73 (64)
n (%)	> 8 years	97 (38.6)	56 (40.9)	41 (36)
Working condition	Not working	227 (90.4)	127 (92.7)	100 (87.7)
n (%)	Working	24 (9.6)	10 (7.3)	14 (12.3)
Income	Low	192 (78.4)	111 (83.5)	81 (72.3)
n (%)	Middle	53 (21.6)	22 (16.5)	31 (27.7)
Total FSFI score	Mean ± SD	23.08 ± 5.18	22.95 ± 5.02	23.25 ± 5.39
FSD present		165 (65.7)	97 (70.8)	68 (59.6)
n (%)				

FSFI = Female sexual function index, FSD = Female sexual dysfunction, SD = standard deviation, BMI = body mass index

Table 3. Comparisons of FSFI total scores according to the trimesters and Female sexual dysfunction rates seen in trimesters

	1. trimester (n = 42)	2. trimester (n = 35)	3.trimester (n = 60)	*p* value
FSFI total score (mean ± SD)	24.24 ± 4.41	22.36 ± 4.61	22.22 ± 5.47	0.16*
FSD (%)	64.3	82.9	68.3	

FSD = Female sexual dysfunction, *Kruskal-Wallis test was done

The female sexual dysfunction rate in the first trimester was 64.3%; it was 82.9% in the second trimester and 68.3% in the third trimester. When the FSFI total scores were compared between the trimesters, there was no significant difference between the trimester groups ($p = 0.16$) (Table 3).

When the androgen levels and FSFI total and domain scores of the women with and without sexual dysfunction were compared, there was not any significant differences according to the serum androgen levels between the groups ($p > 0.05$) (Table 4).

Table 4. Distribution of the participants' sexual dysfunction according to the androgen levels, FSFI domain scores, and total FSFI scores

	Sexual dysfunction present		Sexual dysfunction absent		
	n	Mean ± SD	n	Mean ± SD	*p* value*
Total testosterone	163	0.68±0.47	86	0.69±0.69	0.549
1-4 delta androstenedione	161	2.83±2.22	86	2.55±1.92	0.366
Dehydroepiandrosterone sulfate	162	152.39±73.24	86	172.78±88.99	0.152
Desire domain	165	2.85±0.9	86	3.9±0.82	**< 0.001**
Arousal domain	165	2.95±0.89	86	4.37±0.80	**< 0.001**
Lubrication domain	165	3.75±0.91	86	4.88±0.72	**< 0.001**
Orgasm domain	165	3.52±0.98	86	5.10±0.68	**< 0.001**
Satisfaction domain	165	3.83±1.26	86	5.57±0.54	**< 0.001**
Pain domain	165	3.35±1.28	86	4.65±1.11	**< 0.001**
Total score	165	20.27±3.80	86	28.48±2.5	**< 0.001**

*Mann-Whitney U test was done, SD = standard deviation

Table 5. Distribution of the participants' androgen levels, FSFI domain scores, and total FSFI scores according to the pregnancy situation

	Pregnancy absent		Pregnancy present		
	n	Mean ± SD	n	Mean ± SD	*p* value*
Total testosterone	114	0.46 ± 0.20	135	0.87 ± 0.67	**< 0.001**
1-4 delta androstenedione	113	1.97 ± 1.13	134	3.37 ± 2.52	**< 0.001**
Dehydroepiandrosterone sulfate	114	178.39 ± 79.53	134	143.36 ± 76.06	**< 0.001**
Desire domain	114	3.27 ± 1.03	137	3.16 ± 0.97	0.30
Arousal domain	114	3.51 ± 1.08	137	3.37 ± 1.11	0.22
Lubrication domain	114	3.96 ± 1.07	137	4.28 ± 0.92	0.02
Orgasm domain	114	4.12 ± 1.19	137	4.01 ± 1.14	0.52
Satisfaction domain	114	4.52 ± 1.32	137	4.34 ± 1.38	0.28
Pain domain	114	3.83 ± 1.41	137	3.76 ± 1.34	0.55
Total score	114	23.25 ± 5.38	137	22.95 ± 5.02	0.60

*Mann-Whitney U test was done, SD = standard deviation

Table 6. Correlations between the androgen levels, FSFI domain scores, and total FSFI scores in the participants with sexual dysfunction

Sexual dysfunction present											
		Total testosterone	1-4 delta androstenedione	Dehydroepiandrosterone sulfate	Desire domain	Arousal domain	Lubrication domain	Orgasm domain	Satisfaction domain	Pain domain	Total score
Total testosterone	rho	1.000									
1-4 delta androstenedione	rho	0.536**	1.000								
Dehydroepiandrosterone sulfate	rho	0.107	0.263**	1.000							
Desire domain	rho	0.031	0.032	0.083	1.000						
Arousal domain	rho	0.167*	0.043	0.092	0.513**	1.000					
Lubrication domain	rho	0.264**	0.211**	0.035	0.225**	0.360**	1.000				
Orgasm domain	rho	0.053	0.156*	0.073	0.363**	0.439**	0.387**	1.000			
Satisfaction domain	rho	0.125	0.053	0.006	0.370**	0.456**	0.284**	0.477**	1.000		
Pain domain	rho	0.108	0.065	-0.045	-0.093	-0.069	0.091	-0.036	-0.083	1.000	
Total score	rho	0.212**	0.174*	0.104	0.614**	0.701**	0.610**	0.656**	0.678**	0.260**	1.000

**Correlation is significant at the 0.01 level (2-tailed).

*Correlation is significant at the 0.05 level (2-tailed).

When the androgen levels and FSFI total and domain scores of the pregnant and nonpregnant women were compared, it was found that the pregnant women's total testosterone levels ($p < 0.001$), androstenedione levels ($p < 0.001$), and FSFI lubrication domain scores were significantly high ($p = 0.02$) , while their DHEAS levels were significantly low ($p < 0.001$). There was not any significant difference according to the FSFI total scores between pregnant and nonpregnant women (Table 5).

When the correlation between the androgen levels and the FSFI domain and total scores in the women with sexual dysfunction were evaluated, there were significant correlations between the total testosterone level and the FSFI arousal domain (r = 0.167, $p < 0.05$), FSFI lubrication domain (r = 0.264, $p < 0.01$), and FSFI total score (r = 0.212, $p < 0.01$). Additionally, there were significant correlations between the androstenedione level and the FSFI lubrication domain (r = 0.211, $p < 0.01$), FSFI orgasm domain (r = 0.156, $p < 0.05$), and FSFI total score (r = 0.174, $p < 0.05$) (Table 6).

The independent predictors of sexual dysfunction using the possible factors in the multivariate analysis were examined using a logistic regression analysis (Table 7). Evaluated input factors were age, bmi, gravidity, number of vaginal birth, number of caesarean section, educational attainment, working condition, income, total testosterone, dehydroepiandrosterone sulfate (DHEAS), and 1-4 delta androstenedione. It was observed that an increase in the DHEA level increased the sexual dysfunction by 0.996-fold. The women with one pregnancy had 3.312-fold greater sexual dysfunction than the women without any pregnancies. Those women with more than eight years of education had 0.358 times more sexual dysfunction than those with eight years of education and less. This suggests that with an increasing educational level, sexual dysfunction decreases.

Table 7. Logistic regression analysis for sexual dysfunction

Risk factors	*p* value	OR (95% CI)
Dehydroepiandrosterone sulfate	0.026	0.996 (0.992-0.999)
Gravida 0	referent	
Gravida 1	0.039	3.312 (1,061-10,339)
Gravida ≥ 2	0.073	3.711 (0.886-15.551)
Educational attaintment (≤ 8 years)	referent	
Educational attaintment (> 8 years)	0.001	0.358 (0.193-0.665)

OR = odds ratio, CI = Confidence Interval

DISCUSSION

In the current study, which was performed with a sample of Turkish women, we found that the sexual dysfunction rate was 65.7%, of which 58.8% were pregnant and 41.2% were not. In their meta-analysis, McCool *et al*. [22] evaluated 95 studies of premenopausal sexual dysfunction, excluding pregnant and lactating women, and they found an estimated FSD prevalence of 40.9% (95% CI = 37.1-44.7, I2 = 99.0%). They reported the different FSD prevalence estimates in the different regions of the world as follows: 39.1% in Europe, 40.2% in Asia, 45.5% in Central and South America, 47.0% in the Middle East, and 61.7% in Africa [22]. Ninivaggio *et al*. [23] evaluated the sexual function of 623 nulliparous pregnant women using the FSFI in the first (T1), second (T2) and early third (T3) trimesters. They reported sexual dysfunction rates of 36.3% in T1, 36.8% in T2, and 57% in T3, and that the mean FSFI scores decreased as pregnancy progressed. In the previous studies conducted with reproductive aged nonpregnant Turkish women, Oksuz and Malhan [21] and Aslan *et al*. [5] reported the rates of sexual dysfunction as 48.3% and 43.4%, respectively. In the study by Seven *et al*. [24], which was conducted in pregnant Turkish women, the rate of sexual dysfunction was 77.6%. Eryılmaz *et al*. [25] evaluated 238 Turkish pregnant women, and they reported that in 81.5% of them, their sexual lives were affected during pregnancy. In the studies by Erol *et al*. [26] and Çorbacıoğlu *et al*. [27] conducted with Turkish pregnant women, the total FSFI scores and third trimester FSFI scores were significantly lower than the first and second trimester scores. The high sexual dysfunction rates of the Turkish reproductive aged women could be attributed to their social, cultural, religious, and educational attitudes. Inadequate education about sexual health, shame when talking about sexuality, acceptance when talking about sexuality as a sin, and shame in Eastern populations could be accepted as causes.

When evaluating women with sexual dysfunction present and absent, we did not find any differences according to the androgen levels. In a cross-sectional study by Davis *et al*. [28], the relationships between the androgens and sexual function were investigated in 1,423 non-healthcare-seeking women aged 18-75 years old. They did not find any relationships between the androstenedione, total testosterone, and free testosterone levels and the sexual function scores.

In the present study, we did not find any differences in terms of the total and domain scores, with the exception of the lubrication scores, between the pregnant and nonpregnant women. The lubrication scores in the pregnant women were higher because lubrication intensifies due to the increased genital vasocongestion during sexual excitement in pregnancy [29]. In the comparison of the serum androgen levels between the pregnant and nonpregnant women, we found higher total testosterone and androstenedione levels and lower DHEAS levels. The level of maternal testosterone increases [30] and the level of DHEAS decreases by about two times during pregnancy [31]. In addition, the serum level of the sex hormone binding globulin that binds a large fraction of testosterone increases and the percentage of free testosterone decreases during pregnancy. According to our results, although there were significant differences in the androgen levels between the pregnant and nonpregnant women, the FSFI total scores were not different.

In the current study, we found significant correlations between the androgen levels and the FSFI scores. There were significant correlations between the total testosterone level and the FSFI total, FSFI arousal domain, and FSFI lubrication domain scores. Additionally, there were significant correlations between the androstenedione level and the FSFI total, FSFI lubrication domain, and FSFI orgasm domain scores. Different from our results, Erol *et al*. [26] did not find any correlations between the androgen levels and the FSFI scores in their study of 589 pregnant women. Jacobsen *et al*. [32] studied the relationships between the androgen levels and sexual desire in 560 healthy women aged 19-65 years old, and they found significant correlations between the free testosterone, androstenedione, and FSFI desire domain in the total cohort of women. Garcia *et al*. [2] conducted a study of 101 women aged 18-55 years old, and there was no relationship between the free testosterone level and the FSFI scores. Of those 29 women with androgenic deficiencies, 14 had sexual dysfunction and 15 did not have sexual dysfunction [2]. These heterogeneous

results could be explained by either the lack of sensitivity of the scale or the hypothesis that FSD is much more than just a hormonal problem. In addition to hormonal factors, cultural, social, traditional, psychosocial, developmental, religious, interpersonal, and medical factors are often relevant when measuring FSD [33].

We evaluated the independent predictors of sexual dysfunction using sociodemographic and hormonal variables, and we found that gravida 1, more than 8 years of education, and DHEA were significant predictors. When compared to the women with no pregnancies, the women having one pregnancy had an increased risk of sexual dysfunction. Pregnancy has an effect on the sexual health via a decrease in sexual function throughout pregnancy, particularly during the third trimester [26, 34, 35]. In addition, the women having more than 8 years of education exhibited a decreased risk of sexual dysfunction when compared to the women with 8 years of education and less. Laumann and Paik [36] evaluated the prevalence and predictors of sexual dysfunction among 1,749 women aged 18-59 years old in the United States. They reported that sexual dysfunction was associated with various demographic characteristics, including age and education. Those women who were college graduates had lesser degrees of low sexual desire, problems achieving orgasm, sexual pain, and sexual anxiety when compared to the women who did not graduate from high school [36]. Eryılmaz *et al*.[25], in their study of 238 Turkish pregnant women, reported significant relationships between the changes in sexual life during pregnancy and the marriage duration, educational level, parity, and gravidity. According to our results, an increase in the level of DHEA was related to a decrease in the level of sexual dysfunction. In an Australian study evaluating the relationship between the androgen levels and self-reported sexual function with 1,423 women from 18-75 years old, there was no association between the testosterone and the self-reported sexual function. However, in those women between 18 and 44 years old with decreased sexual desire, the sexual arousal or sexual responsiveness was associated with a DHEAS value below the 10th percentile for age [28].

Limitations

The limitations of this study include the fact that it was a cross-sectional study and not prospective. The comparisons were done among different women, not with the same women before and after pregnancy. In addition, we did not measure the level of free testosterone because of our limited assays. Finally, we did not ask about any history of sexual dysfunction before pregnancy or include questions about the partners' roles or conditions related to sexual dysfunction.

CONCLUSION

Although we evaluated the sexual dysfunction among a small group of pregnant and nonpregnant Turkish women, we found a high prevalence, as reported in the literature. Although the serum androgen levels change during pregnancy, there were no significant differences according to the FSFI total scores between the pregnant and nonpregnant women. In addition, there were no significant differences in the androgen levels of the women with and without sexual dysfunction. There were significant correlations between the total testosterone level and the FSFI arousal domain, FSFI lubrication domain, and FSFI total scores. Additionally, there were significant correlations between the androstenedione level and the FSFI lubrication domain, FSFI orgasm domain, and FSFI total scores. When compared to the women with no pregnancies, the women with one pregnancy had an increased risk of sexual dysfunction. Based on our results, any increase in the DHEAS level and educational level of a woman was observed to decrease the development of sexual dysfunction.

Overall, sexual dysfunction is a multifactorial entity. Future prospective studies evaluating the reasons for sexual dysfunction with larger populations from different cultures and countries could help professionals understand the multifactorial dimensions of this public health problem. In addition, healthcare professionals should give more time for better counselling about sexuality during pregnancy at prenatal visits.

Authors' Contributions

BSA: Study design, data drafting, statistical analysis, interpretation of data writing; IK: Study design, interpretation of data, writing

Conflict of interest

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

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The European Research Journal 2019;5(2):268-273 ORIGINAL ARTICLE

Retrospective evaluation of breast cancer patients with five or more axillary lymph node involvement achieving 5-year overall survival

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ABSTRACT

Objectives: The aim of this study was to analyze high risk breast cancer patients with involvement of five or more axillary lymph nodes with an overall survival of at least five years, and to determine the predictive and prognostic factors by comparing patients by recurrence/metastases status retrospectively.

Methods: From a total of 500 patients those were followed up in Adnan Menderes University, Medical Oncology department, 37 were eligible for the study; 23 were disease free and 14 had recurrence/metastases in the follow up period. The patients were analyzed, for demographical (such as age, menopausal status, obesity), anatomical and histological characteristics of tumor (primary tumor's diameter, stage, grade, Ki-67, hormon receptors and Her-2 status), treatment modalities and prognosis.

Results: Both number of metastatic lymph nodes and (metastatic/sampled) lymph node ratio were not significantly different between the recurrence-free and metastatic patients. In the recurrence-free patients both grade 3 (48% vs none, $p = 0.03$) and p53 negative tumors (64% vs 36%, $p = 0.036$) were significantly more than metastatic patients. Also in the recurrence free patients as compared to metastatic patients, adjuvant chemotherapy was applied more than 6 cycles (87% vs 43%, $p = 0.004$), the regimens included more taxane based regimens (91% vs 64%, $p = 0.042$), aromatase inhibitors were used higher (100% vs 75%, $p = 0.019$) and the period of tamoxifen treatment in switch regimens were shorter.

Conclusion: The results of this study suggested that, high risk breast cancer patients with involvement of five and more nodes that have the predictive factors as grade 3 and/or p53 negative tumors are propably more responsive to adjuvant treatments. Chemotherapy of more than 6 cycles, administering taxane based regimens and aromatase inhibitors in the adjuvant regimens may favourably effect the prognosis.

Keywords: breast cancer, lymph node metastases, predictive and prognostic factors

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Breast cancer is the most frequently diagnosed cancer in women, which consist of many clinical subtypes with distinct biological features [1]. Breast cancer patients, have different response patterns to various treatment modalities and clinical outcomes. Prognostic and predictive factors are critical for the selection of local or systemic therapies. These factors include, tumor histology, clinical and pathologic characteristics of the primary tumor (especially tumor size and tumor grade), axillary lymph node status,

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tumor hormone receptor (ER/PgR) expression, tumor Her-2 status, existance of metastatic disease , patient comorbid conditions, patient age and menopausal status [2].

Patients with metastatic lymph node involvement are the most often candidates for chemotherapy and if the tumor is hormone receptor positive, for the subsequent endocrine therapy [3]. Although multiple metastatic axillary lymph nodes are strong negative prognostic factor for disease recurrence and death from breast cancer, there have been a group of patients with extensive nodal involvement which have five or more years overall survival after local and systemic therapies.

The aim of this study was to analyze high risk breast cancer patients with involvement of five or more axillary lymph nodes with an overall survival of at least five years, and to determine the predictive and prognostic factors by comparing patients by recurrence/metastases status retrospectively.

METHODS

In this study, medical files and pathology reports of 500 breast cancer patients who were on follow up at Adnan Menderes University medical oncology department were screened retrospectively. Thirty-seven patients had breast surgery and axillary lymph node dissection with a final pathology report showing 5 or more metastatic axillary lymph node involvement. All of 37 patients had received adjuvant chemotherapy. Fourteen patients developed metastatic disease, while the other 23 patients were relapse free , after at least 5 years follow up.

Demographic characteristics, pathological features of primary tumor (size, grade, Ki-67, hormone receptor and Her-2 status, stage), treatment modalities (surgery, radiotherapy, chemotherapy, hormonotherapy) were recorded from medical files.

ER and PgR status were tested by immunohistochemistry, and a value ≥ 1% was considered as positive. Her-2 status was obtained by immunohistochemistry or fluorescent in situ hybridization (FISH). IHC 3+ and IHC 2+ that were FISH positive were classified as Her-2-positive tumors; IHC 2+ that were either FISH negative, or IHC 1+ were classified as HER2-negative tumors. Ki-67 levels over 14% are considered high; whereas levels below 14% were considered low. p53 levels considered as positive when > 10% of cells were positive regardless of the intensity.

Eligible patients had five and more metastatic axillary lymph node involvement, breast surgery for non metastatic breast cancer, and at least five years follow-up. Patients with synchronous distant metastases, and taking neoadjuvant treatment were excluded from the study.

Statistical Analysis

The data analysis was performed by using SPSS for Windows, version 22 (SPSS, Chicago, IL, USA). The normality of the distributions of continuous variables was determined via the Shapiro–Wilk test. The data were reported as the mean ± standard deviation or median and range where applicable. The differences in the results between the groups were compared by performing Student's t-test or the Mann–Whitney U test, where appropriate. The categorical data were analyzed by using Pearson's chi-square or Fisher's exact test, where appropriate. A $p < 0.05$ was considered as indicating statistical significance.

RESULTS

Between January 2010 and December 2014, 37 breast cancer patients were enrolled in the study. The baseline characteristics of the study subjects and tumors are summarized in Table 1. There were no difference between menopause status and obesity in patients with and without relapsed disease. Primary tumor was right-sided in 21 (57%) patients and left-sided in 16 (43%) patients. Upper-outer quadrant was the most frequent site for primary tumor.

Grade 3 tumors were higher in patients without recurrence or metastases. There was no significant difference between groups according to metastatic lymph node numbers,histology, pT stage and pN stage (Table 1).

Immunohistochemical characteristics of tumors are shown in Table 2. 87% of tumors were Luminal subtype (Luminal A and Luminal B). The most common subtype was Luminal B (65%). There was no significant difference between patients according to breast cancer molecular subtypes ($p = 0.517$). Patients

Table 1. Patient and tumor characteristics

Characteristics		Relapse free	Relapsed	*p* value
Age (years)		47 ± 9	46 ± 10	
Total lymph node		20 ± 6	20 ± 8	> 0.05
Metastatic lymph node		12 ± 6	13±6	> 0.05
Metastatic/total LN		0.61	0.66	> 0.05
Tumor side	Right	14 (70%)	7%30	> 0.05
	Left	16 (36%)	%64	
Histology	Ductal	21 (92%)	11 (79%)	> 0.05
	Lobular	1 (4%)	3 (21%)	
	Ductal+lobular	1 (4%)	0	
Tumor size	T1	6 (26%)	5 (36%)	> 0.05
	T2	14 (61%)	5 (36%)	
	T3	3 (13%)	5 (28%)	
Tumor grade	Grade 1	1 (4%)	1 (10%)	**< 0.03**
	Grade 2	10 (48%)	9 (90%)	
	Grade3	10 (48%)	0	
Lymph node stage	N2	8 (35%)	5 (36%)	> 0.05
	N3	15 (65%)	9 (64%)	
Perinodal invasion	Yes	13 (44%)	9 (64%)	> 0.05
	No	10 (56%)	5 (36%)	
Menopausal status	Premenopause	10 (43%)	5 (36%)	> 0.05
	Perimenapause	3 (14%)	2 (14%)	
	Postmenapause	10 (43%)	7 (50%)	
Body mass index (kg/m^2)	> 30	6 (26%)	3 (21%)	> 0.05
	< 30	17 (74%)	11 (79%)	

All values are median. Body mass index: weight/height^2

Table 2. Immunohistochemical features of tumors

		Relapse free	Relapsed	*p* value
ER	Negative	6 (26%)	4 (28%)	> 0.05
	Positive	17 (74%)	10 (72%)	
PgR	Negative	4 (17%)	2 (14%)	> 0.05
	Positive	19 (83%)	20 (86%)	
Her-2	Negative	12 (52%)	10 (71%)	> 0.05
	Positive	11 (48%)	4 (29%)	
Ki-67	Negative	8 (35%)	6 (43%)	**0.036**
	Positive	15 (65%)	8 (57%)	
p53	Negative	14 (64%)	5 (36%)	**< 0.05**
	Positive	8 (36%)	9 (64%)	
Tumor subtype	Luminal A	5 (22%)	3 (22%)	> 0.05
	Luminal B	15 (65%)	9 (64%)	
	Her-2	2 (9%)	0	
	Triple negative	1 (4%)	2 (24%)	

ER = estrogen receptor, PgR = progesterone receptor, HER2 = human epidermal growth factor receptor 2

Table 3. Adjuvant systemic treatments

		Relapse free	Relapsed	*p* value
Chemotherapy cycle		8 ± 1	6.4 ± 1.8	**0.001**
Duration of hormonal treatment (months)		75.7 ± 21.7	30.5 ± 21.4	**0.001**
Duration of tmx in switch (months)		22.2 ± 4	39.7 ± 14.6	**0.004**
Chemotherapy	< 6 cycle	3 (13%)	8 (57%)	**0.004**
	> 6 cycle	20 (87%)	6 (43%)	
Taxane regimen	Yes	21 (91%)	9 (64%)	**0.042**
	No	2 (9%)	5 (36%)	
Type of hormonal treatment	Tmx	0	3 (25%)	**0.019**
	AI	10 (50%)	4 (33%)	
	Switch	10 (50%)	3 (25%)	
	Other	0	2 (17%)	
Tmx in switch	< 36 month	10 (100%)	1 (33%)	**0.005**
	> 36 month	0	2 (67%)	

with relapse-free disease have higher rates of p53 negativity as compared with patients who developed metastases (Table 2).

Adjuvant treatment modalities were shown in Table 3. All patients received 3 to 6 cycles of antracycline based chemotherapy first and then, most of patients had taxane based chemotherapy subsequently. Total chemoterapy cycles were higher in recurrence free group. Duration of tamoxifen treatment was shorter in recurrence free group. Patients with recurrence free disease had received more taxane chemotherapy when compared with the others.

DISCUSSION

In this study, we retrospectively evaluated patients who were operated for breast cancer with a final pathology report of 5 or more metastatic lymph node involvement and achieved five year overall survival. All patients received adjuvant chemotherapy. We compared patients who were relapse free at 5 years, with patients who developed recurrence or metastases to analyze prognostic and predictive factors in this high risk patient population.

There are some well-defined risk factors for breast cancer development [4-9]. Breast cancer risk factors such as age, family history , smoking, oral contraceptive use, obesity were not different between groups. At the time of diagnosis, 15 (40%) of the patients were premenopausal, 5 (14%) were perimenopausal and 17 (46%) were postmenopausal and there was no difference in menopausal status between the two groups.

In the group without recurrence, 48% of the patients had grade 3 tumor, whereas the control group had no grade 3 tumor. Although, high tumor grade has a negative impact on the natural course of the disease, high grade tumors may be more sensitive to chemotherapy and radiotherapy. In a retrospective study of 183 patients who received neoadjuvant anthracycline and taxane based chemotherapy, there was a significant correlation between pathologic response and tumor p53 expression and tumor grade [10].

Primary tumor localization was right breast in 70% of the patients in the relapse-free group, whereas left breast in 64% of the recurrent patients. The difference in right/ left breast side was statistically

significant; but there was no difference according to the quadrant. Karatas *et al*. [11] studied 305 non-metastatic women with pathological N3 (pN3) nodal involvement and showed that, left laterality in patients with pN3 non-metastatic breast as an independent risk factor associated with distant metastases and axial bone involvement compared with right laterality.

Tumor diameter is one of the important prognostic factor for the requirement for adjuvant therapy [12, 13]. The risk of recurrence or distant metastasis increases linearly with the increase in tumor size. Tumor diameter is the main prognostic factor, especially in node-negative patients, while this effect decreases in node-positive patients. Many studies have shown an inverse relationship between tumor size and metastasis or survival. There were no significant differences in the number of foci of primary tumor, mean diameter, and T-stage between the groups with and without recurrent disease. Because of the high number of metastatic lymph nodes in our study population, the contribution of tumor diameter to prognosis of these patients was considered to be low. The number of metastatic lymph nodes in breast cancer is considered to be one of the important prognostic factors. In an analysis based on Holland cancer records, 23.315 patients with node-positive breast cancer treated between 1999 and 2005 were evaluated. The overall 5-year survival was 78% in the whole population while 84% in cases with 1-3 metastatic lymph node involvement, and 55% in cases with > 10 metastatic lymph node involvement [14]. In this study; there was no significant difference between groups in terms of presence of perinodal invasion and N stage. This result suggests that groups with relapse free and recurrent patients are homogeneous in terms of lymph node metastasis and that other predictive and prognostic factors are important in our cases.

Hormone receptor positivity was high in the patients (87%), especially Luminal B was the most common tumor type but there was no significant difference between the two groups in terms of tumor subtype. There was no difference in the Ki-67 and Her-2 levels between the groups.

The higher incidence of p53 negativity, suggests that the sensitivity of adjuvant therapy is higher in the relapse free group.

Chemotherapy is the basis of adjuvant treatment in cases, with axillary lymph node metastases. The total number of chemotherapy cycles was found to be higher in the recurrence-free group. When the total number of chemotherapy cycles was categorized as < 6 and > 6, it was found that more patients in the recurrence free group had 6 or more chemotherapy cycles. This finding indicates the importance of the number of chemotherapy cycles in high-risk locally advanced breast cancer.

Taxanes have been extensively given as adjuvant chemotherapy for the treatment of operable breast cancer, particularly in high risk, node-positive patients [15]. Taxane treatment was significantly higher in the relapse free patients than recurrent patients. This suggests the importance of taxane after anthracycline treatment in high-risk breast cancer.

All luminal A and B patients received hormonal treatments. Aromatase inhibitor and switch (aromatase inhibitor after tamoxifen) treatments were in higher in recurrence free patients.

The use of more aromatase inhibitors than tamoxifen may be one of the positive prognostic factors in relapse free patients. The duration of the hormonal treatment was shorter in recurrence free group and it was considered to be related with switching patients to another treatment modality 'mostly chemotherapy', after recurrence.

Limitations

Our study has some limitations. First; this study had a relatively small number of patients and second has a retrospective nature.

CONCLUSION

In conclusion, grade 3 tumor and/or p53 negativity in high-risk locally advanced breast cancer can be used as predictive factors for adjuvant treatment response. Taxane treatment significantly improved clinical outcome. We believe that validation of these results in larger series with similar characteristics may be useful in local advanced breast cancer treatment.

Authorship Declaration

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

Conflict of interest

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

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Comparison of the results of Teflon felt and Dacron strip usage in Stanford type A dissection

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ABSTRACT

Objectives: In patients who undergo surgery for aortic dissection, the anastomotic leakage and the bleeding in these regions affect surgical success and mortality rate significantly. Various surgical materials are used for this purpose. We examined the results obtained from patients in whom Teflon felt strip or Dacron strip was used for creating a more secure anastomotic suture line.

Methods: Twenty-eight patients who underwent surgery for ascending aortic dissection between 2013 and 2017 were examined retrospectively. Teflon felt strip or Dacron strip was used to create a more secure anastomotic suture line and to reduce bleeding in these patients. The patients were divided into the Teflon and Dacron groups according to the materials used. The amount of drainage, the amount of tissue adhesive used, the number of red blood cell (RBC) transfusions, and the morbidity and mortality rates were mainly compared between the two groups.

Results: While Teflon felt strip was used in 13 (46%) patients, Dacron strip was used in 15 (53%) patients. The mean amount of drainage in the first 24 hours postoperatively was 596.15 ± 165.15 ml in the Teflon group and 546.67 ± 217.5 ml in the Dacron group. There was no statistically significant difference between the two groups in terms of mean amount of drainage ($p = 0.509$). Similarly, the mean number of RBC transfusions was 2.54 ± 0.51 units in the Teflon group and 2.33 ± 0.81 units in the Dacron group. There was no statistically significant difference between the two groups in terms of mean number of RBC transfusions ($p = 0.416$). Although the mean amount of tissue adhesive used was relatively higher in the Dacron group, there was no statistically significant difference between the two groups in terms of mean amount of tissue adhesive used ($p = 0.761$). The total mortality rate was 28% (8 patients). There was no statistically significant difference between the two groups in terms of mortality rate ($p = 0.281$).

Conclusion: We concluded that the results obtained from the Teflon and Dacron groups were not significantly superior to each other. We think that Dacron strip may be used as an alternative to Teflon felt strip, which is used routinely in the surgical treatment of aortic dissection.

Keywords: Aortic dissection, Teflon felt strip, Dacron strip

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Aortic dissection is a rare but fatal disease. Early diagnosis and treatment of the disease is very important. If acute aortic dissection is left untreated, the mortality rate increases by approximately 1% per hour

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for the first 48 hours. 70% of patients die within the first week [1]. The Stanford classification divides aortic dissections into 2 types, type A and type B. Type A involves the ascending aorta. Type B does not involve the ascending aorta [2]. The primary goal of urgent surgical intervention in the treatment of Stanford type A ascending aortic dissection is to prevent aortic rupture, to treat aortic valve insufficiency, and to protect life by directing blood flow to dissected branch vessels [3]. Optimal treatment of type A acute aortic dissection is still a difficult challenge for cardiovascular surgeons. Despite all improvements, the mortality rate in conventional surgery of aortic dissection ranges from 10% to 27%. Today, open surgery continues its importance for treatment with acceptable results [4].

In the surgical treatment of aortic dissection, the Dacron graft interposition and the sandwich technique at the anastomotic line are today used in many patients. In the English literature, it is seen that Teflon®-felt strips and biological glues are usually used in the Sandwich technique for providing hemostasis and for creating a more tightly braided suture line [5, 6]. In the surgical treatment of ascending aortic dissection in our clinic, Teflon®-felt strip and Dacron graft strip were used as a surgical material in order to create a more secure anastomotic suture line and to contribute hemostasis in the anastomotic line. The patients grouped according to these two different materials were compared in terms of mortality and morbidity rates. Their results were evaluated.

METHODS

Twenty-eight patients who underwent surgery for Stanford type A ascending aortic dissection between January 2013 and December 2017 were included in the study. The study was performed retrospectively using hospital records. Demographic data and risk factors of the patients were recorded. Teflon felt strip or Dacron graft strip was used for creating a more tightly braided suture line in the patients. The patients were divided into the Teflon and Dacron groups according to the materials used.

Group 1 (Teflon): Teflon®-felt strip was used at the proximal or distal suture line of the aortic graft in tube graft replacement of the ascending aorta.

Group 2 (Dacron): The same procedures were performed with Dacron strip instead of Teflon® felt strip. Dacron strip was obtained from the abundant parts of the graft that we used for replacement of the ascending aorta.

All patients were primarily subjected to a detailed physical examination. Their risk factors were recorded. Before the surgery, the diagnosis was confirmed by computed tomography (CT) and transthoracic echocardiography. The Stanford classification was used to classify aortic dissections. The duration and type of surgery, the amount of drainage, the number of RBC transfusions, the amount of tissue adhesive used, the revision rate, and the hospital and intensive care unit length of stay were recorded for the patients. Postoperative complications such as stroke, multiple organ failure (MOF), and renal dysfunction and mortality rates were statistically compared between the two groups. This study was approved by the Local Ethics Committee.

Surgical Technique

The patients were operated under general anesthesia. All patients underwent a standard median sternotomy and total cardiopulmonary bypass (CPB). Hypothermic antegrade perfusion was performed through right axillary artery cannulation with PTFE side-graft. In distal organ malperfusion, double arterial perfusion was provided with direct femoral artery cannulation in addition to axillary artery cannulation. Antegrad perfusion was established at a rate of 8–10 mL/kg/minute. Venous cannulation was performed through the right atrium. Operations were performed with moderate degree hypothermia of 24-28ºC. In all patients, cardiac arrest was firstly provided with crystalloid cardioplegia. Isothermic hyperkalemic blood cardioplegia was used during the maintenance period. In the surgery, the areas where intimal tears occurred in the ascending aorta were firstly removed by resection. The dissected aortic layers were glued using fibrin tissue adhesive [Tissell® (Eczacıbaşı-BAXTER)]. Teflon® felt strip or Dacron graft strip was used for creating a more tightly braided suture line in the patients. The anastomotic suture line was supported with these materials. Aortic valve pathologies were repaired by methods such as valvuloplasty or the Bentall procedure. A Dacron tube graft of appropriate size was used for replacement of the ascending aorta. After the surgery, in the patients

in whom right axillary artery cannulation with PTFE side-graft was performed, the side graft was connected directly and was sutured on itself with polypropylene. In the patients in whom direct femoral artery cannulation was performed, the arteriotomy was closed primarily after the cannula was withdrawn.

Follow up

The patients were followed up by CT and echocardiography in the postoperative period. Patient follow-ups were conducted through outpatient clinic visits and via telephone.

Statistical Analysis

Statistical analysis data were analyzed with the Statistical Package for the Social Sciences (IBM SPSS Statistic Inc. version 21.0, Chicago, IL, USA).Continuous and ordinal variables were expressed as mean ± standard deviation and nominal variables were expressed as frequency and percentage. Shapiro-Wilk tests of normality were used to identify distribution of variables. Student's t test was used to compare two groups for continuous variables with normal distribution. Chi Square test was used to compare two groups for nominal variables. Mann-Whitney U test was used to compare two groups for continuous variables without normal distribution. For all tests, a p value of < 0.05 was considered statistically significant.

RESULTS

A total of 28 patients were included in the study. There were 13 (46%) patients in the Teflon group and 15 (53%) patients in the Dacron group. The demographic data and risk factors of the patients were evaluated according to the groups. There were 11 (84.6%) male patients in the Teflon group and 13 (86.7%) male patients in the Dacron group. The mean age was 54.15 ± 6.89 years in the Teflon group and 54.0 ± 11.6 years in the Dacron group. There was no statistically significant difference between the two groups in demographic data and risk factors (Table 1).

The intraoperative data of the patients were recorded (Table 2). Eigth patients in both groups underwent isolated replacement of the ascending aorta. The Bentall procedure was applied in 4 (26.7%) patients in the Dacron group but not in the Teflon group. 5 (38.5%) patients in the Teflon group and 3 (20%) patients in the Dacron group underwent ascending aortic replacement plus aortic valvuloplasty. There was no statistically significant difference between the two groups (p = 0.281). Ten (76.9%) patients in the Teflon group and 14 (93.3%) patients in the Dacron group underwent axillary artery cannulation. Three (23.1%) patients in the Teflon group and 1 (6.7%) patient in the Dacron group underwent direct femoral artery cannulation in addition to axillary artery cannulation. There was no statistically significant difference between the two groups in terms of arterial cannulation site (p = 0.216).

Four patients in both groups underwent total circulatory arrest (TCA). The mean duration of TCA was 5.77 ± 10.97 min in the Teflon group and 3.53 ± 8.11 min in the Dacron group. There was no statistically significant difference between the two groups in terms of mean duration of TCA (p = 0.751).

Table 1. Demographic features of the patients

	Teflon group (n = 13)	Dacron group (n = 15)	*p* value
Age (years)	54.15 ± 6.89	54.0 ± 11.6	0.967[#]
Male gender, n (%)	11 (84.6)	13 (86.7)	0.877[*]
Hypertension, n (%)	12 (92.3)	13 (86.7)	0.630[*]
Diabetes mellitus, n (%)	5 (38.5)	5 (33.3)	0.778[*]
CAD, n (%)	-	2 (13.3)	0.172[*]
CVD, n (%)	2 (15.4)	-	0.115[*]
Smoke, n (%)	8 (61.5)	13 (86.7)	0.126[*]

CVD = Cerebrovascular disease, CAD= Coronary artery disease. * Pearson Chi- Suquare, [#] Student's t test

Table 2. Operative variables

	Teflon group (n = 13)	Dacron group (n = 15)	*p* value
Ascendan aortic replecement	8 (61.53%)	8 (53.3%)	-
Benthall procedure,	-	4 (26.7%)	**0.044**[*]
Ascendan aortic replecement + aortic valvuloplasty	5 (38.5%)	3 (20%)	0.281[*]
Arterial cannulation			0.216[*]
Axillary	10 (76.9%)	14 (93.3%)	
Axillary + Femoral	3 (23.1%)	1(6.7%)	
Biological Glue	2.15 ± 0.37	2.20 ± 0.41	0.761[a]
TCA	4 (30.7%)	4 (26.7%)	0.811[*]
CPB time, minutes	138.62 ± 14.75	148.13 ± 18.07	0.143[#]
X-clamp time	58.85 ± 9.49	61.67 ± 11.09	0.480[#]
TCA time	5.77 ± 10.97	3.53 ± 8.11	0.751[a]

CVD = Cerebrovascular disease, CAD = Coronary artery disease, TCA = Total circulatuar arrest, *Pearson Chi-Suquare, [#] Student's t test, [a]Mann-Whitney test

The mean duration of X-clamp was 58.85 ± 9.49 min in the Teflon group and 61.67 ± 11.09 min in the Dacron group. The mean total duration of CPB was 138.62 ± 14.75 min in the Teflon group and 148.13 ± 18.07 min in the Dacron group. There was no statistically significant difference between the two groups in terms of mean duration of X-clamp and mean total duration of CPB ($p = 0.480$, $p = 0.143$).

The postoperative data of the patients were recorded (Table 3). In the postoperative period, atrial fibrillation was observed in 6 (46.2%) patients in the Teflon group and in 1 (6.7%) patient in the Dacron group. Renal dysfunction was observed in 3 patients in both groups.

There was no statistically significant difference between the two groups in terms of atrial fibrillation and renal dysfunction ($p = 0.055$, $p = 0.843$). In the Teflon group, 3 (23.07%) patients had a stroke and 4 (30.76%) patients had MOF. Stroke and MOF were not observed in the Dacron group. The Teflon group had worse results for stroke and MOF. There was a statistically significant difference between the two groups in terms of stroke and MOF ($p = 0.049$, $p = 0.020$). In the postoperative period, low cardiac output was observed in 1 patient in the Teflon group and in 3 patients in the Dacron group. There was no statistically significant difference between the two groups.

The mean amount of drainage in the first 24 hours postoperatively was 596.15 ± 165.15 ml in the Teflon group and 546.67 ± 217.5 ml in the Dacron group. The mean number of RBC transfusions was 2.54±0.51 units in the Teflon group and 2.33 ± 0.81 units in the Dacron group. There was no statistically significant difference between the two groups in terms of mean amount of drainage and mean number of RBC transfusions ($p = 0.509$, $p = 0.416$). The mean amount of tissue adhesive used was 2.15 ± 0.37 in the Teflon group and 2.20 ± 0.4 in the Dacron group. Although the mean amount of tissue adhesive used was relatively higher in the Dacron group, there was no statistically significant difference between the two groups in terms of mean amount of tissue adhesive used ($p = 0.761$).

Sternal dehiscence and mediastinitis were observed in the early postoperative period in 1 patient in the Dacron group. This patient underwent revision. The mean intensive care unit (ICU) length of stay (hours) was 100.31 ± 71.21 hours in the Teflon group and 57.47 ± 38.1 hours in the Dacron group. The mean hospital length of stay (days) was 9 ± 4.76 days in the Teflon group and 7.93 ± 5.03 days in the Dacron group. There was no statistically significant difference between the two groups in terms of mean hospital length of stay ($p = 0.571$). However, there was a

statistically significant difference between the two groups in terms of mean ICU length of stay (p = 0.048). The total mortality rate was 28%. A total of 8 patients including 5 patients in the Teflon group and 3 patients in the Dacron group died. Cause of death was MOF and low cardiac output. There was no significant difference between the two groups in terms of mortality rate (p = 0.281).

DISCUSSION

There are many factors such as heredity, degeneration, atherosclerosis, inflammation, trauma, and toxicity in etiology of aortic dissection. Because of all these reasons weakening the aortic wall, especially the lamina media is exposed to extreme wall stress. As a result, aortic dilatation and aneurysmal formation cause aortic dissection or rupture [7].

The Stanford classification, which is based on involvement of the ascending aorta (type A and type B), is the most frequently used classification today. In patients with type A aortic dissection, severe catastrophic outcomes occur due to progression of rupture or dissection [2, 16].

The main purpose in the surgical treatment of aortic dissection is to remove the torn segments and to maintain vessel continuity by performing replacement with prosthetic vascular graft. For this purpose, it is very important to ensure vessel integrity by gluing the separated aortic layers with various biological glues. Today, the sandwich technique with Teflon felt strip or its modified forms are applied in aortic and prosthetic graft anastomoses in the surgical treatment of ascending aortic dissection. In our study, it was seen that Teflon felt strip and biologic glue were a common denominator for the anastomotic line [6-9].

In a study that evaluated the results of the surgical treatment of aortic dissection, it was observed that the dissected aorta was glued with biological glues in analogy to the literature. Subsequently, it was reported that the dissected aorta was approximated by the sandwich technique using internal and external Teflon felt strips or PTFE strips. However, Teflon felt strip or PTFE strip used to support aortic suture lines were not compared in this study [10].

Our basic principles in the surgical treatment of our patients are the replacement of ruptured ascending aorta with prosthetic tube graft and the appropriate aortic root surgery in presence of the aortic root pathology. There were a few reasons why we used Dacron strip instead of the commonly accepted Teflon® felt strip in order to create a more secure anastomotic suture line. Firstly, it does not bring extra cost to the patient. Secondly, the Dacron graft has blood sealing properties. Finally, it provides a better anastomotic integrity because the material has a ring shape.

Major complications seen after the surgical replacement of ascending aortic dissection are bleeding or infection requiring reoperation, RD, permanent or transient neurological dysfunction, and MOF. All of these reasons lead to an increase in early and late mortality rates in patients [11].

Neurological events seen after the surgical replacement of ascending aortic dissection are a very important cause of morbidity affecting the life of the patient. Many methods have been tried to reduce these neurological events. The main methods such as retrograde cerebral perfusion under deep hypothermia, direct right axillary artery cannulation or right axillary artery side-graft cannulation, and antegrade cerebral perfusion under moderate hypothermia have been used [12]. All of these have advantages and disadvantages to each other [13]. However, although short periods of deep hypothermic circulatory arrest (30-40 min) do not make a significant difference in terms of neurological complications and mortality outcomes when compared with other cerebral protection methods [14]. Antegrade serebral perfusion (ACP) has been reported to allow a more comfortable and secure anastomosis, especially in complex distal reconstructions. Many studies have reported that moderate hypothermia and persistent ACP are effective in protecting against neurological events [10, 11, 14, 15].

When the axillary artery was intact clinically, perfusion was routinely maintained through right axillary artery cannulation with PTFE side-graft. Perfusion was additionally supported by direct femoral artery cannulation if distal organ perfusion was insufficient. After the surgery, the side graft was cut near the anastomotic region and was sutured on itself. Thus, upper limb ischemia was prevented to occur because the axillary artery was not clamped. Moreover, it was aimed to prevent possible arterial

stenosis that may occur after direct axillary artery injury or cannula withdrawal.

In the literature, Sabik *et al*. [16] compared direct cannulation and side-graft cannulation. They found that complications related to side-graft cannulation were less frequently seen. Axillary artery injury and upper limb ischemia due to direct cannulation were more frequently seen[16]. We used PTFE side-graft for axillary artery cannulation in all our patients. Axillary artery injury or upper limb ischemia due to axillary artery side-graft cannulation was not observed in any patient.

The bleeding from especially aorta-graft and graft-to-graft anastomoses in aortic surgery is a very important factor that prolongs the duration of operation, requires additional blood transfusions, and increases risk of patient mortality [17].

Several methods have been described to stop bleeding in the surgical treatment of aortic dissection. These are anastomosis techniques to reinforce a suture line, glues for anastomosis or wrapping methods. A new method used for reducing bleeding in the anastomotic line is the Dacron graft intussusception technique described by Pinheiro *et al*. [18]. The common goal of all these techniques is to create a more secure anastomosis and to reduce surgical bleeding [17, 18]. In a case-series study of Pinheiro BB *et al*. [18], it was found that the mean amount of postoperative bleeding was 654 ml and that the revision rate due to bleeding was 4.1%.

In a case-series study of Emrecan *et al*. [10] in which the sandwich technique was performed using internal and external Teflon® felt strips or PTFE strips for creating a more secure anastomotic suture line, it was found that the mean amount of drainage was 1485 ml and that the revision rate due to bleeding was about 13%.

In our study, the mean amount of drainage in the first 24 hours postoperatively was 596 ml in the Teflon group and 546 ml in the Dacron group. Revision due to bleeding was not observed in both groups. Although the amount of drainage was relatively higher in the Teflon group, there was no statistically significant difference between the two groups in terms of amount of drainage and revision rate. The amount of drainage in both groups was similar to or less than the literature[10, 11, 14-19].

We compared whether there was any difference in mean number of RBC transfusions between the two groups. The mean number of RBC transfusions was similar in both groups. There was no statistically significant difference between the two groups in terms of mean number of RBC transfusions (p = 0.416). Although the mean amount of tissue adhesive used was relatively higher in the Dacron group, there was no statistically significant difference between the two groups in terms of mean amount of tissue adhesive used (p = 0761).

In a surgical series of Rylski *et al*. [3] involving 197 patients with type A aortic dissection, it was observed in two patient groups that the mortality rate was between 10% and 29%, the revision rate due to bleeding was between 7% and 14%, and the stroke rate was between 5% and 9%. The duration of X-clamp was between 97-134 min. Another large series study on the surgical treatment of type A aortic dissection belongs to Caus *et al*. [5]. In their case-series involving 83 patients, it was determined that the operative mortality rate was 37%, the postoperative stroke rate was 22%, the incidence of renal failure was 26%, and the bleeding rate was 7%. In addition, the mean hospital length of stay was found to be 15 days [5].

The postoperative complications in our patients were atrial fibrillation, RD, stroke, MOF, and revision due to infection. From among these complications, MOF (30%) and stroke (23%) were statistically significantly higher in the Teflon group than in the Dacron group (p = 0.020, p = 0.049). The mean intensive care unit (ICU) length of stay was statistically significantly lower in the Dacron group than in the Teflon group (p = 0.048). A total of 8 patients including 5 (38%) patients in the Teflon group and 3 (20%) patients in the Dacron group died. However, there was no significant difference between the two groups in terms of mortality rate.

The patients were similar in terms of age, gender, and preoperative risk factors. When the intraoperative data were evaluated, the mean duration of X-clamp and the mean total duration of CPB were shorter in the Teflon group. However, there was no statistically significant difference between the two groups in terms of mean duration of X-clamp and mean total duration of CPB.

When both groups were evaluated according to the literature, the Dacron group had better results in terms

of complications such as mortality rate, amount of drainage, stroke, and MOF compared to other relevant studies. When compared with similar literature, the Teflon group had similar mortality rate, shorter hospital length of stay, and similar or slightly higher stroke and MOF rates. When compared with the literature, the operative time was shorter in both groups [3-5].

When the patient groups were generally evaluated, the Dacron group had lower stroke and MOF rates but longer operative time. Moreover, although not statistically significant, the revision rate due to infection was higher. In the Teflon group, although not statistically significant, the operative time was shorter, the hospital length of stay was longer, and the amount of drainage was higher. We cannot conclude that the two groups could be superior to each other. Before this study was performed, our most important consideration was whether there would be a difference in amount of drainage and revision rate between the two groups. However, there was also no clear superiority in this regard between the two groups according to our results.

CONCLUSION

As a result of this study in which the results obtained from the patients undergoing surgery for aortic dissection were evaluated, we concluded that the Teflon and Dacron groups were not definitively superior to each other. However, complications of PTFE side-graft used for axillary artery cannulation were not observed in both groups. Therefore, we recommend that PTFE side-graft is used for axillary artery cannulation. There was no statistically significant difference between the groups in terms of amount of drainage, revision rate due to bleeding, and number of RBC transfusions. For these reasons, we think that Dacron strip which does not bring extra cost may be used as an alternative to the commonly accepted Teflon felt strip in order to create a more secure anastomotic suture line.

Conflict of interest

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

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The European Research Journal 2019;5(2):282-290 ORIGINAL ARTICLE

Effect of hospital ethical climate on the nurses' moral sensitivity

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ABSTRACT

Objectives: The study determines the effects of the hospitals ethical climate on the moral sensitivity of nurses.
Methods: The study design is descriptive and correlational. The data was obtained from 99 nurses who voluntarily accepted to fully participate in the surveys conducted. The data was analysed using descriptive statistics and Pearson correlations.
Results: As a result of the study, the ethical climate perception of nurses and their moral sensitivity level was found to be above average. A positive, meaningful and medium relationship was found between the moral sensitivity level of nurses and ethical climate perceptions of nurses.
Conclusions: Our findings support that the ethical climate perception of nurses is an important factor in determining the moral sensitivity. Consequently, building an ethical climate in all the hospitals that provide health care will result in a high moral sensitivity of nurses when giving health care.

Keywords: ethical climate, hospital, moral sensitivity, nurses, nursing ethics

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Today, hospitals strive to receive quality certification and high recognition. In this context, hospitals project the changes and innovations brought by science and technology on health care services, which can power them to carry on good and satisfactory treatment on the patients in their various field. The cost of quality and quantity of these services provided by hospitals are influenced by "moral sensitivity" and its crucial determinant "ethical climate" that reflect on the attitudes and decisions of health care professionals. Ethical climate which has various definitions in literature is described as the perception of atmosphere that increases ethical thoughts, mutual respect and trust in the organization and allows for questioning, discussions and expression of different views [1]. Ethical climate is also defined as common general perceptions related to corporate organizational values, practices and operations. It also includes perceptions related to expected, supported and rewarded behaviors [2]. According to Victor and Cullen [3], ethical climate involves the characteristics that immensely influence decisions and experienced in organizations and this climate requires generating a common approach that seeks answers to the questions which arise when dealing with ethical problems and to accurate approaches that need to be used in terms of ethics.

Ethical climate is a concept related to the degree of implementing ethical norms [4]. Therefore, it is crucial for hospitals to create an ethical climate and ensure the existence of a work environment in which the

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employees adopt ethical principles so that hospitals can sustain quality health services, keep their existence and increase their organizational performances [5]. Creating a positive climate in hospitals and a robust organizational structure and operation born out of practicing ethical values may generate feelings of ownership in employees and decrease feelings of loneliness as well as having positive impact on productivity [6]. It may also have positive reflections on patient satisfaction with health care services.

Nurses who are the leading force in operating health care services are health professionals who are directly affected by the ethical climate patterns adopted by hospitals. Nurses experience despair and incapacity in displaying professional attitudes and behaviors in the ethical decision-making process regarding the ethical dilemmas they face while offering health care services. There are some environmental factors that hinder professional attitudes and generate negative feelings during the process. Although moral distress and ethical climate are the most important factors, there are many other elements such as lack of administrative support, limitations based on organizational procedures and policies and resource control [7, 8]. In a study of nurses' ethical climate perception, McDaniel [9] found that nurses had fewer opportunities to participate in ethical negotiations in their institutions, were not adequately supported in practice, and had inconsistencies in policy and procedures in practice. In another study, it has been determined that nurses' having a more positive ethical climate perception of the institution they work at reduces the moral distress experienced [10]. It is crucial to create a positive work environment in organizations to ensure that employees can carry out their duties effectively because positive climate affects employees' morale, motivation and organizational commitments [6]. The ethical climate of an organization can act like a guide to solving ethical dilemmas experienced by employees and can also affect nursing practices and patient outcomes [10].

It is of important for nurses believe in the ethical climate atmosphere and the existence of an ethical climate approach in the hospital they work so that they can display ethical behaviors when carrying out their duties related to patient care. Ethical climate can also affect making ethically sound decisions while contributing to the development of moral sensitivity during the process. Moral sensitivity enhances individual competence used during ethical decision-making process [11]. In other words, moral sensitivity enables professionals to understand, interpret and appropriately respond to individuals who receive professional services [12]. According to Lovett, moral sensitivity is the skill of noticing moral problems [13] and prevents ethical dilemmas and conflicts in the process of ethical decision-making for patients. Therefore, the first step in displaying ethical behaviors in quality nurse care is to have moral sensitivity [14].

Moral sensitivity in professional practice develops through sensibility, sensitivity and intentness based communication of healthcare professionals in cases where patients experience difficulties and uncertainties as well as vulnerabilities. Moral sensitivity allows nurses and other health care professionals to morally respond to individuals who are receiving professional health care services, who are in pain and who are vulnerable [12]. Patients entrust their lives, bodies, health and their most vulnerable and private aspects to nurses who care for them. In this context, patient-nurse communication based on trust is of important. However, since nurses are relatively the stronger party in this professional relationship and they provide care for vulnerable groups, the moral aspects of care become clearer [15]. Professional care received by patients during their stay at the hospital brings ethical responsibilities for nurses. Since nurses' decisions and choices made by nurses include protecting the pride and supporting the comfort of patients who need care and treatment [16].

In this context, considering the moral aspect of nurse care and the ethical responsibilities it bestows on nurses, the importance of moral sensitivity and the ethical climate atmosphere for quality nurse care will be better comprehended. Policies followed by hospitals in the face of ethical problems and their reflections on organizational climate -i.e. ethical climate atmosphere generated by the hospital- may guide nurses' moral sensitivity and nursing practices and may affect the decisions made by nurses. It is important that nurses' decisions and actions are far from being intuitional, free from prejudices, and based on scientific, objective; and ethical principles. It is necessary to create an ethical climate to ensure professional nursing practices. In atmospheres where professionalism is ignored and ethical climate is not recognized, it is rather

hard to have moral sensitivity in practices related to care, making decisions about the significance and priorities of ethical principles and values, and displaying behaviors with moral standards which are supported by professional attitudes [17]. Hence, creation of an ethical climate in the organization is indispensable for quality health care services more of it provides nurses with the opportunitiy to approach problems faced in patient care with moral sensitivity, effectively follow ethical decision-making process and work by conducting the requirements of professionalism.

Objective

The study aims to determine the effect of hospitals ethical climate perception on the nurses' moral sensitivity.

Research Questions

What is the nurses' perception of ethical climate in their work place?

1. What are the opinions of nurses about moral sensitivity level?
2. Is there a relationship betweennurses' perception of ethical climate in their work place and level of moral sensitivity?

METHODS

Setting and Sample

The study was descriptive and correlational in design. It was conducted in a state and university hospital in Kırıkkale, Turkey. The sample size was estimated using G power analysis for a power level of .90, a significance level of .05 and medium effect size to enable the planned analyses. A sample size of 112 participant was calculated. The data was collected from 99 nurses who voluntarily accepted to participate and returned the surveys fully completed (88% response rate).

Ethical Considerations

For the approval of the study, written permission was obtained from each hospital. Nurses were informed about the aims and methods of the study. They were informed about voluntarily participation and the right to withdraw from the study at any time. Permissions were granted for the use of MSQ and HECS from Hale Tosun and Havva Öztürk respectively and from the Ethical Committee of Bolu Abant Izzet Baysal University (Protocol number: 2012/14).

Data Collection

The data were collected through face-to-face interviews. To obtain the descriptive qualities of the nurses, a personal information form was administered. The Turkish version of the Hospital Ethical Climate Survey was used to determine the ethical climate perception in hospitals, and The Turkish version of the Moral Sensitivity Questionnaire was used to identify the level of moral sensitivity.

Instruments

Moral Sensitivity Questionnaire (MSQ)

The Moral Sensitivity Questionnaire (MSQ) was originally developed by Lutzen [11] in 1994 to assess the moral sensitivity levels of the nurses. The MSQ was adapted into Turkish in 2003 by Tosun [18], and its validation and reliability were confirmed. The Turkish version of the MSQ is a 30-item self-administered survey consisting of six sub-dimension (including autonomy: 7 items, benevolence: 4 items, meaning: 5 items, conflict: 3 items, rules: 4 items, and relation: 4 items) based on the 7-point Likert type scale. Three items are not included into any subdimension in this questionnaire. The scales ranged from 1 (completely disagree) to 7 (completely agree). A total score between 30-210 is possible in this questionnaire. The higher scores indicate the higher levels of moral sensitivity of nurses [18, 19]. With regard to reliability of the instrument, Tosun [18] reported a Cronbach's alpha value of 0.84, Başak *et al*. [20] 0.80, Han *et al*. [21] 0.76, and Kim *et al*. [19] 0.85. In this study, it was calculated as 0.88.

The Hospital Ethical Climate Survey (HECS)

The Hospital Ethical Climate Survey (HECS) was originally developed by Olson in 1995 [22] to assess the ethical climate perception in their work place of nurses. The HECS was adapted into Turkish in 2003 by Bahçecik and Öztürk [23], and it was confirmed to be valid and reliable. The Turkish version of the HECS is a 24-item self-administered survey consisting of 5 sub-dimension (including patients: 4 items, managers: 6 items, hospital: 5 items, peers: 4 items, and

physicians: 5 items) based on the 5-point Likert type scale, from 5 indicating "always true" to "1" indicating "not true" [23]. The total scale score of 24-120 is possible. The higher scores indicate the positive perception of the hospital ethical climate of nurses. With regard to reliability of the instrument, Olson [22] reported a Cronbach's alpha value of 0.91, Bahçecik and Öztürk [23] 0.89, and Karagözoğlu *et al*. [2] 0.92. In this research, the Cronbach's alpha value was estimated as 0.95.

Statistical Analysis

The SPSS, version 17.00 for Windows, was used for data entry and statistical analysis. Numbers and percentages were used in the analysis of socio-demographic data. In order to determine the ethical climate perception and views of nurses on moral sensitivity levels, mean and standard deviation were used. Pearson correlation analysis was used to determine the relationship between the ethical climate of the hospital and the moral sensitivity perception of nurses.

RESULTS

The characteristic features of the participating nurses were shown in Table 1. Most (n = 78; 78.8%) of the participating nurses was female, 48 (48.5 %) were between 27-35 years old, and 40 (40.4%) had a bachelor's degree in nursing. Thirty-one (31.3%) of the participants were working in medical ward, and 29 (29.3%) had 6-10 years of nursing experience, and 44 (44.4%) had 1-5 years of experience in their current wards, and 83 (83.8%) had been working willingly in their current wards (Table 1).

Mean scores related to Nurses' perception of the ethical climate in their work place are shown in Table 2. In this study, the mean score of the nurses related to ethical climate perception was found to be 84.02 ± 19.80 on a scale of 24-120, with range of 38-120. When the subscales were examined, it is also found that from the subscales of the HECS, the nurses got the highest point in peers (15.46 ± 3.69) and patients (15.38 ± 3.70) and the lowest points in hospitals (15.78 ± 4.93) (Table 2).

Table 1. General characteristic of participants (n = 99)

Characteristic	Category	n	%
Sex	Female	78	78.8
	Male	21	21.2
Age	18-26	21	21.2
	27-35	48	48.5
	>36	30	30.3
Educational background	Senior high school	22	22.2
	Associate degree	37	37.4
	Bachelor	40	40.4
Current place of employment	Medical ward	31	31.3
	Surgical ward	27	27.3
	Intensive care unit	27	27.3
	Other*	14	14.1
Experience as a nurse (years)	< 1	7	7.1
	1-5 years	16	16.2
	6-10 years	29	29.3
	11-15 years	23	23.2
	> 15	24	24.2
Experience at the ward (years)	< 1	32	32.3
	1-5 years	44	44.4
	> 5	23	23.3
Work willingly at the ward	Yes	83	83.8
	No	16	16.2

Other* = emengency department, polyclinic, blood center

Table 2. Mean scores of nurses obtained from hospital ethical climate survey (n = 99)

Subscales of HECS	Item	Mean	SD	Total Score
Patients	4	15.38	3.70	4-20
Managers	6	20.96	6.74	6-30
Hospital	5	15.78	4.93	5-25
Peers	4	15.46	3.69	4-20
Physicians	5	16.42	4.67	5-25
Total Score	24	84.02	19.80	24-120

HECS = hospital ethical climate survey, SD = standard deviation

The nurses MSQ average score was found to be 150.05 ± 25.410 on a scale of 30-210, with range of 76-210. When the subscales were examined, it was also observed that from the subscales of the MSQ, the nurses got the highest point in autonomy (38.52 ± 6.80) and relation (21.83 ± 4.55) and the lowest points in conflict (11.29 ± 3.94) (Table 3).

The result of the correlation analysis made to determine whether there is a relationship between nurses' ethical climate perception and their moral sensitivity are given in Table 4. The analysis results showed that there was a positive, meaningful and moderate relationship in between (r = 0.565). According to the correlation values, the highest relationship was found between the patients ethical climate and relation moral sensitivity subscales (r = 0.603) and the lowest was found between peers and conflict (r = 0.208) subscales. According to the correlation values, a meaningful relationship was not found only between managers ethical climate and conflict moral sensitivity subscales (r = 0.121) (Table 4).

Table 3. Mean scores of nurses in moral sensitivity questionnaire (n = 99)

Subscales of MSQ	Item	Mean	SD	Total Score
Autonomy	7	38.52	6.80	7-49
Benevolence	4	20.05	4.11	4-28
Meaning	5	26.44	6.27	5-35
Conflict	3	11.29	3.94	3-21
Rules	4	18.96	4.70	4-28
Relation	4	21.83	4.55	4-28
Total Score	30	150.05	25.41	30-210

MSQ = moral sensitivity questionnaire scores, SD = Standard deviation

Table 4. Correlations among hospital ethical climate survey scores and moral sensitivity questionnaire scores (n = 99)

Subscales of Survey	Patients	Managers	Hospital	Peers	Physicians	Total HECS
Autonomy	0.574**	0.437**	0.522**	0.484**	0.560**	0.609**
Benevolence	0.420**	0.217*	0.310**	0.271**	0.286**	0.348**
Meaning	0.552**	0.365**	0.404**	0.455**	0.434**	0.516**
Conflict	0.211*	0.121	0.233*	0.208*	0.288**	0.246*
Rules	0.372**	0.338**	0.404**	0.380**	0.539**	0.483**
Relation	0.603**	0.377**	0.407**	0.509**	0.375**	0.526**
Total MSQ	0.561**	0.396**	0.470**	0.466**	0.515**	0.565**

Data are shown as Pearson correlation coefficient (r). HECS = hospital ethical climate survey, MSQ = moral sensitivity questionnaire scores, *$p < 0.05$, **$p < 0.01$

DISCUSSION

According to study results, nurses believed that ethical climate in their hospital was above average. Previous studies also pointed to similar findings [2, 10, 24-30]. Ethical climate in an organization can be evaluated by measuring employee perceptions related to organizational practices. Nurse perceptions regarding their work environment affect their approach to colleagues and the ethical problems they face as well as their attitudes towards solutions and their skills in making ethical decisions [1, 31]. Policies, procedures and practices of hospital in ethical matters may affect nurses' resolution to display attitudes and behaviors related to patient care [22, 24]. Ethical climate created in the hospital may cause moral distress in nurses [10, 24, 27, 32] and result in leave of employment [24, 31]. Therefore, ethical climate perceptions of health care professionals and especially of nurses who spend most time with patients and who provide continuous care is an important factor to ensure the provision of desired care and treatment [2]. Ethical climate perceptions of nurses are significant indicators to present nurse care based on moral sensitivity, ethical standards, trust and honesty. At the same time, ethical climate is the determinant factor in creating a robust organizational structure including the quality of organizational life at hospitals, employees' job satisfaction, motivation, commitment, patient and employee satisfaction, conflict prevention, identification of ethical problems and presentation of suitable ethical approaches and in offering quality health care services. In this respect, nurses believes that, they have an ethical climate which can be considered a positive satisfaction in terms of developing their moral sensitivity, taking care of the patients within the ethical approach and supporting the professional nursing roles.

This study found nurses' ethical sensitivity levels to be above average. Results of many studies in the literature are parallel to these findings [19, 20, 33-35]. Value problems experienced in relation to the changes and developments in health care services have resulted in new ethical problems and reflections of these problems on nurse care have made it compulsory for nurses to use ethical decision-making skills. Moral sensitivity has a significant place in using ethical decision-making skills. Moral sensitivity is required to identify ethical dilemmas and determine the appropriate values contained among alternative solutions [19]. However, moral sensitivity requires that the caregiver is sensible enough to comprehend verbal and non-verbal signs and behaviors to identify patient needs [36]. Moral sensitivity is also important to notice ethical dilemmas, produce solutions to problems and prevent conflicts [13, 19]. Decisions and choices made in the context of nurse care encumber nurses with immense responsibilities since they include protecting the pride of individuals in need of professional care and treatment, understanding their vulnerability, being aware of the moral outcomes of the decisions made for them and ensuring their comfort [15, 16, 37]. The findings in the study shows that nurses believing they have above average moral sensitivity may be important since it is an indicator that they will tend to display ethical appropriate behaviors.

The study identified a positive, significant and medium level relationship between nurses' hospital ethical climate perception and their moral sensitivity levels. Based on this finding, it can be claimed that nurses' positive ethical climate perceptions increase moral sensitivity. While ethical climate refers to individual organizational perceptions that affect attitudes and behaviors, it is also a reference to the course of action that will be displayed by employees [1]. Hence, policies, procedures and ethical climate perception related to hospitals are determinant factors for nurses to notice ethical dilemmas experienced in patient care and follows appropriate processes to solve these problems. Organizational obstacles and deadlocks in the process of solving ethical problems may result in less sensitivity in time [38]. Therefore, it is important for employees to believe in the existence of an ethical climate approach in the organization so that their moral sensitivity develops and conflicts and unethical behaviors can be prevented. Based on the results of this study, it can be stated that it is necessary to create ethical climates in hospitals to enhance nurses' moral sensitivity.

The study examined the relationships between hospital ethical climate sub dimension and moral sensitivity sub dimension and the highest level of relationship was found to be between patients and orientation sub dimension. According to this result, it can be expressed that; when nurses' ethical climate

perceptions related to approaches towards patients increase, their interest in actions that can affect their relationships with patients will also rise. People are at the center of nursing practices. To offer high quality services that are humane, it is necessary to work in collaboration and provide nursing practices that do not ignore patient autonym and security. Nurses' positive ethical climate perceptions for their organization are crucial to present patient-centered approaches and sustain professionalism. Positive perceptions will affect nurse orientation and the standard of care provided. According to the result, it can be stated that belief in the existence of an organizational understanding that allows ethical thoughts ethical behaviors and free expression of ideas related to patient care; supports ethical decision-making skills based on trust and respect in the context of team work will positively contribute to orienting to the units where nurses work and the quality of patient care. The study shows that, the lowest degree of relationship between ethical climate sub dimensions and moral sensitivity sub dimensions was found between colleagues and conflict factors. The positive relationship between these two factors is an unexpected outcome when it is considered that communicating with colleagues is effective towards the systematic implementation of operations and conflict prevention. Literature review shows that the majority of nurses have not been trained in ethical issues [20, 34-36] and they often ask the support of their colleagues to solve conflicts experienced during decision making process and to identify the correct action [34, 39, 40]. Since the majority of nurses generally do not receive training in ethics, it can be stated that decisions and actions based on professional seniority, inquisitive and personal judgments may be in effective. In these cases, suggestions provided by colleagues may contradict nurses' own sense of justice and value judgments and consequently the nurses may experience conflicts in approaching ethical problems and making ethical decisions. Appropriate approaches to ethical problems require that nurses are trained in ethical matters, make decisions about each action using their cognitive skills, use a systematic model as a guide and have moral sensitivity and awareness in addition to taking ethical theories and principles into consideration. Based on the results of the study, it can be stated that receiving support from colleagues in ethical issues may create conflicts and in order to eliminate conflicts, nurses should be provided with knowledge and skills in ethical matters and their moral sensitivity should be developed.

CONCLUSION

The perception of nurses related to their work place environment is important since it affects their approach to ethical problems and colleagues, their moral sensitivity, ethical decision skills and the quality of the care. As a result of the study, the ethical climate perception of the nurses and their moral sensitivity level was found to be above average. A positive, meaningful and medium relationship was found between the moral sensitivity levels and the ethical climate perceptions of the nurses. Our findings support that the ethical climate perception of the nurses is an important factor in determining the moral sensitivity. Therefore, that hospitals create an ethical climate will provide the nurses express themselves bravely in patient care, and plan and apply the patient care away from conflicts, coherent to patient rights, aiming to protect people's honour, with moral sensitivitiy and by using their ethical decision-making skills.

Authors' Contributions

BC, and HÖ contributed to the conception, and design of this study. BC. performed the statistical analysis, interpretation of the data, and drafting the manuscript. H Ö. contributed to collection of the data. Both authors approved the final version of the manuscript. All authors are in agreement with the content of the manuscript.

Conflict of interest

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

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The European Research Journal 2019;5(2):291-298 ORIGINAL ARTICLE

Efficacy of adjunctive treatment with trimetazidine for fragmented QRS among patients with ischemic heart failure: a propensity score match analysis

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ABSTRACT

Objectives: Fragmented QRS (fQRS) is an indicator of nonhomogeneous ventricular activity caused by myocardial ischemia and fibrosis. The anti-ischemic agent trimetazidine (TMZ) added to pharmacological treatment appears to have positive effects on cardiac parameters of patients with ischemic heart failure. We aimed to investigate the relationship of fQRS with adjunctive TMZ therapy in ischemic HF patients.

Methods: Four hundred eighty-nine consecutive ambulatory ischemic patients with heart failure eligible for our study were recruited for the study. A 12-lead electrocardiogram with standard chest and limb leads was used to evaluate the presence of fQRS. Further patients were divided into groups according to adjunctive TMZ treatment and fQRS presence. Confounding factors were adjusted by propensity score matching and multivariate logistic regression analysis.

Results: One hundred ninety-seven (40.3%) patients had fQRS on their ECGs and 235 (48.1%) patients were on adjunctive treatment with trimetazidine. Compared to patients without fQRS, patients with fQRS had lower left ventricular ejection fraction (LVEF), higher NYHA classes and more frequent mineralocorticoid receptor antagonist and diuretic usage ($p < 0.05$). Add-on treatment with TMZ was independently associated with fQRS presence (OR, 0.45; (95% CI, 0.29-0.70); $p < 0.0001$).

Conclusion: According to conventional therapy, adjunctive treatment with TMZ among ischemic heart failure patients can be associated with fQRS in 12-lead ECG independent of LVEF.

Keywords: Adjunctive treatment, fragmented QRS, ischemic heart failure, myocardial fibrosis, trimetazidine

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Although advances in acute cardiac care have improved survival after myocardial infarction (MI), there has been a rise in frequency of patients who have a poor prognosis due to the ineluctable progression of contractile dysfunction and left ventricular (LV) enlargement despite the recent introduction of many therapies [1]. As scientific evidence has shown that in addition to hemodynamic alterations, deep changes occur in the metabolism of failing heart; metabolic modulation has become an attractive therapeutic approach to heart failure (HF) [2-5]. Shifting metabolism away from a preference for free fatty acid toward more carbohydrate oxidation by Trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride, TMZ) has suggested to be the mechanism for the beneficial effects of TMZ given to ischemic HF patients as an add-on therapy. TMZ was observed to have a beneficial effect on LV remodeling, cardiac function, exer-

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cise tolerance, endothelium-dependent relaxation and electrophysiological properties for risk of major arrhythmias when added to conventional pharmacological treatment in patients with ischemic HF [2, 6-8]. Recently add-on therapy with TMZ have demonstrated to reduce mortality in these patients [1].

Several clinical parameters have shown association to cardiac death and HF progression including older age, prior MI, and diabetes mellitus [9]. Fragmentation in the QRS complex (fQRS) in 12-lead ECG has also been shown for prediction of cardiac events in patients with coronary artery disease (CAD) [10]. The fQRS is a result of myocardial scarring or ischemia that causes heterogeneous ventricular activation and dyssynchronous contraction [11, 12]. The effect of adjunctive treatment with trimetazidine on the presence of fQRS in ischemic HF patients is obscure. So, in this study, we aimed to investigate the association of add-on therapy with TMZ with the presence and extent of fQRS in patients with ischemic HF.

METHODS

The study population included patients with heart failure who were admitted to the cardiology outpatient clinics for ischemic heart disease and were under treatment with optimal, regular medication modalities for at least 6 months. The etiology of the heart failure was coronary artery disease documented by coronary angiography and a comprehensive echocardiographic examination, including M-mode, two-dimensional and Doppler echocardiography in all of the included patients [13]. Information was obtained by document review and patient interview following patient consent. Patients' medical notes provided patient details, past medical history, laboratory investigations, drug treatment on admission, and other relevant information such as adverse effects and compliance. Patients who have irregular trimetazidine usage (previous usage with cessation or not taken properly), mitral, aort, tricuspid and pulmoner stenosis or other severe valvular heart disease, non-ischemic dilated cardiomyopathy, left ventricular ejection fraction (LVEF) > 50% in echocardiography and New York Heart Association class (NYHA) IV were excluded from the study. Other exclusion criteria were; patients with acute myocardial infarction in the previous 3 months, with atrial fibrillation, chronic lung disease or any systemic disorder, complete or incomplete bundle branch block and pacemaker rhythm on ECG and use of additional antiarrhythmic drugs other than beta blockers.

All subjects were screened with a questionnaire. Demographic information, comorbidities, medications, symptoms, and history of trimetazidine therapy of the patients were obtained. Hypertension (HT) (systolic or diastolic blood pressure > 140 and 90 mm Hg, respectively, or pharmacological therapy with antihypertensive drugs), diabetes mellitus (DM) (fasting glucose plasma concentrations > 126 mg/dL or pharmacological therapy with antidiabetic drugs or insulin), hyperlipidemia (low-density lipoprotein (LDL) cholesterol levels ≥ 130 mg/dl or being treated with lipid-lowering medication) were considered definitions. Smoking was defined as at least 20 cigarettes per month for more than 6 months.

A 12-lead electrocardiogram with standard chest and limb leads was used to evaluate the presence of fQRS. The paper speed and amplitude were set to 25 mm/s and 10 mm/mV, respectively. The low-frequency cutoff (high-pass filter) was set at 0.16 Hz and high-frequency cut off (low-pass filters) was set at 100 Hz. All ECGs were interpreted by two cardiologists who had no knowledge of the patients' clinical information. Fragmented QRS was defined as the QRS complexes with the presence of an additional R wave (R') or notching in the nadir of the R wave or the S wave, or the presence of >1 R' in two contiguous leads, corresponding to a major coronary territory.
The study was approved by hospital Ethics Committee and patients gave their written informed consent.

Statistical Analysis

The SPSS statistical software (SPSS 17.0 for Windows, Inc., Chicago, IL, USA) was used for data analysis. Quantitative data were presented as mean ± standard deviation or median and interquartile range, and categorical variables presented as percentages. After testing data for normal distribution by using Shapiro-Wilk test, Student's t-test or Mann-Whitney U test were used to compare continuous variables. Chi-square test or Fisher's exact test, as appropriate, were used to identify statistically significant differences for categorical variables. To evaluate the

correlations between fQRS and clinical presentation, we used the Spearman's ρ correlation analysis. To minimize the confounding effect of possible factors and to obtain the best balance among groups, we performed a multivariate logistic regression model based on the significant demographic, clinical and treatment characteristic variables [14]. Logistic regression analysis was used to examine the associations between fragmented QRS, additional treatment with trimetazidine and other variables. Variables with a p value of < 0.1 in univariate logistic regression analysis were included in a multivariate logistic regression model. Statistical significance was defined as $p < 0.05$. Statistical tests were two-sided.

Table1. Baseline characteristics of patients with and without fragmented QRS

	All n = 489	**fQRS (+) n = 197**	**fQRS (-) n = 292**	***p* value**
Age, years	61.1 ± 8.4	62.5 ± 8.8	60.1 ± 8.1	**0.003**
Age >65 years, n (%)	133 (27)	80 (41)	53 (18)	**< 0.0001**
Male, n (%)	327 (67)	154 (78)	173 (59)	**< 0.0001**
BMI, kg/m²	27.2 ± 3.2	26.9 ± 2.9	27.4 ± 3.5	0.15
LVEF, %	41.4 ± 8.3	39.3 ± 7.7	42.8 ± 6.3	**< 0.0001**
LVH, n (%)	208 (43)	88 (45)	120 (41)	0.43
NYHA, n (%)				**< 0.0001**
I	337 (69)	88 (45)	249 (85)	
II	126 (26)	83 (42)	43 (15)	
III	26 (5)	26 (13)	0 (0)	
DM, n (%)	143 (29)	73 (37)	70 (24)	**0.002**
HT, n (%)	285 (58)	141 (72)	144 (49)	**< 0.0001**
Dyslipidemia, n (%)	461 (94)	183 (93)	278 (95)	0.28
Smoking, n (%)	349 (71)	136 (69)	213 (73)	0.35
ACE-I, n (%)	299 (61)	125 (64)	174 (60)	0.39
ARB, n (%)	103 (21)	39 (20)	64 (22)	0.57
Diuretic, n (%)	199 (41)	117 (59)	82 (28)	**< 0.0001**
MRA, n (%)	124 (25)	79 (40)	45 (15)	**< 0.0001**
β-Blocker, n (%)	324 (66)	121 (61)	203 (69)	0.07
Digoxin, n (%)	63 (13)	20 (10)	43 (15)	0.14
ASA, n (%)	446 (91)	177 (90)	269 (92)	0.38
Statin, n (%)	309 (63)	133 (68)	176 (60)	0.11
Insulin/OAD, n (%)	130 (27)	68 (34)	62 (21)	**0.001**
HbA1c, %	5.2 (5.1-6.2)	5.7 (5.2-6.3)	5.1 (4.8-5.5)	**< 0.0001**
eGFR, mL/min per 1.73 m²	85.1 ± 28.9	83.5 ± 23.1	86.1 ± 32.3	0.36
No. leads with fQRS	0 (0-3)	4 (3-4)	0 (0-0)	**< 0.0001**
TMZ Treatment, n (%)	235 (48)	72 (36)	163 (56)	**< 0.0001**

ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, ASA = acetylsalicylic acid, BMI = body mass index, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, fQRS = fragmented QRS complex, HbA1c = hemoglobin A1c, HT = hypertension, LVEF = left ventricular ejection fraction = LVH = left ventricular hypertrophy, MRA = mineralocorticoid receptor antagonist, NYHA = New York Heart Association class, OAD = oral antidiabetic, TMZ = Trimetazidine

RESULTS

Of 489 consecutive patients recruited for the study, 327 (67%) were male and 133 (27%) were more than 65 years old. Mean age of the patients was 61.1 ± 8.4. Among the participants, 285 (58%) had hypertension, 143 (29%) had diabetes mellitus, and 461 (94%) had hyperlipidemia. One hundred and ninety seven (40.3%) patients had fQRS on their ECGs. Compared to patients without fQRS, patients with fQRS had lower LVEF, higher NYHA classes and more frequent mineralocorticoid receptor antagonist (MRA) and diuretic usage. Also adjunctive treatment with Trimetazidine was significantly lower in patients

Table 2. Baseline characteristics of the study population according to the treatment modality.

	All n = 489	**Add-on treatment with TMZ n = 235**	**Conventional treatment n = 254**	***p* value**
Age , years	61.1 ± 8.4	61.5 ± 8.5	60.7 ± 8.4	0.29
Age >65 years, n (%)	133 (27)	69 (29)	64 (25)	0.30
Male, n (%)	346 (71)	164 (70)	182 (72)	0.65
BMI, kg/m²	27.2 ± 3.2	27.5 ± 3.3	26.9 ± 3.2	0.07
LVEF, %	41.4 ± 8.3	44.8 ± 4.9	38.2 ± 7.6	**< 0.0001**
LVH, n (%)	208 (43)	98 (42)	110 (43)	0.72
NYHA, n (%)				**< 0.0001**
I	337 (69)	194 (83)	143 (56)	
II	126 (26)	41 (17)	85 (34)	
III	26 (5)	0 (0)	26 (10)	
DM, n (%)	143 (29)	69 (29)	74 (29)	0.96
HT, n (%)	285 (58)	138 (59)	147 (58)	0.85
Dyslipidemia, n (%)	461 (94)	220 (94)	241 (95)	0.55
Smoking, n (%)	349 (71)	176 (75)	173 (68)	0.10
ACE-I, n (%)	299 (61)	143 (61)	156 (61)	0.90
ARB, n (%)	103 (21)	63 (27)	40 (16)	**0.003**
Diuretic, n (%)	199 (41)	73 (31)	126 (50)	**< 0.0001**
MRA, n (%)	124 (25)	33 (14)	91 (36)	**< 0.0001**
β-Blocker, n (%)	324 (66)	171 (73)	153 (60)	**0.003**
Digoxin, n (%)	63 (13)	38 (16)	25 (10)	**0.037**
ASA, n (%)	446 (91)	212 (90)	234 (92)	0.46
Statin, n (%)	309 (63)	139 (59)	170 (67)	0.08
Insulin/OAD, n (%)	130 (27)	61 (26)	69 (27)	0.76
HbA1c, %	5.2 (5.1-6.2)	5.2 (5.0-6.2)	5.3 (5.1-6.3)	0.27
eGFR, mL/min per 1.73 m²	85.1 ± 28.9	83.9 ± 28.6	85.9 ± 29.2	0.45
fQRS, n (%)	197 (40)	72 (31)	125 (49)	**< 0.0001**
No. leads with fQRS	0 (0-3)	0 (0-2)	0 (0-4)	**< 0.0001**

ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, ASA = acetylsalicylic acid, BMI = body mass index, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, fQRS = fragmented QRS complex, HbA1c = hemoglobin A1c, HT = hypertension, LVEF = left ventricular ejection fraction, LVH = left ventricular hypertrophy, MRA = mineralocorticoid receptor antagonist, NYHA = New York Heart Association class, OAD = oral antidiabetic, TMZ = Trimetazidine

Table 3. Characteristics of our matched study group according to the treatment modality

	All n = 176	Add-on treatment with TMZ n = 88	Conventional treatment n = 88	*p* value
Age >65 years, n (%)	40 (23)	20 (23)	20 (23)	1
LVEF, %	41.3 ± 7.8	43.5 ± 8.0	39.2 ± 7.1	**< 0.0001**
NYHA, n (%)				**0.003**
I	129 (73)	74 (84)	55 (63)	
II	44 (25)	14 (16)	30 (34)	
III	3 (2)	0 (0)	3 (3)	
LVEF <30%, n (%)	28 (16)	11 (13)	17 (19)	0.22
LVH, n (%)	80 (46)	43 (49)	37 (42)	0.36
fQRS, n (%)	62 (35)	24 (27)	38 (43)	**0.03**
No. leads with fQRS	0 (0-3)	0 (0-2)	0 (0-3.5)	**0.05**

fQRS = fragmented QRS complex, LVEF = left ventricular ejection fraction, LVH = left ventricular hypertrophy, NYHA = New York Heart Association class, TMZ = Trimetazidine

with fQRS according to non-fQRS group. While HT and DM were more frequent in patients with fQRS, frequency of left ventricular hypertrophy (LVH) did not differ significantly between groups (Table 1). In subgroup of patients with EF ≤ 30% prevalence of fQRS and number of leads with fQRS didn't differed between the treatment modality groups (8 patients (40%) vs. 30 patients (48%) and 0 (0-3) vs. 0 (0-4); $p > 0.05$ respectively).

Number of leads with fQRS on ECG was

Table 4. Association of fragmented QRS with multiple variables in univariate and multivariate logistic regression analyses.

Variables	Univariate OR (95% CI)	*p* value	Multivariate OR (95% CI)*	*p* value
Age > 65 years	3.08 (2.04-4.65)	**< 0.0001**	2.47 (1.53-3.99)	**< 0.0001**
Male Gender	2.48 (1.67-3.70)	**< 0.0001**	2.43 (1.56-3.79)	**< 0.0001**
LVEF	1.05 (1.03-1.08)	**< 0.0001**	1.02 (0.99-1.05)	0.18
LVEF <30 %	1.3 (0.8-2.1)	0.26	-	-
LVH	1.2 (0.8-1.7)	0.43	-	-
DM	1.87 (1.26-2.77)	**0.002**	1.33 (0.83-2.14)	0.24
HT	2.59 (1.76-3.80)	**< 0.0001**	1.77 (1.11-2.83)	**0.02**
ACE-I	1.18 (0.81-1.71)	0.39	-	-
ARB	0.88 (0.56-1.37)	0.58	-	-
β-Blocker	0.70 (0.48-1.02)	0.07	0.66 (0.43-1.00)	0.06
TMZ Treatment	0.46 (0.31-0.66)	**< 0.0001**	0.45 (0.29-0.70)	**< 0.0001**

ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CI = confidence interval, DM = diabetes mellitus, HT = hypertension, LVEF= left ventricular ejection fraction, LVH = left ventricular hypertrophy, OR = odds ratio, TMZ = Trimetazidine.

*Adjusted for: Age > 65 years, male gender, left ventricular ejection fraction, diabetes mellitus, hypertension, β-Blocker and Trimetazidine usage.

significantly correlated with NYHA functional class (r_s =0.47, $p < 0.0001$), LVEF (rr_s = -0.27, $p < 0.0001$), usage of diuretics (r_s =0.30, $p < 0.0001$) and MRAs (r_s=0.33, $p < 0.0001$).

Patients were on standard medical therapy for heart failure (HF) according to current guidelines [15]. Two hundred and thirty five (48.1%) patients were on TMZ treatment added to conventional therapy. When patients were classified according to adjunctive TMZ treatment there were no differences between the 2 groups with regard to the specific drugs used with the exception of diuretics, MRA, β-Blocker, digoxin and angiotensin receptor blockers (ARB). Patients in the conventional treatment group had higher rates of fQRS and higher number of leads with fQRS ($p <$ 0.0001) (Table 2). After matching groups according to demographic, clinical and treatment characteristics, presence of fQRS remained significantly less frequent in adjunctive TMZ treatment group (Table 3). There were no differences between the groups regarding hematologic and biochemical parameters.

In stepwise multivariate logistic regression analyze, age > 65 years, male gender, hypertension and add-on treatment with TMZ were independently associated with fQRS presence (Table 4).

DISCUSSION

Our study results showed the independent association of fQRS in 12-lead ECG with adjunctive TMZ treatment according to conventional therapy among patients with ischemic HF.

In this study, the presence of fQRS was evaluated in ambulatory ischemic systolic HF patients to investigate its relation with clinical symptoms and add-on TMZ therapy. Many studies have demonstrated that the rates of the fQRS widely range between percentages (28%–54%) [10, 11, 16]. This wide range can be explained by the differences in the patients' groups, different treatment methods and variability in the ranges of filters adopted in the ECG imaging of these studies. In this study, the frequency of fQRS was 40.1% in ischemic systolic HF patients. The extent of fQRS on ECG was correlated with NYHA functional class, and both the presence and extent of fQRS were associated with a poor overall clinical presentation besides NYHA class, including increased usage of diuretics and MRAs, and lower LVEF. Because of well documented negative correlation of LVEF with the number of leads with fQRS, we proposed that those patients with increasing number of leads with fQRS had greater myocardial scar tissue or ischemia in our study. Our suggestion was compatible with the scholars as successful myocardial reperfusion by invasive treatment had decreased the number of fQRS leads and the probability of ischemia detection by myocardial perfusion scintigrams was higher in patients whose ECGs have fQRS [17, 18]. Also, while, fQRS was found to be associated with poor functional NYHA class in hospitalized decompensated systolic heart failure patients [19]; different from our study, Cheema *et al*. [20] could not demonstrate a relationship between fQRS and EF in patients receiving ICDs for primary prevention due to ischemic and non-ischemic heart failure. The diffusiveness of probable residual ischemia and the differences in clinical characteristics of the enrolled patients may be likely explanations for this discrepancy.

The fQRS is related to a higher adverse cardiac event and decreased life span in patients with known atherosclerotic heart disease [10]. Myocardial scar and/or ischemia have been implicated in the formation of fragmentation of the QRS complex, leading to inhomogeneous ventricular activations. Different fQRS morphologies are caused by shifting QRS vector during depolarization in and around scars or myocardial ischemic areas, depending on their extent and ventricular locations [16, 21, 22]. The beneficial effects of TMZ on left ventricular systolic function and functional capacity were emphasized more markedly in patients with more severe reversible perfusion defects [23]. Although residual ischemia wasn't evaluated in our study; benefits of adjunctive metabolic treatment was indirectly supported by demonstrating the higher prevalence of the fQRS presence in ischemic HF patients with conventional treatment barring TMZ. The diagnostic accuracy of fQRS has been investigated in different studies in which they have showed that in addition to significant relation with coronary reversible ischemia [17, 18], fQRS was moderately sensitive but highly specific for myocardial scar [24]. The fQRS have also been defined as a predictor of arrhythmic events and

appropriate ICD shocks in patients with cardiomyopathy who received an implantable cardioverter-defibrillator (ICD) for primary or secondary prevention of sudden cardiac death (SCD) [16, 25]. Similarly, increased fragmentation might also serve as a marker of abnormal spread of ventricular activation leading to dyssynchronous contraction and impending HF [26]. In patients receiving cardiac resynchronization therapy for HF, increased number of leads with fQRS predicted response to treatment [26]. Both arrhythmias and worsening HF were demonstrated to be associated with a poor prognosis and prognostic value of add-on therapy with TMZ in ischemic HF patients was determined [1, 11, 12]. Our findings reinforce this evidence by the relatively low prevalence of fQRS presence and higher mean EF values in add-on TMZ treatment group relative to conventional treatment group.

Of interest, patients who had higher number of leads with fQRS were less frequent in adjunctive TMZ treatment group relatively to the conventional treatment group. In another study carried out in ischemic HF patients, the number of leads with fQRS was an independent predictor of cardiovascular mortality or re-hospitalization for HF [27]. We failed to demonstrate a similar association between number of leads with fQRS and treatment modality in subgroup of patients with EF ≤ 30%, although the small number of patients in these subgroups degreases the power of statistical assessment. So, we have postulated that fQRS precisely represents the myocardial scar other than ischemia in patients with EF ≤ 30% and may discriminate patients with poor prognosis.

Limitations

The limitations of the study include cross-sectional and single-center design. It was non-randomized, and thus, subject to selection bias. However, we were careful to include consecutive patients and had strengthened our results by matching groups' with propensity score analysis. The fQRS was not defined in the presence of complete or incomplete bundle branch blocks or paced rhythms, and therefore in this present study these patients were excluded from the study. Also, we did not use other quantitative modalities (myocardial perfusion scanning, stress echocardiography, or magnetic resonance imaging) to show the myocardial ischemia or scarring. Evaluation of residual ischemia wasn't performed with appropriate techniques; therefore contribution of residual ischemia to the trimetazidine treatment efficiency on fQRS prevalence is obscure.

CONCLUSION

In light of the present study by finding a significant association between the clinical presentation, adjunctive treatment with TMZ and higher fQRS frequency; we suggest that the prognostic benefit of add-on TMZ treatment can be at least partly by degreasing the frequency of the fQRS on ECG. Since the presence of fQRS in 12-lead ECG is related to myocardial ischemia or scarring; monitoring these patients closely by myocardial perfusion scanning or magnetic resonance imaging can allow us for discriminating patients who would benefit most from invasive or non-invasive treatment strategies. Nevertheless, future prospectively designed large scale studies going deeper in this discussion are required for investigating the importance of the adjunctive Trimetazidine therapy on FQRS.

Conflict of interest

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

Financing

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The European Research Journal 2019:5(2);299-305 ORIGINAL ARTICLE

Regenerative effect of platelet-rich fibrin on articular cartilage defects in an experimental rat model

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ABSTRACT

Objectives: Different materials are currently being used experimentally to accelerate cartilage healing and to obtain hyaline cartilage. We aimed to investigate the effect of platelet-rich fibrin on joint cartilage healing.

Methods: Twenty rats were used in this study. platelet-rich fibrin was obtained from 4 rats, and the remaining 16 rats were randomly divided into two groups (4 and 8 weeks). Both knee joints were prepared, and an osteochondral defect was created at the femoral condyle in all rats. platelet-rich fibrin was placed into the osteochondral defect of the right knee, while the left knee joint was used as a control. Groups were sacrificed after 4 and 8 weeks, respectively.

Results: According to the O'Driscoll score, there were no significant differences between the right and left knee scores in group 4 weeks ($p = 0.820$). However, the right knee scores were significantly different than the left knee scores in group 8 weeks ($p < 0.001$). Defects were completely filled with cartilage tissue after 8 weeks in the platelet-rich fibrin group.

Conclusions: Similar to its role in various tissues, platelet-rich fibrin is an effective biomaterial that enhances the healing of osteochondral defects.

Keywords: Articular cartilage, chondral healing, experimental rat model, hyaline cartilage, platelet-rich fibrin

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Joint cartilage is a unique tissue, that is involved in joint motion and resistance during weight bearing. However, the lack of primary vascular nutrition renders joint cartilage repair after damage difficult [1]. Chondrocytes have a limited potential for migration to damaged sites, and untreated cartilage lesions can result in degenerative joint diseases. The limited treatment options for focal cartilage defects include microfracture procedures, use of biomaterials, and scaffolds. During microfracture, perforation of the subchondral bone plate is performed to stimulate bone marrow, and to enhance the migration of non-differentiated bone marrow-derived multipotent stem cells to the defective site [2]. The use of biomaterials is widespread, but there is no consensus as to its effectiveness. The cellular and acellular biomaterials that are used currently both have advantages. Acellular biomaterials such as collagen, hyaluronic acid, synthetic polymers, alginate, and chitosan are relatively cheaper than cellular cultures, and are not associated with donor site issues. However, an ideal biomaterial should be rich in cells and growth factors. Platelet-rich fibrin (PRF), a second-generation platelet-rich biomaterial [3] that is rich in platelets, neutrophils, and cir-

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culating stem cells, was developed by Choukron [4-6]. PRF contains several growth factors and cytokines, including transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF)-I and IGF-II, platelet-derived growth factor (PDGF), the inflammatory cytokines interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)-α, and the anti-inflammatory cytokines IL-4 and IL-10 [7, 8]. PRF is the highly effective biomaterial in terms of cellular content, growth factors, and inflammatory cytokines compared with platelet-rich plasma (PRP), plasma rich in growth factors (PRGF), advanced platelet-rich fibrin (A-PRF), and concentrated growth factors (CGF) [9]. Several authors have shown that growth factors, including PDGF and TGF-β, which are constantly released from PRF for at least one week and up to 28 days, support its accelerating effect on tissue healing [4-7, 10]. PRF is obtained by centrifugation of fresh whole blood; therefore, it does not cause allergic reactions. In this experimental study, we investigated the histological effects of PRF on cartilage regeneration.

METHODS

This study was approved by the University Ethical Committee of Laboratory Animals Care and Use (04/01/2014–09/01/2014). The study included twenty mature male Sprague-Dawley rats (average length 18 cm) weighing approximately 300 grams. To obtain PRF, blood samples were collected from four rats using conventional glass tubes without anticoagulants.

Preparation of PRF

The collected blood was centrifuged at 2700 rpm for 12 minutes. Then, the PRF matrix was immediately withdrawn from the tube, and the red blood cell (RBC) fraction was eliminated. A large number of platelets were trapped between the yellow fibrin section and the RBC section with the buffy coat section [7] (Figure 1). When PRP was obtained, first, donors blood was treated with anticoagulants. Then the primary centrifugation was applied (at 1500 rpm for ten minutes) to separate the red cells and the plasma. Second centrifugation was carried out for the concentration of the platelets. (3000 rpm for ten minutes). It has been reported in the literature by the authors who define the original method of PRF preparation that no allogenic reaction occurs [7, 8]. There is no allergic or histological abnormality was observed due to use of allogeneic PRF.

Surgical Procedure

The animals were housed in the Laboratory Animal Care-Augmentation facility of our university in a temperature-controlled room (20-22°C), on a 12-hour light/dark cycle. They were provided with rat pellets and water *ad libitum*. Four animals were housed together per standard cage. The 16 rats used in this study were randomly divided into two groups (groups 4 and 8 weeks). Anaesthesia was induced via an intraperitoneal injection of ketamine (50 mg/kg) and xylazine hydrochloride (10 mg/kg). Both knees of each animal were prepared for aseptic surgery with chlorhexidine gluconate. An anterior longitudinal incision was made in the knee, and the patella was

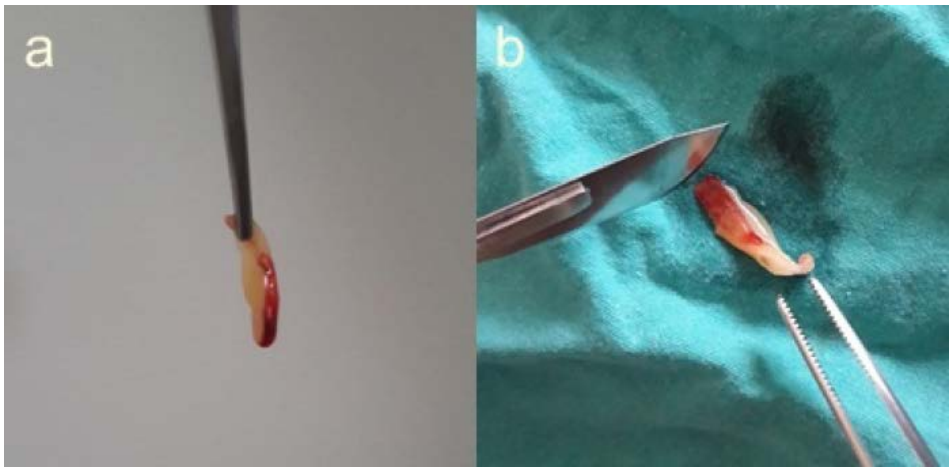

Figure 1. The obtained PRF was separated into eight equal parts (a, b).

Table 1. The O'Driscoll histological cartilage repair scale

Characteristics	Score
Nature of predominant tissue	
Cellular morphology	
Hyaline articular cartilage	4
Incompletely differentiated mesenchyme	2
Fibrous tissue or bone	0
Staining of the matrix	
Normal or nearly normal	3
Moderate	2
Slight	1
None	0
Structural characteristics	
Surface regularity	
Smooth and intact	3
Superficial horizontal lamination	2
Fissures 25-100% of the thickness	1
Severe disruption including fibrillation	0
Structural integrity	
Normal	2
Slight disruption including cysts	1
Severe disintegration	0
Thickness	
100% of normal adjacent cartilage	2
50-100% of normal cartilage	1
0-50% of normal cartilage	0
Bonding to the adjacent cartilage	
Bonded at both ends of graft	2
Bonded at one end or partially at both ends	1
Not bonded	0
Freedom from cellular changes of degeneration	
Hypocellularity	
Normal cellularity	3
Slight hypocellularity	2
Moderate hypocellularity	1
Severe hypocellularity	0
Chondrocyte clustering	
No clusters	2
<25% of the cells	1
25–100% of the cells	0
Freedom from degenerative changes in adjacent cartilage	
Normal cellularity, no clusters, and normal staining	3
Normal cellularity, mild clusters, and slight staining	2
Mild or moderate hypocellularity, slight staining	1
Severe hypocellularity, poor or no staining	0
Total	**24**

dislocated laterally. An osteochondral defect was created at both femoral condyles using a 1.50 mm (0.057-inch)-diameter stainless Kirschner wire (Aysam Samsun, Turkey) to a depth of 2 mm. This procedure was performed in all animals for both knees (Figure 2). The collected PRF was divided into eight equal portions and placed into the defective areas of the right knees, and the joint capsule was repaired.

Cartilage healing is a process that is completed in 6 weeks, similar to fracture healing. Evaluation was made at 4th and 8th weeks to investigate the early and late effects of PRF.Groups were sacrificed 4 and 8 weeks post-surgery, respectively, and the femoral condyles were harvested for histological evaluation.

Histology and Immunohistochemistry

The specimens were fixed in 10% buffered neutral formalin and decalcified in acid solution for two weeks. Following decalcification, the specimens were dehydrated and subsequently embedded in paraffin wax. Sections 10 µm thick were made through the centre of the defect. Cartilage sections were stained with hematoxylin and eosin stain for overall evaluation of the tissue. Histological depth measurement was not performed. Masson's trichrome stain was used for the evaluation of the osteochondral zone, and Toluidine blue stain was used to determine the presence of proteoglycan. The sections were blindly scored by two independent investigators (MHM and CK) and evaluated using the O'Driscoll scale [11] (Table 1).

Statistical analysis

The SPSS software version 22.0 Mining (IBM Corp., Armonk, NY, USA) was used for all analyses. Normally distributed data were analysed using the Shapiro–Wilk test, and variance homogeneity was assessed using the Levene test. Univariate analysis of variance (ANOVA) was used with bootstrap analysis to determine dependent quantitative variables in groups 4 and 8 weeks and for the left and right knees according to the O'Driscoll scores. Quantitative variables are expressed as means ± standard deviations (SD), and categorical variables are expressed as n (%). Variables were examined at a 95% confidence level, and $p < 0.05$ was considered to indicate statistical significance.

RESULTS

The mean value of PRF in the right knees of 8 week group (11.75 ± 1.67) was significantly higher than that of 4 week group (20.38 ± 2.62) ($p < 0.001$).

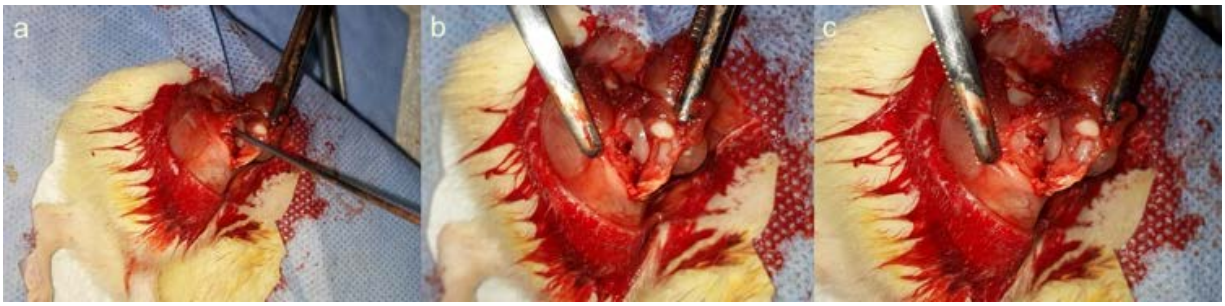

Figure 2. Osteochondral defects were created using a Kirschner wire at the femoral condyles and the right knee defects were subsequently filled with PRF (a-c).

Table 2. Comparison of the right and left knee scores in both groups

Groups	Knee		*p* value[1]
	Right	Left	
	Mean ± SD. / Max.-Min.	Mean ± SD. / Max.-Min.	
4 weeks	11.75 ± 1.67 / 14-9	12.00 ± 2.27 / 15-8	0.820
8 weeks	20.38 ± 2.62 / 24-16	12.25 ± 2.05 / 16-10	**< 0.001**
***p* value[2]**	**< 0.001**	0.820	

Univariate Analysis of Variance (ANOVA) (Bootstrap), SD =Standard deviation

p value[1] = 4 weeks versus 8 weeks groups, *p* value[2] = Right knee versus left knee

There were no significant differences between the control (left) knees of both groups ($p = 0.820$) (Table 2).

The O'Driscoll score of the PRF-treated group (right knees) (20.38 ± 2.62) was significantly higher than that of the control group (12.25 ± 2.05) during the eighth week ($p < 0.001$). There were no differences in the knees of group 4 weeks (p = 0.820) (Figure 3).

Four weeks after surgery, the defects in both groups were filled with 50% fibrocartilage. At the end of 8 weeks, the PRF placed in the defective zone of the right knee was completely resorbed, and the defect was filled with hyaline cartilage (Figure 4). In the control group, differentiated mesenchymal cells and fibrosis cartilage tissue were predominant in some sections (Figure 5).

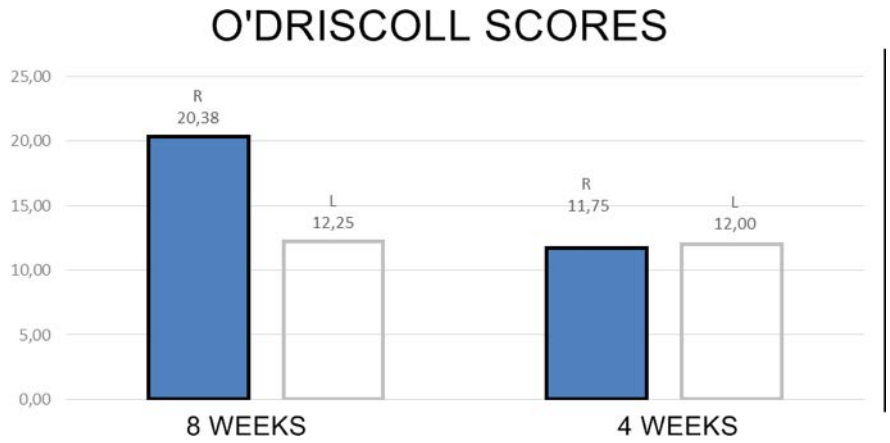

Figure 3. Distribution of right and left knee scores according to the O'Driscoll scoring system in groups A and B.

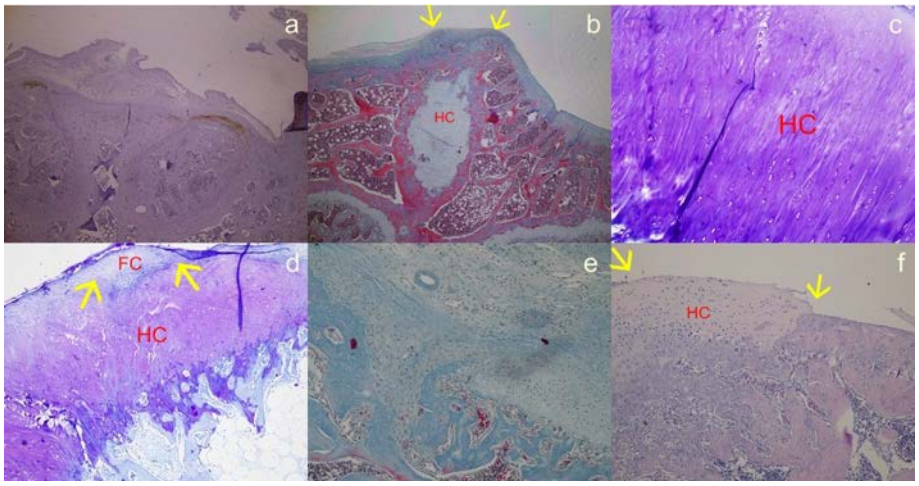

Figure 4. Histological evaluations in the PRF-treated knees of group B (a-f). (a) Hyaline cartilage healing; collagen II (×10), (b, e) Masson trichrome (×20, ×40), (c, d) a fully healed defect; Toluidine blue (×40, ×20), and (f) smooth surface shown with hematoxylin & eosin (×20).

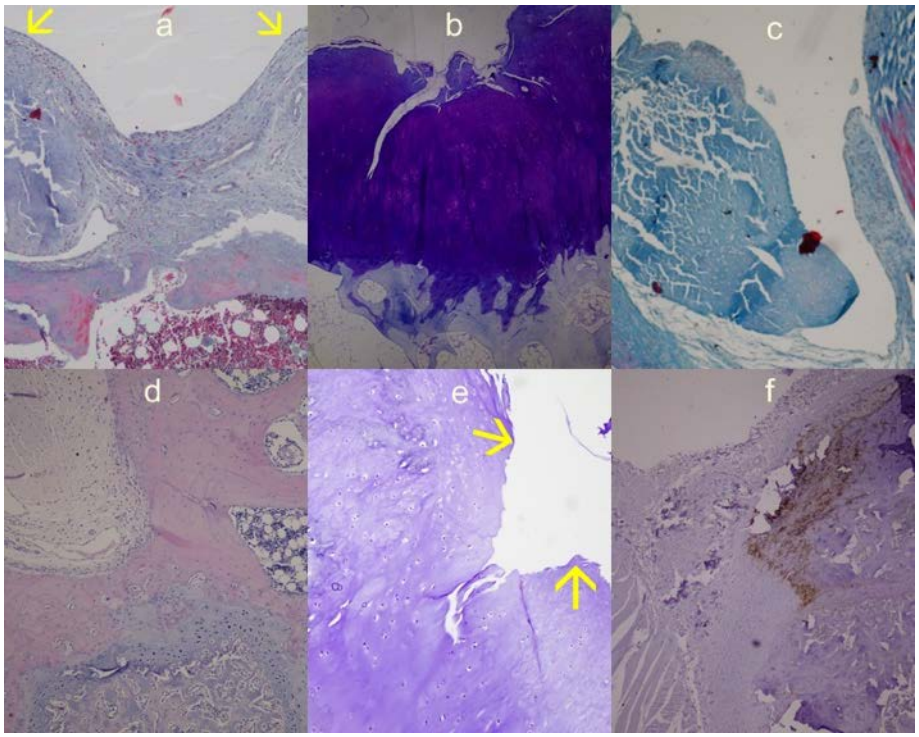

Figure 5. (a-f) Histological assessment of Group A. (a) Defects healed to 50-75% with fibrocartilage; Masson trichrome (×10) and (b) Toluidine blue (×20). (c) Partial healing of the PRF-treated defect; Masson trichrome (×40) and (d) Hyaline cartilage-filled defect; hematoxylin & eosin (×20). (e) Unhealed defect; Toluidine blue (×40) and (f) a partly healed defect; collagen II (×20).

DISCUSSION

The main goal of studies that investigate cartilage healing is to obtain faster production of and better quality hyaline cartilage. With autogenous cartilage grafts, there is a risk of donor area morbidity. Moreover, homogeneous and xenografts have the potential of causing immunological and infectious problems. The focus of this study was to obtain easily produced and reliable biomaterials that accelerate

cartilage healing. The goal was to achieve biomechanical functioning similar to that of normal joint cartilage, with a minimally invasive procedure [12]. Platelet-rich preparations are appealing, as they are autogenous and contain many growth factors [13, 14]. Indeed, the most important components of tissue repair are growth factors, which are released during injury from platelet granules [15]. After a microfracture, subchondral bone haemorrhage occurs, and the fibrin network and platelets aid in recovery; however, these effects are limited. Thus, use of PRF is preferred, as it provides abundant platelets. PRF is an inexpensive and reliable biomaterial used in various disciplines [16, 17]. In the current study, we observed hyaline cartilage in the joint treated with PRP at the end of 8 weeks. The smoothness of the repair surface and proximity to the normal thickness of the cartilage have resulted in high scores for the PRF group. Kazemi *et al*. [18] treated the cartilage defect in dogs with the PRF. Although histological and macroscopic scores were higher but results not statistically significant. Hamanishi *et al*. [19] observed hyaline cartilage after 4 weeks with atelocollagen membrane after drilling. Same study showed that 4 weeks after creation of the defects showed positive immunoreactivity of transforming growth factor beta (TGFb) in the deep layer of fibrous reparative tissue above the area of ingrowth of hyaline cartilage [19].

In our study, osteochondral defects were created in the right and left knees of rats, and only the right knees were treated with PRF. The healing periods of experimental models using different animal groups vary, and a follow-up period of 1-12 months is recommended for adequate macroscopic and histological evaluations [18, 20, 21]. Performing studies in rats is easy, and it provides opportunities for histological examination. However, macroscopic examination may not be possible in rodent studies. Recent studies have achieved satisfactory histological results after study durations of 4 and 12 weeks in rat knee cartilage models [19, 22]. In our study, we demonstrated that injured rat cartilage and subchondral bone healed within 2 months. Significant improvements were observed in the PRF group at 8 weeks, but no significant differences between the PRF and control groups were found during at 4 weeks, according to O'Driscoll scores. A defect of 1.5 mm in diameter is considered large in the rat knee joint; Jackson *et al*. [23] showed that 3 mm diameter defects did not heal spontaneously in sheep knees. Vasara *et al*. [20] obtained spontaneous chondral healing without any augmentation material in injured immature porcine knee joints. In our study, no spontaneous filling of the defects occurred in the control group. However, fibrocartilage was observed in all sections studied, even in the PRF-treated group. Due to the smooth surface of the cartilage and complete filling of the defect, the PRF group received high scores. The average defect-filling rate in the control group ranged from 50 to 75%. In a previous study, Kuo *et al*. [24] showed that PRF improved the healing of cartilage defects. It is desirable to have a defect filled with cartilage with smooth healing.

Limitations

Our study is not without limitations. First, a larger number of experimental animals should be used to perform International Cartilage Repair Society scoring. A defect greater than 1.5 mm could be created. Moreover, a longer follow-up period would have enabled us to better demonstrate the stages and the evolution of cartilage healing. The results of human PRF applications may not be similar to those of rats, and histologic findings may not be correlated with functional outcomes.

CONCLUSION

PRF is a reliable and effective biomaterial for use in the recovery of cartilage defects, as it contains growth factors, cellular material, and a fibrin skeleton.

Conflict of interest

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

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The European Research Journal 2019;5(2):306-310 ORIGINAL ARTICLE

Management of traumatic pneumothorax in isolated blunt chest trauma

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ABSTRACT

Objectives: Pneumothorax is an important complication of blunt chest trauma. The aim of this study was to report our experience in treatment strategy and outcomes of traumatic pneumothorax.

Methods: A total of 78 patients who developed pneumothorax due to isolated blunt chest trauma were evaluated in terms of age, gender, size of pneumothorax, treatment methods, complications and length of hospital stay. The size of pneumothorax was calculated with computer-aided volumetry.

Results: Tube thoracostomy was performed for 48 patients while observation was undertaken for 30 cases. Chest tubes were inserted in 6 patients after 24 hours following the traumatic event. A total of 8 patients who developed prolonged air leakage and hemothorax as complications underwent video-assisted thoracoscopic surgery. None of the patients developed any mortality or morbidity.

Conclusions: Traumatic pneumothorax demands prompt diagnosis and treatment. Monitoring all patients even with small sizes of traumatic pneumothorax for at least 24 hours onset of their initial assessment and applying chest tubes for cases who have pneumothorax larger than 50% at first examination should be an appropriate modality for treatment. Moreover, the minimally invasive approach of video-assisted thoracoscopic surgery benefits to overcome the complications of thoracic trauma.

Keywords: Blunt chest trauma, traumatic pneumothorax, treatment

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A pneumothorax is defined as collection of air in the pleural space. It is present in 40 to 50% of patients suffering thoracic trauma [1]. Prompt diagnosis and treatment of traumatic pneumothorax is essential for these patients.

Massive or tension pneumothorax is frequently recognized clinically before imaging. On the other hand, several studies suggest that large number of pneumothoraces diagnosed by computered tomography (CT) are missed on initial chest X-rays termed occult pneumothorax [2, 3].

Current treatment guidelines recommend urgent chest tube insertion for patients who have unstable clinical conditions and symptoms; such as hypoxia, hypotension or an impaled level of consciousness [4, 5]. However, the optimal management for stable patients continues to be debated considering that complication and failure of inapropriate interventions may rate up to 30% [6].

We report treatment methods, points demanding

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caution and outcomes in patients with traumatic pneumothorax in our institution.

METHODS

We conducted a retrospective study to clarify the treatment strategy and outcomes in patients with the diagnosis of traumatic pneumothorax. A total of 78 patients throughout 1,428 trauma cases who admitted to our emergency unit between December 2011 and April 2017 were included in the study. All cases had pneumothorax due to isolated blunt thoracic trauma.

The patients were divided into 4 groups considering the initial size of pneumothorax diagnosed via thorax CT at the initial assessment: Group A (n = 12, <10%), Group B (n = 18, 10-20%), Group C (n = 22, 20-50%) and Group D (n = 26, >50%). All the patient groups were evaluated in terms of age, gender, treatment method and length of hospital stay. Treatment method included conservative approach and chest tube insertion. Regardless of the way of approach, all patients were closely monitored applying nasal oxygen therapy at 3 L/hour and examined with daily chest X-rays. Patients under observation who developed clinical or radiological deterioration, such as oxygen desaturation or increase in the size of preexisting pneumothorax underwent tube thoracostomy urgently. All tube thoracostomies were performed under local anesthesia using 24 French (F) chest tubes by the same two thoracic surgeons.

Hospital stay revealed the time between the admittance to the emergency unit and the discharge of the patients. Cases treated via tube thoracostomy were discharged the day after chest tube removal. Complications were noted for each group of patients.

Pneumothorax was diagnosed upon CT findings for all patients. Besides, radiological studies were carried out retrospectively by the same radiologist using the same CT and CT computer. Size of the pneumothorax was calculated with the guidance of computer-aided volumetry (CAV).

RESULTS

We have 48 (61.5%) male and 30 (38.5%) female patients with a median age of 35.3 years (range, 6-68 years). Cause of the blunt thoracic trauma was car accident in 34 (43.6%) , fall from heights in 24 (30.8%), beating in 14 (17.9%) and jamming under heavy objects in 6 (7.7%) patients. Accompanying thoracic injuries were pulmonary contusion in 34, fractured ribs in 23, clavicle fracture in 8, scapula fracture in 3 and combination of these pathologies in 14 cases , respectively. Concerning that additional surgery and healing period were necessary, patients who had injuries to thoracic vertebra or diaphragm were not included in this study. Etiology and accompanying injuries are given in Figure 1.

Pneumothorax was right sided in 34 (43.6%) , left sided in 37 (47.4%) and bilateral in 7 (9%) patients. A

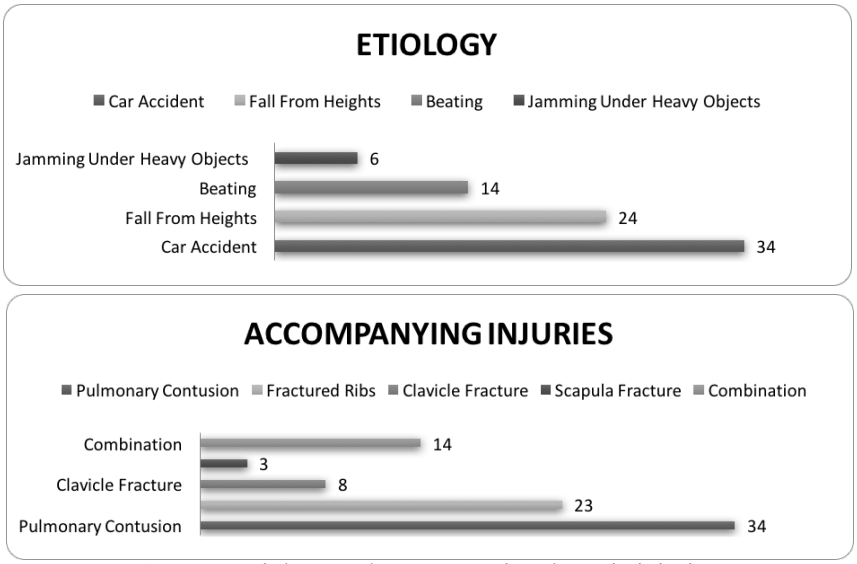

Figure 1. Etiology and accompanying thoracic injuries

Table 1. Distribution of patients

Parameters	Group A	Group B	Group C	Group D	Total
Age (mean, years)	28.4	41.3	32.6	38.8	35.3
Gender (n) (male/female)	9/3	12/6	11/11	16/10	48/30
Treatment (n) (Observative / Chest tube)	10/2	10/8	10/12	-/26	30/48
Hospital stay (mean, days)	1.8	4.1	7.4	10.6	6.1

Group A = the initial size of pneumothorax < 10%, Group B = the initial size of pneumothorax of 10-20%, Group C = the initial size of pneumothorax of 20-50%, Group D = the initial size of pneumothorax > 50%

total of 48 patients underwent tube thoracostomy whilst conservation was undertaken for remaining 30 cases.

Ten patients in Group A were discharged without any surgical procedures. However, 2 patients of this group had chest tubes in 24 hours after their admittance due to the increasese in size of pneumothorax. Group B had observative approach for 10 and tube thoracostomy for 8 patients as the treatment method. Ten patients of Group C were only monitored carefully and the remaining 12 cases of this group underwent tube thoracostomy. Similarly, 2 patients in each of Group B and C had their chest tubes in the next 24 hours following their admittance. Taking a stand on corrupted clinical status, all the patients in Group D were treated with tube thoracostomy in sequel of their initial evaluation in the emergency unit.

Mean hospital stay was 1.8 days for Group A, 4.1 for Group B, 7.4 for Group C and 10.6 for Group D, respectively.

Group C had 2 and Group D had 4 patients who underwent video-assisted thoracoscopic surgery (VATS) with the diagnosis of prolonged air leakage due to parenchymal damage. Moreover, VATS was performed for 2 patients in Group D for hemothorax which emerged subsequently as a delayed complication of fractured ribs.

A total of 6 (12.5%) patients of all tube thoracostomies were treated with additional chest tubes upon the diagnosis of subcutaneous emphysema, malposition of the chest tube and failure in the expansion of the lung. Further surgical intervention was not necessary for these cases. Data related to the general distribution of patients are given in Table 1.

None of the patients developed mortality or morbidity. One patient in Group A and 2 patients in Group C developed recurrence of pneumothorax after the tenth day following discharge, recognized on chest X-ray but showing no related clinical signs and underwent tube thoracostomy again.

DISCUSSION

Management of traumatic pneumothorax is still debatable concerning the watch or act strategy for its treatment. Percentage of the initial traumatic pneumothorax and the general medical status of the patients should be accepted to be the main points for setting up decisions. Although some of the recents studies in the literature advocate tube thoracostomies for pneumothoraxes larger than 20%, our paper suggests that one third of the cases in the same aspect require chest tubes.

Presence of pneumothorax following blunt trauma is related to the severity of the injury. Pnemumothorax may appear upon the laseration of the visceral pleura secondary to fractured ribs or rupture of the alveoli resulting from sudden compression of the chest [7, 8].

Diagnosis of pneumothorax becomes absolute on clinical and radiological findings. Symptoms of a pneumothorax include chest pain, shortness of breath, rapid heartbeat and breathing which may be confused with other pathologies of a trauma patient. Auscultation of the chest reveals decreased or abscent breath sounds over the affected lung. Diagnosis shall be confirmed by chest X-ray, CT or chest ultrasonograhy (US) since the clinical diagnosis of pneumothorax based solely on auscultation is incorrect in 20-30% of cases [9]. Although some authors reported that chest US was more sensitive and accurate than chest X-rays, CT is still accepted to be the reference standard in detection of traumatic pneumothoraces [5, 7, 9]. Chest X-rays are also

appropriate and cost-effective to be scheduled daily for the follow-up of patients.

Success rate of conservative approach in small and anteriorly localized pneumothoraces is 81% [9]. However, it is a well known fact that mechanical ventilation increases the risk of size increment of existing pneumothorax or development of tension pneumothorax in 20% of small pneumothoraces [10]. Recent papers supported that chest tubes are unnecessary for patients who developed less than 2 fractured ribs or pneumothorax smaller than 20% in size or who did not require mechanical ventilation [11-13]. Our current study included 30 patients with a pneumothorax less than 20% in size. Of these, 10 (33%) cases underwent tube thoracostomy proving that size of the initial pneumothorax does not make an exact criteria for treatment. Regardless of the initial size of traumatic pneumothorax, all the patients should be carefully observed in means of increasing or newly developing pneumothoraces for 24 hours at least to reach a final decision for discharge.

Although numerous studies have reported that a chest tube can be used as the sole treatment for traumatic pneumothorax, persistent air leak or failure in lung expansion in 4-23% of cases sometimes require additional treatment and prolonged hospital stay. Furthermore, tube thoracostomy may bring along complications such as nonfunctioning or malposition of chest tube, wound infection, abdominal or thoracic injury and vascular trauma in 2-10% of the patients [4-6]. Advantages of minimally invasive surgery offered by VATS have oriented many institutions to accept this method as the preferred treatment for patients with chest trauma [14]. As noted above, 8 patients with the diagnosis of prolonged air leakage and hemothorax underwent VATS without encountering any further complications or morbidity.

CONCLUSION

Pneumothorax is a life-threatening complication of chest trauma which requires immediate diagnosis and treatment. In our experience, rigorous observation of the trauma patients both clinically and radiologically avoided mortality. We believe that all patients with even small sizes of pneumothoraces shall be monitored for at least 24 hours after the traumatic event, considering that most of the complications occur within this period. Detoriation in clinical status and increase of pneumothorax identified by radiological follow-up studies shall alert surgeons to insert chest tubes. We also suggest that cases who have pneumothorax larger than 50% at their first assessment shall urgently undergo tube thoracostomy. Moreover, our surgical experience with VATS in trauma patients support it as an effective modality for the treatment of complicated thoracic trauma.

Conflict of interest

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Are nasal steroids effective in children with adenoid hypertrophy?

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ABSTRACT

Objectives: Chronic nasal obstruction is a common disease of childhood. Adenotonsillar hypertrophy plays an important role in obstructive sleep apnea. The topical use of the aerosolized forms of corticosteroids therefore seems the most appropriate route to decrease systemic side effects. The aim of our study is to demonstrate the effect of topical mometasone furoate especially on the adenoid volume in patients without any allergic story.
Methods: The study group consisting of 30 males and 25 females was administered topical nasal mometasone furoate steroid treatment. The 20 patients were in the control group where saline solution (0.9% NaCl) treatment was administered consisted of 12 males and 8 females. Nasopharyngeal X-rays before treatment revealed that 25 patients were Grade 2 and 30 patients were Grade 3 according to the Fujioka method.
Results: Flexible endoscopy performed before the treatment revealed that 20 patients were Grade 2, 11 patients were Grade 3 and 24 patients were Grade 4. Nasal endoscopies performed after 6 weeks of intranasal topical steroid therapy revealed that 45 patients were Grade 1 and 10 patients were Grade 2. A statistically significant difference was present between endoscopic grades before and after treatment ($p < 0.0001$). Nasal endoscopies performed after 6 weeks in control group receiving saline solution treatment revealed Grade 2 in 7 patients, Grade 3 in 10 patients and Grade 4 in 3 patients. There was no statistically significant difference between in the prior and later grades of the control group ($p = 0.3125$).
Conclusions: We believe that the use of intranasal steroids (mometasone furoate) for 6 weeks in patients with pediatric chronic nasal obstruction due to adenoid hypertrophy may be an effective treatment modality in alleviating symptoms and decreasing adenoid volume without causing systemic side effects.

Keywords: Nasal steroids, adenoid hypertrophy, flexible endoscopy, nasopharyngeal X-rays, Fujioka method

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Chronic nasal obstruction (CNO) is a common disease of childhood with an estimated prevalence of 2-3% in the healthy pediatric population [1]. Adenotonsillar hypertrophy plays an important role in obstructive sleep apnea (OSA) pathophysiology and reaches its peak incidence between the ages of 2 and 8 years [2, 3]. OSA is the result of increased airway resistance during sleep and characteristically manifests as repeated arousals, hypercapnia, episodic snoring, and periods of oxyhemoglobin desaturation [4]. Ade-

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notonsillar hypertrophy is the most common cause of OSA in preschool children [5]. Allergic exacerbations give rise to the hypertrophy of adenoid tissue but repeated upper respiratory tract infections(URTIs) may also be the cause.

The hypertrophied lymphoid tissue may cause many pathological conditions including snoring, sleep apnea, sinusitis otitis media with effusion and adenoid face [6]. If left untreated, OSA may cause many serious problems such as cognitive and behavioral disorders, systemic and pulmonary hypertension, enuresis, and developmental delay [7]. Adenoidectomy is the definitive treatment modality for upper airway obstruction caused by adenoid hypertrophy but decongestant nasal drops have also been used for its symptomatic management [8].

Structural and neuromuscular pathologies may also cause CNO but the main factor in the pathogenesis of pediatric CNO is the size of the tonsils and adenoid tissue making their surgical excision the primary choice of treatment [9, 10]. Postoperative residual OSAS is found in 20% of the children who have undergone adenotonsillectomy [11].

The nonsurgical treatment options for pediatric CNO are attracting increasing attention due to the potential complications of adenotonsillectomy. Anti-allergic drugs have been used from time to time despite the lack of adequate evidence to support their usage, as allergy is just one of the reasons for obstruction [12]. The efficacy of oral steroids in relieving the obstructive symptoms of adenoid hypertrophy is reported in the literature. They also reduce the size of the adenoid tissue significantly. However, their long-term use is limited due to the significant side effects [12]. The topical use of the aerosolized forms of corticosteroids therefore seems the most appropriate route to decrease systemic side effects, since there will be a minimal amount of systemic absorption from the upper airway [13]. The 6-week administration of triamcinolone acetonide aqueous nasal spray to children with allergic rhinitis aged 6 to 12 years has been reported to have no significant impact on adrenocortical function. Treatment with mometasone furoate aqueous nasal spray (200 micrograms once a day) for 14 days was shown to be safe and well-tolerated in children [14].

Local and systemic inflammatory markers and proinflammatory cytokines, which trigger lymphoid tissue proliferation, are increased in children with adenotonsillar hypertrophy. Systemic or topical anti-inflammatory agents have therefore been recommended to prevent the potential tonsillar hypertrophy in these patients [15, 16]. Topical nasal corticosteroids can alleviate CNO symptoms and nasal obstruction as well as reduce the size of the adenoid tissue [17, 18]. However, the optimal dose and duration of treatment with nasal steroid agents is not clearly defined yet.

The current inadequate evidence on the efficacy of intranasal steroids in children with adenoid hypertrophy and nasal obstruction led us to conduct this study. With this study we evaluated the efficacy of Mometazon furoat (topical nasal steroid) on adenoid hypertrophy in children.

METHODS

Patients

The study was conducted a randomized placebo-controlled children with adenoid hypertrophy who presented to Otolaryngology and Pediatrics outpatient clinics of our hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Institutional review board (IRB) was taken for the patients (Number: 66519339- 900-01/1304). Informed consent was obtained from all individual participants included in the study. Adenoidectomy operation under general anesthesia was suggested as the main treatment of adenoid hypertrophy to all parents or patients and they were informed about the possible complications of the operation. Mometazon furoat as topical nasal steroid was prescribed for the patients who rejected the surgery and for the relief of symptoms in case of preoperative severe symptoms. All the patients included in the study had a complaint of snoring, cessation of breathing and frequent arousals during sleep. They were aged between 6 to 12 years old.

The diagnosis of adenoid hypertrophy was based on endoscopic nasopharyngeal findings (the occlusion degree of the choana with adenoid tissue) and lateral cephalometric X-ray findings (the thickness of soft tissue density in nasopharyngeal airway) in patients

suspected of having adenoid hypertrophy (i.e., having nasal obstruction without septoconchal pathology, snoring, and/or nasal discharge).

The inclusion criteria were as follows:

1. Patients aged between 6 to 12 years old,
2. With a diagnosis of adenoid hypertrophy without tonsillar hypertrophy for a minimum of 12 months,
3. With a follow-up period of 2 months and per 2-week intervals,
4. No sign of improvement despite medical treatment with antibiotics under parental control.

The exclusion criteria were as follows:

1. Use of any nasal or systemic steroid within the past 1 year.
2. Use of any nasal decongestant or anti-allergic medication within the past 2 weeks.
3. History of upper respiratory tract infection within the past 2 weeks.
4. History of one or more of the following conditions: genetic craniofacial, or neuromuscular syndromes, chronic epistaxis, immune disease, asthma, nasal surgery, septal perforation, nasal trauma within the last 3 months and hypersensitivity to mometazon furoat.

The patients with a diagnosis of adenoid hypertrophy who were candidates for surgery with a 6-weeks follow-up saline solution (3-5 drops, three times/day) treatment were included in the study as control group.

After taking a detailed medical history, the symptoms were graded according to the severity of patient's clinic. Pre-treatment a lateral cephalometric X-ray graph and a nasopharyngoscopic image ("MSI Flexible Nasopharyngoscope, Germany" attached to "Karl-Storz Telecam SL II, Tuttlingen, Germany" camera) were obtained from every patient. The hypertrophy of adenoid tissue was graded. Follow up examinations were based on nasopharyngoscopic records. Nasopharyngoscopic examination records were repeated after medical treatment. The difference between pretreatment and post treatment adenoid tissue enlargement were compared.

Diagnostic Criteria

Symptoms

Nasal obstruction, snoring, and nasal discharge

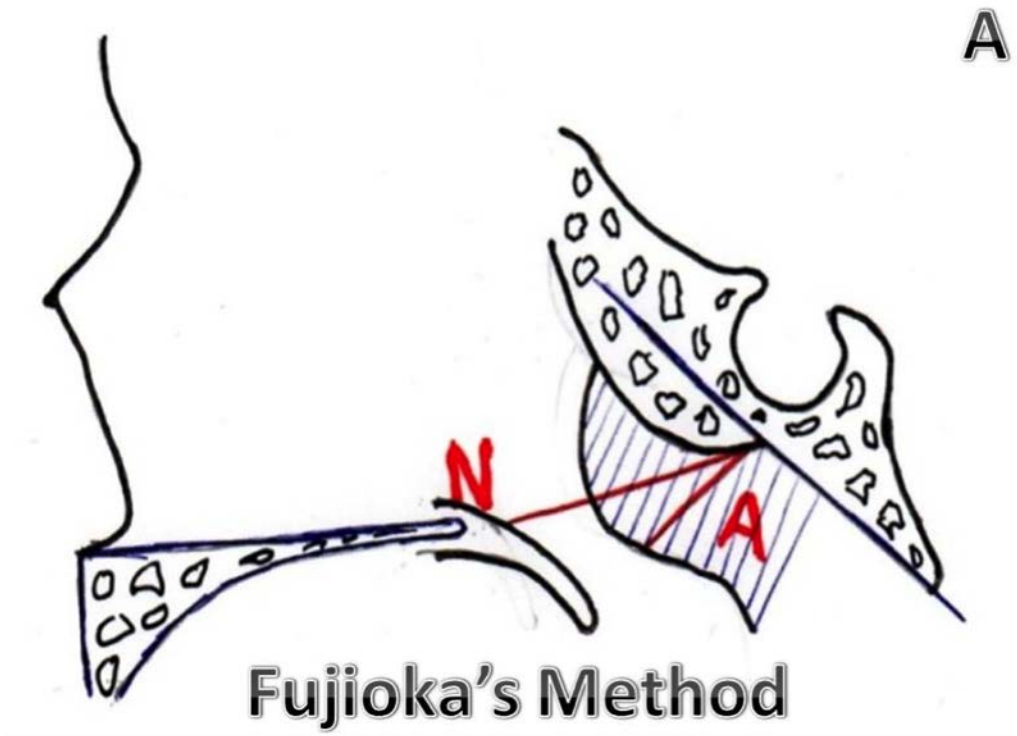

Figure A. Adeno/nasopharyngeal ratio according to the Fujioka method.

were graded according to the frequency reported by the parents (Grade 0: never seen, Grade 1: seen during URTI, Grade 2: frequently seen, Grade 3: always occurs).

Nasopharyngeal X-ray

Adenoid tissue enlargement was graded according to the Adenoidal-nasopharyngeal ratios (ANR). The distance of adenoid tissue density was measured along a line dropped perpendicularly from point of maximal convexity of adenoid tissue to its point of intersection with line drawn along the straight part of the anterior margin of the basiocciput. Then the nasopharyngeal space was measured as the distance between posterior superior edge of hard palate and the anterior inferior edge of the spheno basioccipital synchondrosis. The ANR was obtained by dividing the measurement for adenoid tissue density by the value for nasopharyngeal space in millimeters as described by Fujioka *et al.* [19]. It was rated as: Grade 1: > 6 mm, Grade 2: 4-6 mm, and Grade 3: < 3 mm. Nasal endoscopy: Performed with a Flexible Nasopharyngoscope following topical anesthesia with 4% lidocaine without any decongestant. Graded according to the rate of obstruction of the choanal aperture by the adenoid tissue as Grade 1: 25%, Grade 2: 50%, Grade 3: 75%, and Grade 4: 100% occlusion. Adeno/nasopharyngeal ratio according to the Fujioka method has been indicated in Figure A.

The children with a diagnosis of adenoidal hypertrophy were then prescribed topical mometasone furoate for 6 weeks, once a day, two puff to each nostril (50 mcg/puff), comprising a daily total dose of 200 mcg. The nasal endoscopic evaluations were repeated 6 weeks after the initial diagnostic workup. Operation were not recommended to the control and study groups with grade 2 adenoid hypertrophy, however medical treatment was given.

Statistical Analysis

The data were analyzed with the SPSS for Windows v.16.0 software by IBM, USA.using the appropriate nonparametric tests for nominal and ordinal data. In all analytical evaluations, $p < 0.05$ was the significance limit value.

RESULTS

The study consisted of 75 patients (42 male, 33 female) with adenoid hypertrophy aged between 6 to 12 years old. Demographic characteristics and Body Mass Index (BMI) and Percentiles of the study group and the control group have been indicated in Table 1. Fifty-five patients (30 male, 25 female) who had topical nasal steroid accepted as study group and 20 patients (12 male, 8 female) who had preoperative follow up record for 6-weeks were accepted as control group. Endoscopic appearances before and after topical steroid treatment were indicated in Figures B, C and D.

The study group consisting of 30 males and 25 females was administered topical nasal Mometasone Furoate steroid treatment. Nasopharyngeal X-rays before treatment revealed that 25 patients were Grade 2 and 30 patients were Grade 3 grade according to the Fujioka method. Flexible endoscopy performed before the treatment revealed that 20 patients were Grade 2, 11 patients were Grade 3 and 24 patients were Grade 4. Nasal endoscopies performed after 6 weeks of

Table 1. Demographic characteristics and BMI and percentiles of the study group and the control group

	Study Group (n = 55)	**Control Group (n = 20)**
Age (year)	7.92 ± 1.81 (6-12)	7.80 ± 1.36 (6-11)
Gender (M/F)	30/25	12/08
Height (cm)	125.47 ± 11.30	123.15 ± 6.89
Weight (kg)	28.72 ± 7.09	27.55 ± 5.88
BMI	17.94 ± 1.58	17.95 ± 1.94
Percentile	77.89 ± 16.88	78.95 ± 13.83
BMI as a multiple of the mean BMI	1.11 ± 0.07	1.10 ± 0.08

BMI = Body Mass Index, F = Female, M = Male

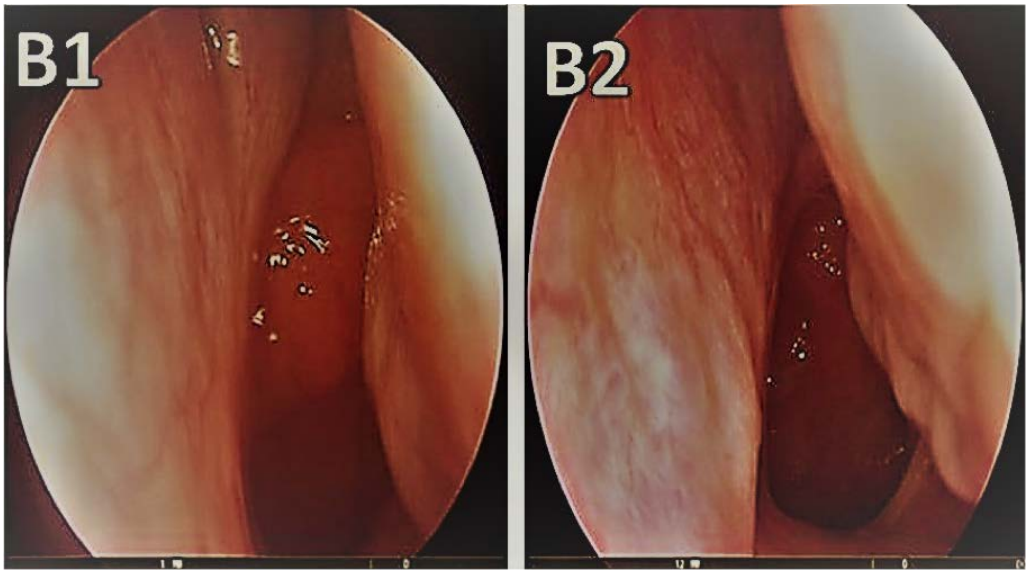

Figure B. Endoscopic appearance before (B1) and after (B2) topical steroid treatment.

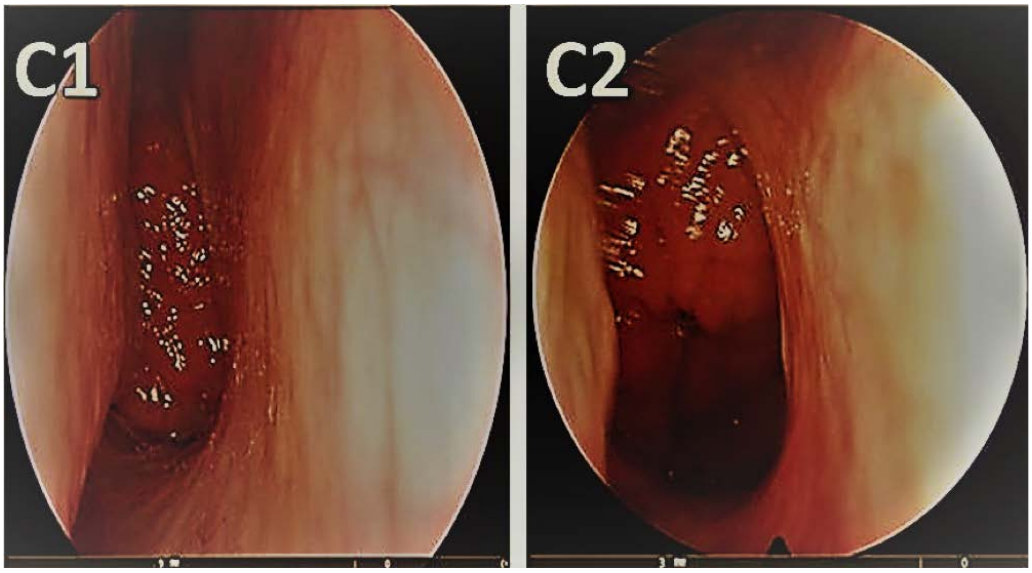

Figure C. Endoscopic appearance before (C1) and after (C2) topical steroid treatment.

intranasal topical steroid therapy revealed that 45 patients were Grade 1 and 10 patients were Grade 2. Nasopharyngeal X-rays were not requested for follow-up to avoid the additional harmful effects of X-rays. A statistically significant difference was present between endoscopic grades before and after treatment ($p < 0.0001$) (Table 2). Non-severe epistaxis was observed in three patients who administrated topical steroid therapy.

The 20 patients in the control group where saline solution (0.9 % NaCl) treatment was administered consisted of 12 males and 8 females. Nine patients was Grade 2 and Grade 3 in 11 patients on nasopharyngeal X-rays at first presentation according to the Fujioka method in this group. Flexible nasal endoscopy performed simultaneously revealed that there were Grade 2 in 6 patients, Grade 3 in 9 patients and Grade 4 in 5 patients. Nasal endoscopies performed after 6 weeks in control group receiving saline solution treatment revealed Grade 2 in 7 patients, Grade 3 in 10 patients and Grade 4 in 3 patients. There was no statistically significant difference between in the prior and later grades of the control group ($p = 0.3125$) (Table 2).

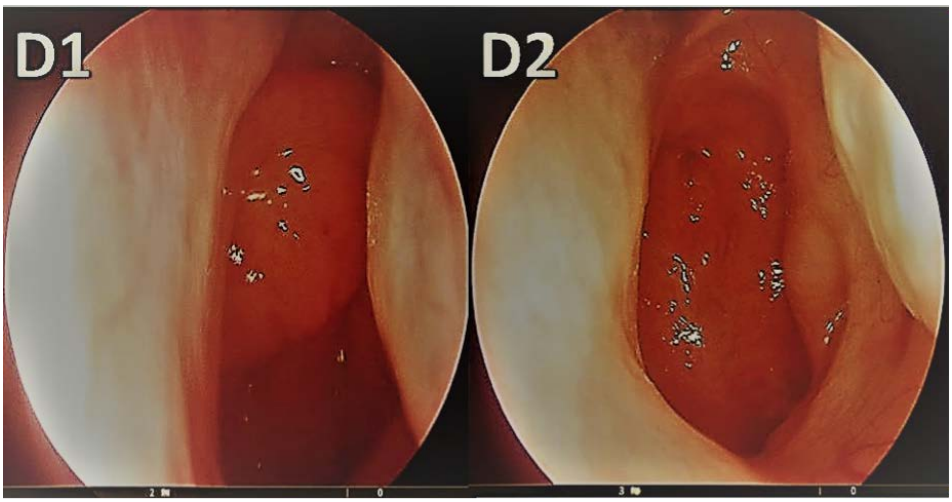

Figure D. Endoscopic appearance before (D1) and after (D2) topical steroid treatment.

Table 2. First and second endoscopic grades in the study group and in the control group

Grade n (%)	Study (n = 55) First	Study (n = 55) Second	Control (n = 20) First	Control (n = 20) Second
Grade 1	0 (0%)	45 (81%)	0 (0%)	0 (0%)
Grade 2	20 (36%)	10 (18%)	6 (30%)	7 (35%)
Grade 3	11 (20%)	0 (0%)	9 (45%)	10 (50%)
Grade 4	24 (43%)	0 (0%)	5 (25%)	3 (15%)
Endoscopic grade (mean ± SD)	3.07 ± 0.89	1.18 ± 0.38	2.95 ± 0.75	2.80 ± 0.69

*Wilcoxon test (paired samples).

DISCUSSION

Demain and Goetz [20] used beclomethasone nasal spray for 8 weeks (338 microgm/day) followed by a lower daily dose (168 microgm/day) in the next 16 weeks for the treatment of adenoid hypertrophy and reported a decrease in adenoid size in all the study subjects. A history of atopy was reported in previous studies but they excluded those with such a history in this study [20]. We treated 55 children between the ages of 6 and 12 years with mometasone furoate nasal spray at a daily dose of 200 mcg for 4 weeks [20]. Lepcha *et al*. [21] reported no significant improvement in X-ray and endoscopy findings of subjects administered intranasal topical beclomethasone for 8 weeks while there was a 6% improvement in nasal congestion. However, there was an improvement in adenoidal obstruction and clinical findings when compared with placebo after 24 weeks of treatment [21]. In our patients, we also observed a decrease in the endoscopic findings of adenoid tissues.

Kheirandish-Gozal and Gozal [4] showed intranasal budesonide to decrease the severity of respiratory distress and the size of the adenoids, although mildly, with 6 weeks of use in children with mild OSA. Brouillette *et al*. [17] observed an improvement in the respiration of patients despite no noticeable change in the adenoid tissue mass after 6 weeks of treatment with intranasal fluticasone before T&A surgery in patients with moderate-to-heavy OSA. No significant change was found in the size of adenoids and tonsils and in the symptoms as reported by the parents but there was a significant reduction in apnea and hypopnea frequency among children treated with fluticasone.

Similar positive effects in OSA patients were reported in later studies. It is interesting that the effect on OSA symptoms continued even after the treatment was discontinued during 9 months of follow-up in the Alexopoulos *et al*. [18] study on 27 patients. The general results regarding OSA severity are strikingly similar despite differences in patient selection criteria

and treatment methods, indicating that nasal corticosteroids can be used as the first treatment option in pediatric OSA. However, there is no clear consensus on the appropriate steroid dosage and treatment duration at present [16, 22]. Junk *et al*. [23] have reported a significant improvement in loud snoring, breath holding, frequent awakening from sleep, breathing from the mouth, URTI frequency and nasal discharge after 4 weeks of intranasal mometasone furoate treatment in children. We also chose mometasone furoate among the various steroid nasal sprays commercially available for this study. The reason was the absence of reports on any negative effect of this spray on the nasal mucosa or side effects related to the hypothalamus-pituitary-adrenal axis and growth with long-term use [24]. The systemic effect of the drug is lower than other steroids after topical administration [25]. Berlucchi *et al*. [26] recently evaluated the effectiveness of 40 days of mometasone furoate treatment in adenoid hypertrophy and found symptomatic improvement in 77.7% of the patients. Fujioka *et al*. [19] described the A/N ratio as an indicator of adenoid hypertrophy in 1979 and the method has been used in many studies. Jung *et al*. [23] showed that the A/N ratio on lateral neck graphs decreased in 22 (71%) of 31 children after 4 weeks of treatment ($p = 0.006$). Cengel and Akyol [27] reported shrinkage of adenoid tissue in 67.2% of the children after 6 weeks of treatment with intranasal mometasone furoate treatment in 2006. However, there is no proven mechanism explaining adenoid shrinkage. The presence of inflammation in the soft palate mucosal surface has been shown in OSA patients [28]. Jung *et al*. [23] thought that this type of upper respiratory tract inflammation could also involve the adenoid mucosa and that 4 weeks of local steroids could decrease this inflammation, causing the adenoids to shrink.

There are several methods to evaluate the size of the adenoids causing sleep-disordered breathing. The most commonly used techniques are lateral neck radiograph and direct videorhinoscopy. Mlynarek *et al*. [29] reported video rhinoscopy to be more useful for the evaluation of symptom severity in 2004. However, the nasopharyngeal examination of small children with fiberoptic devices can be difficult. The above results indicate that intranasal steroids can be used to reduce symptoms in children with sleep-disordered breathing, regardless of allergy or sinusitis. The results of our study were also consistent with the literature. However, a limitation of our study is the lack nasal airway patency evaluation with objective methods such as acoustic rhinometry.

CONCLUSION

We believe that the use of intranasal steroids (mometasone furoate) for 6 weeks in patients with pediatric chronic nasal obstruction due to adenoid hypertrophy may be an effective treatment modality in alleviating symptoms and decreasing adenoid volume without causing systemic side effects. Placebo-controlled studies are required to investigate the long-term effect of short-term steroid use in the treatment of pediatric sleep disorders in the future.

Conflict of interest

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

Financing

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

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The European Research Journal 2019;5(2):319-325 ORIGINAL ARTICLE

Cu/Zn superoxide dismutase enzyme immunoreactivity in the stomach tissue of rats fed with mussels (Mytilus galloprovincialis)

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ABSTRACT

Objectives: Mussels accumulate heavy metals in their tissues. Although there are few data about the toxicity of seafood that is exposed to environmental pollution, there are no animal studies about the gastric toxicity of mussels grown in the Dardanelles. The antioxidant Cu/Zn superoxide dismutase (Cu/Zn SOD) enzyme catalyzes the hydrogen peroxide dismutation of superoxide radicals and removes the effects of free radicals which cause oxidative stress. The purpose of the study was to demonstrate the Cu/Zn SOD in the stomach tissues of rats which are fed with mussels that are collected from the Çamburnu region of the Dardanelles.

Methods: A total of 24 male Wistar albino rats were randomly divided into four groups: Group 1 (n = 6), control group fed with standard rat food; Group 2 (n = 6), 75% mussels and 25% standard rat food daily; Group 3 (n = 6), 75% mussels and 25% standard rat food every two days; and Group 4 (n = 6), 75% mussels and 25% standard rat food every three days. To detect Cu/Zn SOD localization in the tissues, the LAB-SA Detection System was used.

Results: Cu/Zn SOD enzyme immunoreactivity was not detected in Group 1 and in samples without Cu/Zn SOD primer antibody. Cu/Zn SOD enzyme immunoreactivity was detected 82% in Group 2, 79% in Group 3, and 61% in Group 4. There was statistically significant difference between the Cu/Zn SOD immunoreactivity of epithelial cells in the gastric mucosa of the rats in the experimental and control groups ($p< 0.05$).

Conclusions: Determination of the increase of Cu/Zn SOD enzyme in the gastric mucosa of mussel-fed rats that we used in our study suggests that it triggers the antioxidant defense mechanism against mussel toxicity.

Keywords: Immunohistochemistry, Dardanelles, mussel, Cu/Zn superoxide dismutase, stomach

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Heavy metals, such as mercury (Hg), cadmium (Cd), lead (Pb), copper (Cu), nickel (Ni), zinc (Zn), chromium (Cr) and arsenic (As), have gained significance because they are toxic on certain concentrations and can increase their concentration during transition from one organism to another. Mussels are living organisms that are fed by filtering organic matter and phytoplankton in the water. The mussels can also filter toxic substances during water filtration. Pollution travels along food chains and can harm all living things, including humans [1, 2]. In sea chestnuts growing in Dardanells, the values of aluminium (Al), Zn, and iron (Fe) in samples taken from Gelibolu Hamzakoy station are high. Al and Fe values are higher in samples taken from Çardak region of the Dardanelles. Al, Fe and Zn values are higher in

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samples taken from Umurbey region of the Dardanelles. Al, Fe and Zn values are higher in samples taken from Çamburnu region of the Dardanelles [3]. International Agency for Research on Cancer (1987) has explained that heavy metals may affect and cause chronic degenerative changes and, in some cases, teratogenic and carcinogenic effects, especially by affecting the nervous system, liver and kidneys [4].

Heavy metals are toxic because they may have cumulative deleterious effects that can cause chronic degenerative changes [5], especially to the nervous system, liver, and kidneys, and, in some cases, they also have teratogenic and carcinogenic effects [4]. The mechanism of toxicity of some heavy metals still remains unknown, although enzymatic inhibition, impaired antioxidants metabolism, and oxidative stress may play a role. Heavy metals generate many of their adverse health effects through the formation of free radicals, resulting in DNA damage, lipid peroxidation, and depletion of protein sulfhydryls (e.g., glutathione) [6].

Cu/Zn superoxide dismutase (Cu/Zn SOD) enzyme is believed to play a major role in the first line of antioxidant defence [7]. SOD is the antioxidant enzyme that catalyses the dismutation of the highly reactive superoxide anion to O_2 and to the less reactive species H_2O_2. Peroxide canstroyed by CAT or GPX reactions [8-10]. The antioxidant enzyme SOD, which provides an important means of cellular defence against free radical damage [11].

Antioxidant enzymes are capable of stabilizing, or deactivating free radicals before they attack cellular components. They act by reducing the energy of the free radicals or by giving up some of their electrons for its use, thereby causing it to become stable. In addition, they may also interrupt with the oxidizing chain reaction to minimize the damage caused by free radicals. For the past decade, countless studies have been devoted to the beneficial effects of antioxidant enzymes. It has been found that a substantial link exists between free radicals and more than sixty different health conditions, including the aging process, cancer, diabetes, Alzheimer's disease, strokes, heart attacks and atherosclerosis. By reducing exposure to free radicals and increasing the intake of antioxidant enzyme rich foods or antioxidant enzyme supplements, our body's potential to reducing the risk of free radical related health problems is made more palpable [12].

The purpose of the study was to demonstrate Cu/Zn SOD immunoreactivity in the stomach tissues of rats which are fed with mussels that are collected from the Çamburnu region of the Dardanelles (Çanakkale, Turkey) (Figure 1).

METHODS

Animal Model

A total of 24 male Wistar albino rats, weighing 290-310 g, were used in the study. The study protocol was approved by the Çanakkale Onsekiz Mart University Ethical Council of Animal Research

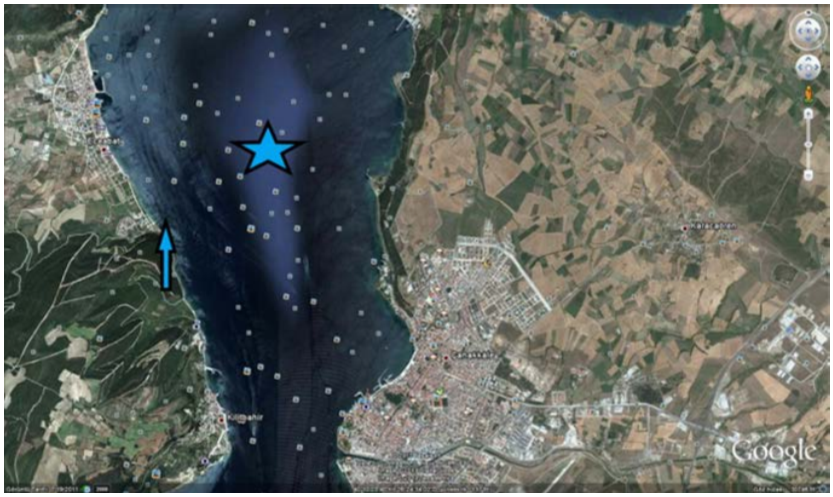

Figure 1. The area where the mussels are collected. Star shows Dardanelles. Arrow shows Çamburnu region (Çanakkale, Turkey).

(Protocol number-2010/09-03). The rats were kept for 30 days under appropriate conditions of temperature/humidity and a 12-h light cycle while being provided sufficient water and feed. The rats were randomly selected and divided into 4 groups: Group 1 (n = 6), control group fed with standard rat food; Group 2 (n = 6), 75% mussels and 25% standard rat food daily; Group 3 (n = 6), 75% mussels and 25% standard rat food every two days; and Group 4 (n = 6), 75% mussels and 25% standard rat food every three days.

Rats were fed twice daily for 30 days at 15% of their weight every morning and evening at the same time. The mussels given as food to the rats were removed from Çamburnu region in the Dardanelles (Figure 1). Average 100±10 g weight were selected. After the beaks were overcooked, the meat broke off and the meat at 100 degrees was dried.

It was weighed into each rat's weight and 10 mg/kg intraperitoenal ketamine hydrochloride (Ketalar, Eczacibasi, Istanbul, Turkey), and 20 mg/kg of xylazine 2% (Rompun, Bayer Turkey Pharmaceutical Ltd., Istanbul, Turkey) were anesthetized. The rats were anesthetized and then sacrificed. After the rats have received the stomachs other organs were also taken for further research.

Histological Evaluation

The stomach tissues were maintained in immunofix (Leica) for 24 hours for histopathological examination. The paraffin embedded stomach tissues were stained with hematoxylin and eosin (H&E) at a thickness of 5 microns. Immunohistochemical staining method was applied by cutting the paraffin embedded stomach tissues 3 microns in thickness.

The LAB-SA Detection System, (Histostain-Plus Bulk Kit, Invitrogen) was applied to determine immunohistochemical localization of Cu/Zn SOD enzyme in tissues. Sections taken from paraffin blocks were deparaffinized and rehydrated. Subsequently, tissue samples were resuspended in 0.2% Triton × 100 (Santa Cruz Biotechnology) solution prepared with Phosphate Buffer Saline (PBS, Invitrogen) for 5 min. were kept. This allowed better passage of solutions from the pores in the cell and nucleus membranes. The tissue samples confined to the Pap pen were washed three times with PBS for 3 min. Subsequently, 3% H_2O_2 was applied to the sections to block endogenous peroxidase activity. The sections were incubated in citrate buffer (0.1 M, pH: 6.0) in the microwave (800 watt, 10 min) for antigen retrieval, and the samples were washed with phosphate buffer solution (PBS, 0.1 M, pH: 7.2). After the samples had been incubated in the blocking buffer for 10 min, they were washed with PBS. Next, slides were incubated with polyclonal rabbit anti-superoxide dismutase (Cu/Zn SOD1, Enzo Life Sciences) antibody, which was diluted 1:50 for the stomach tissue, for an hour at room temperature in the humidity chamber, and they were then washed with PBS. Afterwards, biotinylated secondary antibody was applied to the samples for 30 min (Ultravision Detection System, Thermo Scientific, Fremont, USA). Then the samples were washed with PBS again and incubated with Broad Spectrum Antibody (Invitrogen, USA) for 30 min. After washing the samples, diaminobenzadine-tetrahydrochlorid (DAB, Invitrogen Corporation) was applied to them. Negative control was used to determine specific Cu/Zn SOD immunoreactivity, and hematoxylin stain was used as a nuclear counter stain.

Dye samples were evaluated on the Zeiss AXIO Scope 1 brand research microscope. Analysis of Cu/Zn SOD immunoreactive cells in the stomach tissue was performed using the Leica LAS V3.8 image analysis system. Five of the sections from the blocks containing the stomach tissues of all the rats in all groups were stained. From the stained sections, 1000 cells were counted and immunoreactive cells were identified among these cells. For this purpose; immunopositive cells / total cell count (1000) × 100 % = % formula were used [13-15].

Statistical Analysis

SPSS 15 version was applied for the statistical evaluation of the results obtained with the applied formula. Kruskal-Wallis test was used for nonparametric tests to determine the differences between Cu/Zn SOD immunoreactivity groups. The difference between the groups was considered significant in the results of $p < 0.05$.

RESULTS

In immunohistochemical staining with Cu/Zn SOD, a significant difference was observed in the

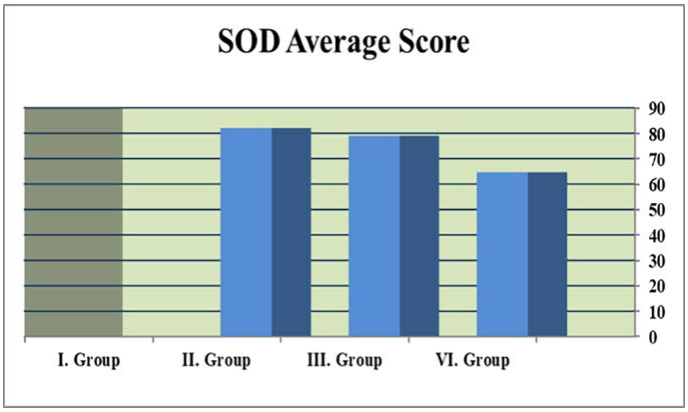

Figure 2. Cu/Zn SOD immunoreactivity ratios between control group and mussel groups.

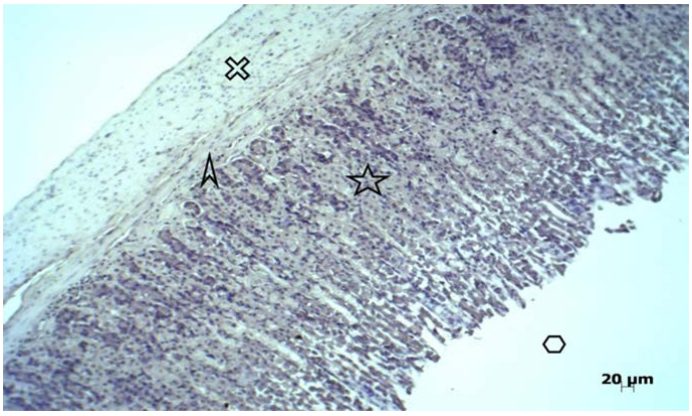

Figure 3. Group 1 (control group); standard rat diet was given every days. Rat stomach, (Cu/Zn SOD × 10, Bar = 20 µm). Hexagon = Gastric lumen, Star = Lamina propria mucosa, Pointed arrow = Lamina muscularis mucosa, Crossed = Tunica muscularis mucosa

gastric mucosal epithelial cells of the rats given mussels per day, every other day and every three days compared to rats fed with normal feed ($p < 0.05$) (Figure 2).

Cu/Zn SOD immunopositive cells could not be detected in epithelial cells of gastric mucosa of rats fed with standard rat diet (Group 1) (Figures 2 and 3). Dark brown staining in the cytoplasm of the cells was considered positive. Cu/Zn SOD immunopositive cells were found in 82% of the gastric mucosal epithelial cells of rats fed with mussels every day (Group 2) (Figures 2 and 4). Cu/Zn SOD immunopositive cells were found in 79% of the gastric mucosal epithelial cells of rats fed with mussels every other day (Group 3) (Figures 2 and 5). Cu/Zn SOD immunopositive cells were found in 61% of the gastric mucosal epithelial cells of rats fed with mussels every three days (Group 4) (Figures 2 and 6). In the epithelial cells of the gastric mucosa of the rats fed with mussels every day, Cu/Zn SOD immunopositive cells could not be detected by negative staining (Figure 7).

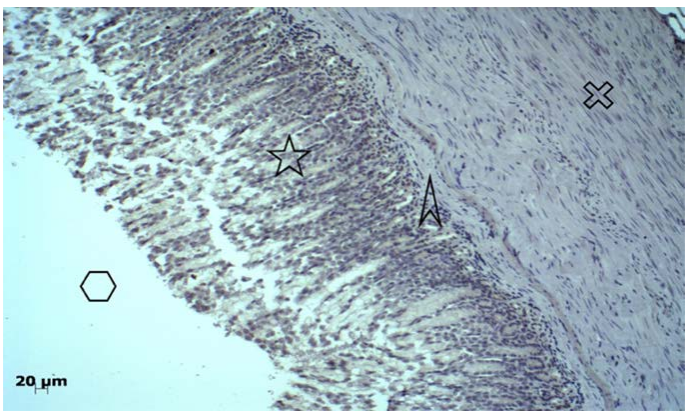

Figure 4. Group 2; 75% mussel + 25% standard rat diet standard rat feeds were given daily. Rat stomach, (Cu/Zn SOD × 10, Bar = 20 µm). Hexagon = Gastric lumen, Star = Lamina propria mucosa, Pointed arrow = Lamina muscularis mucosa, Crossed = Tunica muscularis mucosa, Arrows = Cu/Zn SOD positive gastric gland cells

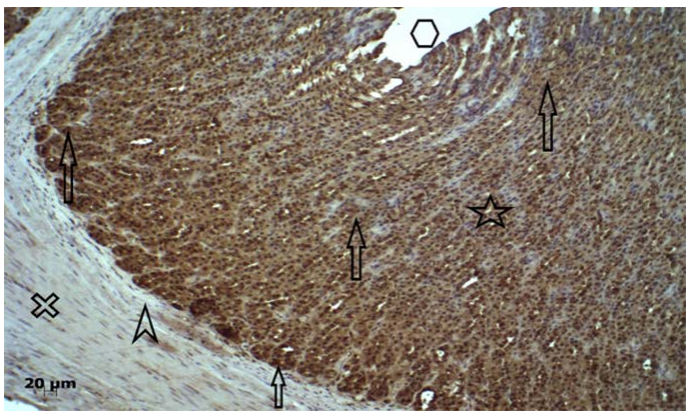

Figure 5. Group 3; 75% mussel + 25% standard rat diet was given every two days. Standard rat diet was given the other day. Rat stomach, (Cu/Zn SOD × 10, Bar = 20 µm). Hexagon = Gastric lumen, Star = Lamina propria mucosa, Pointed arrow = Lamina muscularis mucosa, Crossed = Tunica muscularis mucosa, Arrows = Cu/Zn SOD positive gastric gland cells

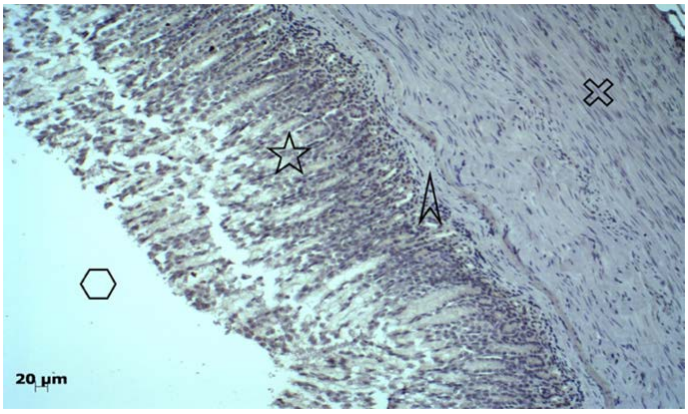

Figure 6. Group 4; 75% mussel+ 25% standard rat diet was given every three days. Standard rat diet was given the other two day. Rat stomach, (Cu/Zn SOD × 10, Bar = 20 µm). Hexagon = Gastric lumen, Star = Lamina propria mucosa, Pointed arrow = Lamina muscularis mucosa, Crossed = Tunica muscularis mucosa, Arrows = Cu/Zn SOD positive gastric gland cells

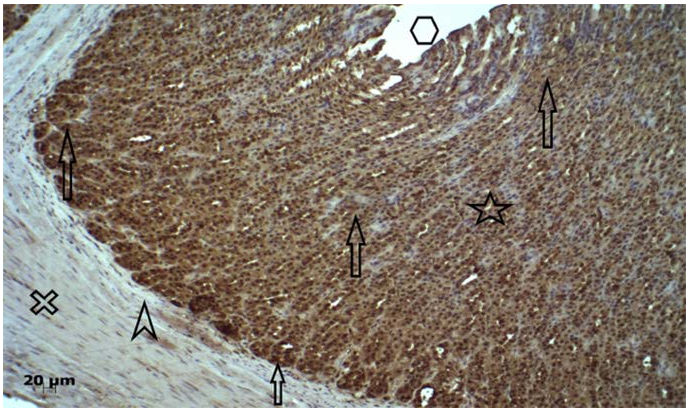

Figure 7. Group 2; 75% mussel + 25% standard rat diet standard rat feeds were given daily. Rat stomach, negative control, (Cu/Zn SOD × 5, Bar = 20 µm). Hexagon = Gastric lumen, Star = Lamina propria mucosa, Pointed arrow = Lamina muscularis mucosa, Crossed = Tunica muscularis mucosa

DISCUSSION

We have found that the levels of heavy metals in bivalve and sea water in the Dardanelles throat are higher than acceptable levels in our previous researches [3, 16, 17]. All heavy metals are potentialy harmfull to most organisms at some level of exposure and absorption. Aquatic animals are also exposed to elevated levels of heavy metals. Some trace metals are essential in low concentrations for the metabolism of animals, but in the excess all trace metala are toxic [18]. International Agency for Research on Cancer has explained that heavy metals may affect and cause chronic degenerative changes and, in some cases, teratogenic and carcinogenic effects, especially by affecting the nervous system, liver and kidneys [4]. Toxic effects of heavy metals causes oxidative stress, mitochondrial damage, cellular death and apoptosis. In chronic Pb intoxication loss of kidney function, hypertension, anemia and hyperuricemia without tofus were reported [19]. Oxidative stress plays a major role in the pathogenic of many disorders including aging, cancer, diabetes, Alzheimer's, strokes, viral infections (that cause airway epithelial inflammation), neurodegenerative processes (including cell death, motor neuron diseases and axonal injury) and infarction, and brain edema. Antioxidant enzyme plays an important role in protecting oxidative injury to the body [20].

Mussels are living organisms that are fed by filtering organic matter and phytoplankton in the water. The mussels can also filter toxic substances during water filtration. Pollution travels along food chains and can harm all living things, including humans.

Oxygen species are key participants in damage caused by virus infections (that cause airway epithelial inflammation), progression to cancer (tumor invasion, and metastasis injuring local tissues), neurodegenerative processes (including cell death, motor neuron diseases and axonal injury), and both infarction and brain edema. Therefore, tissues must be protected from this oxidative injury by expression of stress-response genes and genes encoding antioxidant enzymes and activation of other related transcriptional regulatory proteins. Those abnormalities appeared in the cellular regulation and expression of antioxidant enzymes play a main role in cell division cycle and in the balance of life. This fact shows us the importance of the ROS scavenging and the antioxidant defence system in maintainging normal cellular physiology, facing diseases and promoting immunity. In fact, the regulation of gene expression by means of oxidants, antioxidants and the redox state, has emerged as a novel target that promises therapeutic implications [21].

Gezen stated that immunohistochemical staining methods are used to detect damage to cells and tissues

[22]. In this study, immunohistochemical staining method was used to detect Cu/Zn SOD enzyme production.

CONCLUSION

In this study, a high amount of Cu/Zn SOD was detected in the stomach tissues of the rats fed from the Çamburnu region from the Dardanelles. It is considered that the increase of Cu/Zn SOD production is thought to occur because heavy metal containing mussels may cause oxidative stresses. The first defense against free radicals in organism is the SOD enzyme, so Cu/Zn SOD production is thought to increase excessively.

Conflict of interest

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

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Footnote

At the time of this research, the author (AM) worked at Department of Pathology of Çanakkale Onsekiz Mart University.

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The European Research Journal 2019;5(2):326-334 ORIGINAL ARTICLE

Nursing professionals' attitudes toward biostatistics: an international web-based survey

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ABSTRACT

Objectives: The present study, an international web-based survey, was focused on four aims: to obtain nursing professional's self-reported statistical knowledge levels and how this knowledge varies by research area, to investigate and specify when biostatistics courses should be taught in nursing education and to identify the key statistical methods relevant to nursing education.

Methods: A total of 448 nursing professionals from five continents and 52 countries participated in our study. For the data comparison, Kruskal-Wallis test and Mann-Whitney U test were applied.

Results: The results indicate that while nursing professionals place an emphasis on biostatistics education, the majority state that biostatistics education should be taken both at the undergraduate and postgraduate level and the participants also believe that taking a biostatistics course is useful for their occupation. A biostatistics education should also emphasize the necessity of consulting to a biostatistician when planning a study.

Conclusion: Our study provides information regarding self-reported levels of biostatistical knowledge of nursing professionals by research area and academic position, and provides guidance regarding the ideal semester for administering a biostatistics course.

Keywords: Biostatistics course, biostatistics knowledge, nursing education, nursing professionals, web-based survey

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Statistics have been an integral part of nursing practice and researchas well as other health science disciplines since the days of *Florence Nightingale* (1820-1910), the first known nurse statistician and founder of professional nursing. Statistics is an important tool in the conduct of clinical, basic, and outcomes research in nursing and allied health that are required at every stage of research, from planning to completion, to produce scientifically important and reliable results [1, 2]. Health professionals need at least a basic level of statistical knowledge and the support of a biostatistician to contribute to ongoing discussions in their research area and advance in their academic career. Furthermore, since the majority of journal articles are accompanied by statistics, readers who do not conduct research but follow the innovations in their own specialized area also need a working knowledge of biostatistics, which

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may help them to easily and clearly understand what they read [3, 4].

Being a health researcher is an extensive process that starts with undergraduate education. It is a common experience with health sciences students to generally accept statistics, as a difficult and non-popular subject, mostly because of inadequate mathematical background, which leads to a decrease in interest and ability towards the course [5-7]. Hence, in undergraduate education, the student's main objective is success in statistical courses, and students cannot gain a clear understanding of the importance of biostatistics [8]. At this point, another set of reasonable questions emerges: how to teach statistics, what statistics to teach, when to teach statistics and what statistics are common in the literature, to provide students with basic data comprehension that will enable them to interpret statistical results [9].

In undergraduate education, if the key concepts that would be most meaningful to students as they enter professional practice were identified and then coupled with the additional statistical knowledge gained during postgraduate education, health professionals would be better prepared about how to make intelligent choices based on their data, and how to evaluate it specifically for their research areas. As with other health field disciplines, nurse scientists also need to develop a statistical mindset for their own research, to be able to analyze clinical phenomena in a systematic manner, and to be able to use and generate research in the clinical setting for enhanced patient care [10, 11].

The present study, an international web-based survey, was focused on four aims:to obtain nursing professional's self-reported statistical knowledge levels and how this knowledge varies by research area, to investigate and specify when biostatistics courses should be taught in nursing education and to identify the key statistical methods relevant to nursing education.

METHODS

In the present study, nursing professional data were obtained by a web-based survey. Participants were selected randomly from the PubMed (www.ncbi.nlm.nih.gov) database for the years 2005-2016 using the keywords "*school of nursing, nursing school, faculty of nursing, nursing faculty*", by screening the nursing journals. Therefore, the participants were determined by searching the keywords in the corresponding or the first author's address information of the articles. After the participants were identified, they were also confirmed to be nursing professionals from their institutional web page or from their previous studies. The participants were invited to participate in the survey via e-mail, and the respondentswere directed to the survey at Survey Monkey (https://www.surveymonkey.com).

In the first part of the survey, subjects were asked whether a biostatistics course would be useful for their future careers (from "completely disagree: 0"; to "completely agree: 4"), at which semester or semesters should biostatistics be administered, and how much importance they placed on biostatistics (from "not important: 0"; to "very important: 10"). In the second section of the survey, the subjects were asked which statistical methods, tests and techniques they knew, out of 54 methods and techniques which referenced based on our previous studies [4, 12, 13]. Only self-reported general knowledge about the procedures was assessed. In the questionnaire, methods, tests and techniques were grouped as "general statistics knowledge." Subgroup statistical methods, tests and techniques were classified as follows: "parametric tests", "non-parametric tests", "multivariate methods", "sampling methods" and "survival analysis methods". The self-reported statistics knowledge of each participant was converted to a ratio by dividing the number of methods, tests and techniques that the participant knew by the total number of methods, tests and techniques in that subject group.

Statistical Analysis

In this study, the Shapiro-Wilk normality test was applied to determine whether the variables were normally distributed. For comparison, Kruskal-Wallis test and Mann-Whitney U test were applied using a significance level of $\alpha = 0.05$. For post hoc comparisons, Dunn-Bonferroni tests were considered. Dueto the use of nonparametric tests for comparison, data were represented with median and interquartile range(IQR), which is equal to the difference between the 25th and 75th percentile value. Statistical analyses were performed by using SPSS(IBM Corp. Released

Table 1. Distribution of the participants according to continents and countries

Continent	Country
Africa n = 19 (4.20%)	Nigeria (5), Ethiopia (4), South Africa (4), Botswana (2), Egypt (1), Malawi (1), Uganda (1), Zambia (1)
America n = 206 (46%)	United States (162), Canada (22), Chile (3), Brazil (19)
Asia n = 112 (25%)	Turkey (30), China (14), Iran (14), Jordan (12), Israel (8), Japan (7), Saudi Arabia (6), India (5), Republic of Korea (4), Indonesia (2), Malaysia (2), Oman (2), Lebanon (1), Qatar (1), Thailand (1), United Arab Emirates (1), Vietnam (1), Yemen (1)
Europe n = 81 (18.10%)	Spain (15), United Kingdom (14), Italy (9), Ireland (6), Norway (6), Greece (5), Sweden (4), Switzerland (4), Cyprus (3), Belgium (2), Finland (2), Lithuania (2), Netherlands (2), Poland (2), Austria (1), Germany (1), Malta (1), Serbia (1), Slovakia (1)
Oceania n = 30 (6.70%)	Australia (27), New Zealand (3)

2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

RESULTS

Of the 10.000 e-mail invitations sent, 866 were rejected by the server due to e-mail addresses being either incorrectly spelled or no longer valid, leaving an estimated 9,134 email recipients. Those who responded with the intention of participating numbered 463, reflecting a responserate of 5.07%. Additionally, of 463 respondents, 15 were excluded from the study due to their failure to complete the survey.

Participant median age was 49 (IQR = 18) years (range: 20 to 77 years). The majority of participants were female (n = 359, 80.10%). A total of 448 nursing professionals from five continents and 52 countries participated in our study (Table 1).

Of the total, 141 were academic staff, including 44 (9.80%) Assistant Professors, 54 (12.10%) Associate Professors and 43 (9.60%) Full Professors. The rest of the participants, who also had academic careers but were not academic staff, were distributed as follows: Doctor of Philosophy (Ph.D.) (n = 260,

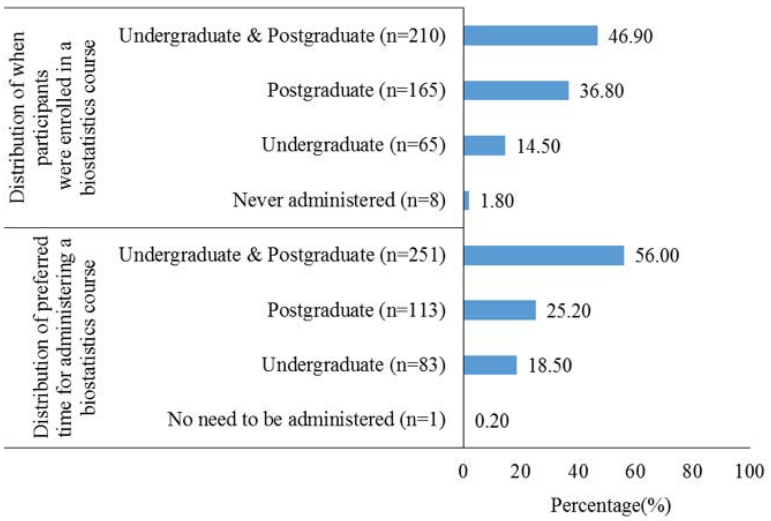

Figure 1. Percentage of when the participants enrolled a biostatistics course and preferred time line.

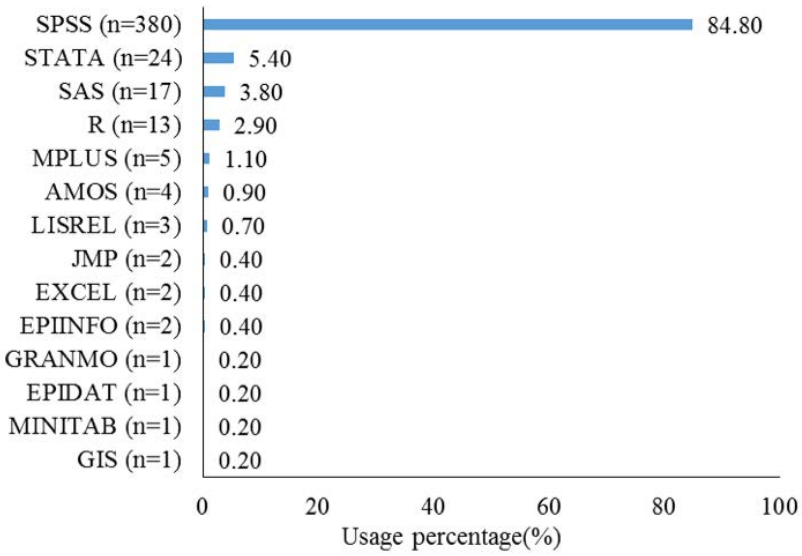

Figure 2. Usage percentage of preferred statistical software by nursing professionals.

58.00%) and Master of Science (M.Sc.) (n = 47, 10.50%).

Nearly half of the participants (n = 210, 46.90%) stated that they have administered a statistics course in both undergraduate and postgraduate education. This is followed by the percentage of those (n = 165, 36.80%) who only administered such courses at the postgraduate level. The distribution of the responses of the remaining participants, by the time periods in which they were administered a biostatistics course,

Table 2. Descriptive values and comparisons of whether enrolling in a biostatistics course is useful for one's occupation and the importance placed on biostatistics in nursing science according to academic staff and research area

Academic Statue	Do you agree with the idea that taking a biostatistics course is beneficial for a nurse's profession? (min-max: 0-4)	What is the importance of biostatistics in nursing science? (min-max: 0-10)
Academic Staff (n = 141)	4 (0)	10 (1)
Non-academic Staff (n = 307)	4 (0)	10 (2)
***p* value**	0.978[a]	0.351[a]
Research Area		
Fundemantel Nursing & Basic Science (n = 28)	4 (1)	10 (2)
Surgical Nursing (n = 31)	4 (0)	10 (2)
Medical Nursing (n = 119)	4 (0)	10 (1)
Obstetrics and Gynecological Nursing (n = 40)	4 (0)	10 (2)
Family and Community Health Nursing (n = 87)	4 (0)	10 (1)
Pediatric Nursing (n = 35)	4(0)	10 (2)
Psychiatric and Mental Health Nursing (n = 44)	4(0)	10 (0)
Nursing Management (n = 46)	4 (0.25)	10(2)
Nursing education (n = 18)	4 (2)	8(3)
***p* value**	0.532[b]	0.200[b]

Data are presented as median(Interquartile range). [a]: Mann Whitney U test, [b]: Kruskal Wallis test

was as follows: 14.50% (n = 65) took a biostatistics course only during undergraduate education, and the remaining 1.80 % (n = 8) stated that they never took a statistics or biostatistics course (Figure 1).

More than half of the participants (n = 251, 56.00%) preferred that biostatistics courses be taken at both the undergraduate and postgraduate levels. The choice of the biostatistical course, only in postgraduate education, was the second most-preferred option (n = 113, 25.20%). The rest of the preferred opinions were as follows: 18.50% (n = 83) of the participants preferred that the course be administered only at the undergraduate level, and 0.20% (n = 1) stated that there was no need to administer the course (Figure 1).

It was determined that SPSS is the most preferred statistical software for statistical analysis (Figure 2). The three most-preferred statistical software are as follows: SPSS (84.80%), STATA (5.40%) and SAS (3.80%).

Academic and non-academic participants think that the biostatistics course is very important for them and that administering the course will definitely benefit the profession in the future (Table 2). There was no difference in responses between academic and non-academic staff. Furthermore, all participants also agreed on the importance of biostatistics in nursing science with the median point 10 (IQR: 2). Regardless of whether they were academic staff or not, there was also no difference between participant's responses to the importance of biostatistics and its usefulness, even when examined only in the research fields of nursing science (Table 2).

The comparison of self-reported statistical knowledge level according to academic status is given in Table 3. Although there is no difference between the academic and the non-academic staff, according to the level of information, interestingly, there is a difference between statuses (Table 3).

There was a difference between the status groups according to the information levels in all of the sub-

Table 3. The comparisons of the level of self-reported statistics knowledge possessed by academic statues and research area

Academic Statue	Sampling methods (%)	Parametric tests (%)	Non-parametric tests (%)	Multivariate Methods (%)	Survival Analysis Methods (%)	General Statistics (%)
Academic Staff (n = 141)	33.33 (75)	85.71 (28.57)	50 (35.72)	33.33 (41.66)	0 (66.67)	46.30 (38.89)
Non-academic Staff (n = 307)	41.67 (66.67)	100 (28.57)	50 (28.58)	41.67 (41.66)	33.33 (66.67)	51.85 (35.19)
***p* value**	0.125[a]	0.264[a]	0.656[a]	0.513[a]	0.181[a]	0.357[a]
(1) M.Sc. degree (n = 47)	25 (58.33)	85.71 (42.86)	42.86 (35.71)	16.67 (25)	0 (33.33)	35.19 (83.34)
(2) Ph.D. degree (n = 260)	50 (66.67)	100 (100)	50 (28.58)	41.67 (41.67)	33.33 (66.67)	53.70 (35.19)
(3)Assistant Professor (n = 44)	20.84 (50)	85.71 (71.43)	42.86(42.86)	29.17 (50)	0 (33.33)	40.74 (37.50)
(4) Associate Professor (n = 54)	33.33 (58.33)	85.71 (28.57)	50 (28.57)	33.33 (20.83)	0 (66.67)	43.52 (28.24)
(5) Professor (n = 43)	75 (66.66)	85.71 (28.57)	64.29 (35.71)	41.67 (33.34)	33.33 (100)	61.11 (38.89)
***p* value**	**< 0.001[b]**	**0.011[b]**	**0.001[b]**	**< 0.001[b]**	**0.002[b]**	**< 0.001[b]**
	Pairwise Comparisons Among Academic Statues					
Sampling methods (%)	$\boldsymbol{p_{2\&3}=0.041}$, $\boldsymbol{p_{3\&5}=0.003}$, $\boldsymbol{p_{4\&5}=0.007}$, $\boldsymbol{p_{1\&5}=0.050}$, $p_{1\&4}=1.00$, $p_{1\&3}=1.00$, $p_{2\&4}=0.101$, $p_{1\&2}=0.689$, $p_{2\&5}=0.644$,					
Parametric tests (%)	$\boldsymbol{p_{1\&2}=0.014}$, $p_{1\&4}=0.943$, $p_{1\&5}=0.358$, $p_{3\&4}=1.00$, $p_{3\&5}=1.00$, $p_{2\&3}=0.386$, $p_{4\&5}=1.00$, $p_{2\&4}=1.00$, $p_{2\&5}=1.00$,					
Non-parametric tests (%)	$\boldsymbol{p_{1\&2}=0.014}$, $\boldsymbol{p_{1\&5}=0.001}$, $\boldsymbol{p_{3\&5}=0.043}$, $p_{1\&3}=1.00$, $p_{1\&4}=0.712$, $p_{3\&4}=1.00$, $p_{3\&5}=1.00$, $p_{2\&4}=1.00$, $p_{4\&5}=0.157$, $p_{2\&5}=0.344$,					
Multivariate Methods (%)	$\boldsymbol{p_{1\&2}<0.001}$, $\boldsymbol{p_{1\&5}<0.001}$, $p_{1\&3}=0.135$, $p_{1\&4}=0.110$, $p_{3\&4}=1.00$, $p_{2\&4}=0.182$, $p_{4\&5}=0.153$, $p_{3\&5}=0.239$, $p_{2\&5}=1.00$					
Survival Analysis Methods (%)	$\boldsymbol{p_{3\&5}=0.027}$, $\boldsymbol{p_{4\&5}=0.043}$, $p_{3\&4}=1.00$, $p_{1\&3}=1.00$, $p_{2\&3}=0.129$, $p_{1\&4}=1.00$, $p_{2\&4}=0.209$, $p_{1\&2}=0.388$, $p_{1\&5}=0.074$, $p_{2\&5}=1.00$					
General Statistics (%)	$\boldsymbol{p_{1\&2}=0.001}$, $\boldsymbol{p_{1\&5}<0.001}$, $\boldsymbol{p_{3\&5}=0.009}$, $\boldsymbol{p_{4\&5}=0.023}$, $p_{1\&3}=1.00$, $p_{3\&4}=1.00$, $p_{2\&3}=0.064$, $p_{2\&4}=0.179$, $p_{2\&5}=1.00$					

Data are presented as median(Interquartile range). [a]: Mann Whitney U test, [b]: Kruskal Wallis test

Table 4. The comparisons of the level of self-reported statistics knowledge possessed by academic status and research area

Research Area	Sampling methods (%)	Parametric tests (%)	Non-parametric tests (%)	Multivariate Methods (%)	Survival Analysis Methods (%)	General Statistics (%)
Fundamental Nursing & Basic Science (n = 28)	33.34 (83.33)	92.86 (39.29)	57.14 (37.50)	25 (47.92)	50 (100)	52.78 (39.81)
Surgical Nursing (n = 31)	33.33 (75)	85.71 (28.57)	50 (42.86)	25 (33.33)	0 (66.67)	44.44 (40.74)
Medical Nursing (n = 119)	33.33 (66.67)	85.71 (28.57)	50 (28.58)	33.33 (41.66)	0 (66.67)	50 (37.04))
Obstetrics and Gynaecological Nursing (n = 40)	25 (72.92)	85.71 (28.57)	50 (35.72)	33.33 (33.33)	16.67 (66.67)	45.37 (37.97)
Family and Community Health Nursing (n = 87)	50 (66.67)	100 (28.57)	50 (35.72)	41.67 (41.67)	0 (66.67)	53.70 (31.48)
Paediatric Nursing (n = 35)	58.33 (83.34)	100 (28.57)	50 (21.43)	50 (41.66)	33.33 (66.67)	59.26 (38.89)
Psychiatric and Mental Health Nursing (n = 44)	41.67 (58.34)	92.86 (28.57)	50 (28.58)	33.33 (41.66)	0 (33.33)	49.08 (35.19)
Nursing Management (n = 46)	41.67 (75)	85.71 (28.57)	50 (35.72)	50 (35.42)	0 (66.67)	53.70 (32.87)
Nursing education (n = 18)	25 (100)	92.86 (32.14)	42.86 (51.79)	37.50 (75)	0 (66.67)	49.08 (59.73)
***p* value**	0.370[b]	0.799[b]	0.908[b]	0.246[b]	0.411[b]	0.650[b]

Data are presented as median(Interquartile range). [b]: Kruskal Wallis test

subjects identified. It was determined that the level of professor knowledge about sampling was higher than participants with M.Sc. degrees, assistant professors and associate professors. It was also determined that the level of knowledge about sampling is higher for participants with Ph.D. degrees than assistant professors. For the sub-subject, group-titled parametric tests, the only difference was found between participants who had MSc. degrees and those who had Ph.D. degrees. Again, professor knowledge levels about non-parametric tests were found to be higher than participants with M.Sc. degrees and assistant professors, while participants with Ph.D. degrees also had higher self-reported knowledge levels than participants with M.Sc. degrees. In terms of multivariate methods, it was determined that participants with M.Sc. degrees had lower levels of knowledge than participants with Ph.D. degrees and professors. As for survival analysis methods, it was determined that the self-reported knowledge levels of professors were higher than assistant professors and associate professors.

When assessed in terms of general knowledge level, it was determined that except for participants with PhD. degrees, professor knowledge levels were higher than all other statuses. It was also observed that participants with Ph.D. degrees had higher self-reported knowledge levels than participants with M.Sc. degrees. It can be seen that the differences achieved in the sub-group subjects, according to academic status, also could not be observed among the research areas in nursing science (Table 4).

DISCUSSION

In the nursing profession, the use of statistics directly affects patient care and advocacy efforts to advance the profession. However, for evidence-based practice to become well established, nursing professionals must have a basic understanding of statistics to be able to read, understand, and interpret the relevant literature. Although there are a multitude of studies [4, 6, 8, 12-17] assessing statistics and biostatistics education in the field of medicine and other health science fields, there are fewer studies [7, 10, 18] particularly in nursing science.

Nearly half of the participants stated that they completed statistics or biostatistics courses at both the undergraduate and postgraduate levels. In fact, this finding is consistent with our previous studies in literature [12, 13]. In these studies, nearly half of the

participants in medicine (n = 128, 46%) and veterinary medicine (n = 66, 42.60%) also stated that they had taken such courses during similar periods. In another similar study focused on academic dentists, Ocakoglu *et al*. [4] also reported that the majority of participants (n = 111, 44%) stated that they took the statistics or biostatistics course during the undergraduate period. These studies reflect that in the subfields of health science, statistics is considered part of postgraduate education as well as undergraduate education. Participants were also asked their opinions about when the course should be provided. Furthermore, over half of the participants (n = 251, 56%) were united in the idea that a nursing practitioner who wanted to have an academic career should take statistics at both the undergraduate and postgraduate levels. In similar studies [4, 12, 13], on the direction of their experience in academic life, participants from various health science fields also suggested that the course should be administered during both the undergraduate and postgraduate periods.

Nurses should be trained in basic statistics during their career. Nurses who pursue masters or Ph.D. degrees in nursing science especially need to know advanced statistical techniques, as they are required to do a research thesis or to publish their study. Utilization and the use of statistics in nursing practice helps nursing professionals to determine the effectiveness of their work.

Statistical software is a useful tool that transfers the statistical skills of nurses to research reports. With a solid understanding of statistical fundamentals, combined with appropriate statistical software, evidence-based nursing research has much to offer the healthcare community [19]. In the present study, it was found that SPSS is the most preferred statistical software for statistical analysis. The same preference has been obtained in similar studies applied to other disciplines in the field of health sciences [4, 12, 13, 20].

It is an unfortunate truth that statistics and biostatistics courses are the courses in which most health professionals are unwilling and do not give adequate attention to during their undergraduate education [21, 22]. After graduation, when these former students participate in research, even if only temporarily, there is considerable motivation to obtain a sufficient understanding of basic statistical methodology [8, 13]. In this study, academic and non-academic nursing professionals stated the importance of biostatistics in nursing science and its acceptance as a useful tool for the profession. Beyond the difference between academic and non-academic, regarding the importance of statistics courses and their role in career advancement, there was also no difference among research areas of nursing professionals.

In the present study, participants were also asked to indicate whether they have awareness or knowledge about subjects that are harmonized within biostatistics or statistics lessons that are commonly taught in other health science disciplines. In similar studies [4, 12, 13], the low level of participant's self-reported knowledge, especially about sampling methods, was remarkable; surprisingly, this finding does not exist in the present study of nursing professionals. It can be concluded that nursing professionals realize that data collected from given samples, and its interpretation, will accurately reflect conditions found in the general population.

There was no difference between academic and non-academic nursing staff professionals in terms of self-reported knowledge of biostatistics subjects. Moreover, there was no difference in the level of knowledge by nursing professional's research areas. The remarkable finding is that the level of knowledge varies according to academic status. This finding can be interpreted as the product of more publications with an increase of vocational skills and experience, and in this regard, the increase of biostatistics knowledge level.

The biostatistics curriculum should be adaptable and include specialized statistical methods appropriate to the data characterization and analysis,and for the research areas of the target group enrolled in the course. In other words, it may be unnecessary to teach the same set of statistical methods to every field within the health sciences [4]. For this reason, it can be accepted that the level of knowledge differs according to the statistical methods used by different disciplines in health sciences. In the present study, while the topic with the lowest level of self-reported knowledge was declared as survival analysis methods, the topic with the highest level of knowledge was reported as parametric tests. In contrast, with parametric tests, nursing professionals were less informed about the

non-parametric statistical methods, yet nonparametric tests must be used when the assumptions for parametric tests are not satisfied. Imperatively, this situation leads us to the following questions: Are parametric tests used, by nurses within the habit of analyzing the data? Are the parametric procedures being tested to ensure that they meet the necessary assumptions, such as normality, for their application? Therefore, research related to this topic should be conducted according to the result of these studies, if it is indeed needed, more importance should be given to parametric and nonparametric distinction in the courses [12]. Even if health professionals take biostatistics courses, they should not implicitly trust themselves in the field of statistics. It is important to remember that the design of each study and the characteristics of the data obtained may be different and specific to a particular study, so each study may require different statistical methods, with which the researchers may be unfamiliar [4].

It is clear that medical study that involves any aspect of the collection, summarization, analysis and/or interpretation of clinical quantitative information requires statistical support and guidance. This input may be provided by the health professionals themselves if properly trained but is most appropriately and commonly achieved by a collaboration with a biostatistician. The biostatistician can be an assistant, consultant, or colleague co-investigator [23]. In 1938, R.A. Fisher said "*To consult the statistician after an experiment is finished is often merely to ask him to conduct a post mortem examination. He can perhaps say what the experiment died of*". Therefore, obtaining the services of a biostatistician in the planning stage of a study is strongly encouraged, to assist in the stages of "proper study design" and "conducting the study" in the research process, before finally setting up the database and statistical analysis [24].

Limitations

One of the main limitations of this study is the low response rate (< 10%). The low response rate is not surprising, given that response rates to surveys have dramatically declined over time, due to the proliferation of junk mail, the rapid growth and ease of large-scale surveys, and resulting complaints that people feel "bombarded" with internet-based surveys in the face of increasing demands on their time [25]. However, our response rate of 5.07% is similar to that of web-based studies in previous research aimed at medical providers (4%) [26], academic veterinarians (4.38%) [13], primary care physicians (5.7%) [27], dental physicians(9.1%) [4], and a group of urologists (9.3%) [28]. When similar studies are considered, our response rate is acceptable.

CONCLUSION

The present study is significant in terms of its international scope, intent and originality due to the uniqueness of this scope. Our study provides information regarding self-reported levels of biostatistical knowledge of nursing professionals by research area and academic position, and provides guidance regarding the ideal semester for administering a biostatistics course. This study can also make a contribution interms of revising higher education nursing curricula by including frequently used statistical methods as a part of nursing research to enable nursing professionals to understand current research and contribute to its ongoing discussion.

Conflict of interest

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

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The European Research Journal 2019;5(2):335-340 ORIGINAL ARTICLE

Comparison of spinal and cerebral oxygen saturation with near-infrared spectroscopy method during spinal surgery in prone position

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ABSTRACT

Objectives: To assess spinal and cerebral oxygenation with near-infrared spectroscopy method during spinal surgery in prone position.

Methods: This prospective study included 64 patients, who were prepared for posterior spinal instrumentation and laminectomy surgeries. Group 1: 31 patients who had posterior spinal instrumentation; Group 2: 33 patients who had at least two levels of disk operation (Laminectomy). The following were recorded for all patients before and after anesthesia induction in supine position, after induction in prone position, during operation (beginning, middle and end of surgery) in prone position and before waking up in supine position: cerebral oxygen saturation (NIRSs) measurements, spinal oxygen saturation (NIRSp) measurements, peripheral oxygen saturation (SpO_2), heart rate (HR), invasively monitored systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP) values.

Results: There was no significant difference between two groups in terms of the variables of age, weight, anesthesia and surgery duration ($p > 0.05$). MAP values were significantly different in both groups before induction, during operation and postoperative periods ($p < 0.05$). NIRSs were significantly lower at mid-operation and at the end of operation ($p < 0.05$). NIRSp values had no significant difference in any period ($p > 0.05$). We found no significant difference between groups in HR, SAP, DAP, MAP, NIRSs and NIRSp parameters ($p > 0.05$) compared at different times.

Conclusions: MAP dropped depending on induction and prone position. Cerebral oxygenation significantly decreased at the time of mid-operation and at the end of operation but spinal oxygenation had no significant decrease. Compared to laminectomy, posterior stabilization surgery did not pose an additional risk to the patients in terms of spinal and oxygen saturation.

Keywords: prone position, spinal surgery, cerebral oxygenation, near-infrared spectroscopy

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To prevent the possible complications, it is important to recognize symptoms such as ischemia and hypoxia at an early stage which might develop during spinal surgery due to surgical intervention or pre-existing trauma. Spinal surgeries are mostly performed in prone position. Spinal surgery presents a complex

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situation where surgery trauma, general anesthesia and prone position generate hemodynamic and respiratory effects. It is important to follow the changes in cerebral and spinal perfusion and oxygenation. Compared to discectomy and laminectomy, posterior stabilization surgeries pose more risk in terms of cerebral and spinal oxygen saturation due to more compression and bleeding risk.

In near-infrared spectroscopy (NIRS) method, infrared light is used to penetrate the tissue, and the optic values of oxyhemoglobin and deoxyhemoglobin in capillary bed are used to calculate the oxygen saturation in tissue [1]. It is a noninvasive method. It enables the measurement of cerebral tissue oxygen saturation with the help of the sensors placed on frontal region. Possibility of measurement mistakes prevents getting the real values for cerebral oxygen saturation and limits its use [2, 3]. Many factors such as the arterial and venous vascular density of the region where sensor is applied, arterio-venous shunts, hemodilution, edema, and patient's bilirubin level might prevent finding the real oxygenation value not only in cerebral tissue but in all measured tissues [2]. However, it is advantageous in terms of the real-time monitoring of oxygenation and its trend follow-up [4, 5]. It has also been reported that, in the light of the insufficiency of standard monitoring methods in following the changes in tissue oxygenation, NIRS monitoring of spinal cord will be a useful warning system for reducing ischemic spinal cord damages, which might occur due to spinal cord surgery [6-9].

In this study, our purpose was to find out whether patients' spinal and cerebral oxygenation values varied before induction, during operation and after operation, and to assess the relation between tissue oxygenation changes and hemodynamic changes in two different survey groups which had posterior spinal instrumentation and at least two levels of disk operation (laminectomy).

METHODS

The study started after getting the Local Ethics Council Approval from the Medical School of Celal Bayar University (26/02/2014, No: 20478486-100) and CBU BAP support (project no. 2014-076).

The study was prospective and included 64 patients who were prepared by the Neurosurgery Clinic for posterior spinal instrumentation and laminectomy, ASA I, II and III (American Society of Anesthesiologists classification) between May 2014 and May 2016. The patients aged between 18 and 70 years, were included in the study after their informed consents were received. Those who did not consent to take part in the study, pregnant patients, those with pre-diagnosed vascular operation and diseases (abdominal aorta surgery, etc.) or a history of cardiac surgery or any intracranial pathology were excluded. The patients, who were included in the study for their spinal surgeries were divided into two groups based on the surgery they underwent; Group 1: 31 cases who had posterior spinal instrumentation (Group 1, n = 31) and Group 2: 33 cases who had at least two levels of disk operation (Laminectomy) (Group 2, n = 33).

All patients were monitored for heart rate (HR), invasive arterial blood pressure, peripheral oxygen saturation (SpO2), and end-tidal CO2 (EtCO2) after being taken into the operating room. In addition, Group 1 cases were monitored for central venous pressure (CVP). For monitoring tissue oxygenation, NIRS (NONİN-Somanetics, Nonin Medical Inc. Minnesota, MN) probes were placed on frontal region and on the distal of spinal segment to be operated.

Pre-oxygenation was performed for all cases with 100% oxygen. Then, the same general anesthesia induction and anesthesia maintenance were applied to both groups. General anesthesia induction was performed with: fentanyl 1-2 µg/kg, propofol 2-3 mg/kg, rocuronium 0.9 mg/kg. After endotracheal intubation, mechanic ventilation parameters were set to keep the tidal volume at 7 ml/kg and end-tidal CO2 value at 30-40 mmHg. Anesthesia maintenance was provided with sevoflurane 1-2%, 40/60% O2/N2O mix and remifentanil infusion. After the patient was put in prone position, endotracheal tube location was verified; eyeballs, nose and other possible pressure locations were checked; and proper position preventing abdominal pressure was confirmed.

Cerebral oxygen saturation (NIRSs) was measured with the NIRS device (NONIN-Somanetics) by placing probes on the foreheads of patients in both groups; and spinal oxygen saturation (NIRSp) was measured by placing NIRS probes which were sterilized by immersing into ethylene oxide on the distal dermis of the spinal segment to be operated.

Table 1. Descriptive demographical information of groups

	Group 1 (n = 31)	Group 2 (n = 33)	*p*
Age (years)	53.77 ± 13.90	52.87 ± 13.29	0.690
Weight (kg)	78.70 ± 14.56	79.66 ± 12.31	0.590
BMI (kg/m^2)	26.69 ± 6.11	27.03 ± 5.27	0.610
Gender (male/female)	17/14	19/11	
ASA (1/2/3)	10/16/5	11/15/7	
Anesthesia duration (min)	154.35 ± 38.29	160.15 ± 39.30	0.710
Surgery duration (min)	137.25 ± 38.79	137.72 ± 35.99	0.680

Data are shown as mean ± standard deviation or number. Group 1 =cases who had posterior spinal instrumentation, Group 2 = cases who had at least two levels of disk operation (Laminectomy), ASA = American Society of Anesthesiologists classification, BMI = body mass index

Simultaneously; SpO2, HR, invasively monitored systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP) values were recorded.

Measurement times include T1: Before induction (Supine position), T2: After induction (Supine), T3: Right before surgery (after turning to prone position), T4: After starting the surgery (Prone), T5: Mid-surgery (Prone), T6: End of surgery–at the time of skin suturing (Prone), and T7: After the final positioning of the patient (Supine).

When there is an instant changing in the recorded cerebral oxygenation values the surgery teams were simultaneously warned.

Statistical Analysis

SPSS (statistical package for social sciences for Windows 15.0) program was used for the statistical analysis of the study. Data were evaluated through descriptive statistical analysis by using mean, standard deviation, minimum, maximum, interval and percentage distributions. Analytically, the two groups were evaluated by applying T test in independent groups. Pearson correlation test was applied for comparing numeric data. In all analytical evaluations, $p < 0.05$ was the significance limit value.

RESULTS

We found no significant difference between two groups in terms of the variables of age, weight, anesthesia and surgery duration ($p > 0.05$) (Table 1).

In inter-group comparisons, there was no significant difference between two groups in HR, SAP, DAP, MAP, NIRSs and NIRSp parameters compared at all times ($p > 0.05$). But, there were significant differences between the values taken different measure-times for each group of patients.

Among group 1, there was a significant difference between T1 and T2 MAP values ($p < 0.001$). T2 MAP value was significantly different from T3 MAP value ($p = 0.0019$). Among group 2, there was a significant difference between T1 and T2, T2 and T3 MAP values ($p < 0.001$ and p = 0.015, respectively). Group 1 and Group 2 MAP values were given in Table 2.

Among group 1, there was a significant difference between T1 NIRSs value and T3 NIRSs value ($p = 0.04$). T3 NIRSs value was significantly different from T5 and T6 NIRSs values ($p = 0.018$ and $p = 0.032$,

Table 2. Group 1 and Group 2 MAP values

	Group 1 (mean ± SD)	Group 2 (mean± SD)
MAP T1	96.48 ± 15.09	97.33 ± 14.96
MAP T2	79.58 ± 12.70	80.60 ± 13.52
MAP T3	73.19 ± 12.73	74.39 ± 13.96
MAP T4	75.16 ± 11.85	74.90 ± 11.51
MAP T5	71.54 ± 8.64	72.06 ± 8.70
MAP T6	76.48 ± 15.83	77.24 ± 15.64
MAP T7	91.83 ± 11.44	91.87 ± 11.07

Group 1 =cases who had posterior spinal instrumentation, Group 2 = cases who had at least two levels of disk operation (Laminectomy), MAP = mean arterial pressure, SD = standarddeviation

Table 3. Group 1 and Group 2 NIRSs values

	Group 1 (mean ± SD)	Group 2 (mean ± SD)
NIRSs T1	77.83 ± 12.84	77.15 ± 12.76
NIRSs T2	73.80 ± 11.42	73.63 ± 11.10
NIRSs T3	71.25 ± 12.89	70.84 ± 12.65
NIRSs T4	69.06 ± 9.50	68.81 ± 9.29
NIRSs T5	66.67 ± 9.77	66.57 ± 9.52
NIRSs T6	67.06 ± 11.75	67.37 ± 11.51
NIRSs T7	70.76 ± 11.69	71.00 ± 11.15

Group 1 =cases who had posterior spinal instrumentation, Group 2 = cases who had at least two levels of disk operation (Laminectomy), NIRSs = cerebral oxygen saturation, SD = standard deviation

respectively). Among group 2, there was a significant difference between T1 and T3, T3 and T5 NIRSs values ($p = 0.038$ and $p = 0.021$, respectively). NIRSs values of Group 1 and Group 2 patients were detailed in Table 3.

The correlation analysis of the intra-group comparisons of Group 1 MAP and NIRSs values indicated a positively (r=0.427) significant ($p = 0.017$) relation between T5 MAP and T5 NIRSs, and a positively (r=0.486) significant ($p = 0.006$) relation between T6 MAP and T6 NIRSs (Tables 2 and 3)

The correlation analysis of the intra-group comparisons of Group 2 MAP and NIRSs values indicated a negatively (r= -0.375) significant ($p = 0.032$) relation between T1 MAP and T1 NIRSs; a positively (r= 0.383) significant ($p = 0.028$) relation between T5 MAP and T5 NIRSs; and a positively (r= 0.504) significant ($p = 0.003$) relation between T6 MAP and T6 NIRSs (Tables 2 and 3).

DISCUSSION

We found that, compared to the MAP values measured before induction, MAP values dropped with anesthesia induction and significantly dropped in prone position during operation. With respect to NIRSs; while there was no difference in supineposition before and after induction, there was a decline after turning to prone position. We found a positively significant relation between MAP and NIRSs during the time of ongoing surgery. This finding was also supported by other studies in literature. The study by Babakhani *et al*. [4], which enrolled 50 patients undergoing lumbar spine surgery in prone position, concluded that cerebral oxygenation can be maintained in prone position and it is very crucial in preventing bradycardia and arterial hypotension. The study by Trafidlo *et al*. [10], which covered 43 patients, that underwent lumbar spondylosis surgery in prone position to assess postoperative cognitive functions, indicated a positive correlation between MAP and cerebraloxygensaturation. The study by Meng *et al*. [11] reported that this change was actually associated with cardiac output (CO) while it was affected by other hemodynamic parameters. In our study, we thought thatthe change in NIRSs actually derived from prone position while it was affected by the decline inMAP. We can say that this effect of prone position is a complex combination of many effects such as increased abdominal pressure, thoracic compression, disrupted venousturn, cardiac output return, effects on respiratory dynamics, and effects on intracranial circulation, as well as MAP. Studies reported that pulmonary infiltration and atelectatic regions, which concentrated in posterior lung in supine position, dissolved in prone position, intrapulmonary shunting decreased, and perfusion increased in ventral [12]. The clear conclusion of all these was an increased oxygenation in prone position [12]. However, the obstruction that occurred in inferior vena cava in prone position caused a decrease in cardiac venous return [13], and resulted in decreased cardiac index and cardiac output [13, 14]. With the help of auto-regulation mechanisms, systemic vascular resistance (SVR) was increased and MAP was maintained [13, 15]. However, anesthesia induction might disrupt the rise in SVR and auto-regulation thereby causing a drop in MAP [16]. When we consider the results of our study and all effects of prone position on systems, we might conclude that cerebral oxygenation might be affected negatively. The study by Babakhani *et al*. [4] indicated the decrease in cerebral oxygenation in prone position while it was within the margin of safety.

Compared to laminectomy, posterior stabilization operations require applying more compression for placing rots and they pose a bleeding risk. The study by Park [17], which covered 40 patients that underwent spinal surgery in prone position, reported that an increase in intraabdominal pressure caused an

increase in blood loss in surgery region. Due to those differences, posterior stabilization operations might have a more negative effect on average arterial pressure change, cerebral and spinal oxygen saturation due to venous return and volume loss, compared to laminectomies. By including these two types of surgeries performed in prone position in our study, we aimed to compare the oxygenation values before, during and after operation in these groups. In our study, the groups had a homogenous distribution in terms of demographic data. The comparison of two groups indicated no difference in terms of hemodynamic data, NIRSs and NIRSp values. This led us to think that compared to laminectomy, stabilization surgeries did not pose an additional risk to the patient in terms of cerebral and spinal oxygen saturation values. It is possible to say that accurate surgery technic and proper bleeding intervention decreased cerebralo xygenation risk.

In our study, we saw no significant difference in NIRSp values in any period. Similar to the NIRSs values, NIRSp values had a statistically insignificant decrease in proneposition. This might have resulted from an increase in venous blood rate in the region covered by NIRSp sensor as a result of venous stasis. Moreover, NIRSp measurement might be affected by differences in skin, subcutaneous fat tissue and muscle tissue volume and blood build-up. There are studies indicating that paravertebral muscle volume changed based on age and gender [18]. However, since our study found no statistically significant difference between groups in terms of age, gender and BMI, we think that NIRSp measurements were not affected by those factorsin our study.

Limitations

The limitations of NIRS method in the other studies have also limited our study. Many factors such as the arterial and venous vascular density of the region where sensor is applied, arterio-venous shunts, hemodilution, edema, and patient's bilirubin level might have affected the real value of oxygenation.

CONCLUSION

In conclusion, MAP dropped depending on induction and prone position. Cerebral oxygenation decreased significantly at the time of mid-operation and at the end of operation but there was no significant decrease for spinal oxygenation. Compared to laminectomy, posterior stabilization surgeries did not pose an additional risk to the patient in terms of cerebral and spinal oxygensaturation.

Conflict of interest

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

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The European Research Journal 2019;5(2):341-349 ORIGINAL ARTICLE

The awareness of healthcare workers about hazardous substances used in a tertiary hospital

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ABSTRACT

Objectives: Potentially hazardous materials are commonly used during health practices in the hospital environments. Management of hazardous substances is of great importance. Inadequate training of personnel for use and disposal of hazardous materials were reported by some studies. The aim of present study was to create awareness among healthcare workers for hazardous substances.

Methods: A survey was carried out on 204 healthcare workers (125 females and 79 males; mean age: 33.8 ± 12.9 years) to measure their level of knowledge about hazardous substances used in hospitals.

Results: Hospital departments were investigated and it was found that listing of dangerous substances were missing, their locations were not fixed, and they were not stored in isolated areas. Sixty percent of the participants considered themselves not having enough knowledge about hazardous materials. Ninety percent of the respondents thought that warning signs and symbols placed on hazardous material storage cabinets are useful. It was determined that warning signs for flammable, hazardous for environment, corrosive and explosive were significantly less known compared to symbols ($p = 0.037$, $p = 0.018$, $p < 0.001$ and $p < 0.001$, respectively).

Conclusions: It was concluded that healthcare workers did not have sufficient information about hazardous substances. Healthcare workers should be trained effectively on hazardous substances issue.

Keywords: hazardous substance, healthcare workers, hospital environment

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Hospitals play a significant role in health sector as institutions providing treatment, rehabilitation and care for sick and wounded people as well as for people who want to have their health status checked or who want to have health information on a 7/24 basis. These institutions are also important because they employ considerable number of medical, administration and support personnel. Hospital sector has highest risk for occupational hazards. Individuals who work in a hospital are required to be adequately informed about the physical and health hazards present in the hospital, the known risks, and what is to be done if an accident occurs [1].

Potentially hazardous materials are used during implementation of health care services. Explosive, oxidizing, flammable, irritant, harmful, toxic, carcinogenic, corrosive, infectious, teratogenic, mutagenic and environmentally hazardous materials are considered dangerous materials, and their wastes are referred to as hazardous waste. Costa and Felli [2]

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showed that healthcare workers detected 145 chemical substances and the most frequent health problems were related to skin problems. Hazardous materials used in hospitals are halogenated and non-halogenated organic compounds, inorganic compounds, corrosive materials, some prescription drugs, disinfectants, and other compounds containing carcinogenic or mutagenic toxins. Occupational exposure to hazardous drugs can cause harmful effects on health professionals and several protective measures must be taken [3]. These materials are frequently used for works in operation rooms, in-room services, laboratories and sterilization units. Use of hazardous materials and production of hazardous wastes are inevitable for hospitals and their management is crucial. A study by Terekli *et al*. [4] showed that education of personnel for use and disposal of hazardous materials is insufficient both in amount and scope.

The aims of the presents study were to determine and take under control hazardous materials used in hospital environment, to create awareness for them among healthcare workers, to set rules to minimize possible injuries that could arise from use of hazardous materials and to ensure safety for the healthcare workers, the hospital working environment.

METHODS

Data collection tool / questionnaire form of the study was conducted on a total of 204 health workers (125 females, 79 males, mean age: 33.8 ± 12.9 years) in clinics, intensive care services, emergency rooms, laboratories, hospital storages, pathology, radiology, nuclear medicine and radiation oncology departments of the a tertiary hospital in order to determine what they know about hazardous materials in hospital environment. Questionnaire forms included questions categorized in six main groups about what the hazardous materials are and what care must be observed about them.

Formal request was made to Gaziosmanpaşa University Health Research and Practice Hospital. Administration for visits to departments before the study, and permission was granted. Health workers to participate in the study were informed in advance and interviews were made with ones willing to participate. Data were collected by a single investigator through face-to-face interviews and observation techniques. This study was carried out by the safety committee and the quality committee. The Tertiary Hospital management was informed about the study results.

Statistical Analysis

Statistical analysis was performed using IBM-SPSS 20 program. The results were expressed as mean ± standard deviation (SD). The differences among groups were analyzed by one-way analysis of variance (ANOVA), and Tukey test was used as post-hoc test. $p < 0.05$ was considered statistically significant.

RESULTS

Survey of departments of Gaziosmanpaşa University, Health Research and Practice Hospital by Worker's Safety Committee and Quality Committee started with inspection of hospital storage which supplies all material needs of the hospital. Hazardous materials that could be found in hospital environment were determined. Hazardous symbol and signs to be used for labeling of hazardous materials and products given in Table 1 were distributed to all departments. A list of dangerous materials that could be found in hospital environment was prepared. List of hazardous materials by different hospital departments were given in Table 2.

Two hundred four health workers employed in clinics, intensive care service, emergency room, laboratories, hospital storage, pathology, radiology, nuclear medicine and radiation oncology departments participated in the questionnaire study. Occupations of the participants were as follows: nurse (n = 95, 46%), cleaning staff (n = 43, 21%), radiology and surgery technicians (n = 32, 16%), physician (n = 18, 9%), assistant health personnel (secretaries and other administrative personnel) (n = 16, 8%). Distribution of participants in questionnaire study by occupation was given in Figure 1.

The first question of the awareness questionnaire was "In your opinion, what are the hazardous materials used in hospital?" Sixty percent of the participants could name 3, 4 and 5 materials, which was significantly higher than those who could name 0, 1 and 2 materials (p = 0.03). There was significant

Table 1. Symbols and signs to be used for labeling of hazardous materials and preparations

HAZARD FEATURE	SIGN	SYMBOL
EXPLOSIVE	E	
OXIDİZING	O	
FLAMMABLE	F	
TOXIC	T	
HARMFUL	Xn	
CORROSIVE	C	
IRRITANT	Xi	
ALLERGIC	Xn Xi	
CARCINOGENIC	T Xn	
MUTAGEN	M Xn	
TOXIC FOR REPRODUCTION	T Xn	
HAZARDOUS FOR ENVIRONMENT	N	

difference between people who could name 3, 4 and 5 materials and people who could name 0, 1 and 2 materials in both nurse and assistant health personnel groups ($p < 0.001$). Data for this question was given in Figure 2.

When the meanings of hazardous material signs of Flammable (F), Irritant (Xi), Hazardous for Environment (N), Corrosive (C) and Explosive(E) participants were asked to participants, it was revealed that C and E signs were less known compared to other signs ($p < 0.001$) (Figure 3).

C was known only by 26% of the health workers. When the analysis was repeated after the participants were grouped by their profession, C was the sign least known by all professions. Percentages of knowing E in physician and assistant personnel groups were similar to percentages of knowing all other signs (Figure 4).

When the participants were asked to match the symbols and meanings of warning signs, success rate of 70% for Xi was much lower than those of other signs ($p < 0.001$) (Figure 5).

Analysis after grouping the participants by their profession revealed that Xi was again the least known symbol (Figure 6).

Answers of participants given to questions about signs and symbols of hazardous materials were compared. It was determined that warning signs for F, N, C and E were significantly less known compared to other symbols ($p = 0.037$, $p = 0.018$, $p < 0.001$ and $p < 0.001$, respectively). Sign and symbol of Xi, on the other hand, was known at the same rate ($p = 0.798$) (Figure 7).

Answers given by the participants to the question of "Dou you consider yourself knowledgeable enough about hazardous materials used in hospital?" were studied. Sixty per cent of them considered themselves to have enough knowledge about hazardous materials. Analysis of participants by their professions showed that percentages of workers who considered

Table 2. List and warning signs of the hazardous materials

department	NAME OF HAZARDOUS MATERİAL	WARNING SING
HOSPITAL WAREHOUSE	TOOL DISINFECTANT	Xi
	SKIN DISINFECTANT	F
	SURFACE DISINFECTANT	Xi, N
	ETHYL ALCOHOL 96%	
BIOCHEMISTRY AND MICROBIOLOGY LABORATORY	ANALYTIC MACHINE SOLUTION	C, Xi
	HAND DISINFECTANT	F
	LPG TANK	E
PATHOLOGY LABORATORY	FORMALDEHYDE 37-40%	Xn, T
	XYLENE	F, Xn, Xi, T, M
	ETHYL ALCOHOL 96%	F
	METHANOL	F, T, M
	TISSUE STAINS	F, T, M
	HAND DISINFECTANT	F
INSERVICE	HAND DISINFECTANT	F
	SKIN DISINFECTANT	XI
	TOOL DISINFECTANT	XI
	SURFACE DISINFECTANT	Xi, N
	ETHYL ALCOHOL 96%	F
	OXYGEN TANK	E
LAUNDRY	ALKALINE WASHING MATERIAL	C

themselves not having enough knowledge were significantly higher in cleaning staff, physician and assistant personnel ($p = 0.046$, $p < 0.001$ and $p < 0.001$, respectively) (Figure 8).

Answers given by the participants to the question of "Would you like to get information about the hazardous materials used in hospital?" were examined. Seventy five per cent of the participants told they

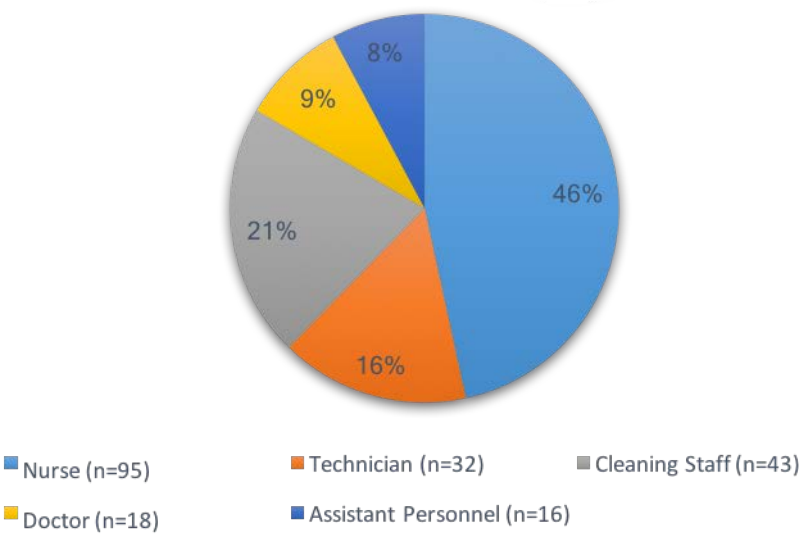

Figure 1. Distribution of 204 health personnels by profession who participated in the questionnaire conducted for awareness of hazardous materials in hospital environment.

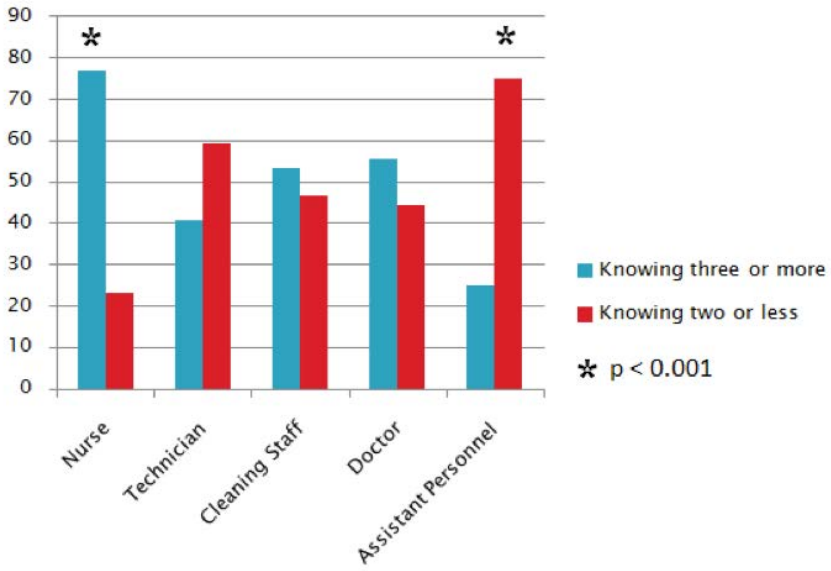

Figure 2. Distribution of health personnel based on knowing hazardous materials.

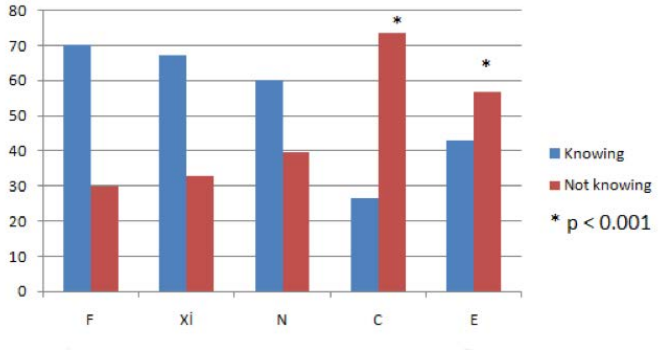

Figure 3. Percentages of questionnaire participants knowing hazardous material warning signs [Flammable (F), Irritant (Xi), Hazardous for Environment (N), Corrosive (C) and Explosive (E)].

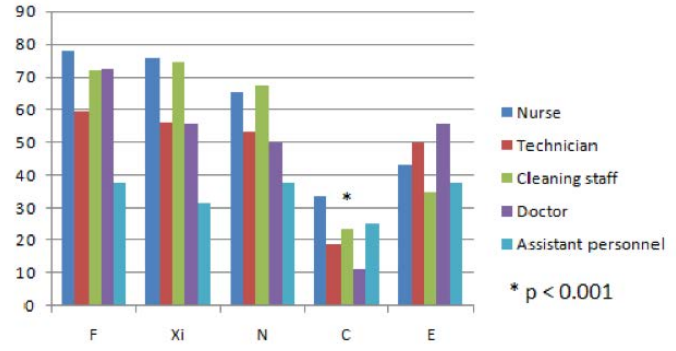

Figure 4. Percentage of knowing hazardous material warning signs by professions [Flammable (F), Irritant (Xi), Hazardous for Environment (N), Corrosive (C) and Explosive (E)].

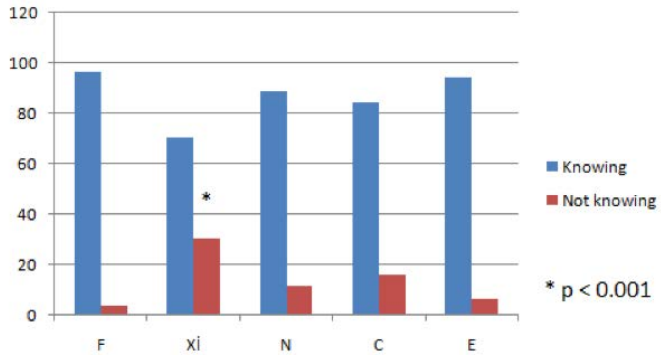

Figure 5. Percentages of questionnaire participants knowing symbols and meaning of hazardous material warning signs [Flammable (F), Irritant (Xi), Hazardous for Environment (N), Corrosive (C) and Explosive (E)].

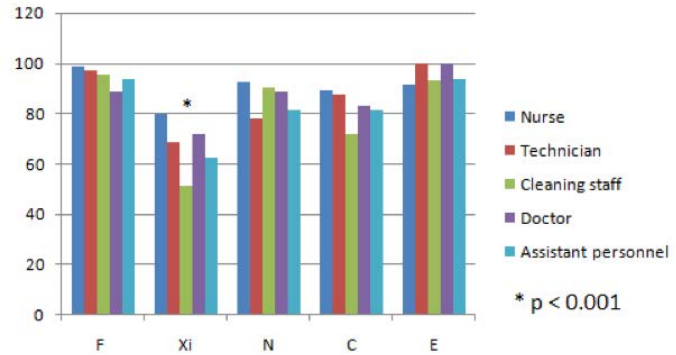

Figure 6. Percentage of knowing symbols of hazardous material warning signs by professions [Flammable (F), Irritant (Xi), Hazardous for Environment (N), Corrosive (C) and Explosive (E)].

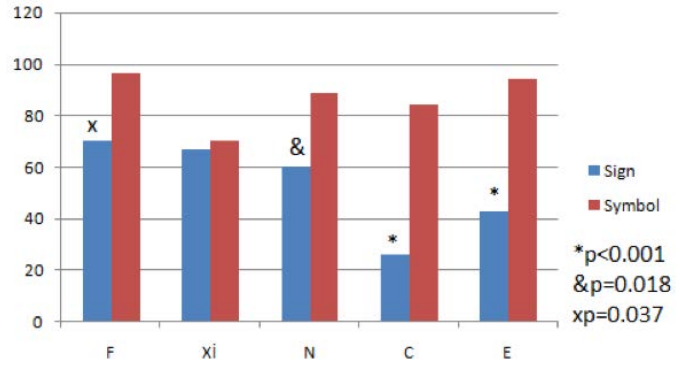

Figure 7. Percentages of knowing the warning signs and symbols of hazardous materials [Flammable (F), Irritant (Xi), Hazardous for Environment (N), Corrosive (C) and Explosive (E)].

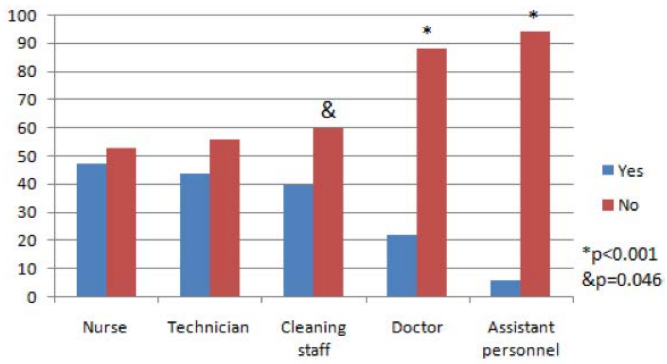

Figure 8. Percentages of questionnaire participants considering themselves knowledgeable enough about hazardous materials used in hospital.

wanted to get detailed information about hazardous materials. An analysis of participants after grouping by their profession showed that workers demanding detailed information for hazardous materials were high in all professions (Figure 9).

Finally, participants were asked to mention whether the signs put on hazardous material cabinets in hospital were useful. Ninety per cent of them thought that the warning signs and symbols put on cabinets were useful. Analysis after grouping participants by their professions revealed that workers who considered the signs were useful were clearly high in all groups ($p < 0.001$) (Figure 10).

All departments of the Tertiary Hospital were surveyed and hazardous materials in working environments were determined. Areas where hazardous materials were kept and stored in the hospital were re-organized according to the current regulations.

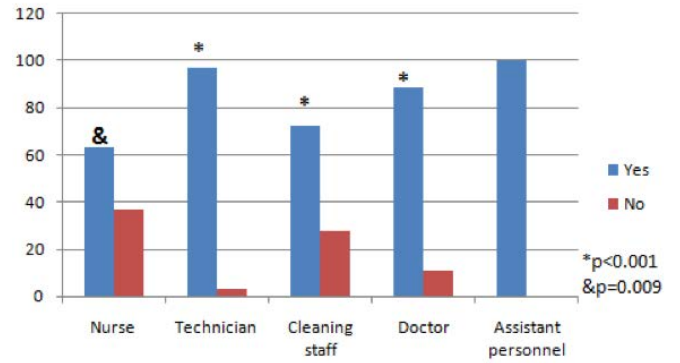

Figure 9. Distribution of answers given by questionnaire participants from different professions to the question of "Would you like to have detailed information about hazardous materials used in hospital?"

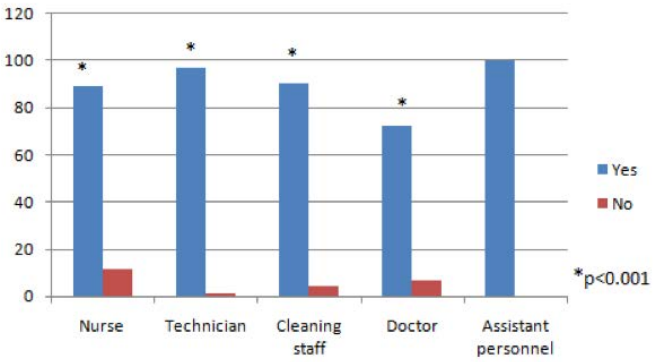

Figure 10. Figure 10. Comparison of answers given by questionnaire participants from different professions to the question of "Whether warning signs and symbols put on hazardous material cabinets in hospital are effective?"

DISCUSSION

The health care industry is one of the largest employers, and hospital workers face safety risks comparable to some of most dangerous jobs in the worldwide. Health and safety risks in a healthcare environment not only put at risk the health of workers. They also impose significant costs on healthcare institutions, increasing the cost of medical care for everyone and compromising the quality of patient care. Awareness of occupational health and safety among the employees is important in the hospital. The work environment must be free from hazards and all employees should be aware of their health and safety.

There are thousands of chemicals and other toxic substances which nurses are exposed in practice. Hazardous chemical exposures can occur in a variety of forms including aerosols, gases, and skin contaminants from medications used in practice. Materials which have one or more of the features of explosive, oxidizing, very easily flammable, easily flammable, flammable, genotoxic, toxic, harmful, corrosive, irritant, allergic, carcinogenic, mutagenic and dangerous for environment are considered hazardous since they can pose risk for health and safety of workers. Management of these materials is crucial for hospitals because the process from release to destroying them is a part of daily hospital activity [5-9].

From the various reviews available on occupational health hazards and their precautions, various problems of physical, chemical, biological, and psychological nature were identified [10-12]. Hazardous material management, also an inseparable part of environment management, should have strict standards to be observed. These standards should include monitoring through written procedures of obtaining, transporting, storing and disposal of hazardous materials. Potentially hazardous materials should be evaluated and approved before use. Product safety and information forms containing the potential dangers of hazardous materials used in hospital should be obtained from producers and sellers. For an appropriate management of hazardous materials, a written procedure should be produced which carries information about the name, explanation, synonyms, area of use, risks for human and environment, directions for use, protective precautions, emergency and first aid directions and appropriate disposal methods. Elimination or decrease of hazardous materials could be facilitated through establishment of hazardous material management systems in hospitals; thus, impacts of materials dangerous for human health could be lowered both inside and outside hospital. Hospitals can also prevent potential dangers through replacing hazardous materials with less hazardous ones to be used during hospital operations. Hazardous materials should be transported with care not to leak, spill or scatter around. Their transport should be carried out based on product safety information form and hazardous materials inventory list. Workers in all hospital departments should be trained about the presence and use of hazardous materials [13]. In this study, knowledge of healthcare workers was investigated about on hazardous materials. Participants expressed their inadequacy in this regard. The tertiary hospital workers in the present study demanded detailed information about hazardous materials. The self-report survey was conducted in a tertiary hospital research hospital and cannot be generalized without replication to other settings.

Most of the hazardous materials used in laboratory studies are harmful for health. Ensuring a safe working environment through establishment of proper recording and using procedures and organizing training programs for the use of these materials mean prevention of potential dangers for workers, patients and environment. Many chemicals used have the potential to be dangerous and they carry various signs on their packages showing this feature. The present study showed that health workers did not know characteristics of dangerous materials used in hospital and were not aware of the dangers posed to them. Efforts to reduce health and safety risks in the healthcare workplace may have positive impact on workers, patients and communities. Institutions that focus on developing and maintaining a culture of safety could effectively reduce most of the risks. A safety culture can also lead to significant process improvements, creating greater operational efficiencies and increasing profitability [14].

Storages in hospitals designated for hazardous materials should be kept locked and access of unauthorized people to them should be prohibited. Chemicals in stores should be kept in their original packages. Temperature of storages should be 18-20 °C. Storage areas for harmful chemical materials and products should be equipped with necessary heating, isolation, aeration, warning and fire extinguishing systems considering the possible harms caused by the materials stored. Conditions suggested by the supplier should be taken into account in storing the material [15]. Therefore, we designated a separate part for hazardous materials in hospital storage within the context of the present study based on safety considerations.

Flammable and combustible liquids should be stored in places such as cabinets or shelves with

protection against fire. If chemical material to be used is hazardous, amount of purchase should be suitable for anticipated duration of use. In places where storing facilities are limited frequent purchasing should not be made. Hazardous materials should be stored based on their expiration date. Shelves should be labeled specifying class symbols of hazardous material. Storage and cabinets should be labeled according to danger posed by the materials they contain. Cabinets where hazardous materials were stored were labeled using danger warning signs in the present study. The questionnaire study showed that workers found the danger warning signs placed on hazardous material cabinets useful.

Healthcare workers have a significant role in provision of a safe and quality service in health institutions. It is necessary for health workers to know what the hazardous materials and their risks are, where they are located, in what stage of the study they are used, what are the contact and entrance ways into the body and the way they affect the worker. Awareness of occupational safety plays an important role in the prevention of occupational diseases [16]. Number of studies aiming to determine the dangers and risks of hospital environment is quite limited [17]. Healthcare workers must receive adequate information and training about the risks derived of the presence of any hazardous chemical agent present in their working place, as well as about the prevention and protection measures to be adopted [18]. The present study revealed that health workers did not consider themselves having enough knowledge about hazardous materials used in hospital and demanded detailed information on this issue. Aspects such as periodical training and evaluation are key factors in order to achieve the objective in a satisfactory way.

Limitations

The self-report survey was conducted in a tertiary hospital research hospital and cannot be generalized without replication to other settings. Results of the present study should not be generalized for all health workers since it was carried out only on workers in Gaziosmanpaşa University Health Research and Practice Hospital. It should also be kept in mind that results could be subjective since evaluations were made solely based on the responses by workers.

CONCLUSION

The present study was conducted in a tertiary hospital. Hospital workers did not have enough information about hazardous materials. Nevertheless, meaning of warning signs of hazardous materials were not known well by health workers. Warning signs and symbols of hazardous materials should be known for all workers. Nevertheless, meaning of warning signs of hazardous materials were not known well by health workers in the present study. Interestingly, symbols of hazardous materials were known more than warning signs. It was concluded that, in order to clearly indicate the cabinets containing hazardous materials, they need to be labeled using hazardous material warning signs and symbols. Health workers need effective trainings for these materials. Warning signs and symbols of hazardous materials should be known for all workers. In order to clearly indicate the cabinets containing hazardous materials, they need to be labeled using hazardous material warning signs and symbols.

Authorship declaration

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

Conflict of interest

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

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The European Research Journal 2019;5(2):350-354 ORIGINAL ARTICLE

Evaluation of the effect of hypnobirthing education during antenatal period on fear of childbirth

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ABSTRACT

Objectives: The objective of this research was to analyse the effect of hypnobirthing education given to pregnant women during antenatal period on fear of childbirth.

Methods: This is an educational interventional case-control study. A total of 51 pregnant women were studied together during the 12th week of pregnancy. Ethical Committee and related consents were taken. Data was evaluated by using descriptive statistics.

Results: The age average of the pregnant in the control group was 28.70 ± 5.42 years while it was 25.74 ± 5.16 years for the case group. Women's gestational week averages were 20.87 weeks for study and 24.10 weeks for control group. In the study, the pre-training scale scores of the cases and control groups were compared with the average level of birth fear of the groups (t = 1.848, $p = 0.073$). There was a significant difference between pre- and post-hypnotic scale scores in the birth preparation class (t = -5.329, $p < 0.001$). Before the training; 48% of the case group. Fifty-two percent of the control group is adequately informed about the hypnobirthing problem.

Conclusions: It was found that among the pregnant women who had attended birth preparation classes, positive labour perception of the intervention group pregnant women was higher than that of the control group pregnant women who hadn't had hypnobirthing education and there was a significant difference between them.

Keywords: Birth preparation, fear of childbirth, hypnobirthing, midwife, pregnant

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Pregnancy and labour are normal physical events which are emotionally, psychologically and culturally important for women and their families [1]. Many pregnant women's concerns about the approaching delivery increase throughout pregnancy. However, some women experience certain significant fear and anxiety about giving birth [2].

Fear affects a woman's decision making process. According to Dick Read's "fear-tension-pain syndrome", fear causes muscular and psychological tension which results in prolonged labour and increase in pain perception. A woman who has decided upon hypnobirthing learns how to relax her whole body, especially perineal and uterus muscles, and keep them under control [3].

Reasons for fear of childbirth vary, current literature shows that there are many reasons like infant death or impairment during delivery, experiencing pain, compulsory delivery by caesarean section, death, episiotomy, being helpless at delivery, the baby being

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malformation, not trusting delivery staff, damage or laceration at expulsion phase, thinking herself incapable of giving birth, panicking during delivery, involuntary screaming, losing self-control, being alone during delivery and not knowing how delivery will be [4]. Fear of childbirth is a preliminary factor for elective and urgent caesarean section. Maximum effort is required to prevent traumatizing negative delivery experience especially in women who have never given birth before [2].

The objective in birth preparation training is to help mother-to-be and couples make accurate decisions about pregnancy, labour and postnatal periods and go through these periods in the most pleasant way [5]. It was found in a study by Melender [6] that 78% of the women had fears about pregnancy and labour. It has been observed that doctors, nurses and midwives working at delivery rooms today provide support to delivery with two philosophies. One of them is "the pregnant cannot do delivery alone and so intervention is required". Although rare, the second is "delivery is done by the pregnant herself, but it should be reinforced" [7].

The frequently used descriptive treatment modalities for labour pain can be listed as yoga, meditation, hypnosis, relaxation, imagery and breathing exercises [8]. Rather than being a technique, hypnobirthing can be called a labour philosophy that prepares the pregnant for delivery physically and psychologically. This approach is getting more and more prevalent in many countries around the world as HypnoBirthing Institutes, set up by Marie F. Mongan with its headquarters in the USA, regularly train practitioners [7].

Hypnobirthing focuses on teaching self-hypnosis, breathing slowly, letting oneself go and the art of enjoying labour calmly and serenely, discovering the method of delivery without stress, forming a positive expectation, trust and faith in the spontaneity of labour. Midwives enable the pregnant to live the natural process of labour by teaching the basic labour philosophy, physiological and chemical consequences of fear, how to do away with the hitches of fear and stress and how to relax before and at the time of delivery [7]. A pregnant woman who has decided for hypnobirthing learns how to relax her whole body, perineal and uterus muscles in particular, and how to keep them under control [9]. Current literature has shown that by decreasing childbirth fear and anxiety, hypnobirthing decreases pain perception and use of analgesic and oxytocin, increases vaginal delivery rate and level of labour satisfaction, decreases postpartum depression rate and is a safe method for it does no harm to mother or newborn[10]. The objective of this research was to analyse the effect of hypnobirthing education given to pregnant women during antenatal period on tokophobia. The research hypotheses are as follows: H0: There is no significant difference in terms of childbirth fear between women who have had hypnobirthing training and who haven't. H1: Fear of childbirth in women who have had hypnobirthing training is less than those who haven't had this training.

METHODS

Study Population

This educational interventional case-control study was conducted in February 2015 at Özgül Gündüz Public Health Building of Bornova Municipality in İzmir. The research population consisted of pregnant women during the 12th week or more at the time of the research who applied to pregnancy class at Özgül Gündüz Public Health Building of Bornova Municipality in İzmir.

The control group was determined as at least 30 participants in accordance with parametric tests and later its capacity was assessed using power analysis. With I. Type error $\alpha = 0.05$ and II. Type error $\beta = 0.1$ (power = 90%), the sampling size was determined as total 60 participants; 30 study group and 30 control group.

Upon the approval and consent of Ege University Medical Faculty Clinical Research Ethics Committee, the case group involved 31 pregnant women who applied to the institution for antenatal education at the time of the research but didn't have hypnobirthing education.

The control group involved 20 pregnant women chosen among the population who had previously participated in antenatal education but hadn't had hypnobirthing education, resided at the stated residence at the time of the research and accepted to participate in the research willingly.

The education was given one hour a week totalling

four hours in four weeks. The data gathering tools used in the research were a questionnaire developed by the researchers within the scope of literature review involving 36 questions for descriptive characteristics of the women (socio-demographic, obstetric) and 25 questions to determine the knowledge of the women about hypnobirthing and "Wijma Delivery Expectancy/ Experience Questionnaire (W-DEQ)-A Version", whose reliability and validity had been done by Körükçü *et al*. [12], to measure the fear of childbirth level of the pregnant women.

The dependent variable was fear of childbirth score while the independent variables were the case of having hypnobirthing education, pregnancy number, delivery type and educational status.

Data Gathering

The research data were gathered in three stages. The 1st stage was conducted with only the study group in birth preparation class at the institution at the start of the four-week training process and the 2nd stage was conducted with only the control group by calling the group who had previously had birth preparation education to the institution while the 3rd stage was conducted with the study and control groups at the end of the four-week education.

Data Gathering Tools

The entire data gathering forms of the study were gathered by the researcher through face-to-face interview and observation methods. The study and control groups were applied:

1. Informed Voluntary Consent Form
2. Case Report Form-1 involving descriptive characteristics (Appendix I)
3. Case Report Form-2 involving information about hypnobirting (Appendix I)
4. Wijma Delivery Expectancy/ Experience Questionnaire (W-DEQ)-A Version (Appendix II)

Statistical Analysis

The analyses of the data were conducted on the computer using Statistical Package for Social Science 16 (SPSS 16.0). For number and percentage (%) distributions of the descriptive data in parametric conditions, t-test was used in dependent and independent groups while chi-square test was used for the data acquired by counting. The results were analysed at 95% reliability interval and 0.05 significance level.

RESULTS

Socio-Demographic Findings

The age average of the pregnant in the control group was 28.70 ± 5.42 years (the youngest: 21, the oldest: 37) while it was 25.74 ± 5.16 years (the youngest: 17, the oldest: 39) for the case group. The gestational week average of the pregnant in the case group was 20.87 weeks, while it was 24.10 weeks for the control group. 35.50% of the women in the case group were secondary school graduate while 35.50% were high school graduate or above. Whereas 20.00% of the women in the control group were secondary school graduate, 10.00% were high school graduate or above. The case of voluntary pregnancy in the women in the case group was 90.30% and it was the same in the women in the control group (90.00%). While 35.50% of the pregnant women in the case group stated that they had given at least one live birth, 70.00% of those in the control group stated that they had given at least one live birth. 49.10% of the pregnant revealed that they were anxious and added that the first reason for their anxiety was the fear that their baby would get harmed during delivery. While

Table 1. The mean (W-DEQ)-A points for study and control group before hypnobirthing education

Pre-Education	Case Group (n = 30)		Control Group (n = 30)		t test	
	Mean	SD	Mean	SD	*t*	*p*
(W-DEQ)-A	79.47	11.58	84.60	16.71	-1.38	3.71

(W-DEQ)-A = Wijma delivery expectancy/ experience questionnaire-A version

Table 2. The mean (W-DEQ)-A points of study group before and after hypnobirthing education

Case Group	Pre-Education (n = 30)		Post-Education (n = 30)		t test	
	Mean	SD	Mean	SD	*t*	*p*
(W-DEQ)-A	79.47	11.58	67.10	11.00	5.21	**< 0.001**

(W-DEQ)-A = Wijma delivery expectancy/ experience questionnaire -A version

76.48% of the women stated that they hadn't heard of hypnobirthing before, it was also determined that 56.86% had a bath when they experienced pain during pregnancy.

Findings of Hipnobirthing and Fear of Childbrth

Fear of childbirth was found that similiarly between case and control group pre- hypnobirthing education (t =-1.38, p = 3.71) (Table 1).

In case group pregnancies who get hypnobirthing education in the birth preparation class, it was found that there was a significant difference between pre and post education scale mean scores. (t = 5.21, $p < 0.001$) (Table 2).

Table 3 shows level of hypnobirthing knowledge pre-hypnobirthing education in case and control groups. In terms of knowledge status, 48% of the case group and 52% of the control group were found to be sufficient.

DISCUSSION

In terms of some individual characteristics of the pregnant, it was found that age average of the pregnant in the case group was 25.74 ± 5.16 years, while it was 28.70 ± 5.42 years for those in the control group. In terms of the age average of the women who had participated in birth preparation classes, among the studies in Turkey, Şeker and Sevil [12] found the age average 27.47±3.62 years in her study and among the international studies, Bergström *et al*. [13] found the age average of 28 ± 8 years. The age average of the pregnant in our study shows similarities to the other study results. While 35.50% of the women in the case group were secondary school graduate and 35.50% of them were high school graduate or above, 20.00% of those in the control group were secondary school graduate and 10.00% of them were high school graduate or above. In line with our study, it was found in a study by Coşar and Demirci [14] that education level of the pregnant in the case group (77.20% university graduate) was higher than education level of those in the control group (51.40% elementary school graduate).

The groups also showed similarities in gestational week and the case of voluntary pregnancy. It was determined in an intergroup comparison before education that 6.50% of the case group and 20.00% of the control group were found adequate in knowledge status. When the scale score averages of the pregnant before education were compared according to groups, the difference wasn't found to be significant ($p > 0.05$). When the averages of "Wijma Delivery Expectancy/ Experience Questionnaire" scores of the groups in birth preparation class before and after Hypnobirthing education were compared, scale score averages of the pregnant after education were found

Table 3. Comparison of hypnobirthing knowledge level of case and control groups pre- education

Group	Sufficiency Level of Hypnobirthing Knowledge				TOTAL	
	Sufficient (X ≥ 70)		Insufficient (X ≤ 69)			
	n	%	n	%	n	%
Case	14.3	47.7	15.7	52.3	30	100.0
Control	15.7	52.3	14.3	47.7	30	100.0
TOTAL	30	100.0	30	100.0	60	100.0

(Chi-square: 0.267, $p = 0.606$)

to be lower than those before education. The difference between the score averages was statistically significant (t = .329, $p < 0.001$). After education, there was a decrease in fear perception of the pregnant. It was determined that after hypnobirthing education, knowledge scores of the pregnant increased (t = -9.117, $p < 0.001$) and their fear of childbirth perception decreased. In the literature, it is stated that having education during antenatal period decreases fear of childbirth.

CONCLUSION

In our study, a significant difference was found between fear of childbirth perception of the pregnant before and after education, which in line with the literature. This study will yield more extensive discussions about the evaluation of the effect of antenatal education based on hypnobirthing philosophy on birth perception and delivery adaptation process and will thus become a basis for future studies. It was determined that birth perception of the pregnant became more positive when they attended antenatal education and birth preparation classes and were given labour support. It is suggested that birth preparation classes based on hypnobirthing philosophy should be implemented and made more common and that birth preparation education should be included in the curriculum to teach hypnobirthing philosophy to students of midwifery and nursing.

Ethical Explanations

Approval and consent of Ege University Medical Faculty Clinical Research Ethics Committee were obtained. Official consent was obtained from Bornova Municipality. Consent of Öznur Körükçü, who adapted W-DEQ-A scale to Turkish, was obtained to use the scale. Written and oral consent of the pregnant women who accepted to participate in the research was obtained.

Authors' Contribution

AB: Conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscriptand final approval of manuscript; **EÇF:** Analysed data, did review and critical revision; **NS:** Did review and critical revision.

Conflict of interest

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

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The European Research Journal 2019;5(2):355-360 ORIGINAL ARTICLE

The association between lipid profile and bone mineral density in subjects with ankylosing spondylitis

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ABSTRACT

Objective: This study aims to investigate the relationship between serum lipids and bone mineral density in ankylosing spondylitis patients.

Methods: A total of 94 ankylosing spondylitis patients fulfilling the 1984 Modified New York Criteria who had serum lipid levels and bone mineral density scores in medical records were included in this study. These patients treated with nonsteroid antiinflammatory drugs. Their files were examined in detail. Later demographic and laboratory features were recorded to the research form. Dual-energy X-ray absorptiometry was used to assess bone mineral density in two bone sites of femur (neck, intertrochanteric zone and trochanter) and spinal lumbar vertebras (Lumbar 1-Lumbar 4).

Results: Significant and positive correlation was found between high density lipoprotein and femoral neck bone mineral density (r = 0.356, p = 0.021) in osteopenic group and in osteoporotic group (r = 0.005, p = 0.040).

Conclusion: According to our study significant and positive correlations are found between high density lipoprotein and femoral neck bone mineral density in osteopenic and osteoporotic group. However, we believe that more studies are needed about this research.

Keywords: Ankylosing spondylitis, lipid profile, bone mineral density

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Ankylosing spondylitis (AS) is an inflammatory rheumatic disorder and a prototype of spondyloarthritis, characterized by axial skeleton and sacroiliac joint involvement. In 90% of patients, the first symptoms develop before 40-45 years and the mean average age is 28.3 years [1].

The incidence of osteopenia or osteoporosis in these patients is reported to be 19-62% [2]. Bone loss in AS appears to be multifactorial and involves different mechanisms at different stages of disease [3]. Also there is association between inflammation and lipid changes [4]. The association between serum lipids and bone mineral density (BMD) has been investigated in previous studies [5-7] but these relationships have not yet been described in AS.

In our study, we investigated the relationship between serum lipids and BMD in AS patients. To the authors' knowledge, this is the first study in AS patients which evaluated the relationships between serum lipids and BMD.

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METHODS

Our study was carried out at Department of Physical Medicine and Rehabilitation, Division of Rheumatology, Aydın, Turkey from January 2017 to June 2017. The ethics committee of the Institution approved the study and all patients signed the Informed consent form. 94 male patients who were diagnosed with AS according to the 1984 Modified New York criteria and who had serum lipid levels and BMD scores in medical records were included in this study. The all medical records of these patients in our hospital were analysed and later ages, gender, body weight and height, body mass index (BMI), serum lipid levels [high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), total cholesterol (TC) and total triglyceride (TG) and BMD scores of the patients were recorded to the research form. AS patients (94 male) were treated with nonsteroid antiinflammatory drugs (NSAIDs).

Dual-energy X-ray absorptiometry (DXA) was used to assess BMD in two bone sites of femur (neck, intertrochanteric zone and trochanter) and spinal lumbar vertebras (Lumbar 1- Lumbar 4). Calibration of bone densitometer (Hologic, Inc., Waltham, MA, USA) was performed weekly by using appropriate phantoms. The precision rror (PE) is usually expressed as the coefficient of variation (CV), which is the ratio of the standard deviation to the mean of the measurements [8]. The PE for BMD measurements was 2 to 3% in the femoral and 1 to 1.5% in the lumbar regions. All scans were performed according to the manufacturer's guidelines. In patients with spinal implant the involved lumbar vertebras were excluded and the mean BMD of noninvolved vertebras was entered into the analysis.

Baseline characteristics and differences of basic features among male subjects with AS were presented in Table 1.

HDL cholesterol (HDLc), LDL cholesterol (LDLc), TC and TG were measured by spectrophotometric enzymatic colorimetric tests using Abbott Diagnostics and VLDL cholesterol (VLDLc) by using the formula VLDLc = Triglycerides /5. Normal ranges were considered to be: 35-55 mg/dL for HDLc, 30-130 mg/dL for LDLc, 0-200 mg/dL for TC and 0-149 mg/dL for TG. Body mass index (BMI) was calculated by the formula BMI = weight/height2, where height is expressed in meters and weight in kilograms. We considered patients with a T-score etween -1.0 and -2.49 to be osteopenic and those with a T-score < -2.5 to have osteoporosis.

Inclusion criteria were male AS subjects. Because of some conditions which could potentially affect serum lipid levels, the patients who had some disorders of neurologic, endocrinologic and cardiovascular systems, and a history of using some drugs (e.g., oral contraceptives, corticosteroids, lipid lowering drugs, hormones, thyroid hormones, anticonvulsive drugs, heparin, aluminum containing antacids, lithium, omega-3 fatty acids, or other nutrients supplements) and smoking or alcohol consumption were excluded from the study.

Statistical Analysis

Normally distributed variables were tested by T-test in AS patients. To compare the correlations between serum lipids and BMD. Spearman correlation test was used. Partial correlation with adjustment for weight, height, BMI and age was used to determine the association between BMD in different bone sites and serum lipids. Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS), ver 19.0 (IBM Corp.; Armonk, NY, USA) and $p < 0.05$ was considered to be statistically significant.

RESULTS

Ninety four patients (age 42.44 ± 10.75 years, 94 male) diagnosed with AS were enrolled in the study. Mean weight was 84.04 ± 13.22 kg, mean height was 167.74 ± 25.79 cm, mean BMI index was 28.76 ± 4.94 kg /m2, mean disease duration was 16.3 ± 9.8 years. Mean TG was 146.70 ± 91.01 and mean of TC was 195.64 ± 41.22. Means of HDLc, LDLc and VLDLc were 41.65 ± 9.84, 123.67 ± 36.28 and 29.03 ± 18.30, respectively (Table 1).

Significant correlations were not found between HDLc, LDLc, VLDLc, TC, TG and BMD scores of the patients in normal group (Table 2).

Significant and positive correlation was found between HDLc and femoral neck BMD (r = 0.356, p = 0.021) in osteopenic group and in osteoporotic group (r = 0.005, p = 0.040) (Table 2).

Table 1. Baseline characteristics and differences of basic features among male subjects with ankylosing spondylitis

	Male subjects with ankylosing spondylitis (n = 94)
Age (year)	42.44 ± 10.75
Gender	
Male, n (%)	94 (100)
Female, n (%)	0 (0)
Weight (kg)	84.04 ± 13.22
Height (cm)	167.74 ± 25.79
BMI (kg /m^2)	28.76 ± 4.94
Disease duration (year)	16.3 ± 9.8
TG (mg/dL)	146.70 ± 91.01
TC (mg/dL)	195.64 ± 41.22
HDLc (mg/dL)	41.65 ± 9.84
LDLc (mg/dL)	123.67 ± 36.28
VLDLc (mg/dL)	29.03 ± 18.30
BMD of femoral neck T-score	-0.89 ± 0.95
BMD of spinal lumbar vertebras T-score	-1.10 ± 1.62

Data are shown as mean±standard deviation or number (%). BMD = bone mineral density, HDLc = high density lipoprotein, LDLc = low density lipoprotein, TC = total cholesterol, TG = total triglyceride, VLDLc = very low density lipoprotein

DISCUSSION

The association between serum lipids and BMD has been investigated in previous studies [5-7]. Hadis *et al*. [5] investigated the relationships between serum lipids and BMD in 85 male patients with spinal cord injury (SCI). As a result of this study a positive correlation between HDL and femoral neck BMD (r = 0.33, p = 0.004) was found although any a relation between others and BMD scores had no. Their study does not support a strong association between serum lipids and BMD in patients with SCI. Garg *et al.* [6] studied the relationships of lipid parameters with BMD in 2,347 participants. In this investigation, a total of 924 male,788 premenopausal and 635 postmenopausal female participants were included. As a result of this study, BMD of male participants at femoral neck, femur total and lumbar spine were negatively correlated with TC and LDLc and positively with TG. In premenopausal women, there was no correlation of any lipid parameters with BMD. In postmenopausal women, a significant negative correlation was found between femur total BMD with TC and LDLc. Furthermore, there was a negative correlation between TG and femur BMD, while a positive correlation was found between HDLc and the same region in these women. They reported a weak correlation between lipid parameters and BMD at various sites in men, pre- and post-menopausal women. Catalina *et al*. [7] investigated lipid profile in 610 postmenopausal women with osteoporosis. Authors were grouped according to the age (< 50 years, 51-60 years, 61-70 years and >0 years) and presence or absence of a history of fragility fracture of patients. In this research, they determined significant correlations between BMD with BMI and lipid profile. The results presented in this report provide support for an association between osteoporosis and the circulating lipid profiles. Makovey *et al*. [9] investigated the association between TC and BMD in 497 female patients (224 premenopausal and 273 postmenopausal women). They showed that BMD is significantly negatively correlated with TC and LDLc in postmenopausal

Table 2. The relationship between serum lipids and bone mineral density in male subjects with ankylosing spondylitis

Category	**Male subjects with ankylosing spondylitis (n = 94)**				
Normal Group	**TG**	**TC**	**HDLc**	**LDLc**	**VLDLc**
Femoral neck BMD T-score					
r	0.036	0.129	0.176	0.136	0.030
p	0.857	0.523	0.381	0.499	0.881
Spinal lumbar vertebras' BMD T-score					
r	0.132	0.042	0.186	0.041	0.139
p	0.510	0.834	0.353	0.838	0.489
Osteopenic Group	**TG**	**TC**	**HDLc**	**LDLc**	**VLDLc**
Femoral neck BMD T-score					
r	0.195	0.214	0.356	0.017	0.174
p	0.216	0.174	**0.021**	0.915	0.270
Spinal lumbar vertebras' BMD T-score					
r	0.264	0.072	0.280	0.123	0.317
p	0.091	0.648	0.072	0.437	0.479
Osteoporotic Group	**TG**	**TC**	**HDLc**	**LDLc**	**VLDLc**
Femoral neck BMD T-score					
r	0.233	0.110	0.005	0.109	0.237
p	0.262	0.142	**0.040**	0.604	0.254
Spinal lumbar vertebras' BMD T-score					
r	0.164	0.301	0.006	0.068	0.163
p	0.433	0.144	0.978	0.746	0.437

BMD = bone mineral density, HDLc = high density lipoprotein, LDLc = low density lipoprotein, TC = total cholesterol, TG = total triglyceride, VLDLc = very low density lipoprotein

women not receiving hormone replacing therapy (HRT) and with HDLc in postmenopausal women receiving HRT [9]. Orozco *et al*.'s [10] study included 52 overweight early postmenopausal women, with no history of HRT, or any current or past pathology or treatment that could alter bone or lipid metabolism. As a result of their study early postmenopausal women with atherogenic lipid profile, defined as TC ≥ 240 mg/dl or LDLc ≥ 160 mg/dl or lipoprotein (a) ≥ 25 mg/dl have lower lumbar and femoral BMD and have an increased risk of osteopenia than those with normal lipid profile. They suggested that hyperlipidemia could be associated with osteoporosis and bone status should be evaluated in women with hyperlipidemia. Tankó *et al*'s [11] study included 340 postmenopausal women between 50-75 years. They showed that serum TC is significant negative correlated with BMD at the lumbar spine (r = -0.21, $p < 0.0001$) and distal forearm (r =- 0.14, $p = 0.013$), but not at the hip. They suggested that the weak associations between spine BMD and TC can be explained by the fact that both variables are simultaneously affected by estrogen deficiency rather than by a direct influence of serum cholesterol on osteoblast function. Uyama *et al.* [12] investigated the relation of carotid atherosclerosis to BMD in 30 postmenopausal women aged 67 to 85 years. They demonstrated a significant correlation of plaque score with TC level and low total BMD. In the prospective study of Samelson *et al.* [13] assesed the association between TC and BMD in 712 female and 450 male patients. No significant association between TC and BMD was found in female and male patients for any of the bone sites considered. Solomon *et al*'s [14] study included 13,592 patients. In crude analyses,

higher TC and LDLc levels were associated with lower BMD (both p values for trend <0.001), whereas higher HDLc levels were associated with higher BMD (*p* value for trend <0.001). However, in fully adjusted models, there was no significant relationship between TC, LDLc, or HDLc levels and BMD (all *p* values for trend > 0.1). Wu *et al*. [15] enrolled total 5,000 individuals (2,170 male and 2,830 female patients) to their study. These patients were divided into three groups. Group 1 was composed of male subjects; group 2, female subjects under 50 years; and group 3, females aged over 50 to exclude pre-menopausal females. The results of this study showed that BMD is negatively correlated with TC, LDLc, TG for females in Group 2. But it is only negatively related to TG for females in Group 3. In this mentioned study as a result, any a correlation was not found between BMD and lipid levels.

The responsible mechanisms about the association between osteoporosis and the lipid profile was announced in some studies [16, 17]. Franceschi *et al*. [16] explained this association as a molecular level "inflammaging" theory which can lead to osteoporosis. In another theory, osteoporosis is based on the "osteo-lipo-vascular interactions". Mesenchymal stem cells are capable of differentiating into osteoblasts, vascular smooth muscle cells and adipocytes. As a result of this study bone, adipose and vascular systems provide the epidemiological link between hyperlipidemia and osteoporosis [17].

CONCLUSION

As a result of our study we aimed to investigate the relationship between serum lipids and BMD in AS patients. We enrolled a total of 94 AS patients fulfilling the 1984 Modified New York Criteria who had serum lipid levels and BMD scores. We found significant and positive correlations between between HDL and femoral neck BMD in osteopenic and osteoporotic group. Our study supported the association between osteoporosis and the lipid profile. We can suggest that lipid reducing medications such as statins increases BMD and statins can be used in OP treatment.

Authorship Declaration

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

Conflict of interest

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

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The European Research Journal 2019;5(2):361-368 ORIGINAL ARTICLE

The relationship between hypernatremia and breast milk sodium levels in newborns with hypernatremic dehydration

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ABSTRACT

Objectives: Breast-feeding with high sodium content milk may cause hypernatremic dehydration in neonates (NHD). The number of cases with NHD tends to increase particularly in the higher temperature seasons. In this prospective case-control study, the relationship between NHD and breast milk sodium (Na) levels and demographic features of NHD were investigated during the summer season.

Methods: The study included term newborns admitted to the neonatal intensive care unit of our hospital with the diagnosis of hypernatremic dehydration between June 2009 and October 2009. Serum sodium level ≥ 150mEq/L was accepted as hypernatremia. Among 109 NHD patients, breast milk sodium level was evaluated in 50 cases. Term infants without hypernatremic dehydration were taken as the control group (50 cases).

Results: Postnatal age at admission ranged between 2 and 12 days and mean serum Na concentration was 152 mEq/L (150-173 mEq/L). A significant weight loss of >10% was determined in 85% of cases. Breast milk Na was significantly higher in the hypernatremic group (24.3 ± 20.3 mEq/L) compared to the control group (12.6 ± 6.79 mEq/L) ($p < 0.001$). In primiparous mothers, the mean breast milk Na level was statistically higher than that of multipara mothers (21.16 ± 19.9 mEq/L vs 15.48 ± 9.96 mEq/L, $p < 0.016$).

Conclusions: In this study, we demonstrated that high breast milk sodium level was closely related with NHD and being a primiparous mother appeared as a significant factor for high breast milk sodium content. In this respect, all pregnant women especially primiparous should be educated about infant nutrition and neonatal dehydration. Health care providers should emphasize importance of frequent milking and more fluid intake, especially in summer.

Keywords: Breast milk sodium, hypernatremic dehydration, newborn

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Hypernatremic dehydration of the newborn (NHD) is mostly observed in breast-fed newborns and can cause serious complications [1, 2]. Hypernatremia in all ages may occur in association with reduced fluid intake, excessive fluid loss, or excessive Na intake [3]. Neonatal hypernatremic dehydration has mostly been reported in the infants of primiparous mothers with the lack of education on breast-feeding [4]. The etiology of NHD has been suggested to be related to the insufficiency and high sodium content of breast milk. The inadequate volume and high sodium concentration of breast milk have been linked with a delay in the maturation of breast milk [4, 5]. The number of cases with hypernatremic

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dehydration (HD) tends to increase particularly in the summer because of higher temperatures, which can cause dehydration in both the mother and her infant [6, 7]. In the literature, a relationship was reported between weight loss was more than 10% and high serum sodium concentration [8].

In this study, demographic data, as well as clinical and laboratory findings of newborns with HD were evaluated and the relationship between hypernatremia and breast milk sodium (Na) level was investigated during a summer season. It was also aimed to provide suggestions to reduce the number of NHD cases.

METHODS

One hundred and nine term newborns hospitalized for NHD between June and October 2009 at the neonatal intensive care unit (NICU) of Dr. Behçet Uz Children's Hospital (İzmir, Turkey) were enrolled. Neonates with congenital anomalies, chromosomal abnormalities, congenital heart diseases, perinatal asphyxia, metabolic or endocrine disorders, sepsis, prematurity and those born to mothers with intrauterine infections were excluded. Serum Na level > 150 mEq/L and > 160 mEq/L were considered to indicate hypernatremia and severe hypernatremia, respectively [3]. A detailed maternal and infant history was taken, including gestational age, birth weight, postnatal age at admission, presenting symptoms, feeding type, maternal parity, mode of delivery, maternal age, and education level. Physical examination findings, body weight on admission, and percentage weight loss were evaluated. Length of hospital stay, presence of any accompanying comorbidities and complications (renal failure, disseminated intravascular coagulation (DIC), intraventricular hemorrhage, seizure, dural thrombosis, brain damage), and the mortality rate were determined. Complete blood count and serum sodium, glucose, blood urea nitrogen (BUN), creatinine, potassium, chlorine, calcium, serum alanine amino transferase (ALT), serum aspartate amino transferase (AST), total bilirubin, arterial blood gas, C-reactive protein (CRP), and urinalysis were obtained from all patients. Metabolic acidosis was defined as a serum pH < 7.35 and a base deficit ≥ 5 (with normal CO2 level) [3, 9]. Serum glucose level < 40 mg/dL was defined as hypoglycemia and > 125 mg/dL was defined as hyperglycemia [7, 9]. DIC was defined as prolonged activated partial thrombin time (aPTT) and prothrombin time (PT), increased fibrin degradation products, and a thrombocyte count < 100,000/mm^3 [9].

Physiological body weight loss was described as 1-3% per day or < 7% in the first week after birth [10]. The free water deficit was calculated for all patients and added to their daily required fluid intake. Fluid therapy for the patients was adjusted to Na concentration of 77 mEq/L. Hypernatremia was corrected at a maximum decline of 0.5-1.0 mEq/L/h. Serum Na measurements were repeated every 4-6 hours. Treatment period was arranged according to initial serum Na levels. Any complication observed during treatment were recorded.

The fractional sodium excretion (FeNa) was calculated in order to differentiate pre-renal and renal etiology of kidney failure in patients with acute kidney injury. Pre-renal azotaemia for newborns was defined as a fractional excretion of sodium < 2.5%. A renal failure index ≥ 2.5% was considered to indicate acute intrinsic renal failure. Fever was defined as axillary body temperature ≥ 38°C. Blood and urine cultures were obtained in cases with fever or any suspected infection. In patients with neurological symptoms, transfontanel ultrasonography (USG), magnetic resonance imaging (MRI) and electroencephalogram (EEG) were performed.

Healthy mothers without any contraindications for breast-feeding (such as chronic diseases or use of certain medications) were included in the study. Mothers using diuretics while breastfeeding were excluded. Samples of 3-5 ml breast milk were obtained from each mother using an AmedaSMB 50 breast pump. Each sample was placed in dry-flat biochemistry tubes and centrifuged at 3,500 rpm for 5 minutes and the supernatant was stored at -20° C until assayed. The samples were thawed at room temperature before the assay. Breast milk Na concentration was analysed with the indirect ion selective electrodes (ISE) method using a Beckman UnicelDxC 800 Chemistry Analyzer. The results were reported as mEq/L. The control group consisted of normonatremic, normovolemic healthy term newborns whose serum sodium levels were < 150 mEq/L and whose weight losses were no more than 6% in the first week of life. Breast milk Na concentrations were

classified according to the day of the sample collection and were compared with normal values determined in previous studies [9]. The study and control groups were compared to detect any risk factor that might lead to high breast milk sodium concentration, such as parity, delivery mode, maternal age and educational level. Approval for the study was granted by the ethics committee of Dr. Behçet Uz Children's Hospital (İzmir, Turkey) (date/number: 06.11.2009/7) and informed consent was obtained from each contributing mother before enrollment.

Statistical Analysis

Statistical analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA). Qualitative and quantitative (continues) variables were shown as the number of cases (n) with percentages (%) and mean ± standard deviation (SD), respectively. The t-test and Analysis of variance (ANOVA) were used for comparison of continuous variables between the study groups. Pearson correlation analysis was applied to examine the relationship between variables of interest. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

Among 1,235 term infants hospitalized at the NICU during a 5-month period, 109 cases having NHD were included in the study. The incidence of NHD was 8.82% during the study period. With the exception of two cases, all the other infants were born in a hospital. The mean gestational age of the NHD patients was 38.9 ± 1.12 weeks. Postnatal age at admission ranged from 2 to 12 days, with 91.7% of cases being in the first five days of life and a median age of three days. The mean percentage weight loss of NHD patients was 13.7% ± 4.7% and more than two-thirds of infants had > 10% weight loss. Fifty-six (51.3%) infants were delivered by C-section, 61.5% of the mothers were primiparous and 82.6% of the infants were exclusively breast fed. Nearly half of the mothers were graduated from a primary school and when they were questioned about the amount of their milk, only seven were aware of an insufficiency of amount of breast milk. The demographic and clinical

Table 1. The characteristics of the all neonatal hypernatremic dehydration patients (n = 109)

Characteristics	Data
Birth weight (g)	3,319.10 ± 507.93
Gestational age (week)	38.9 ± 1.12
Admission age (day)	3.6 ± 1.93
Admission weight (g)	2,863.57 ± 450.84
Weight loss (%)	13.7 ± 4.73
Maternal age (year)	27.8 ± 5.3
Gender, female	54 (49.5%)
Delivery mode, cesarean section	56 (51.3%)
First-time mothers	67 (61.5%)
Primary school educated mothers	59 (54.2%)
Feeding type	
Only breast milk	90 (82.6%)
Mix (breast milk+ formula)	17 (17.6%)
Only formula	2 (1.8%)
Weight loss degree ≥ 10%	92 (84%)
Weight loss degree < 10%	17 (16%)
Presenting symptom	
Jaundice	76 (68.5%)
Fever	72 (65%)
Poor infant suck	28 (24%)
Decreased urine output or bloody urine	8 (7.3%)
Weight loss	6 (7.3%)
Lethargy	3 (2.7%)
Seizure	1 (0.9%)
Others[a]	5 (4.5%)
Complications	
IHB	78 (72%)
Acute renal failure	70 (65%)
Pre-renal-renal asotemia	53 (49%)
Acute intrinsic renal failure	17 (16%)
Elevated liver enzymes	40 (37%)
DIC	10 (9.2%)
Hypoglycemia on admission	5 (4.6%)
Hyperglycemia on admission	4 (3.8%)
Metabolic acidosis on admission	15 (13.7%)
Seizure	2 (1.8%)
Intracranial hemorrhage	1 (0.9%)
Mortality	0 (0%)

Data are shown as mean± standard deviation or number (%). [a]Others: Vomiting, diarrhea, cutaneous eruption, respiratory distress, DIC = Disseminated intravascular coagulation, IHB = Indirect hyperbilirubinemia

Table 2. Mothers and infant characteristics of the study and control groups

Characteristics	Study group (n = 50)	Control group (n = 50)	*p* Value
Gestational age (week)	38.7 ± 1.14	38.5 ± 0.97	0.440
Birth weight(g)	3,263 ± 538	3262 ± 446	0.996
Gender (female/male)	27/23	29/21	0.687
Admission age (day)	3.6 ± 1.9	5.8 ± 4.7	**< 0.001**
Admission weight(g)	2,831.4 ± 457.9	3,215.8 ± 397.7	**< 0.001**
Cesarean section delivery mode	29 (58%)	23 (46%)	0.234
Maternal age(year)	27.8 ± 5.08	28.56 ± 5.04	0.467
First-time mothers	32 (64%)	21 (42%)	**0.028**
Primary school educated mothers	27 (54%)	26 (52%)	0.841
Serum sodium (mEq/L)	153.60 ± 4.84	138.08 ± 2.70	**< 0.001**
BUN (mg/dL)	25.57 ± 24.82	9.94 ± 5.42	**< 0.001**
Creatinine (mg/dL)	1.16 ± 0.45	0.56 ± 0.47	**< 0.001**
Glucose (mg/dL)	67.50 ± 23.79	83.0 ± 18.9	**< 0.001**
Breast milk Na concentration, (mEq/L)	24.38 ± 20.54	12.62 ± 6.79	**< 0.001**
High breast milk Na concentration	26 (52%)	13 (26%)	**0.008**

Data are shown as mean± standard deviation or number (%). BUN = Blood urea nitrogen

features of all NHD patients are summarized on Table 1.

The mean serum sodium level of the all NHD patients was found 153.19 ± 4.08 mEq/L (range; 150-173 mEq/L). Severe hypernatremia was observed in seven cases. While serum sodium concentration was positively correlated with the amount of weight loss and postnatal age on admission (r = 0.596, $p < 0.05$ and r = 0.549, $p < 0.01$, respectively), it was not related to gestational age, birth weight, gender or mode of delivery ($p > 0.05$). A positive correlation was determined between serum sodium and BUN, creatinine, and uric acid levels (r = 0.675, $p < 0.01$; r = 0.586, $p < 0.01$; and r = 0.452, p < 0.01, respectively). The mean length of hospital stay was 4.3 ± 2.03 days. The average time for the normalization of serum Na level was 30.52 ± 20.09 hours for all cases with hypernatraemia, and 64 ± 30 hours for cases with severe hypernatraemia. There was a positive correlation between the duration of treatment and the serum sodium level as well as the percentage weight loss (r = 0.515, $p < 0.01$ and r = 0.498, $p < 0.01$, respectively).

Transfontanel USG was applied to seven patients with neurological symptoms (hypotonia, seizure, cephalhematoma, cyanosis, lethargy). Only one had grade one subependimal haemorrhage, while the others were totally normal. Seizures were observed in two (1.8 %) patients within the first 48 hours of rehydration therapy. No abnormalities were observed on EEG, transfontanel USG, or MRI.

A total of 50 single samples were collected from the mothers of the NHD group at postpartum 2-14 days. Mean breast milk Na concentration was 24.48 ± 20.54 mEq/L, with respect to the sample collection day, 52% of cases had high breast milk Na content. The control group was composed of 50 cases, and the sample collection days were identical to the study group. In the control group, mean breast milk Na concentration was 12.62 ± 6.79 mEq/L and 26% of cases had a high breast milk Na content with respect to the day of sample collection. The characteristics of both groups are summarized on Table 2. The breast milk sodium concentrations were significantly higher in the mothers of dehydrated infants compared to the control group ($p = 0.008$). A statistically significant

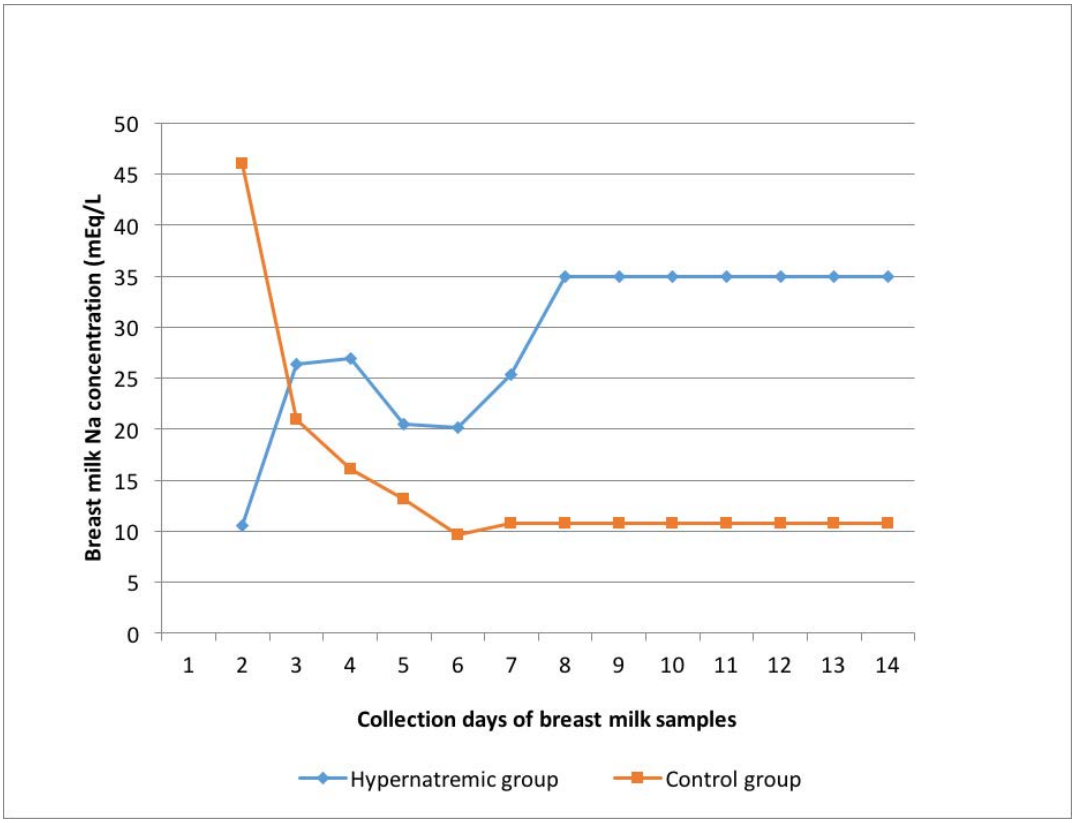

Figure 1. Postpartum changes in mean breast milk sodium level.

correlation was determined between breast milk Na concentration and primiparity ($p < 0.05$). The mean breast milk Na concentration of primiparous women (21.16 ± 19.9 mEq/L) was statistically higher than that of multiparous women (15.48 ± 9.96 mEq/L ($p < 0.016$). Postpartum changes in the mean breast milk sodium level of the study and control groups are demonstrated in Figure 1. No statistically significant correlation could be demonstrated between breast milk Na concentration and maternal age or mode of delivery.

The highest breast milk Na concentration was 98 mEq/L, which was measured on the 14th postpartum day. This infant was hospitalized with complaints of vomiting, fever, and sleepiness on day 13. His birth weight was 3100 g and his total weight loss was 27%. His serum sodium was measured to be 170.6 mEq/L. His mother was subjected to a detailed education on adequate fluid intake and breastfeeding. After regular feeds and milking, her breast milk sodium level decreased gradually to 10 mEq/L on the 20th postpartum day. There was a positive correlation between serum sodium level and postnatal age on admission, degree of weight loss, and breast milk sodium level. Gender, type of delivery, gestational age, birth weight, and maternal age were not related to the development of hypernatremia ($p > 0.05$).

DISCUSSION

Hypernatremic dehydration in the neonatal period is an important problem which can lead to serious, life-threatening complications [9]. This single-center study with a large cohort want to evaluate demographic features of NHD patients and to evaluate the relation of breast milk and NHD. The results of this study showed that breast milk sodium content is closely related to NHD and the breast milk sodium concentrations were significantly higher in the mothers of dehydrated infants compared to the control group.

Lactation failure is the most important etiological factor in NHD. Some of the risk factors associated with lactation failure include prematurity, primiparity, C-section delivery, low maternal education level, infrequent breastfeeding, nipple problems and breastfeeding incompatibility between mother and her

infant [11-13]. In the current study, 61.5% of mothers were primiparous and nearly half of the mothers were graduated from a primary school. There was a statistically significant correlation between primiparity and NHD (p = 0.028). However, the correlation between NHD and low maternal education level was not significant (p = 0.841).

In the current study, the breast milk sodium concentrations adjusted to the postpartum day showed a statistically significant difference between the groups. The mean breast milk sodium concentration of primiparous women was statistically higher than that of multiparous women. Although most reports showing a higher incidence of NHD included neonates delivered by C-section, which is known to decrease breast milk production, some reports have claimed that delivery type does not have any influence [5, 14, 15]. In the current study, the proportion of neonates delivered vaginally or by C-section were similar and hence we concluded that delivery type does not have any effect on NHD (p = 0.07).

Although most publications have emphasized that the amount of breast milk is more important than the milk sodium content, a high level of sodium in breastmilk has been reported to lead to clinical symptoms in some hypernatremic neonates [7, 16]. In a study by Koo and Gupta [17], the electrolyte composition of breast milk was evaluated from the 1st to the 28th postpartum days. The mean sodium concentration of breast milk immediately after delivery was reported to be 64.8 mEq/L and this level continued to decrease progressively. On postpartum third day, it was measured as 21.4 mEq/L and at the end of the second week it was measured 7 mEq/L [17]. A gradual decrease in breast milk sodium level is considered as an indication of successful breast-feeding [17, 18]. The opposite is accepted to be true for unsuccessful breast-feeding [2, 19]. Breast milk having high levels of sodium and low free water portion has been reported to cause a hyperosmolar status in infants [5]. In a study involving 208 mothers by Manganaro *et al*. [20], it was claimed that hypernatremic dehydration was related to insufficient daily milk output rather than high sodium concentration in breast milk. Likewise, Ingram *et al*. [21] showed that primaparous mothers have a lower volume of milk than multiparous mothers especially in the first four postpartum weeks.

The present study was carry out during a summer season for our country and the incidence of hypernatremic dehydration was found to be higher than incidence of NHD reported in literature. In the literature, the incidence of breast feeding-associated NHD ranges between 0.6-4.1% [5, 11, 22]. Although in some studies, alterations of seasonal heat were considered to be an important contributing factor, in others no statistical significance was reported [6, 7]. In neonatal hypernatremic dehydration, the most frequent time of hospital admission is the first 10 days of life [4, 5]. In the current study, the postnatal age at admission ranged from 2-12 days, where 91.7% of infants were between 2-5 postnatal days. Positive correlations were found between the degree of weight loss and the postnatal age at admission and serum Na levels in our study (p = 0.019 and p = 0.022; respectively). Therefore we believed that seasonal heat changes may be considered as a causative factor for dehydration in both newborns and their mothers and newborns may become dehydrated more earlier in heat seasons. The American Academy of Pediatrics (AAP) emphasizes that all newborns who are discharged from hospital before 48 hours of age must be seen by a physician for the evaluation of jaundice and dehydration over the first 3-5 days [10]. It is also suggested that possible feeding problems should be investigated in infants who have lost ≥ 7% of their birth weight within the first week of life and a more intensive evaluation of breast-feeding efficiency is required [10]. In some studies, it has been reported that dehydration is detected during a routine pediatric examination and most families are not aware of the condition and as a mother is not informed well enough, she cannot understand that her milk is insufficient [4]. In our study, 93% of mothers of dehydrated infants believed to have sufficient amount of breast milk. In this respect, we believe that evaluation of all neonates for weight loss and signs of dehydration in the first 3-5 days of life is very important for the detection and prevention of NHD.
The treatment regimen should be planned according to the initial serum Na level and monitorized closely because the degree of hypernatremia is very important for prognosis [1, 23, 24]. Seizure in NHD may occur as a presenting symptom but it usually develops during dehydration therapy with hypotonic fluids [1, 23]. Seizure rates have been reported to vary from 6%

to 38% [6, 9, 23]. In the current study, only one patient was admitted with seizure and two patients had seizures during rehydration period. The overall seizure rate was 2.7%. The mortality rate of NHD is unclear but severe hypernatremia may lead to adverse outcomes and increase the mortality rate [24]. In the current study, we did not have any patient loss. Due to our careful treatment regimen, we did not observe any life-threatening complication either.

Limitations

This single-center study is a large cohort study involving comparative measurements of breast milk sodium in mothers of hypernatremic infants and healthy term infants. The major limitations of the study are that we could not obtain milk samples from mothers of all NHD patients and we did not evaluate the breast milk volume which might have influenced our interpretation of milk sodium levels and we could not obtain milk samples from mothers of all NHD patients in this study. A large, multicenter, prospective study which evaluated milk sodium content and milk volume together including control group may give further information about lactation failure.

CONCLUSION

In conclusion, hypernatremic dehydration in the neonatal period is an important problem which can lead to serious, life-threatening complications. High breast milk sodium content may closely related to NHD. Early recognition and an adequate treatment approach are important to prevent complications. In this respect, we suggest all pregnant women should be educated, both prenatally and postnatally, about infant nutrition and neonatal dehydration. All neonates should be evaluated for weight loss and any sign and symptom of dehydration in the first 3-5 days of life. This is very important for early detection, prevention and proper treatment of NHD.

Authorship Declaration

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

Conflict of interest

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

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The European Research Journal 2019;5(2)369-374 ORIGINAL ARTICLE

The utility of the neutrophil-to-lymphocyte ratio in predicting urolithiasis in acute abdominal pain accompanied by flank pain

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ABSTRACT

Objectives: To evaluate whether the neutrophil-to-lymphocyte ratio (NLR), can differentiate between urinary stone disease and inflammatory conditions in patients admitted to emergency department having acute abdominal pain accompanied by flank pain.

Methods: Data of 191 patients with acute abdominal pain accompanied by flank pain admitted to emergency department in a single institution during 1 year period was retrospectively reviewed. Complete blood count and urine analysis were evaluated, the definitive diagnosis was established radiologically. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The cut off value for the NLR in relation to stone status was calculated.

Results: Of the 191 patients 51.3% (n = 98) were males, 48.7% (n = 93) were females ($p > 0.05$). White blood counts of the patients according to the presence of stone does not show a statistically significant difference ($p > 0.05$). NLR measurement of patients according to the presence of stone shows a statistically significant difference ($p = 0.009$). NLR of patients with urinary stones were significantly lower than patients without urinary stones. NLR measurements did not differ significantly according to stone location. A cut-off point of ≤ 2.16 for the NLR was determined according to the stone status of the patients. NLR values were higher in patients with acute abdominal pain/flank pain due to inflammatory pathologies.

Conclusion: As the diagnosis and treatment of urolithiasis take long time and require elaborate methods, NLR may be used as a simple method in the differential diagnosis of pain due to urinary stone disease or inflammatory condition.

Keywords: Acute abdominal pain, emergency medicine, flank pain, neutrophil-to-lymphocyte ratio (NLR), urolithiasis

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Acute abdominal pain (AAP) is one of the leading symptoms among emergency department (ED) admissions and its diagnostic and management process takes long time [1]. AAP incidence is 7-10% among ED admissions [2, 3]. According to the Statistical Institute in Turkey, 5% of hospitalized patients presenting to the emergency department are cases of AAP admitted to the emergency department, among them 30% cannot be diagnosed [4].

AAP may be due to multiple inflammatory and

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noninflammatory conditions such as intestinal obstruction, acute appendicitis, pancreatitis and urinary stone diseases, aortic aneurysm rupture, mesenteric ischemia, ectopic pregnancy rupture [1].

AAP accompanied with flank pain suggest urinary stone disease and considered among the non-inflammatory pathologies [5, 6]. The abdominal pain is theoretically classified in textbooks as right/left/upper/lower quadrant pain, but the signs and symptoms are mostly presented as intermingled pictures [2].

Although pain localization, intensity and examination findings may be guiding for a probable diagnosis, a wide range of diagnostic tools from the simple urinalysis and complete blood count up to higher cost computerized tomography and magnetic resonance imaging may often be needed. A wide variety of pathologies are considered in the differential diagnosis of flank pain, AAP and many diseases which require elaborate work-up. Higher costs of these sophisticated diagnostic tools have led investigators to study cost-effective simple diagnostic methods including the neutrophil-to-lymphocyte ratio (NLR). Initially, The NLR was developed in 2001 by Záhorec [7] in order to provide a readily measurable parameter reflecting the severity of the stress and systemic inflammation in intensive care patients with shock, multiple trauma, major surgery or sepsis.

Previously, the NLR was considered to be an indicator in inflammatory diseases, however, different conditions are currently known to cause NLR alteration as well [8-10]. The NLR has been reported to be a useful indicator in the diagnostic and treatment evaluation of many benign and malignant diseases [9, 11, 12]. A few limited studies have been recently published in which the diagnostic value of NLR in AAP was reported [13-15].

The aim of the present study is to evaluate the diagnostic distribution of patients with abdominal and flank pain admitted to ED with diagnosis of urinary stone disease and other inflammatory conditions as well as to compare them in terms of NLR and other parameters.

METHODS

After receiving approval from the ethics committee, data of patients having right and/or left flank pain accompanied with AAP admitted to the emergency department of our institution between February 2015-February 2016 were retrospectively reviewed in the study. Demographic characteristics such as age, sex, medical history, comorbidities as well as blood count and urinalysis results immediately taken in the ED were noted. Additionally, definitive diagnoses of urinary stone disease, acute cholecystitis, appendicitis, ovarian cyst, urinary tract infection and cholecystitis, obtained with abdominal ultrasound (US), computed tomography (CT) and other laboratory work-up results in all patients were recorded. The NLR were calculated using data from the complete blood count (CBC). CBC and urinalysis were performed using a full assessment Sysmex XT-2000 and Erba Mannheim Uro-dipcheck 400e devices respectively.

Endocrinological, cardiological and other systemic comorbidities; regular medication; drug/alcohol abuse; nonsteroidal anti-inflammatory drug use within the last week; steroid use including ointment formulas within the last three months; upper respiratory infection within the last three weeks; pregnancy; insufficient history information on the evaluation form and any hematological, biochemical or serological abnormalities such as hyperlipidemia, hyperthyroidism, anemia, vitamin deficiency (D3 and B12), leukocytosis or leukopenia according to laboratory studies were exclusion criterion.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) program for statistical analysis were used for statistical analyses. In order to evaluate study data, Mann-Whitney U test was used in descriptive statistical methods (mean, standard deviation, median, frequency, rate, minimum, maximum) as well as in the two-group comparisons of quantitative data with non normal distribution. For three or more groups with normal distribution Kruskal Wallis test was used. In the comparison of qualitative data, Pearson's chi-square test and Fisher-Freeman-Halton test were used. To determine cut-off values for parameters, diagnostic screening tests (sensitivity, specificity, PPV, NPV) and ROC curve analysis were used. Significance was considered when $p < 0.05$.

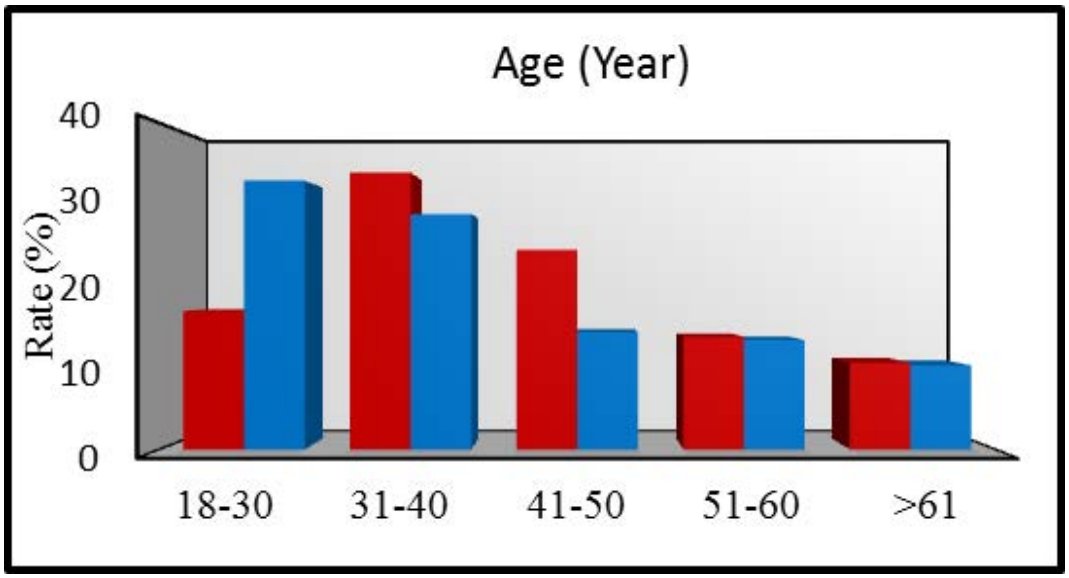

Figure 1. Age intervals according to stone status [Red: Stone (+), Blue: Stone (-)]

RESULTS

Of the 191 patients 51.3% (n = 98) were males, 48.7% (n = 93) were females ($p > 0.05$). The age ranged from 18 to 86, with average of 40.30 ± 13.96 years. Stone status according to gender was statistically significant ($p < 0.01$). Urinary stone disease incidence was frequent between ages 31-40 (Figure 1).

The diagnoses of the patients with flank pain admitted to emergency department were urolithiasis (48.7%), urinary tract infection (26.4%), unidentified abdominal pain (13.7%), acute appendicitis (3.6%), ovarian cyst (1%) and acute cholecystitis (0.5%). The white blood cell count (WBC), NLR and platelet (PLT) counts of the patients included in the study were evaluated. WBC and PLT values of patients did not show a statistically significant difference related to stone status (p = 0.456; and $p = 0.876$; respectively) (Table 1). NLR of stone patients showed a statistically significant difference without gender discrimination ($p = 0.009$; $p < 0.01$) and NLR values of the patients

Table 1. CBC evaluation of the patients

		Total (n = 191)	Stone (+) (n = 94)	Stone (-) (n = 97)	*p* value
WBC	Min-Max (Median)	2.8-29.1 (9.3)	4.6-16.5 (9.1)	2.8-29.1 (9.5)	*0.456
	Mean ± SD	9.89 ± 3.45	9.64 ± 2.88	10.14 ± 3.92	
NLR	Min-Max (Median)	0.7-20.8 (2.4)	0.7-10 (2)	1-20.8 (2.9)	***0.009****
	Mean ± SD	3.37 ± 3.00	2.68 ± 1.86	4.04 ± 3.67	
PLT	Min-Max (Median)	80-571 (238)	106-400 (243)	80-571 (235)	*0.876
	Mean ± SD	248.52 ± 62.54	245.71 ± 56.28	251.25 ± 68.25	

CBC = complete blood count, NLR = neutrophil-to-lymphocyte ratio, PLT = platelet, SD = standard deviation, WBC = white blood cell, *MannWhitney U Test: ***$p < 0.05$

Table 2. Diagnostic screening tests and ROC curve results

	Diagnostic Scan					ROC Curve	
	Cutoff	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Area	95% Confidential Interval
NLR	≤ 2.16	59.57	61.86	60.20	61.20	0.610	0.530-0.689

NLR = neutrophil-to-lymphocyte ratio

with stone were significantly lower than those without stone. After radiological examinations performed in 94 patients with stone, it was seen that 29.8% of the stones were in the kidney, 23.4% in the proximal ureter and 46.8% in the distal ureter (NLR respectively; 2.45 ± 1.41; 3.28 ± 2.60; 2.52 ± 1.65). The anatomic location of urinary stone and the NLR values did not show a statistically significant relationship ($p = 0.667$).

Considering the significance of NLR, a cut-off point was calculated using ROC analysis and diagnostic screening tests; NLR cut off points for stone (+) patients was assessed as ≤ 2.16. Standard error of 61.1% under ROC curve was 4.1% (Table 2 and Figure 2).

There is a statistically significant relationship between NLR cut-off value 2.16 and stone status ($p = 0.003$). When NLR value is 2.16 or less, the risk of stone positivity is 2.34 fold increased. Odds ratio for NLR was 2.390 (95% CI: 1.337-4.272).

DISCUSSION

In this study the relationship between NLR, WBC and PLT measurement and urinary tract stones (renal and ureteral stones) was evaluated in patients admitted to ED with abdominal pain accompanied by flank pain. Lower NLR was found to be more significant than WBC and PLT assessment in patients with stones compared to those without stones.

Urinary tract stones usually develop between the ages of 20-49 and make peak in 3rd and 4th decades. It is usually more common in men than in women [16]. In our study, the mean age was 31-40 years and most of the patients with urinary stones most were male as well (n = 65/94, 69.1%).

NLR, platelet/lymphocytes ratio (PLR) and systemic immune inflammatory index have been subject of many studies [17-20]. Previously the link between NLR ratio and cardiovascular diseases as well as malignancies were evaluated in numerous

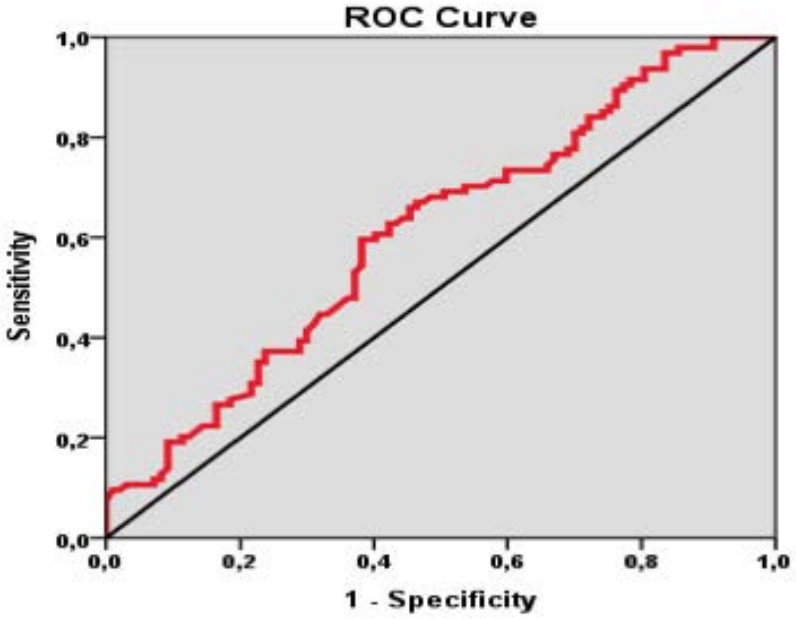

Figure 2. ROC curve according to stone status

reports [21-23]. Later, the importance of NLR among diagnostic and prognostic parameters of miscellaneous illnesses were reported [10, 24-26]. In our study, we investigated the role of NLR in differential diagnosis of patients presenting with flank pain to ED. There are relatively few publications evaluating NLR in patients admitted to ED due to abdominal pain, flank pain and similar symptoms [13, 14, 27-29].

In a study of Acar *et al*. [6] in which acute appendicitis and renal colic were compared, NLRs for acute appendicitis and renal colic were calculated as 8.48 ± 0.39 and 4.96 ± 0.16 respectively with a cut-off value of 3.30. Likewise, inflammation markers such as WBC, red cell distribution width (RDW), mean platelet volume (MPV), PLR and NLR were cited to be useful in the differential diagnosis of renal colic with acute appendicitis in this study.

In 2014 Uyeturk *et al*. [27] grouped patients in urinary stone positive and stone free arms, they have found a higher NLR [app. 2.5 (0.7-8.4)] in stone arm versus stone free arm. In parallel to these data, NLR value in our study was lower in flank pain due to urinary stone disease compared to no stone group (2.68 ± 1.86) which was statistically significant. However, our cut-off value was 2.16 and lower than those of Acer *et al*. [6] and Uyeturk *et al*. [27]. Additionally, WBC and PLT results were not statistically significant in the present study.

There were mostly inflammation related cases in the group which we compared to stone cases. In renal colic, intraluminal pressure increases due to ureteral obstruction during the acute phase and then, nerve endings in the mucosa and muscular layer are stimulated, leading to pain. Evidence of inflammation is not usually observed [30].

In a similar study, WBC and neutrophil ratio varied depending on stone size and location, additionally these values were higher in secondary renal colic cases [28]. In the present study NLR was lower in urinary stone cases and yet, neither the location (kidney or ureter) nor the size had a significant effect on these values. This data remains to be evaluated in further prospective studies.

Limitations

Our study has some limitations; first, the comparative group displayed a wide variety of diagnoses in contrast to urolithiasis patients, hence different statistical evaluation would be more suitable for each of these conditions but the number of patients in our subgroups were low. However, all these subgroups had inflammatory pathologies which lead us to assign inflammatory conditions as the comparison group. The retrospective nature of the study is another limitation. Since smoking and obesity have been previously reported to have a link with increased NLR, the fact that we did not take body mass index and smoking status into consideration in our patients is another limitation [18, 19]. Lastly, not all patients with AAP and flank pain, but only the patients undergone advanced imaging methods were included in the study due to retrospective nature of the study.

CONCLUSION

In conclusion, as the diagnosis and treatment of urolithiasis cases are time consuming and require elaborate methods, NLR may be a simple method in the differential diagnosis of pain due to urinary stone disease or inflammatory condition. Our results should be further evaluated with comprehensive prospective studies.

Conflict of interest

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

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The European Research Journal 2019;5(2):375-381 ORIGINAL ARTICLE

The impact of nutritional status on the outcomes of cancer patients such as mortality, survey and length of hospitalization in palliative care

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ABSTRACT

Objectives: The aim of this study was to determine the effects of nutritional status of the cancer patients in the palliative unit on some important outcomes such as mortality, hospitalization periods and survey.

Methods: The study was carried out through a retrospective review of 65 cancer patients who were treated at the palliative care center. The age and gender of the patients, the type of cancer, the place where they are referred to the palliative unit (from home or from the hospital), from which unit they came from (oncology, intensive care unit, other services), the length of stay, how long they lived after discharge, how long each patient lived after the palliative unit hospitalization day and the NRS-2002 scores were recorded.

Results: There was a statistically significant difference between the median hospital duration of the home-based patients and the median duration of hospital-based patients (11 [2-42] days versus 22 [2-180] days) (p = 0.001). The mean survival time of the home-based patients was median 87.5 (2-323) days, while this was 9 (2-104) days in hospital-based patients (p = 0.017). While 29.5% (n = 13/27) of the patients coming from the house died in the palliative care center, it was 70.5% in the patients taken from the hospital (p = 0.002). The NRS-2002 scores of the cancer patients who were followed up at the palliative unit were correlated with the age of the patients (r = 0.365, p = 0.003).

Conclusions: We concluded that the patients who came to palliative care from home have better surveys than the ones came from the hospital.

Keywords: Palliative care, mortality, nutrition, NRS-2002

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Malnutrition can be described as "a decrease in physical and mental functions resulting from inadequacy of intake or irregular diet, loss of body composition (reduction in lean mass) and deterioration of body cell mass, and worsening of the clinical outcome of the disease" [1]. Malnutrition is an important cause of hospital mortality [2].

Although many methods are used, a single method of recognizing malnutrition alone has not yet been established. The most useful tests in malnutrition screening are Subjective Global Assessment (SGA), "Nutritional Risk Screening-2002 (NRS-2002)" and Mini-Nutritional Assessment (MNA) [3]. For hospitalized patients, the NRS-2002 test is a more appropriate screening method [4].

In recent years, intensive efforts have been made

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to predict patients' return to home in palliative care units. Many factors in the past Meta-analyzes have been proposed as predictors. These include advanced age, mobility limitation, cognitive impairment, living alone, lower activities of daily living (ADL), male gender, medical needs and dysphagia [5-7]. In addition to these factors, nutritional factors were also investigated as factors affecting return to home. Parenteral nutrition has been reported to reduce home return [5]. In another study, it was reported that there was no significant relationship between home return and mini-nutritional assessment [8]. In a recent study, it was reported that survivals of cancer patients with better muscular strength were better.

The association of the NRS-2002 score with the mortality and morbidity of hospitalized patients has been demonstrated in previous studies [9-11]. In addition, the association of the NRS-2002 score with survival has also been demonstrated in a number of diseases such as metastatic cancer patients [12], congestive heart failure patients [13].

In this study, some parameters of cancer patients who were hospitalized in palliative unit were investigated according to nutritional status, including length of stay, survival time, return to home.

METHODS

The study was carried out through a retrospective review of 65 cancer patients who were treated at the Palliative Care Center of the University of Health Sciences, Kayseri Training and Research Hospital.

The age and gender of the patients, the type of cancer, the place where they are referred to the palliative unit (from home or from the hospital), from which unit they came from (such as oncology clinics, intensive care units and other services), the length of stay, how long they lived after discharge, how long each patient lived after the palliative unit hospitalization day and the NRS-2002 scores were recorded.When the patients were discharged, they were looked at from the official population system for how long they lived after discharge. Besides, total cholesterol, LDL, HDL and triglyceride values of the patients on admission day were recorded.

NRS-2002 Screening Tool

NRS-2002 is a nutritional screening method that uses parameters such as Body Mass Index (BMI), weight loss in the last 3 months, current serious diseases and age. Increases in the NRS-2002 scores indicate that patients have more nutritional risks [4]. The NRS-2002 screening is routinely performed on each patient in our palliative unit.

Statistical Analysis

The continuous data were analyzed with mean, standard deviation, median and percentages. Student's t test was used to compare continuous variables between the groups. Mann-Whitney U test was used to compare median numerical variables with a skewed distribution. Chi-square test was used to compare categorical variables. Pearson correlation analysis was utilized to determine the relations between the patient and control groups. Kaplan-Meier survival analysis was used to estimate the frequency of death from high NRS-2002 score.A p value of <0.05 was considered as significant. All statistical analyses were performed by using Statistical Package Program for Social Sciences 21.0 (Statistical Package for Social Sciences Inc., Chicago, Illinois).

Table 1. Distribution of cancer types in the group

CANCER TYPE	RATIO
Colon cancer	26.2% (n = 17)
Stomach cancer	15.4% (n = 10)
Lung cancer	20.0 % (n = 13)
Pancreatic cancer	9.2 % (n = 6)
Cancer with unknown primary site	6.2 % (n = 4)
Renal cell carcinoma	3.1 % (n = 2)
Malign melanoma	3.1 % (n = 2)
Parotis gland cancer	3.1 % (n = 2)
Nasopharynx cancer	3.1 % (n = 2)
Ovarian cancer	3.1 % (n = 2)
Breast cancer	3.1 % (n = 2)
Basal cell cancer of the skin	1.5% (n = 1)
Squamous cell cancer of the skin	1.5% (n = 1)
Hepatocellular carcinoma	1.5% (n = 1)
Duodenum cancer	1.5% (n = 1)

RESULTS

There were a total of 65 cancer patients included in the study. The mean age of these patients was 66.86 ± 13.9 years. Of these patients 63.1% (n = 41) were female and 36.9% (n = 36.9) were male. There were advanced cancer in all of them. The distribution of patients according to cancer types is given in Table 1. The distribution of the patients according to the NRS-2002 score on the application days is given in table 2. There was severe malnutrition (≥ 3) in 89.2% of the patients.

Previous Place of the Patients Before Palliative Unit

The distribution of the patient due to previous place is given in Table 3. There was no statistically significant difference in terms of gender when the patients were divided into two groups as the ones coming from the house and the ones coming from the hospital ($p = 0.225$).

There was a statistically significant difference between the median hospital duration of the home-based patients and the median duration of hospital-based patients (11 [2-42] days versus 22 [2-180] days) ($p = 0.001$). Similarly, if the patients could be discharged, their post-discharge survival was more in favor of home-based patients. The mean survival time of the home-based patients was median 87.5 (2-323) days, while this was 9 (2-104) days in hospital-based patients ($p = 0.017$).

Although the lipid parameters of home-based patients differ from those of hospital-based patients, there is no statistical significance. The median LDL values of the home-based patients were 93 (47-223) mg / dL, which was 71 (20-139) mg / dL for hospital-based patients ($p = 0.069$). While the median triglyceride values of home-based patients were 174 (41-227) mg / dL, this value was 110 (20-139) mg / dL in hospital-originated patients ($p = 0.083$).

While the median HDL values of home-based patients were 22 (15-64) mg / dL, this value was 27 (10-50) mg / dL in patients coming from the hospital ($p = 0.221$). The mean serum albumin level of the home-based patients was 2.73 ± 0.57 mg / dL, which was 2.57 ± 0.56 mg / dL in hospital-based patients ($p = 0.266$). While 29.5% (n = 13/27) of the patients coming from the house died in the palliative care center, the death rate in the palliative care center of the patients taken from the hospital was 70.5% (n = 31/37). The difference between these two ratios was statistically significant ($p = 0.002$).

Although the NRS-2002 values were better for the patients from the home, the difference between the median NRS-2002 scores of home-based cancer patients and those taken over from hospital services was not statistically significant (3.0 [1-5] versus 3.58 [1-5]), ($p = 0.675$).

Table 2. NRS-2002 scores on the day of admission

NRS-2002 scores	Ratio
1	3.1 % (n = 2)
2	7.7 % (n = 5)
3	40.0 % (n = 26)
4	32.3% (n = 21)
5	16.9 % (n = 11)

Table 3. The distribution of the patient due to previous place

Patients' origin	RATIO
Home	43.1% (n = 28)
Oncology	38.5% (n = 25)
Intensive Care Unit	1.5% (n = 1)
Other services	16.9% (n = 21)

Distribution of Patients According to Their Place of Death

Forty-four (68.8%) patients died at the palliative unit. Twenty (31.3%) were discharged from the palliative unit. When the study was over, 1 patient was still being followed in the palliative unit. Of the 20 discharged patients, 17 died at home and 3 were still alive. In total, 61 of 65 patients eventually died.

Place of Death and Gender

Distribution of deaths by gender did not show any statistical difference. Sixteen (69.6%) female patients died at the palliative unit. In males this rate was 68.7% (n = 28/41) ($p = 0.916$). There were no statistically significant differences in terms of hospital stay,

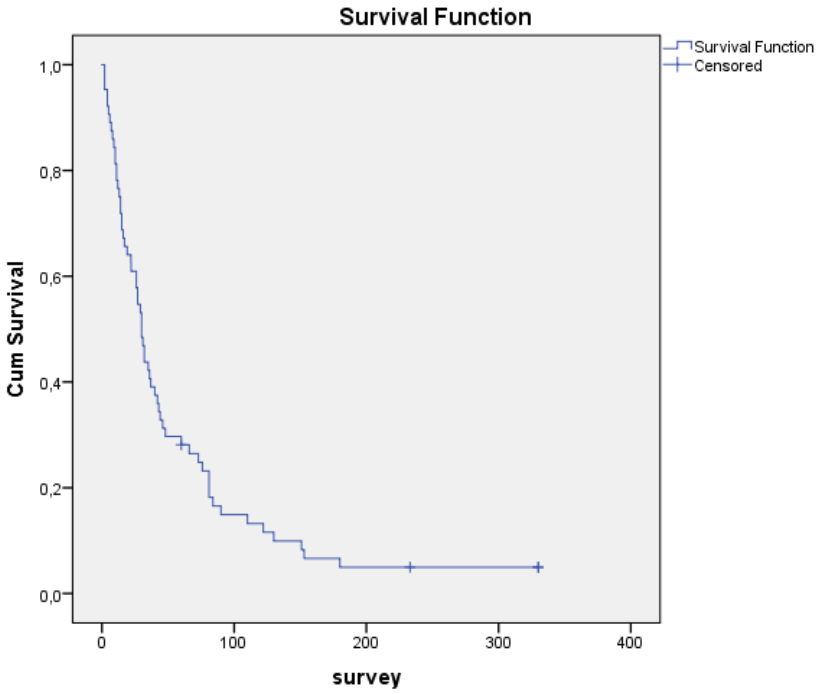

Figure 1. Survival functions of 65 cancer patients those hospitalized in palliative care.

survival from first admission to the palliative unit, and survival after discharge from the palliative unit in terms of gender (*p* values of 0.856, 0.886 and 0.575, respectively).

NRS-2002 and Gender

NRS-2002 scores of the patients did not differ between sexes. The median NRS-2002 score in male gender was 4 (1-5) while in female gender this score was 3 (2-4) ($p = 0.139$).

Correlation Analysis

The NRS-2002 scores of the cancer patients who were followed up at the palliative unit were significantly correlated with the age of the patients at the mild level ($r = 0.365$, $p = 0.003$). There was no statistically significant correlation between NRS-2002 score and hospital stay ($r = -0.147$, $p = 0.246$). There was no statistically significant correlation between the NRS-2002 score and survival after admission to the palliative unit ($r= -0.237$, $p = 0.061$). There was no correlation between NRS-2002 scores and serum albumin levels ($r= -0.159$, $p = 0.205$).

Survival Analyses

Only 61/65 patients were alive when the study was completed. On the 15th day after admission to the palliative unit, only 75% of the patients were alive. On the thirtieth day, this rate had fallen to 48%. On day 73, the survival rate was 25%. At 180 days this rate was around 3% (Figure 1).

In 65 patients who were hospitalized in the Palliative care unit, Kaplan-Meier plots demonstrated that there was a no significance in survival between cancer patients who had NRS-2002 score ≥ 3 or < 3 on admission (Figure 2).

DISCUSSION

According to ESPEN guidelines, there should now be an approach to nutritional support, continuity and frequent reassessment of patients at the end of life. The effects of nutritional status on mortality have been studied in many disciplines. However, in fact, the main goals are not much different from an acute malnutrition treatment [14].

In a study conducted last month, some results were obtained that some predictors in palliative care centers (PBM) may affect the length of hospitalization. According to this, the conditions that increase the length of stay in the hospital are as follows: cancer,

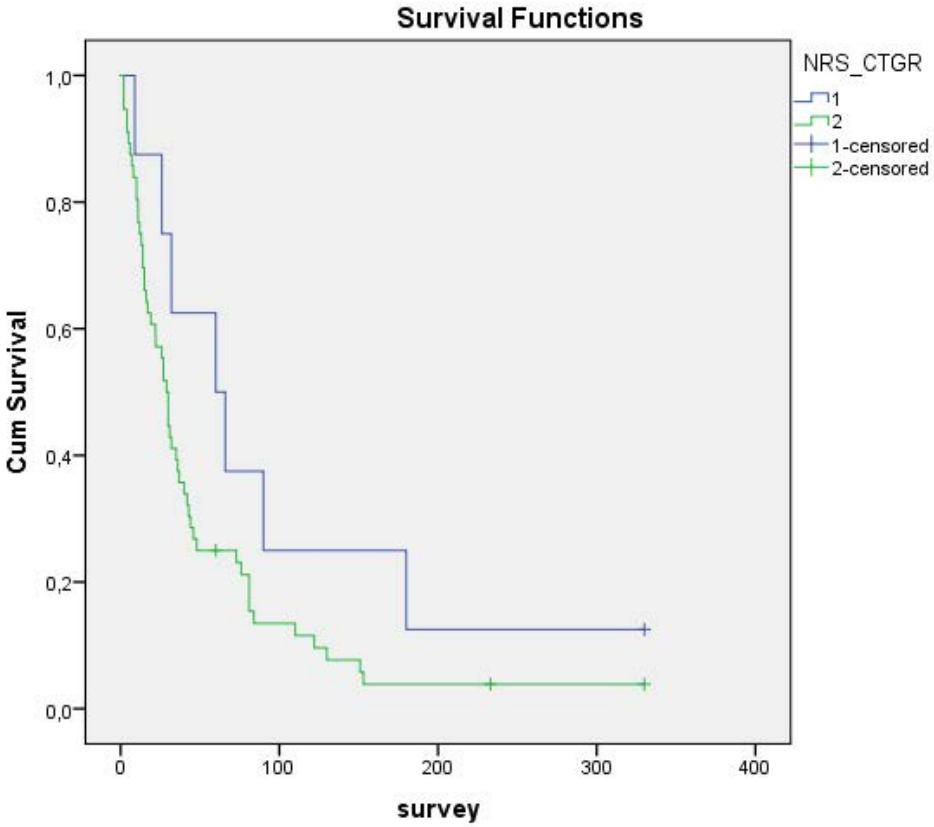

Figure 2. Kaplan-Meier Plots demonstrating Survival of Patients. Kaplan-Meier survival analysis demonstrated a longer hospital survival in cancer patients with Nutritional Risk Screening 2002 (NRS 2002) score <3 compared with patients who had NRS 2002 score ≥ 3 on admission to the palliative unit, but there is no statistical significance (p = 0.127).

hypoxic brain, elderly patients are affected negatively; Infection causes such as PEG (percutaneous endoscopic gastrostomy), total parenteral nutrition (TPN); chronic diseasessuch as hypertension and agents such as E. coli, proteus, Pseudomonas and Acynetobacter affect long hospital stay [15]. Another study, which was published a few months ago, emphasized that the median survival in significant malnutrition end-stage cancer patients was significantly reduced [16]. Decreased phase angle is positively correlated with nutrition of end stage cancer patients in palliative care. Decreased phase angle indicates decreased survival [17].

A weight loss of ≥ 5 kg in patients receiving palliative chemotherapy has been shown to significantly reduce survival [18]. Inanother research, it was concluded that a weight loss of %10 of total body weight is related with a worsened survival [19].

In the present study, a number of parameters were examined, including nutrition scores, length of hospital stay, and length of life after discharge, and dischargeability of 65 end-stage cancer patients. NRS-2002 scores were ≥ 3 in almost 90% of patients who received PBM. The age of the patients followed in the palliative unit and the NRS-2002 scores were mildly and significantly correlated in positive direction.

Home-based patients had a significantly longer hospital stay. It should be noted that terminal cancer patients often die in PBM, so it is not wrong to say that patients with longer hospitalization times are in better condition. This may be due to the fact that home-based patients may be relatively far away from terminal. It is highly probable that the patients taken from the hospital have spent this period in other services. Similarly, median survival times after discharge from home-based patients were significantly higher than those from hospital. It may be possible to link this to the same reasons.

As is known, serum triglyceride levels are inversely proportional to survival in critically ill patients [20]. In this group, the serum triglyceride levels of the patients from the home were 174 (41-227)

mg / dL, which were 110 (20-139) mg / dL in patients coming from the hospital. Serum LDL levels were also higher in favor of the patients coming from the home. Serum LDL levels were median 93 (47-223) mg / dL in patients coming from the home, while this value was 71 (20-139) mg / dL in patients coming from the hospital. There was no statistical significance here, but it could be changed by increasing the number. We attributed the LDL level to be higher in favor of the patients from the home to better nutritional performance of the patients them. There was no statistical difference in serum HDL and albumin levels.

The outcome of death in patients admitted to the palliative unit from the home was also statistically significantly lower than in patients admitted to the hospital. 29.5% (n = 13/27) of the patients coming from home died in the palliative care center while 70.5% (n = 31/37) of the palliative care center of the patients taken from the hospital died. The difference between these two ratios was statistically significant. The difference was not statistically significant between the median NRS-2002 score of 3 (1-5) patients who were admitted from home and the NRS-2002 scores of 3.58 (1-5) of the patients from hospital services.

CONCLUSION

Both palliative care and nutrition are concepts that are of importance in recent times and seem to be in strong interaction with each other. In addition to this study showing that the nutritional status is important in the prognosis of the palliative care patient, it is also true that the nutrition in the palliative care is directly related to the prognosis of terminal cancer patients. We concluded that the patients who come to palliative care from home have better surveys than the ones from the hospital.

Conflict of interest

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

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The European Research Journal 2019;5(2):382-388 REVIEW

Current approaches in gestational diabetes mellitus

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ABSTRACT

Gestational diabetes mellitus (GDM) is one of the most common medical complications in pregnancy and has become a global public health issue in terms of causing fetal and maternal morbidity and mortality in short- and long-term. The number of cases of GDM all over the world has been increasing day by day and they include risks for mother and baby health compared to healthy pregnancies. GDM screening and diagnostic phase has complete different approaches and there is no common consensus. Once GDM is diagnosed, pharmacologic treatment can be necessary in addition to strict blood sugar follow-up, regular exercise, and diet regulation. In postpartum period, medical monitoring is also necessary due to increased risk of diabetes mellitus in women with GDM. In this paper, we will also discuss approaches suggested in the GDM in the context of current guidelines and literature.

Keywords: Hyperglycemia, pregnancy, gestational diabetes mellitus, current approaches

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Gestational diabetes mellitus (GDM) is the most common complication of pregnancy and is defined as glucose intolerance at various grades beginning in pregnancy in women with carbohydrate intolerance or diagnosed for the first time during pregnancy [1]. The incidence of GDM has been increasing worldwide with the effect of factors such as increased obesity rates and advanced maternal age [2]. The prevalence of GDM varies widely depending on the population and diagnostic criteria. The global prevalence of GDM varies from 1% to 28%, depending on population characteristics (maternal age, socioeconomic status, race, body composition, etc.), screening methods and diagnostic criteria [3]. In a limited number of studies conducted in different regions of Turkey, it was reported that the prevalence of GDM varied between 3% and 9.2%, and this ratio increased up to 11.4% depending on the diagnostic criteria used [4-6].

Pathophysiology

In the formation of gestational diabetes, the main problem is a decrease in maternal insulin sensitivity [7]. In normal pregnancy, fasting blood sugar and HbA1c levels are lower than those of non-pregnant women due to peripheral use of glucose, increased glycogen storage in tissues and increased fetal glucose utilization. A decrease in maternal HbA1c and fasting blood sugar are caused by the supply of glucose into fetus with active transport through facilitated diffusion and trophoblasts via glucose transporter-1 (GLUT-1), in other words, are caused by the diffusion of glucose over a wider area [8]. During pregnancy, a progressive insulin resistance occurs due to the effects of diabetogenic hormones secreted from the placenta (growth hormone, corticotropin-releasing hormone [CRH], placental lactogen, progesterone), maternal postprandial blood glucose level is elevated, and this

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process leads to fetal glucose transport [9]. The formation of maternal insulin resistance is also influenced by agents that decrease insulin sensitivity such as tumor necrosis factor alpha (TNF-α), leptin, adiponectin, and resistin [10]. In a recent study, it was reported that Interleukin-6 (IL-6), an inflammatory marker, could be used as a predictor of GDM development regardless of adipose tissue, especially in the first 3 months [11]. Insulin secretion increases especially in the first trimester of pregnancy depending on the change in insulin sensitivity during this physiological adaptation during pregnancy. This increase in insulin secretion is crucial for cellular proliferation, tissue development and differentiation. If increased insulin requirement cannot be met in the long-term, GDM develops due to impaired beta-cell function [12].

Genetic Factors Associated with GDM

The increased risk of type 2 diabetes mellitus (DM) in patients with GDM in the later stages of life suggests that this disease is a polygenic, heterogeneous disease similar to type 2 DM. Genetic studies suggested that some genes associated with insulin secretion, insulin and insulin receptors, GDM and play a role in the pathogenesis of GDM, especially mutations in KCNJ11 and ABCC8 genes, which causes impairment of insulin secretion [13].

Fetal and Maternal Consequences of GDM

Many studies in the literature indicate that increased maternal glucose levels have negative consequences for both mother and fetus. As noted in the Hyperglycemia and Adverse Pregnancy Outcome study (HAPO), increased maternal blood glucose level can cause multiple complications for both fetus and mother, independent of factors such as body mass index (BMI) and weight gain [14]. If gestational beta-cell compensation secondary to decreased insulin sensitivity is not achieved in the long term, it causes beta-cell insufficiency and loss of function, resulting in progression of hyperglycaemia and DM. The fact that the women developed GDM have intolerance to high levels of insulin secretion for a long time, is associated with mild inflammation such as obesity, and decreased adiponectin released from adipose tissue, and the addition of factors related to individual susceptibility to this condition. Type 2 DM occurs as a result of long-term destruction of beta-cells and loss of function. In addition, pregnancy causes a threefold increase in the risk of developing DM following GDM and a prolonged period with insulin resistance, independent of the well-known effects of weight gain [15-17]. It was reported that the prevalence of hypertension development secondary to hyperinsulinemia associated with weight gain and sodium retention in women with GDM has been increased [18]. In the HAPO study, women with GDM with a high body mass index were reported to have a significantly higher risk of developing preeclampsia than women with GDM with a low body mass index [14]. It was shown that the risk of preeclampsia in women with GDM due to the presence of adverse factors such as impaired angiogenesis, endothelial damage, oxidative stress, and abnormal cytotrophoblastic invasion were higher compared to healthy pregnancies [19]. In particular, women with type 1 or type 2 DM were advised to use aspirin at a low dose of 60-150 mg/day (normal dose 81 mg/day) from the end of first trimester until delivery to reduce the risk of preeclampsia. The US Preventive Services Task Force recommended the use of low-dose aspirin (81 mg / day) as a prophylactic agent after 12 weeks of gestation in women at high risk of preeclampsia, based on the results of clinical trials [20]. Women with GDM have a increased risk of preterm labor, shoulder dystocia, polyhydramnios, urinary system and pelvic infection compared to the normal population [21]. It has been reported that if glycemic control is not achieved in GDM, the risk of stillbirth is increased 4-fold. In recent years, lower stillbirth rates have been observed with close follow-up of GDM and insulin treatment. In a study population consisting of women with GDM, the stillbirth rate was found to be about 1.4 per 1000 births [22, 23]. Although the mechanism of pregnancy induced retinopathy is not clearly demonstrated, it has a severe clinical course, so women who have previously type 1 or type 2 DM and planned to become pregnant or conceived should be informed about the risk of developing and/or progressing diabetic retinopathy. Comprehensive eye examinations should be performed before pregnancy or in the first trimester. Patients should also be followed-up in terms of grade of retinopathy in each trimester and within 1 year after birth [24].

Fetal Complications

Complications such as macrosomia, shoulder dystrophy, brachial plexus injury, spontaneous abortion, hyperbilirubinemia, neonatal hypoglycaemia, hypocalcemia, neonatal respiratory distress, hypertrophic cardiomyopathy and congenital malformations may be seen as a result of fetal hyperinsulinemia caused by maternal hyperglycemia in GDM [25]. According to the Pedersen hypothesis, the incidence of obesity and Type 2 DM in infants born from women with GDM was shown to be increased compared to those born from women without GDM due to effects of intrauterine hyperglycemia-related fetal β-cell hypertrophy on adipose tissue [26].

Screening and Diagnosis for GDM

Although there is no common consensus among GDM guidelines in the GDM screening, it is very important to determine the clinical risk in terms of GDM during the first visit of the patient during pregnancy, and to progress rapidly to screening if the patient has a high risk in order to prevent complications related to GDM [27].

Risk Factors for Gestatıonal Diabetes Mellitus [28]

- The presence of GDM in prior pregnancy,
- The diagnosis of glucose intolerance in the pre-pregnancy period,
- A family history (especially in the first-degree relatives) of T2DM,
- A history of macrosomia and polyhidramnios in the previous pregnancy,
- Maternal wait gain (> 20 kg) in the previous pregnancy,
- The presence of a fasting blood glucose level > 95 mg/dL and glucosuria,
- Overweight (BMI > 25 kg /m2),
- Advanced age (> 40 years),
- Polycystic over syndrome

If the patient has one of the high risk factors in first prenatal visit, an oral glucose tolerance test (OGTT) should be performed based on the diagnostic criteria for diabetes mellitus in the non-pregnant population for unidentified diabetic patients [28].

Overt Diabetes Mellitus Diagnostic Criteria [28]

- A fasting plasma glucose (≥ 8 hours fasting) level ≥ 126 mg/dL
- OGTT second hour Plasma glucose PG ≥ 200 mg/dL (with 75 g glucose)
- Random Plasma glucose PG ≥ 200 mg / dL + Symptoms of diabetes
- HbA1c ≥ 6.5%

If high risk factors have not been identified, the recommendations of current guidelines are to make OGTT at 24-28 weeks in all pregnant women. The suggested approach for OGTT is pre-screening with a 50 g glucose test, switching to a 100 g glucose loading test if the 1- h glucose value is identified between 140-180 mg/dL. GDM is diagnosed if at least two values of the cut-off values of 95, 180, 155 and 140 of blood glucose levels at fasting, 1, 2 and 3-hours, respectively, in the 100-gr glucose loading test. If 50 g OGTT is higher than 180 mg/dL in the 1-hour blood glucose test, the patient is diagnosed directly with GDM without a 100 g blood glucose test [28]. Another approach recommended for diagnosis of GDM is one-step procedure using a 75 g OGTT. GDM can be diagnosed if at least one of the cut-off values of 92 mg/dL, 180 mg/dL and 153 mg/dL, respectively, of 0, 1 and 2 hours blood glucose levels are detected following a 75 g glucose loading glucose test. The one-step approach was proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in 2010 and is still in use today. A 75 g OGTT is advantageous because the cut-off points are based on fetal complications of GDM [27]. In the American Diabetes Association (ADA) guidelines published in 2015, a one- or two-step approach is suggested based on selected community characteristics [30]. The approach adopted by the Society of Endocrinology and Metabolism of Turkey (SEMT) is the application of two-step diagnostic and screening criteria. SEMT recommends that at first two-step approach should be followed, as the 75-gram single-step OGTT may lead to pregnancies with a large number of GDM diagnoses and may cause financial problems [28].

Treatment

In order to control the maternal hyperglycemic state in GDM treatment, medical nutrition therapy (MNT), enhancement of physical activity and weight management programs are recommended. If blood

glucose level cannot be regulated with these lifestyle changes, additional medical treatment should be initiated [31].

Prevention of GDM

The prevalence of GDM is increasing and most of GDM patients have a history of type 1 and type 2 diabetes mellitus. There is an increase in GDM and type 2 diabetes in parallel with an increased risk of obesity worldwide. According to ADA 2018 guidelines, preconceptual counselling should be considered as an integral part of primary care for all diabetic patients in the age of fertility starting from the puberty period, family planning should be recommended and effective contraception should be provided for women with childbearing potential. Preconceptional counseling using appropriate training tools should prevent unplanned pregnancies and inform the patient about the complications that may occur in pregnancy due to poor glycemic control [24]. Preconceptional glycemic control as close to normal as possible [ideally HBA1C, below 6.5% (48 mmol/mol)] reduces the risk of congenital anomalies [24]. Pre-pregnancy obesity is a risk factor for GDM and it has been suggested that dietary counseling and lifestyle modification with physical activity in the pre-pregnancy period can cause a decrease in the incidence of GDM [32].

Medical Nutrition Therapy

In the ADA 2018 guidelines, it was suggested that an individualized nutrition plan should be developed by a dietitian who is a specialist in the management of GDM for medical nutrition therapy in GDM. Dietitian nutrition plans should focus on maintaining adequate maternal and fetal health, achieving glycemic goals, and ensuring adequate caloric intake to promote proper gestational weight gain. For all pregnant women, a daily meal plan including a minimum of 175 g carbohydrate, at least 71 g protein and 28 g fiber should be designed [24]. In women with GDM, the daily energy requirement is recommended as 24 kcal per day for ideal weight in obese pregnant women, 30 kcal at the first trimester and 35 kcal from the second trimester until delivery in non-obese pregnant women. The number of meals was recommended as 7 meals including main meals and collations [28].

Exercise

It has been reported that the regular exercise in GDM in conjunction with medical nutrition therapy would reduce the need for insulin, which increases insulin sensitivity [33]. In the American Congress of Obstetricians and Gynecologists (ACOG) 2018 guidelines, women with GDM were advised moderately aerobic exercise for at least 5 days for 30 minutes a week or for at least 150 minutes a week [34].

Medical Treatment

If hyperglycaemia cannot be controlled (a fasting plasma glucose level > 105 mg/dL or 1-hour postprandial >140 mg/dL) despite 2 weeks of medical nutrition therapy and exercise in GDM, medical treatment should be initiated [28]. It was stated that the most appropriate agent to choose in medical treatment is insulin and oral antidiabetics may be used in place of methformin and glyburidine [24]. Metformin has been shown to increase risk of prematurity, although the risk of newborn hypoglycemia is lower, and the risk of maternal weight gain is reported to be less than insulin [35-37]. The use of metformin, which is used for ovulation induction in women with policystic over syndrome, during pregnancy was also reported to have no benefit to prevent spontaneous abortion and GDM [38]. Gliburidine, another oral antidiabetic agent, has been shown to have a higher rate of neonatal hypoglycemia and macrosomia than insulin in the studies conducted [35]. Similarly, in a recent retrospective study of 110.879 women with GDM, neonatal comorbidities were more common in patients receiving glyburidine when compared to those treated with insulin [39]. NICE, ACOG and IDF guidelines have indicated that these two agents can be used safely and effectively during pregnancy [34, 40, 41] although the use of oral antidiabetic agents in the ADA guideline is limited due to limited safety in the long term [24]. Although there is no common consensus and there are different suggestions for the use of oral antidiabetic agents among guidelines, clinicians should determine the optimal treatment strategy by considering the risk-benefit profile of different treatments. The medicinally approved insulins in pregnancy include an intermediate acting human *NPH* and a long-acting insulin analogue *detemir*, a short-acting human regulatory insulin and rapid-acting analogues, insulin *aspart* and *lispro*.

A long-acting insulin analogue *glargine* and a rapid-acting insulin analogue *glulisine* have not yet been approved for use in pregnancy [42].

Individualized treatment should be planned when insulin therapy is to be started, because insulin dose may vary according to the patient's blood glucose level, weight, ethnicity and demographic characteristics. Insulin titration is often required to achieve targeted glucose levels due to physiological changes in pregnancy, and it is very important that the blood glucose is self-monitored on a daily basis [24]. There is usually a reduction in total daily insulin requirements during the first trimester and women, especially with type 1 diabetes, may experience increased hypoglycemia. In the second trimester, rapidly increasing insulin resistance requires an increase in insulin dose once or twice a week to achieve glycemic goals. Total insulin requirement can be planned as 0.7 U/kg/day in the first trimester, 0.8 U/kg/day in the second trimester, 0.9 U/kg/day in the third trimester, 1.0 U/kg in the term (36-40 weeks) and 1.5-2.0 U/kg in the severe obese women [43]. Generally, a daily total dose recommended includes less than 50% of the total dose should be given as basal insulin and more than 50% of the total dose as prandial insulin, and dose titration is necessary because there is usually a slight decrease in insulin requirements towards the end of the third trimester [24].

Treatment Targets and Postpartum Follow-Up

Suggested targets at GDM include a fasting blood sugar level of < 95 mg/dL, the 1- hour postprandial level of < 140 mg/dL, 2-hour postprandial level of < 120 mg/dL and HbA1c level of <6-6.5% [28]. If HbA1c can be achieved without risk of hypoglycaemia, <6% is the most appropriate targeted value, but if the risk o hypoglycemia is high, the targeted HbA1c can reach up to 7% [24]. National and international guidelines recommend long-term follow-up of women with GDM and all women with GDM history should receive 75 g glucose OGTT in terms of overt diabetes mellitus in postpartum 4-12 weeks. If plasma glucose (PG) concentrations in these assessments are normal, a new assessment should be made after 1-3 years, and patients should be trained in terms of symptoms of hyperglycemia and they should be advised to come to control if they experience such symptoms [24, 34].

CONCLUSION

As a result, GDM is a common complication that we frequently encounter in clinical practice of internal diseases and a disease that can cause severe problems in perinatal period and long term for both fetus and mother. Although there is no full consensus among international guidelines, the general approach is to screen pregnant women who have a high-risk on the first prenatal examination and all other pregnancies between 24-28 weeks for GDM. Early diagnosis and close follow-up should be aimed to reduce metabolic risks and prevent GDM-related complications.

Conflict of interest

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

Financing

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The European Research Journal 2019;5(2):389-398 REVIEW

Cardiac rehabilitation

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ABSTRACT

Cardiovascular diseases are one of the majorcause of mortality globally. Coronary heart disease is the largest subset of cardiovascular disease. Although mortality rates decline during time, hospital discharge data as a measure of morbidity rates are stable, leading to larger pool of patients eligible to benefit from cardiac rehabilitation. Cardiac rehabilitation is a multi-disciplinary approach including exersize training, patient counselling, education and nutritional guidance. Despite the many known benefits of cardiac rehabilitation, refferal and participation rates remainlow and interventions to increase its use need to be developed.

Keywords: Coronary, rehabilitation, exercise

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Coronary heart disease (CHD) is the leading cause of morbidity and mortality worldwide with annual mortality over 17 million people. It is expected that, more than 80 million individuals will be diagnosed with cardiovscular disease by 2030 worldwide [1, 2]. The increasing prevalence of CHD is due to the many risk factors that are becoming more endemic (type 2 diabetes mellitus [T2DM], obesity, sedentary lifestyle, hypertension [HTN]) and aging of the population [2].

While cardiovascular diseases' (CVD) mortality are decreasing, by improved emergency response and early intervention, medical and surgical management and to a lesser degree and risk factor reduction, it is still an important cause of disability around the world. Hospital discharge data as a measure of morbidity has been relatively stable since 2004 [3-5]. The percentage of years lived with disability has increased by 25% globally since 2005 [6].

Individuals with CVD are at high risk for subsequent major cardiac events and death [7], thus secondary prevention is very important. The impact of CVD are, increase in morbidity and mortality and the disturbing effects of secondary disability, decreased quality of life, and elevated health and social costs [8]. Cardiovascular rehabilitation (CR) is an effective and low-cost model of care for secondary prevention of CVD. It is an outpatient chronic diseasemanagement program, delivering the core components of assessment, medical risk factormanagement, structured exercise training (ET), patient educationas well as psychosocial and behavioral counselling [9].

CR consists of three phases. Phase I refers to inpatient rehabilitation during the index hospitalization. Due to the shortening durations of hospital stay, phase I CR has become less formalized. Phase II refers to physician supervised, outpatient monitored physical activity during the 2-16 weeks after discharge. Patients usually undergo up to 36 sessions in anexercise program. After this phase, patients may continue into phase III, which is an unmonitored exercise program. CR programs additionally provide nutritional, psycho-

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logical and smoking cessation counseling, besides lipid and blood pressure management.

Indications, Contraindications and Attendance

Most patients reffered for CR are eligible to participate. Common indications for CR are acute coronary syndrome, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), valve surgery, and chronic stable heart failure with reduced ejection fraction (HFrEF) (Table 1) [11-13]. HF is a relatively new addition, as there were long-standing concerns that exercise therapy (ET) would exacerbate HF. However, more recent studies by Wisløff *et al.* [14] and others [15] have shown that ET can elicit beneficial peripheral metabolic adaptations in patients with HF, resulting in a paradigm shift in favor of structured ET as a therapy for HF patients. The American Heart Association (AHA) and American College of Cardiology (ACC) decide CR is a Class I indication for these conditions. Contraindications for CR are listed in Table 2 [16]. The other preclusive reasons of participation include musculoskeletal problems, severe illnesses, co-morbid diseases, acute infections and inflammatory states that limit ET.

Despite favorable data and Class I recommendations, less than 30% of eligible CHD patients participate in CR programme. Commonly, referrals for these programs are not usually the part of routine daily care for many physicians. Frequently, access to facilities is difficult in rural areas. The other reason may be the significant advances in both medical and revascularization therapies, which have seen faster adoption by the cardiologists, because of a combination of physician reimbursement and marketing by pharmaceutical and device companies. Although CHD is a major cause of morbidity and mortality, interest in conventional and alternative approaches to the delivery of CR has grown and adoption is increasing [17, 18]. Decreased attendance of patients has been noted especially among women, non-whites, the elderly, the rural population, and individuals with low socio-economic status [19]. Additionally, the existence of comorbidities such as higher body mass index, poor functional capacity and exercise habits, tobacco use, and depression before starting CR has been associated with lower attendance and higher dropout rates from CR programs [20, 21]. Strong recommendation from primary care physicians and CVD specialists plays a critical role in patient participation and adherence to CR programs, and helps the patient understand the value of this treatment option [22, 23]. Patients adviced to see a cardiologist or a cardiac surgeon at the time of hospital discharge had > 2-fold higher odds of being referred to CR when compared to patients adviced to see with a family physician ($p < 0.05$) [24]. The other fact is that, only 40%-60% of patients referred to these programs complete the prescribed course of CR [25].

Table 1. Indications for CR

Acute myocardial infarction
Stable angina pectoris
Coronary artery bypass graft surgery
Heart valve repair or replacement surgery
Heart valve repair or replacement surgery
Percutaneous transluminal coronary angioplasty
Chronic congestive heart failure
Peripheral arterial disease
Heart transplantation
Heart-lung transplantation

CR = cardiac rehabilitation

Table 2. Contraindications for CR

Unstable angina
Severe or symptomatic aortic stenosis
Decompensated HF
Severe obstructive cardiomyopathy
Acute cardiac mural thrombus
Acute deep venous thrombus
Pulmonary embolism

CR = cardiac rehabilitation

Exercise Modes and Intensity

The exercise prescription therapy starts with a symptom limited, exercise tolerance test. Thereafter, workouts typically consist of a short warm up period, followed by supervised individualized aerobic exercise, and a short cool down phase. The aerobic exercise includes a 20-60 min workouts 3-5 days a week at 50-80% of maximal exercise capacity [26]. Relatively recent data suggest that high intensity interval training (HIIT) produces larger and more rapid in-

creases in exercise capacity [14, 27, 28]. Weston *et al*. [29] have studied ET intensity and in reviewed a collection of meta-analysis data of 1468 patients enrolled in high versus moderate intensity protocols, and conclude that the benefits of HIIT in improving cardiorespiratory fitness (CRF) exceed those gained from moderate intensity continuous training (MICT) protocols utilized as the current standard of care for CR. In a study comparing moderate intensity continuous training MICT and HIIT protocols in patients with stable ischemic cordiomyopathy demonstrated a significant increase in peak oxygen consumption (VO2MAX) in the HIIT group [30]. HIIT also improved endothelial functions, reversed left ventricular remodelling and increased ejection fraction more than continous training. Similar superior improvements have been noted in other studies too [14, 27, 28]. The differentiating factors between HIIT and MICT; that usual therapy involves continuous maintenance of workload at an intensity of 50%-65% of the peak, often measured as VO2MAX or peak HR. HIIT protocols consist of shorter high-intensity intervals (75%-95% of maximal effort) interrupted by periods of rest [31]. In a similar comparative meta-analysis including 277 patients with CHD, Elliot *et al*. [32] and colleagues demonstrated that HIIT was associated with a significantly higher VO2, which is independently associated with reduced CVD mortality.

PREhabilitation is a new approach to ET-based therapy which is suggested to optimize post-CABG outcomes. The CR programme starts pre-operatively, that is, before bypass surgery, to decrease post-CABG morbidity and mortality. In a study, implementing preoperative ET led to improved performance on a 6-minute walk test, a shorter hospital stay, fewer pulmonary complications, and a significantly lower incidence of postoperative atrial fibrillation [33].

Additionally to ET intensity, frequency and optimal "dosing" of ET also play an important role. Michaelides *et al*. [34] found that 30 min of ET increased vascular elasticity and improved antioxidant balance; however, these benefits were lost when the ET duration was extended to 60 min. Recent data suggest that when applied to vigorous ET, more moderate amounts of ET may provide added benefits at reduced risk (< 5 h of ET per week) [35, 36]. These physiologic findings supported by a cohort study of near 13,000 patients conducted by Blair *et al*. [37]. It was found that a plateau in benefits above 9-10 metabolic equivalents (MET) above which adjusted all-cause mortality no longer improved [37]. Similarly, increases above levels of moderate ET frequency in women were not associated with reductions in the risk of vascular diseases in a prospective study of women in the United Kingdom [38]. These findings support the 2013 ACC/AHA recommendations for reducing CVD risk; 150 minutes of weekly moderate intensity exercise or 75 minutes of vigorous aerobic activity weekly in conjunction with moderate-to-high intensity muscle strengthening exercises twice per week [16].

Effects of Exercise Training on Cardiovascular Physiology

Regular physical activity (PA) has multiple effects on health, including improved endothelial function, increased maximal aerobic capacity with better oxidative efficiency, and higher anti-oxidant activity. These physiological changes are the causes of improvements in both diastolic dysfunction and contractility, lower resting blood pressure (BP) and HR, increased muscle mass and even better cognitive performance. Increased metabolic demands during ET cause upregulation of mitochondrial division and modify energy pathways within the organelles [31]. Increased mitochondrial content in muscle promotes fat oxidation especially on carbohydrate oxidation [39]. This adaptation decreases lactate as a byproduct and leads to longer duration of ET at increased aerobic capacity [40]. Additionally, ET favorably impacts cardiac remodeling and results in improvements of the performance of the myocard [41]. The mechanisms are; reversal of metabolic decoupling processes with decreases in glucose uptake in patients with metabolic syndrome and postulation of angiogenesis in working muscles mediated by β-adrenergic stimulation of capillary growth by vascular endothelial growth factors and platelet-derived growth factors [42-44]. More recent studies have shown that ET-associated post-transcriptional gene regulation via micro-RNA reduce remodeling through interactions among metabolic, contractile and epigenetic genes [45]. ET modifies sympathovagal signaling results in an increase in parasympathetic tone, leading to increased HR variability which confers a better prognosis [46, 47]. Accordingly, ET increases the threshold for ventricular ectopic activity, and controlled trials have shown that ectopic beats are less common in

trained than untrained post-MI patients [48]. Via alterations in systemic vasoconstriction, sodium and water retention, angiotensinogen II modulation, aldosterone production and decreasing aldosterone lowers sympathetic tone, complementing the effect of other ET-induced modulators of parasympathetic activity [46, 49]. The other mechanism for regulation of sympathetic tone is via adrenomodullin and atrio/brain-natriureticpeptides which are related closely to aerobic consumption. As a result BP reduction by suppressing noradrenaline and endothelin-1, and improving endothelial responsiveness and function [50-52]. ET also protects against oxidative stress and leads to increase in nitric oxide levels which have anti-hypertensive effects [53]. Ranković *et al*. [54] reported a group of patients participating in a 6-week ET program (a combination of center-based followed by home-based delivery) had C-reactive protein levels which declined by 23.7% ($p < 0.001$), and plasma vascular cell adhesion molecule-1 levels that decreased by 10.2% ($p < 0.05$) when compared to the sedentary cohort.

Many patients with CHD do not have optimal levels of lipids including high density lipoprotein cholesterol (HDL-C) and triglycerides (TGs). Also, there is evidence to suggest that these patients may have improvement in these parameters with CR. Improvements may range between +6% and −15% and for HDL-C and TGs, respectively after CR. However, much better improvements have been seen in subgroups of patients who have more abnormal baseline lipid values [55-57]. Aditionally, it is common for individuals with CHD to have "isolated" low levels of HDL-C with relatively normal to borderline-elevated low-density lipoprotein levels (LDL-C) and/or TGs. These individuals are often thought to be resistant to non-pharmacological and pharmacological regimens. But, there is evidence to support prominent improvements in HDL-C (+17%) and LDL-C/HDL-C (−11%) following formal CR[58]. Although, most CHD patients with elevated LDL-C are already being treated by statin, from which they gain effective LDL-C reduction. That's why CR leads to smaller benefit among isolated LDL-C decrease [59-60].

The Effect of CR on Mortality

In the early era of CR, two pilot meta-analyses, which involved 10 to 22 randomized clinical trials and > 4000 participants revealed that ET-based CR was associated with significant reductions in all-cause and CVD mortality of ~20%-25% as compared with usual care. However, these early studies primarily included smaller trials that involved mostly middle-aged male post-MI survivors. Women and elderly populations were largely absent from the analyses, which limited the generalizability of these reports [61, 62]. In subsequent systematic reviews and meta-analyses, higher risk patients and improved methodology and reporting were employed. These demonstrated a similar reduction in mortality rates associated with CR, as high as 13%-27% for all-cause mortality and 26%-36% for CVD mortality [63-66]. A large meta-analysis of 25 randomized and non-randomized studies from 1995 onward evaluating 219,702 patients supported the benefit of CR in overall mortality reduction in patients who were post-acute coronary syndrome, post-CABG, and in mixed CHD populations [67]. In a recent Cochrane review and meta-analysis of 63 RCTs between 1970 and 2014, including 14,486 CHD patients, CR was associated with an absolute risk reduction for CVD mortality from10.4% to 7.6% with no difference in all-cause mortality [68, 69]. Another meta-analysis that only involved RCTs from 2010 to 2015 (18 trials, 7691 patients) supported the impact of supervised ET programs on CVD mortality (Hazard risk 0.58, 95% CI 0.21-0.88), but also did not find a significant effect on all-cause mortality. Interestingly, the investigators also showed that a subgroup analysis of trials involving comprehensive CR programs (i.e., ET program along with close monitoring and management of major risk factors for CHD) both all-cause and CVD mortality were significantly decreased [70]. Cardiac rehabilitation was found effective on reducing Tpe interval, Tpe/QT and Tpe/QTc which is related with ventricular arrythmia and sudden cardiac death [71].

In different group of patients, the effect of CR on all-cause and CVD mortalitysuch as stable CHD or stable angina and acute coronary syndrome, including unstable angina, ST elevation MI and non-ST elevation MI, with or without revascularization, remains unclear. A few randomized control trials (RCT) have focused on these subcategories of CHD, because of the small number of cases that are too small to study-mortality effects, benefits are unclear. Studies about individuals those with impaired left ventricular function, and patients with incomplete coronary revascularization will be important in determining optimal

therapy for those at high risk of decompensation and death. Aditionally, most previous studies followed patients for 12-36 months, which may not have allowed enough time to observe the associated mortality benefits from CR. As the healthcare fundings are shrinking, it will be crucial to identify the types of patients who will benefit from CR, as this will improve resource utilization in the long-term management of CVD patients [16].

Cardiac Rehabilitation and Rehospitalization

There are a little number of trials that investigated the hospital readmissions during the early studies of CR. Heran *et al*. [66] showed that total readmission rates were reduced in patients who underwent ET-based CR when compared with usual care in studies that followed patients for up to 12 months. A Cochrane review reported rehospitalization risk reduction with CR from 30.7% to 26.1% [68].Some recent trials and observational studies confirmed that, optimal medical management and early intervention may have a major impact on reducing recurrent hospitalizations in CHD and CR failed to show any benefit of CR. In contrast, the benefit of CR in reducing hospitalization has been shown for HF patients [67].

Cardiac Rehabilitation and Non-fatal Myocardial Infarction

In previous, some meta-analyses and systematic reviews did not show benefit of CR on recurrent non-fatal MI rates [62, 64-66]. Only two meta-analyses demonstrated a reduction by 47% in non-fatal MI rates [63, 72]. A lack of benefit in the prevention of recurrent non-fatal MI in the CR group was reported by others [67, 68]. It was thought that this was due to the conversion of fatal to non-fatal MIs, thereby decreasing mortality rates once CR was incorporated into routine cardiac care.

Van Halewijn *et al*. [70] reported the reduction of MI rates by 30% in ET-based CR as compared with usual care, and that cerebrovascular events were decreased by 60%, with the number needed to treat being 45 and 82 for MI and cerebrovascular events, respectively. This study was the first to show a significant reduction in stroke rates in this population after CR; however, this may be due to more comprehensive CV care, medication optimization, and improvements in CVD risk factors, such as BP control, smoking cessation, and reduced cholesterol levels, rather than the effects of ET alone [70].

Health-related Quality of Life and Psychosocial Stress in Cardiac Rehabilitation

The role of CR in enhancing patients' wellness is related to restoring or improving functional capacity. This relates to both physical work capacity and cognitive function. The latter is important because ~25% of CVD events are associated withphyscosocial stress (PSS), which has been shown to be associated with prolonged hospitalization, delayed return to work, and

Table 3. Mechanisms by which moderate-to-vigorous exercise training may reduce the risk for nonfatal and fatal cardiovascular events

Cardioprotective mechanisms of physical activity				
Psychologic	Anti-arrhytmic	Anti-thrombotic	Anti-atherosclerotic	Hemodynamics
↑Social interactions	↑Heart rate variability	↑Fibrinolysis	↑Insulin sensitivity	↑Cardiac remodelling
↓Psyhcosocial stress	↓Adrenergic activity	↓Platelet adhesion	↑HDL/LDL	↑Coronary flow
↓Depression	↑Vagal tone	↓Fibrinogen	↓Triglycerides	↑EPC's and CAC'S
		↓Blood viscosity	↓Blood pressure	↓Myocardial O2 demand
			↓Adiposity	↓Endothelial dysfunction
			↓Inflammation	↑Nitric oxide

BP = blood pressure, EPCs = endothelial progenitor cells, CACs = cultured/circulating angiogenic cells, ↑ = increased, ↓ = decreased, O2 = oxygen. *Nitric oxide also has antithrombotic effects.

increased mortality. The effects of PSS is inversely related to health-related quality of life [73-75]. A cohort study showed a tendency to return to work earlier than those in the conventional care group [76].

Cardioprotective Effect of Cardiac Rehabilitation

A meta-analysis of CHD patients, lipid profile including total cholesterol and LDL-C levels were significantly lower in patients in the comprehensive CR group, but not the ET-only group. Another meta-analysis based on this population demonstrated reductions in total cholesterol and triglycerides, without improvements in LDL-C and HDL-C levels [64, 65]. Additionally, patients' systolic BP significantly reduced following CR. Similarly, another RCTs demonstrated significant reductions in LDL-C and systolic BP values [70]. Kasapoglu Aksoy *et al*. [77] found that CR was found to be effective and safe in terms of functional capacity, daily life activities and anxiety in both obese and non-obese patients. In addition, one RCT that addressed ≥ 6 CVD risk factors during CR demonstrated a reduction in overall mortality, but no differences in overall mortality were present in studies that addressed fewer risk factors. According to these findings, the improvement in CHD risk factors are closely related with concomitant medical management during the ET-based programs, suggesting a critical role of risk factor modification in the secondary prevention. The overall benefits of CR programs for CHD are summarized in Table 3 [16, 70].

Complications of Exercise Therapy

Vigorous physical exercise is a CV stressor, it it can trigger both non-fatal and fatal arrhythmias, especially in patients with known or occult CVD. The 2007 American Heart Association scientific statement on exercise and acute CVD events, the risk of any major CV complication (sudden cardiac death, total mortality or MI) is 1/60.000 - 80.000 patient-hours [78]. In a study of > 25,000 patients participating in 65 CR centers, there was one CVD event for every 8,484 exercise tests performed, one CVD event for every 50,000 patient hours of ET, and 1.3/million cardiac arrests for every patient hours of ET [79]. In a review of 4,846 CHD patients enrolled in interval and continuous CR regimens in Norway, the difference in event rates were 1 in 129,456 h of moderate ET and 1 in 23,182 h of high intensity ET [80]. Although the benefits of structured CR clearly outweigh the risks, additional data on risk stratification and prophylactic strategies (e.g., value of warm-up/cool-down, education of warning signs or symptoms) may help reduce the infrequent, ET-related CVD events. These efforts are already under-way with the development of the Physical Activity Intelligence score, a validated physiologic metric that predicts CVD and all-cause mortality based on aerobic capacity; this is discussed further elsewhere in this issue [81].

CONCLUSION

CR is a cost effective strategy in secondary prevention of CVD. CR has been widely used for over forty yearsin different countries worldwide, with a robust evidence, effective improvements in cardiopulmonary fitness, PSS, quality of life and reduction in morbidity and mortality. It is also a strategy for reducing hospital readmitions. Despite these evidences, CR still remain underutilized not only because of the low patient referral, but also high discontinuation rates. Further randomized controlled research is necessary to evaluate long-term outcomes to assess the persistence of change observed in supervised CR of relatively short duration. Finally, a vigilant approach to primary prevention utilizing the expertise found in CR programs is needed.

Conflict of interest

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The European Research Journal 2019;5(2):399-402 CASE REPORT

Unusual location of lichen striatus in an adult patient

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ABSTRACT

Lichen striatus is a rare inflammatory dermatosis that influences mostly children, being rare reports in adults. The pathogenesis is unknown. In addition, lichen striatus is demonstrated as T-cell mediated inflammatory cutaneous disease. It is characterized by linear tendency, usually on the extremities. Its most typical property is the linear arrangement of slightly raised, lichenoid papules. A 28-year-old woman presented with a 3-month history of an asymptomatic linear erythematous violaceous papular lesions on her left abdominal area. Skin biopsy was performed in terms of differential diagnosis from other linear distributions of inflammatory dermatoses. Histopathological examination revealed hyperkeratosis, acanthosis, focal parakeratosis, exocytosis, subbasal dissociation of an area, vacuolar degeneration of the basal membrane, perivascular and lichenoid lymphocytic infiltration. As a result, our case was diagnosed as lichen striatus, clinically and histologically. Topical pimecrolimus ointment twice a day therapy was preferred in the patient.

Keywords: Lichen striatus, unusual location, pimecrolimus

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Lichen striatus is a rare inflammatory dermatosis that influences mostly children, being rare reports in adults [1]. The pathogenesis is unknown. In addition, lichen striatus is demonstrated as T-cell mediated inflammatory cutaneous disease [2]. It rarely influences adults, and it is characterized by linear tendency, usually on the extremities. Its most typical property is the linear arrangement of slightly raised, lichenoid papules [3]. The linear eruption of inflammatory lesions appears usually over 2 to 3 weeks.

We want to present here case of an adult woman with erythematous violaceous papules on the left abdominal area, diagnosed with lichen striatus by clinical and histopathological correlation.

CASE PRESENTATION

A 28-year-old woman presented with a 3-month history of an asymptomatic linear erythematous violaceous papular lesions on her left abdominal area (Figure 1). The patient's other skin areas, mucosa, hair and nail examination were normal.

The patient was completely healthy. There was no atopy history in her family and herself. Laboratory tests were normal.

Skin biopsy was performed in terms of differential diagnosis from other linear distributions of inflammatory dermatoses. Histopathological examination revealed hyperkeratosis, acanthosis, focal parakeratosis, exocytosis, subbasal dissociation of an

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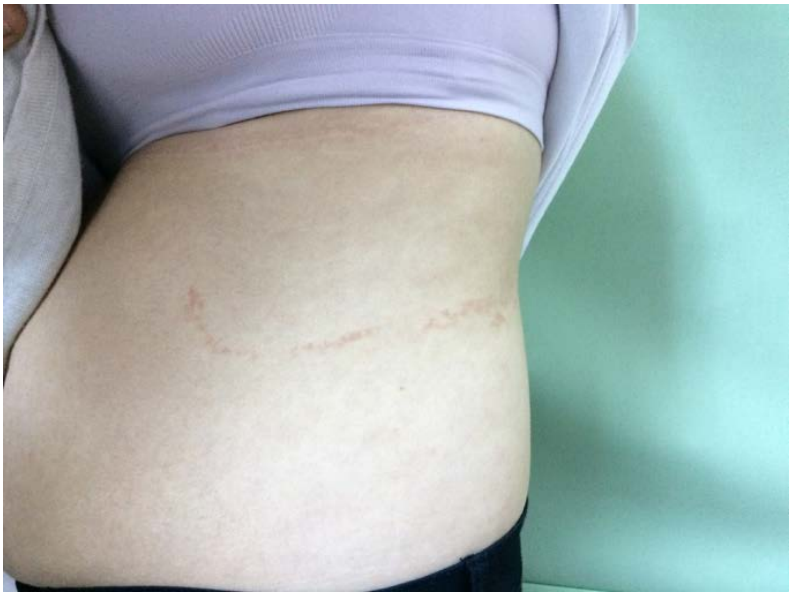

Figure 1. Asymptomatic linear erythematous violaceous papular lesions on her left abdominal area

area, vacuolar degeneration of the basal membrane, perivascular and lichenoid lymphocytic infiltration (Figure 2). The histopathological diagnosis was lichen striatus.

As a result, our case was diagnosed as lichen striatus, based on clinical and histological characteristics. Topical pimecrolimus ointment twice a day therapy was preferred in the patient.

DISCUSSION

Lichen striatus is defined by erythematous papules with a flattened surface that are constantly scaly in appearance. The lesions are generally solitary and unilateral and have a linear distribution following Blaschko's lines, usually on the extremities [4]. In the pathogenesis, T-cell mediated autoimmune reaction

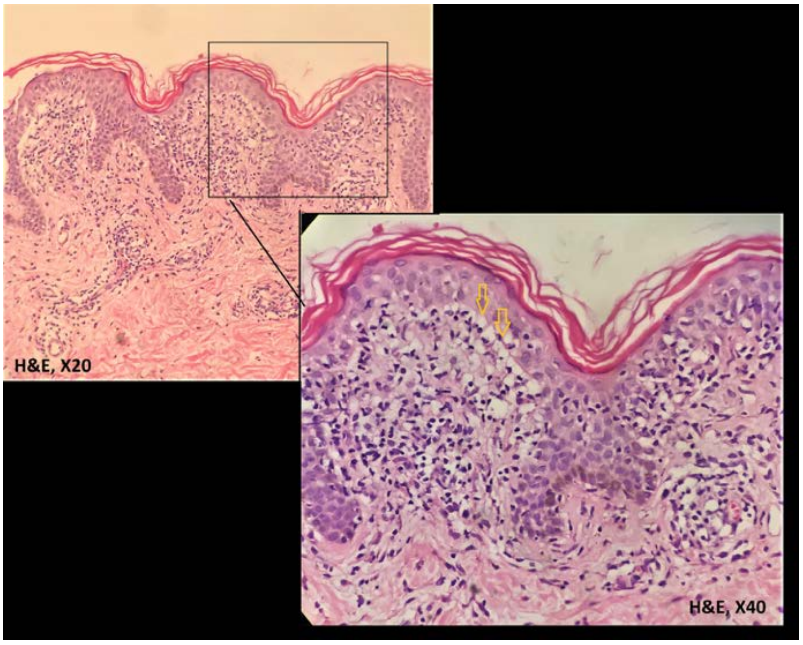

Figure 2. Histopathological examination revealed hyperkeratosis, acanthosis, focal parakeratosis, exocytosis, subbasal dissociation of an area, vacuolar degeneration of the basal membrane, perivascular and lichenoid lymphocytic infiltration.

against Malpighi cells showing genetic mosaicism and distributed throughout the Blaschko lines is accused [5]. The etiology is mysterious, thought ıt have been associated with a personal history of atopy. Viral infections, vaccinations, pregnancy, emotional stress, medications, skin trauma, stem cell transplantation and contact dermatitis are the triggering factors [6]. In our case, there is no history of drug use or viral infection that may trigger.

Inflammatory linear lesions have a variety of clinical and histological appearances, and may look like inflammatory linear verrucous epidermal naevus (ILVEN), linear lichen planus, adult blaschkitis, linear morphea, linear psoriasis, linear Darier's disease, linear porokeratosis, verruca plana and linear lichen nitidus [7]. Differential diagnosis of other inflammatory linear lesions is based on histopathology. Histopathologically, lymphocyte-rich, sometimes band-like intense perivascular inflammatory infiltrates, parakeratosis and hyperkeratosis are seen in lichen striatus [8]. All who claim a clear difference between adult blaschkitis and lichen striatus emphasize that lichen striatus predominantly shows papules and histological lichenoid changes [9]. Likewise, histopathology was lichenoidpatern in our case. In addition, adult blaschkitis usually has multiple dermatomal involvements, whereas lichen striatus usually has only one dermatome [10]. In our case, there was only one dermatomal involvement in the same way.

Lichen striatus is very similar clinically and histopathologically to lichen planus. However, histopathological evidence of clustered infiltrates in the hair follicles and the eccrine glands is a distinctive finding for lichen striatus [2]. In our case mononuclear cell infiltration was also detected around hair follicles. Because lichen striatus is a self-limiting dermatosis, the patients may be left to heal spontaneously on treatment. Topical potent steroids are the first choice for treatment in patients with severe itching [11]. In recent years, topical pimecrolimus and topical tacrolimus(topical calcineurin inhibitors) have been successfully used in therapy [11, 12]. Topical calcineurin inhibitors block interleukin-2 transcription and thus prevent local T lymphocyte activation [13]. Thus, we used topical pimecrolimus in our case.

CONCLUSION

We think that our case of lichen striatus, which we treated with topical pimecrolimus treatment, was suitable for presentation because of its rare occurrence in adult patients and the rare occurrence of abdominal involvement. We think that further studies are needed about the use of pimecrolimus cream in the treatment of lichen striatus.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

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

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The European Research Journal 2019;5(2):403-406 CASE REPORT

Endoscopic management of a foreign body inserted through the urethra into the bladder in a male patient: a case report

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ABSTRACT

Foreign body in the urethra is a rare condition, which is caused by the placement of a foreign object in the person's own urethra, with different causes, and requires immediate intervention. We present a 16-year-old male case of self-insertion of a pencil into the urethra migrating into the bladder. The pencil was in prostatic urethra and pulled by holding it with forceps endoscopically. Open surgery is usually required for the foreign body in the urethra and bladder. In the appropriate patients, the foreign body can be removed with endoscopic management.

Keywords: Foreign body, urethra, endoscopic management

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Foreign body in urethra is a rare condition, which is caused by the placement of a foreign object in the person's own urethra, with different causes, and requires immediate intervention. In most cases, sexual or erotic stimulation providing, psychiatric disorders, mental disorders appear to be the most common reasons.

Objects have commonly included metal rods, bones, screws, pellets, safety pins, a plastic cup, straws, a marble, cotton tipped swab, needles, pencils, ball point pens, pen lids, garden wire, copper wire, speaker wire, Allen keys, wire such as objects (telephone cables, rubber tubes, feeding tubes, straws, string), tooth brushes, household batteries, light bulbs, marbles, cotton tip swabs, plastic cups, thermometers, plants and vegetables (carrot, cucumber, beans, hay, bamboo sticks, grass leaves), parts of animals (squirrel tail, snakes, bones), toys, pieces of latex gloves, blue tack, intrauterine contraceptive devices, tampons, pessaries, powders (cocaine), and fluids (glue, hot wax) [1, 2].

Patients usually apply with the complaints of dysuria, pollakuria, hematuria, urinary retention, penile pain and swelling. The most frequent symptom is dysuria. Hematuria accompanies dysuria. Most patients apply to doctor late because of shame and the fear of social stigma [1-3]. The treatment is not only the retrieval of the foreign material. Also, it consists of the patient long period follow for complication and psychiatric controls.

We present a case of self-insertion of a pencil into the urethra for sexual pleasure during masturbation, and then migrating into the bladder and endoscopic intervention for management.

CASE PRESENTATION

A 16-year-old boy presented to the emergency service with complaints of pain in the perineum and

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hematuria. He had no previous history of any significant psychiatric illness. In the anamnesis, he said that he had placed the pencil into the urethra in the case of erection, and after putting the whole of the pencil in it, he had pressed it down through the penis. The pencil had been pushed into the penis. He said that he had tried with the pen in the same way and he had felt sexual pleasure. On clinical examination, he had severe local tenderness and something was palpable in the perineal region. Abundant erythrocytes were present in urinalysis. Computerized tomography (CT) was performed to evaluate organ injury. The foreign body migrated in the bladder was seen in CT. Endoscopy was planned for the patient with abundant erythrocytes in urine analysis. We entered urethra with an endoscope. Mucosal hyperemia and mucosal damage were present in the urethra. The pencil was seen in prostatic urethra and pulled by holding it with forceps (Figures 1, 2, and 3). The patient was catheterized postoperatively and the catheter was taken the post-operative first day. The patient was discharged with oral antibiotic therapy. There was no urological complaint in the first week control after surgery. The psychiatric evaluation was recommended. Borderline personality disorder was detected after the psychiatric evaluation.

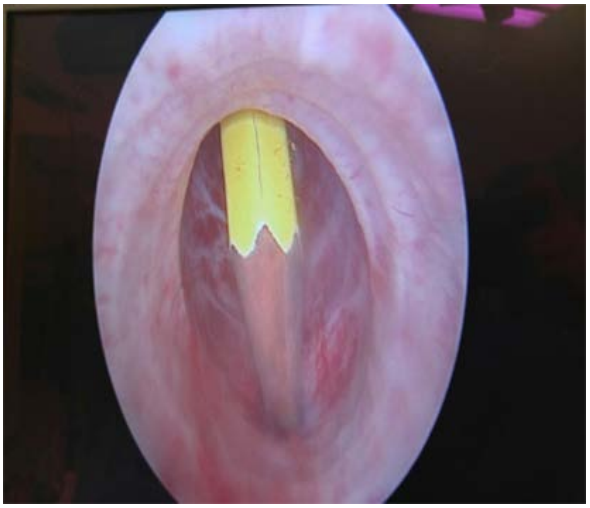

Figure 1. Endoscopic appearance of a foreign body in the urethra.

Figure 2. Pencil removed from the urethra.

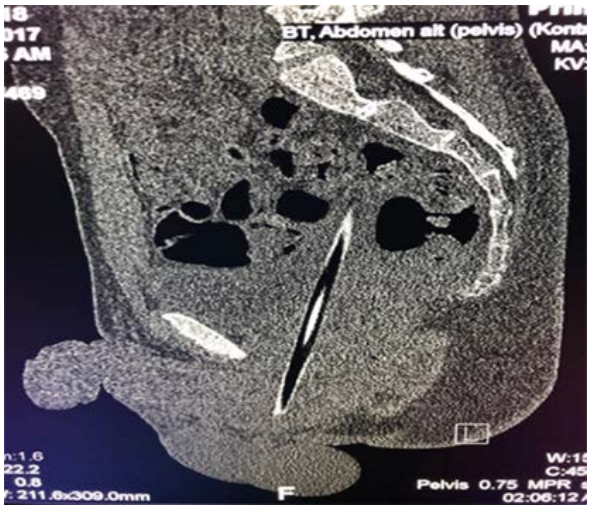

Figure 3. Computerized tomography appearance of a foreign body in the urethra.

DISCUSSION

Although insertion of foreign materials into the lower urinary tract has a rare occurrence, the number of cases reported in male patients has increased in the last 10 years. Patients are often embarrassed to seek medical care initially so they make interventions to retrieve the foreign material themselves. These interventions can lead to a change of position and further injury [1]. Endoscopic intervention is usually insufficient in the treatment of foreign materials. Also, open surgical intervention is usually required [1-3]. In our study endoscopic intervention was achieved without any complication in open surgery requiring patient.

Patients often have pain and anxiety during admission, so if necessary premedication should be performed to relieve the patients and evaluate with appropriate imaging methods [1]. Ultrasonography (US) or CT can be used to assess the location of the foreign material and organ integrity. The most common reason for inserting a foreign material into the urethra is autoerotic and sexual pleasure, especially during masturbation [35].

Aliabadi *et al*. [6] reported their experience in 15 patients who self-inserted foreign material into the urethra over a 42-year period. The endoscopic intervention was successful in six patients who had foreign material in the anterior urethra. Open surgery was required in five of the remaining nine patients with foreign materials in the posterior urethra and bladder. Only one patient required perinealurethrotomy. The differences in our treatment approach can be explained by the variation in the type and location of the materials.

Rahman *et al*. [1] reported their experience; Endoscopic retrieval was successful in 16 of the 17 patients. In one case endoscopic retrieval was unsuccessful and perineal urethrotomy was required.

Sexual exotic predispositions, impaired schizoid personality, and borderline personality disorder are common comorbidities reported in patients presenting with foreign materials [7]. In our case, borderline personality disorder was detected after psychiatric consultation. The medical intervention is delayed due to the feeling of guilt and shame in the majority of the cases. Most cases are associated with a psychiatric disorder, drug intoxication, mental disorder, sexual curiosity, or the desire to get rid of urinary symptoms [1, 4, 5].

In a series of 10 self-inserted urethral foreign material cases reported by Mahadevappa *et al*. [3], the manic depressive psychiatric disorder in two patients, mental retardation in one patient, impulsive behavior in one patient and autoerotic stimulation in two patients were recorded. Lack of partner or spouse and misunderstanding about masturbation were noted as a cause in three patients. Although controversial, psychiatric assessment of each patient is important. This assessment can be beneficial not only in the diagnosis and treatment of any underlying mental illness but also in avoiding self-harmful situations that may arise.

CONCLUSION

Foreign materials in the urethra and bladder can rarely be treated endoscopically. Open surgery is required in many cases. In our case we achieved open requiring patient endoscopically and patient was discharged postoperative first day without any complication. In these patients, besides removing the foreign material, the underlying and triggering events should be defined and appropriate treatment should be performed.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

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

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The European Research Journal 2019;5(2):407-409 CASE REPORT

A rare case of left ventricular lead stabilization utilizing a coronary stent placement during CRT-D implantation

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DOI: 10.18621/eurj.397159

ABSTRACT

During cardiac resynchronization therapy implantation, left ventricular lead placement involves transvenous placement of leads via the coronary sinus and into a tributary branch. At present, the most widely used method for left ventricular (LV) lead placement involves a transvenous LV lead placement via the coronary sinus into a tributary branch. Lead dislodgement is a common cause for reoperation. We describe a case where a coronary stent was placed to stabilize the lead against the vessel wall.

Keywords: Lead dislodgement, CRT, lead stabilization, coronary sinus, dyssynchrony

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Cardiac resynchronization therapy (CRT) has been used successfully to decrease the mortality and morbidity in heart failure patients with cardiac dyssynchrony. CRT effectiveness is significantly hindered in 30% of recipients for several reasons; beyond the patient's selection issue, loss of left ventricular (LV) stimulation plays an important role. Loss of LV stimulation occurs mainly because of LV lead dislodgement that is reported to range from 2 to 12% of patients in different reports [1]. Lead dislodgement is a common cause for a reoperation and continues to be a frequently experienced problem despite advances in the equipment and operator techniques.

CASE PRESENTATION

A 59-year-old female patient, post biventricular-defibrillator (CRT-D) implant 6 months back at another hospital, now presented with worsening of dyspnea for past 1 month. Her device interrogation revealed failure of LV pacing & fluoroscopy revealed dislodgement of LV bipolar lead into coronary sinus. Patient was taken up for LV lead reimplantation. Pacemaker pocket was dissected, LV lead was separated from its pectoral attachments and removed without any resistance. Coronary sinus was accessed with Medtronic attain command (6250, MB2, Medtronic, Minneapolis, MN, USA) catheter. Coronary sinogram revealed only a single large posterolateral vein of approximately 2.5 mm diameter (Figure 1). Her prior coronary sinus venograms or LV lead positions at prior implantations on fluoroscopy were not available for comparison. However, in view of solitary suitable vein available, it was decided to place the lead into this particular vein. A Whisper ES guidewire (Abbott vascular, Santa Clara, LA USA) was placed in the vein, over which the Medtronic attain ability 4196 lead was placed deep in the vein (Figure 2). However, in view of discrepancy between the vein diameter (~ 2.5 mm) and lead diameter (lead

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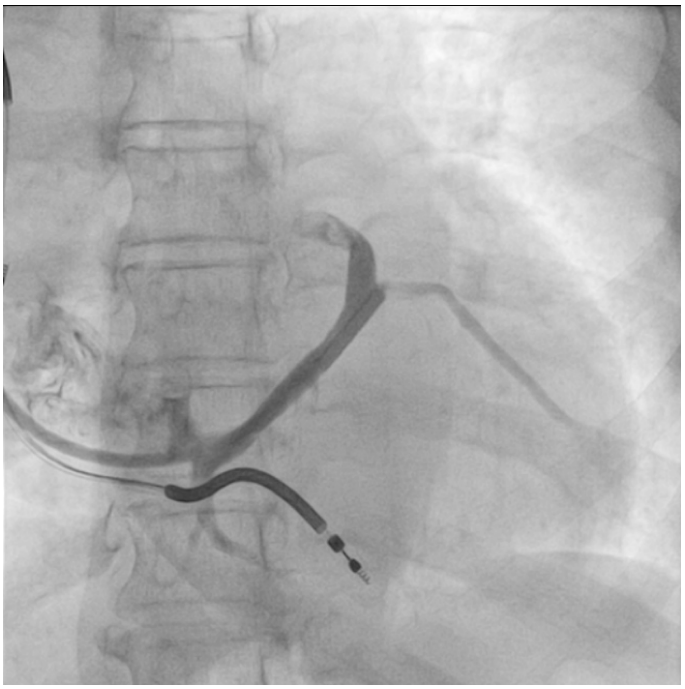

Figure 1. Coronary sinus angiogram showing a large postero-lateral vein.

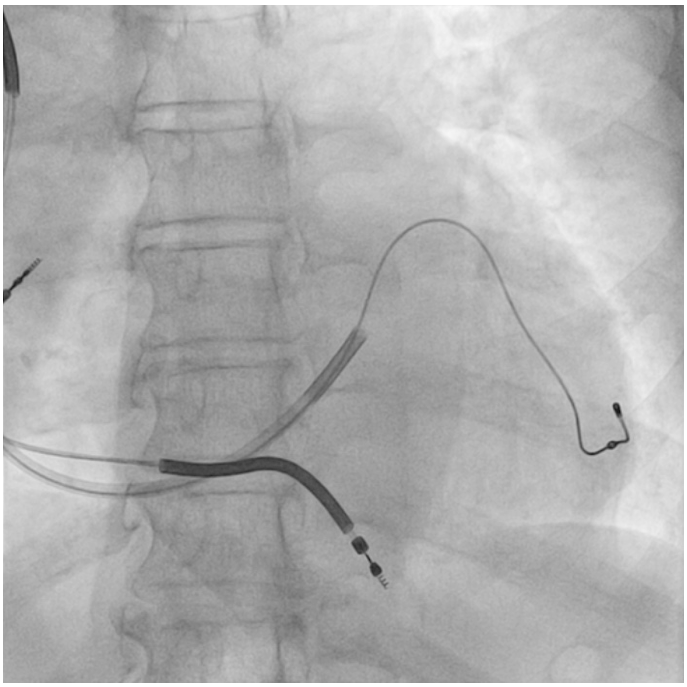

Figure 2. LV lead placed in the desired vein.

tip 4.6F [1.7 mm], lead body 4F [1.3 mm]), lead was not stable inside the vein after spontaneously displaced during withdrawal of coronary sinus guide catheter. Larger diameter lead as well as Medtronic active fixation leads were not available at that time in the cath-lab. Taking into account the target vein - lead diameter mismatch and history of lead dislodgement, it was decided to stabilize the lead with the help of percutaneous stent.

An additional coronary sinus access was obtained with an Amplatz left (AL 1.0) launcher guiding catheter (Medtronic, Minneapolis, MN, USA) and the posterolateral vein was wired with balanced middle weight universal II guidewire (Abbott vascular, Santa Clara, LA, USA). A coronary stent (Xience Prime 2.5 × 8 mm, Abbott vascular, Santa Clara, LA USA) was

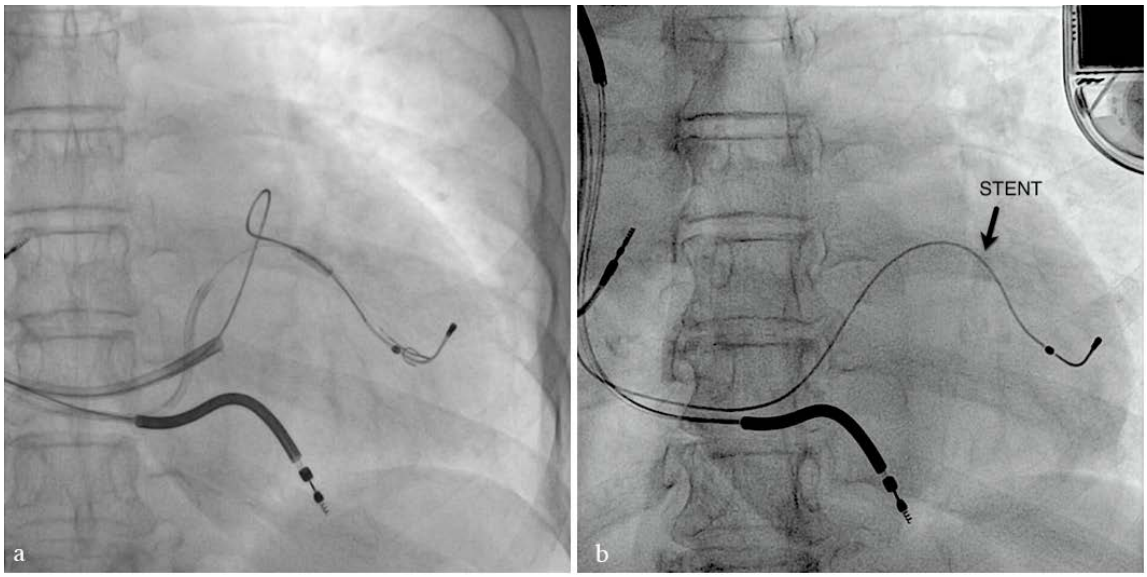

Figure 3. Coronary stent being deployed in the vein adjoining the lead (a), final LV lead position with stent in situ (b).

placed over the guidewire and implanted into the proximal vein adjoining LV lead (Figures 3a and 3b). The guidewire was removed. The LV lead was checked for stability using gentle traction on the lead. There was no LV lead movement. Coronary sinus sheath was removed and wound closed in two layers. Patient was observed in the hospital for 48 hours and lead parameters and position were found to be stable. At one month follow -up, LV lead parameters were found to be satisfactory.

DISCUSSION

LV leads are passively placed in coronary sinus veins in epicardial location. In spite of improvements in lead design and delivery system a high incidence of intraoperative and postoperative lead dislocations of 2-12% are seen leading to loss of LV capture and undesirable diaphragmatic stimulation [1]. The use of coronary stent technique has been proposed as an alternate method for stabilization of the LV lead in patient who experience repeated dislocation as in our case.

Main disadvantages of lead stabilization using acoronary stent are lead damage, coronary venous obstruction by thrombosis, and inability of repositioning or extraction [2].

First case report of utilization of a coronary stent to stabilize the lead in the coronary sinus was published by Cesario *et al*. [3] in 2006. Szilagyi *et al*. [4] studied lead stabilization with stenting technique. During mean follow-up of 12 months, no lead dislocation was found by fluoroscopy [4].

A recent study published by Biffi *et al*. [5] in 2014 about left ventricular lead stabilization to retain CRT at long term. Lead stabilization guided by vein anatomy was prospectively tested on consecutive patients from October 2009 to December 2010. Patients with stabilized LV leads were more likely to be CRT responders than the others: 19 of 26 (73%) vs. 34 of 58 (59%, p = NS), and had a significantly higher proportion of super-responders: 12 of 26 (46%) vs. 12 of 58 (21%, $p < 0.005$). They concluded that lead stabilization by stenting, based on coronary vein anatomy, can effectively reduce dislodgement rate from 10% to 1%. Lead performance was unaffected by the stenting procedure, and extraction was possible in a single patient 27 months after implantation [5].

CONCLUSION

Stent implantation to stabilize the left ventricular lead position seems to be a useful and safe procedure in the treatment of patients with complicated coronary sinus anatomy or lead instability.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

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

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The European Research Journal 2019;5(2):410-412 CASE REPORT

Tingling in tongue due to alprazolam and paroxetine-induced hypergabaergic activity

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ABSTRACT

Paroxetine is a commonly used serotonin-reuptake inhibitor for the treatment of various psychiatric disorders. Available literature is sparse with cases of paresthesia that occur during withdrawal of paroxetine, there are fewer reports of paresthesia during the initiation. Here we report a case of panic disorder who experienced tingling of the tongue during the initiation phase of paroxetine, and whose paresthesia resolved only after the withdrawal of the drug. When paroxetine was introduced, the patient was already on alprazolam monotherapy. Therefore, the previously activated GABAergic state with alprazolam was probably further augmented with paroxetine. We suggest that the serotonin receptor supersensitivity related to panic disorder might have been a vulnerability factor for paresthesia, and the hypergabaergic state caused by alprazolam and paroxetine combination made the paresthesia evident in our case. This is the first report of a case with paresthesia in a combination of alprazolam and paroxetine. We might suggest that in patients who develop paresthesia during psychotropic use, the clinician's first step might be to just decrease the dosage of the drugs before further clinical and laboratory evaluation of the patient for paresthesia.

Keywords: paresthesia, paroxetine, alprazolam, hypergabaergic state

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Paroxetine is a commonly used serotonin-reuptake inhibitor (SSRI) for the treatment of various psychiatric disorders. Besides the side-effects common to all SSRIs during the initiation phase, paroxetine is also well-known for discomforting initiation and discontinuation symptoms [1], one of which is paresthesia [2-4]. Paroxetine has been reported to increase the risk difference for paresthesia in 1.7% of users [1]. While available literature is sparse with cases of paresthesia that occur during withdrawal of paroxetine, there are fewer reports of paresthesia during the initiation [5, 6].

Here we report a case who experienced tingling of the tongue during the initiation phase of paroxetine, and whose paresthesia resolved only after the withdrawal of the drug. Written informed consent was taken from the patient prior to reporting.

CASE PRESENTATION

A 47-year-old female patient with a diagnosis of panic disorder was followed-up by the first author. She had been medication free for two years because she

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had benefited from cognitive therapy and was able to deal with her daily worries. However, after the sudden death of a close relative her anxiety levels increased, insomnia and appetite loss developed and continuous palpitations, and shortness of breath started. After working through her loss and supporting her with alprazolam 0.5 mg twice daily her symptoms continued by the end of one month, and she began experiencing panic attacks. Therefore, paroxetine 10mg/day was added to the treatment. She had used and benefited from paroxetine 30 mg/day previously without any initiation or discontinuation symptoms, however, this time when the dosage was increased to 30 mg/day by the third week she started complaining about tingling sensations in her tongue. A full blood count and blood biochemistry including vitamin B12, folic acid, magnesium, calcium, iron, vitamin D3, thyroid function tests, liver function tests were all in the normal range. The patient was examined by a neurologist. Cranial imaging was not necessary because the patient was functioning well generally and her neurological symptoms included only the tingling in the tongue.

She had thought this tingling might be related to anxiety and increased alprazolam to 1.5 mg/day daily without any benefit. Therefore we suspected that paroxetine might be causing the tingling, and it was decreased to 20 mg/day, but the tingling sensation stopped only after paroxetine was discontinued altogether. She was started on escitalopram. However, after six weeks of escitalopram 20 mg/day she wanted to give paroxetine another try because her anxiety was still very discomforting and she admitted that her anxiety would seem to get better only after she took alprazolam. Unfortunately, she reported the same tingling sensation on her tongue again after switching to paroxetine. Tingling disappeared after stopping paroxetine. She was started on duloxetine 30 mg/day which was increased up to 60 mg/day. She has not reported any tingling sensations in her tongue and is anxiety free for the past eight months. Naranjo's adverse effect scale was applied retrospectively [7]. The score was 8.

DISCUSSION

As a general rule, for the treatment of psychiatric disorders, it is convenient to choose the molecule that the patient had benefited from during previous episodes, that is why paroxetine was selected for our patient. Reappearance and disappearance of the tingling sensation when paroxetine is used and stopped suggests that this paresthesia was caused by paroxetine. Naranjo's adverse effect scale was applied retrospectively. The score was 8. A score of 5-8 for the scale indicates "probable" relation between the drug and the adverse event [7]. Therefore, we can't say that the relation between tingling in the tongue and paroxetine and alprazolam use is not definite but probable. It is of note that she had not previously experienced any important side-effects related to paroxetine before.

Some of the factors that may contribute to adverse drug reactions are age, gender, maternity status, smoking, alcohol use, polypharmacy, drug dosing and drug frequency or the pathophysiology of the disease [8]. Paroxetine is a potent inhibitor of CYP2D6, and this may be responsible for some side-effects related to its use in combination with other drugs. Paroxetine was combined with alprazolam in our patient which is a conventional approach, especially in panic disorder patients to accelerate treatment response at the initiation of SSRI treatment [9]. Alprazolam is neither a substrate nor an inducer of the CYP2D6 system. Therefore alprazolam is not supposed to interact with the metabolism of paroxetine. In a previous study, the combination of paroxetine with alprazolam at steady state in healthy volunteers, there were no pharmacological interactions [10]. Our patient was not on any other drug than alprazolam, was not using alcohol and was not a smoker.

Serotonin receptor supersensitivity has been suggested for the pathophysiology of paresthesia experienced during withdrawal from SSRIs [4]. It has also been reported that patients with panic disorder show serotonin receptor supersensitivity [11]. Therefore, the patient's clinical syndrome of panic disorder itself might have increased her vulnerability to the drug-related paresthesia.

Due to anticholinergic and other receptor features, paroxetine can cause jitteriness or activation syndrome. However, the drug was titrated slowly, starting with 10 mg the first week and reaching 30 mg/day by the third week. Therefore, probable activation syndrome through 5HT2C receptor was not

considered [12]. The patient had no other neurological signs other than the tingling in the tongue. She did not describe increased irritability or any myoclonic activity that would suggest jitteriness.

Benzodiazepine withdrawal may cause paresthesia, but alprazolam dosage remained the same when paroxetine was introduced [13]. When benzodiazepines bind to the GABA A receptor, the receptor is allosterically modulated, and GABA exerts a greater effect on the chloride channel, resulting in stronger inhibition. Benzodiazepines activate GABA receptors [14]. SSRIs increase cortical GABAergic activity [15].

When paroxetine was introduced, she was already on alprazolam monotherapy. Therefore, the previously activated GABAergic state was probably further augmented with paroxetine.

It might be argued that serotonin receptor supersensitivity related to panic disorder might be a vulnerability factor for paresthesia, and the hypergabaergic state caused by alprazolam and paroxetine combination made the paresthesia evident.

CONCLUSION

This is the first report of a case with paresthesia in a combination of alprazolam and paroxetine. We might suggest that in patients who develop paresthesia during psychotropic use, the clinician's first step might be to just decrease the dosage of the drugs before further clinical and laboratory evaluation of the patient for paresthesia.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

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

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The European Research Journal 2019;5(2):413-417 CASE REPORT

An interesting co-existence of celiac disease and idiopathic pulmonary hemosiderosis: Lane-Hamilton syndrome

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ABSTRACT

Idiopathic pulmonary hemosiderosis is characterized by hemoptysis resulting from recurring alveolar hemorrhage attacks, iron deficiency anemia, and parenchymal infiltrations as seen on chest radiographs. The clinical course may consist of silent and asymptomatic attacks, or it may sometimes exhibit a fulminant course with rapidly developing anemia and hypoxemia. Celiac disease is an autoimmune enteropathy triggered by the consumption of gluten-containing foods in genetically predisposed individuals. Co-existence of idiopathic pulmonary hemosiderosis and celiac disease is defined as Lane-Hamilton syndrome. We describe a case of Lane-Hamilton syndrome with growth and developmental delay; complete remission of pulmonary symptoms was achieved with a gluten-free diet.

Keywords: Idiopathic pulmonary hemosiderosis, celiac disease, anemia, gluten-free diet

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Idiopathic pulmonary hemosiderosis (IPH) is characterized by hemoptysis resulting from recurring alveolar hemorrhage attacks, iron deficiency anemia, and parenchymal infiltrations as seen on chest radiographs [1]. It is generally observed in children, but rarely, may occur in adults. Recurring intra-alveolar bleeding constitutes the pathophysiology of the disease. Reticulonodular infiltrates associated with this bleeding are observed on chest radiographs. Iron deficiency anemia occurs secondary to massive hemoptysis. The etiopathogenesis of the disease is unclear [2, 3]. Vasculitis, connective tissue diseases, various autoimmune diseases, infections, and some drugs can lead to recurring alveolar hemorrhage attacks, while a clinical picture of IPH arises when no underlying cause can be shown. The clinical course may consist of silent and asymptomatic attacks, or it may sometimes exhibit a fulminant course with rapidly developing anemia andhypoxemia. Late complications such as pulmonary fibrosis and cor pulmonale may develop following recurring attacks and adversely affect the course of the disease.

Celiac disease (CD) is an autoimmune enteropathy triggered by the consumption of gluten-containing wheat, rye, barley, and oats in genetically predisposed individuals. It may occur with classic symptoms such as chronic diarrhea, weight loss, growth delay, and malabsorption or with non-gastrointestinal symptoms such as refractory iron deficiency anemia, isolated short stature, osteoporosis, and hepatitis. Intestinal

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injury with inflammation occurs because of specific T cell response to gluten. Co-existence of idiopathic pulmonary hemosiderosis and celiac disease is defined as Lane-Hamilton syndrome. This is a rare condition that generally accompanies symptomatic clinical CD findings [4]. IPH responds well to corticosteroids, while a gluten-free diet can reduce the need for corticosteroids in comorbid IPH-CD [5]. We describe a case of Lane-Hamilton syndrome with growth and developmental delay; complete remission of pulmonary symptoms was achieved with a gluten-free diet.

CASE PRESENTATION

An 8-year-old girl was referred to us due to a hemoglobin (Hb) value of 2.7 g/dL from an external clinic to which she presented with lethargy, respiratory difficulty and occasional hemoptysis over the previous 6 months. The patient's past medical history and her family medical history were unremarkable. Tachycardia (heart rate > 140/min) was noted during physical examination. She weighed 19.3 kg (<3 p) and her height was 112.5 cm (<3 p). Her skin and mucosa were significantly pale. Pronounced rales were present in both hemithoraces at respiratory examination. A 2-3/6 systolic murmur was present. Three centimeters of the liver was palpable. Results of other organ system examinations were normal. Complete blood count values were Hb: 2.7 g/dL, hematocrit (Hct): 12%, erythrocyte mass: 1.2 million/mm3, mean erythrocyte volume (MCV): 54.1 fL, mean erythrocyte concentration: 31.6 g/dL, erythrocyte distribution width: 16.2%, white blood cell (WBC) count: 7300/mm3, and platelet count: 532,000/mm^3. Peripheral smear results showed that granulocytes (58%), lymphocytes (34%), and monocytes (8%) were present. Erythrocyte morphology was compatible with hypochromic microcytic anemia. No atypical cells were observed. Serum iron level was 3 µg/dL, total iron binding capacity was 471 µg/dL, and ferritin was 2.89 ng/dL. Transferrin saturation was 0.6%. Liver and kidney function tests and arterial blood gas analyses results were normal. Activated partial thromboplastin time was 23.6 s, and prothrombin time was 13.5 s. C-reactive protein was 1 mg/L (0-8 mg/L) and erythrocyte sedimentation rate was 12 mm/h. There were no acid-resistant bacilli in sputum. Immunoglobulins (Ig) M, G, A and, serum complements 3 and 4 levels were normal. Anti-nuclear antibody, double-stranded DNA antibody, anti-neutrophil cytoplasmic autoantibodies (p-ANCA and c-ANCA) and anti-glomerular basal membrane antibody test results were normal. Respiratory function tests results were normal. The sweat test using the Macroduct method yielded normal results at 33 mmol/L (0-40: normal, 40-60: repeat test, >60: high). Bilateral basal infiltration was determined using a posterior-anterior chest radiograph (PACR) (Figure 1a). Thoracic tomography revealed a patchwork of bilateral diffuse ground glass densities with irregular

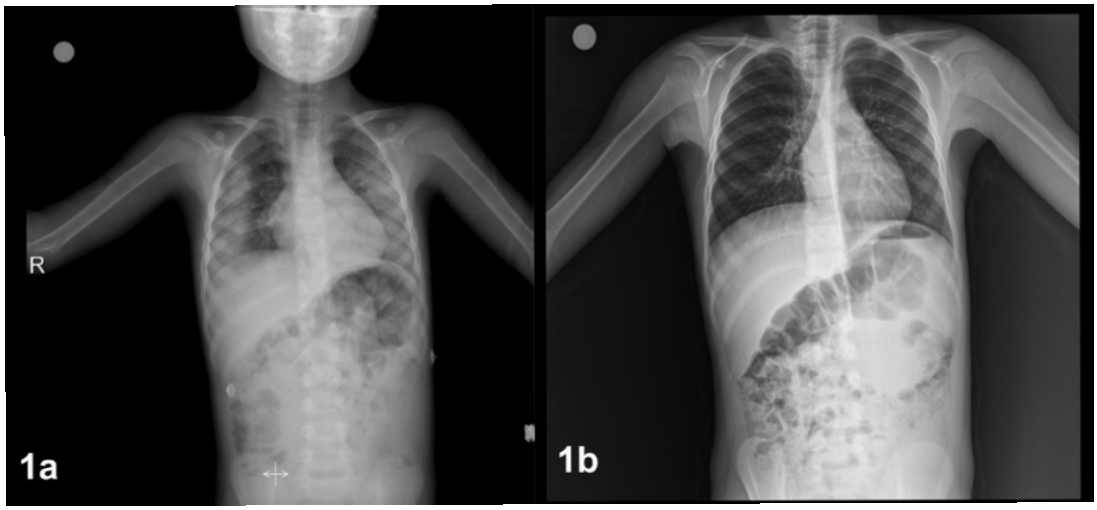

Figure 1. (a) Bilateral basal infiltration on posterior-anterior chest radiograph, (b) Posterior-anterior chest radiograph after gluten-free diet.

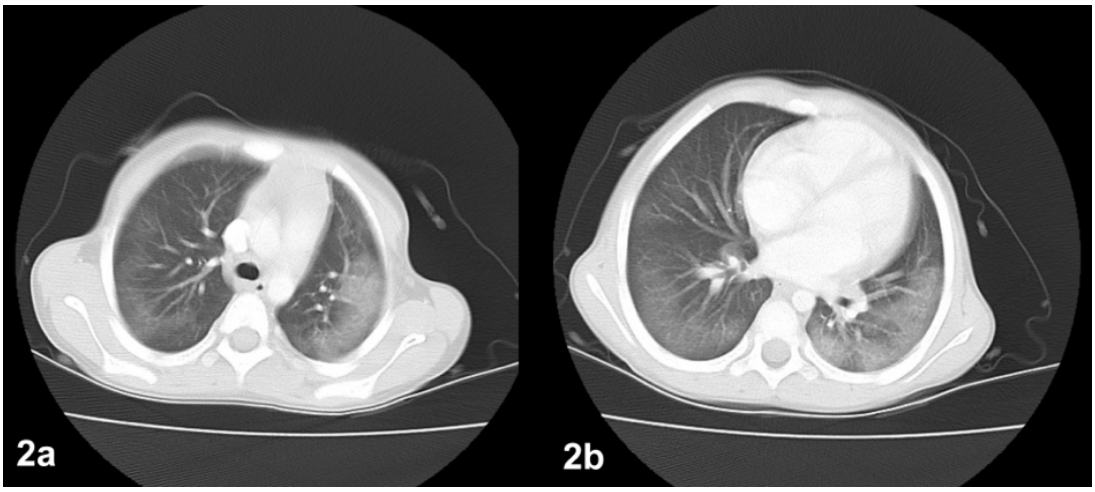

Figure 2. (a, b) Bilateral diffuse ground glass densities with irregular margins in a localization compatible with the vascular tracts and consolidation in the lower lobe of the right lung on thoracic tomography.

margins in a localization compatible with the vascular tracts and consolidation in the lower lobe of the right lung (Figures 2 a and 2b). Erythrocyte suspension was administered three times, and subsequently Hb value was measured to be 12.7 g/dL. Tachycardia attributed to heart failure and liver enlargement was resolved. A bronchoscopy was performed because of the absence of an etiological cause and since the clinical, laboratory, and radiological findings supported pulmonary hemosiderosis. The bronchial mucosa was hyperemic at bronchoscopy, and bronchoalveolar lavage (BAL) fluid was pink in color. The patient also exhibited growth and development delay, and serum celiac antibodies were requested on suspicion of CD accompanying pulmonary hemosiderosis. Anti-tissue transglutaminase IgA (tTg IgA) level was >200 U/ml and anti-endomysial antibody (EMA) level was 1/320 (+). Cytopathological analysis of BAL fluid revealed abundant hemosiderin-bearing macrophages (Figures 3a and 3b). Endoscopic examination revealed millimetric eroded areas covered with exudates on the bulbus duedoni and a scalloped appearance in the folds of the second part of the duodenum. Intense lymphocytic infiltration, total villous atrophy and, and crypt hyperplasia (MARSH 3C) were determined at pathological examination (Figures 4a and 4b). Lane-Hamilton syndrome was suspected in this patient with comorbid pulmonary hemosiderosis and CD, and she was started on a gluten-free diet. Respiratory difficulty improved after transfusion. The existing bilateral basal infiltration improved at PACR performed 14 days after the initiation of iron and B12 supplementation and a gluten-free diet (Figure 1b). At 3-month check-up examination the patient weighed 22.5 kg (10th p) and

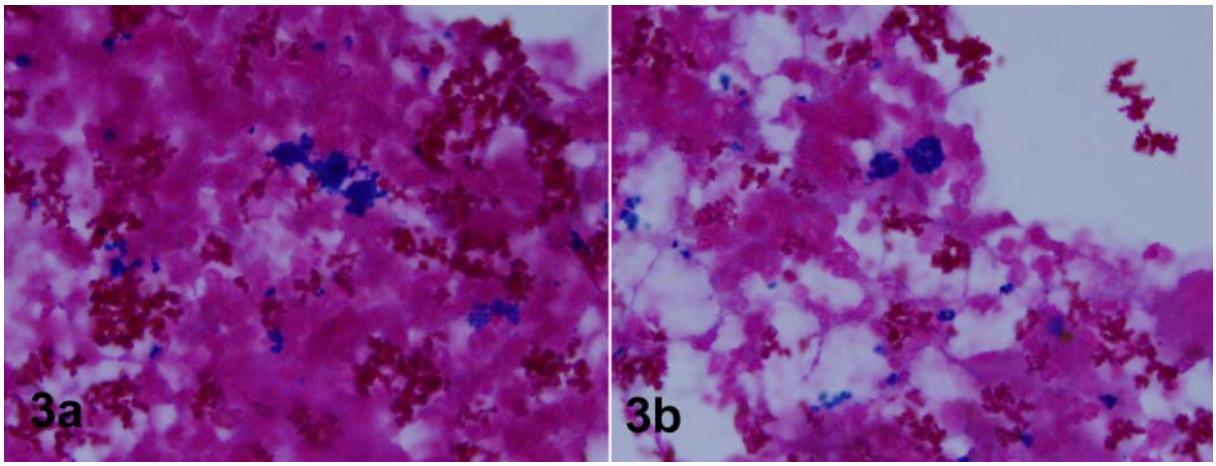

Figure 3. (a, b) Cytopathological analysis of BAL fluid with abundant hemosiderin-bearing macrophages.

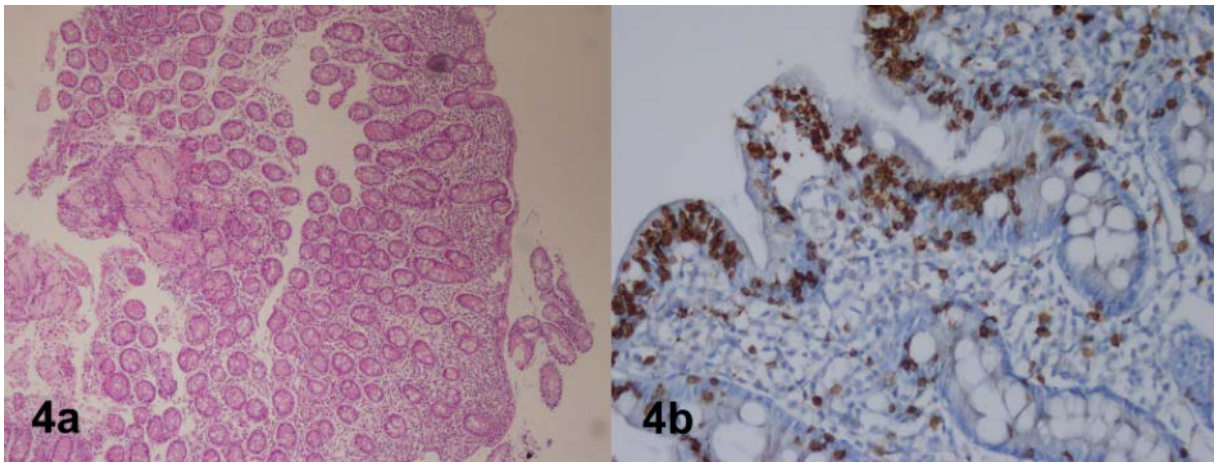

Figure 4. (a, b) Pathological examination of duodenum (Intense lymphocytic infiltration, total villous atrophy and, and crypt hyperplasia).

was 124 cm in height (10thp). Her Hb value was 13.8 g/dL, Hct was 39%, MCV was 84.1 fL, WBC count was 5300/mm3, and platelet count was 332,000/mm3. Her serum iron level was 78 µg/dL, total iron binding capacity was 204 µg/dL, ferritin was 22.19 ng/ml, and tTg IgA was 24.5 U/ml, EMA (-). The patient has been symptom-free at follow-ups at the pediatric hematology and pediatric gastroenterology over the past year.

DISCUSSION

IPH is a rare disease frequently seen in children. Eighty percent of cases appear in the first decade, while 20% can begin in adulthood. There is no marked gender difference, although a male predominance is observed as age increases [6, 7]. Patients generally present with hemoptysis, parenchymal infiltrations at pulmonary radiography and iron deficiency anemia [1, 8].

The etiology of IPH is unclear. The first description of the disease as immunological in nature was made by Steiner in 1954 [9]. Additionally, a good response to immunosuppressive treatment is generally achieved, which suggests that immunological mechanisms are involved in its pathophysiology [10]. Although no immune complex deposition has been shown in the lungs, the presence of immune complex in the circulation in some cases supports the idea of an immunological mechanism being involved in the development of the disease [11]. Recurring hemorrhages resulting from the triggering of unidentified immunological mechanisms cause free iron to be stored in lung tissue. This deposited free iron leads to pulmonary fibrosis via a mechanism similar to fibrosis of the liver in hemochromatosis [12].

CD is characterized by small bowel mucosa injury resulting from cellular and humoral system activation following the consumption of gluten-containing food [13]. The molecular similarity between gluten and nutrition antigens is thought to CD by triggering an immune response. It is generally characterized by diarrhea and growth delay, particularly in childhood. It may appear with non-gastrointestinal symptoms or in milder forms. Transglutaminase 2 (TG2) is a multi-functional protein found in the cell cytoplasm and outside the cell in various tissues. Functional impairment is seen in various organs, including the liver, bowel, lung, kidney and placenta, because of TG2 dysregulation through several mechanisms [14]. TG2 plays a significant role in the pathogenesis of CD by deamination of gluten proteins. anti-tTG IgA used in the diagnosis of CD are 91-100% specific and EMA are 100% specific [11].

The comorbidity of IPH and CD is known as Lane-Hamilton syndrome. This was first described by Bailey, and the focus has been on an immunological etiology since it may also be comorbid with other connective tissue diseases [1, 9, 13]. Perelman *et al*. [15] proposed three hypotheses concerning the comorbidity of IPH and CD. The first is the deposition of immune complexes containing food allergens in the

basal membrane of the alveolar capillaries. The second is the relationship between alveolar basal membrane antigens and anti-reticulin antibodies. The third involves the effect of adenovirus 12, a potential etiological factor in CD, in IPH [15]. Pulmonary hemorrhage attacks have been reported to decrease following gluten-free diet therapy in cases of comorbid IPH and CD. The level of anti-tTG IgA in the circulation decreases with diet therapy, and the patient's clinical findings improve. This suggests that, similar to the immunological mechanism of CD, anti-tTG IgA that form lead to pulmonary hemosiderosis and can trigger fibrosis by impairing the functioning of the TG2 in the lungs. In our case, growth and developmental delay was present in addition to pulmonary hemosiderosis. CD was determined with a small bowel biopsy performed when anti-transglutaminase IgA was positive. Pulmonary hemosiderosis generally responds well to corticosteroids. Because of high long-term recurrence levels, other immunosuppressive agents are also recommended when corticosteroids are insufficient [16]. In addition to cases in which comorbid IPH and CD have been brought under control with a gluten-free diet alone, there are other cases in which steroid therapy has been used together with a gluten-free diet [1]. Complete remission was achieved with a gluten-free diet in our case.

CONCLUSION

In conclusion, CD must be investigated serologically in cases of IPH with growth and developmental delay despite the absence of digestive system symptoms. A positive result for anti-transglutaminase IgA is, to a large extent, diagnostic. Cases with accompanying CD can first be managed with a gluten-free diet before corticosteroid therapy if respiration function tests are normal or close to normal. However, free iron accumulation in the lungs can lead to interstitial fibrosis, and the addition of corticosteroid therapy to a gluten-free diet should be considered in patients with impaired respiratory functions.

Informed consent

Written informed consent was obtained from the patient's family for publication of this case report and any accompanying images.

Conflict of interest

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

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The European Research Journal 2019;5(2):418-420 CASE REPORT

Giant gluteal lipoma in childhood: a case report

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ABSTRACT

Lipomas are the most common benign tumors of mesenchyme. They are soft tissue neoplasm and mobile, well-encapsulated tumors. Lipomas are usually grow slowly and rarely reach a size of more than 2-3 cm. Lesions larger than 5 cm, called giant lipomas. They often appear after 40 years old but rarely can occur in childhood. A 12-year-old male patient had a mass showing rapid growth in the right gluteal region at 6 months. Mass was removed with total excision. Postoperative period was uneventful. In the pathology report, it was confirmed that the lipid tissue was composed of mature adipocytes.

Keywords: Lipoma, giant lipoma, childhood

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Lipomas are the most common benign tumors of mesenchyme; they are composed of mature lipocytes [1]. They are soft tissue neoplasm and mobile, well-encapsulated tumors [2]. Although they can origin in any location where fat cells are found commonly found in the subcutaneous plane of the head, neck, shoulders and back [3]. Lipomas are usually slow growing and rarely reach a size of more than 2-3 cm [2]. Lesions larger than 5 cm, called giant lipomas [4]. They often appear after 40 years old but rarely can occur in childhood [5]. Herein we report a case of 12-year-old male with giant mass showing rapid growth in the his right gluteal region at 6 months.

CASE PRESENTATION

A 12-year-old male patient presented with complaints of swelling in the right gluteal region. There was a slowly growing mass in the right gluteal region about 6 months. There was no known disease, trauma and family history in his history. He had no active complaints other than aesthetic complaints and were normal the laboratory parameters. Ultrasonography revealed a 5×6 cm lipoma in the right gluteal region. The patient underwent total excision under general anesthesia. Approximately 8×9 cm yellowish encapsulated lipoma was removed from the subcutaneous fat tissue by excision (Figure 1). The layers were closed one by one after hemostasis. The patient was discharged the same day. There was no problem after a week's checkup. Histopathological examination revealed that the lesion was composed of mature adipocytes, and lipoma diagnosis was confirmed (Figure 2). There was no recurrence in the 6-month follow-up period. The patient's follow-up continue regularly.

DISCUSSION

Lipomas are the most common benign

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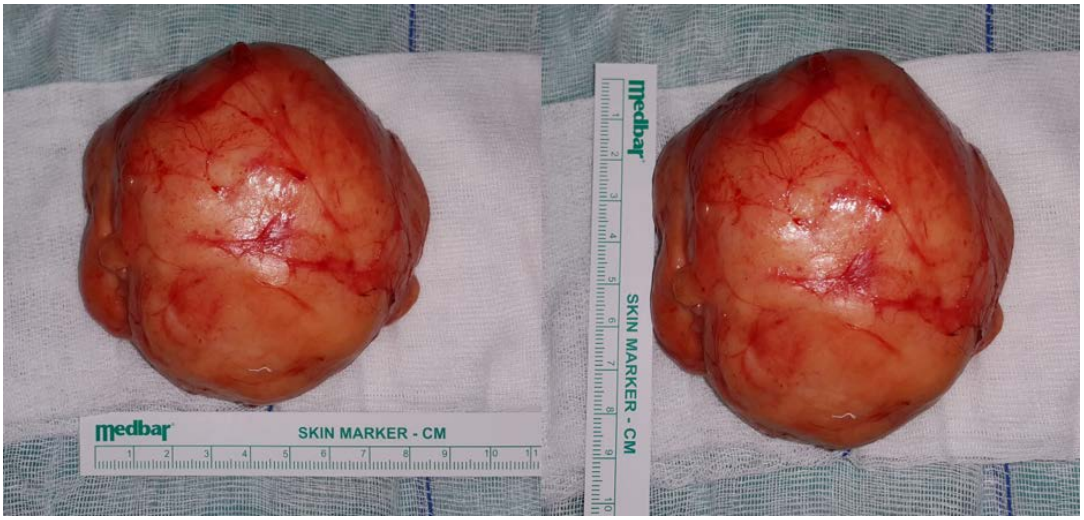

Figure 1. The macroscopic appearance of the lesion

mesenchymal tissue tumors and can arise from every region where fatty tissue is involved [1-3]. It is most common in the upper half of the body, especially in the trunk and neck, although it also presents in other regions [1]. These tumors may be of any age, but they are most commonly encountered in the middle ages between 40 and 60 years [3]. Lipomas are rarely seen in the first 2 decades of life, and if they consist, they can see any place in the body [6]. The etiology of lipomas are unclear. They are known as both sporadic and hereditary [1]. They can be seen after previous blunt traumas rarely [3]. In our case, there was no known prior history of trauma. The differential diagnosis of childhood masses include lipoblastoma, liposarcoma, angiolipoma, embryonal rhabdomyosarcoma, mycosis and myxoid malignant fibrous histiocytoma [6].

Lipomas are usually 2-3 cm in size. Sometimes lipomas can be greater than 5 cm and called are giant lipomas [2]. In our case, it was giant lipoma and its size was also about 8×9 cm. Lipomas are often asymptomatic but giant lipomas may cause cosmetic troubles. There can be symptoms which are related to vessels and nerves pressure [3]. In our case the patients had only cosmetic troubles.

Imaging methods can be used for the diagnosis of lipomas. The most commonly used and first preferred method is ultrasonography [8]. Computerized tomography (CT), magnetic resonance imaging (MRI) or thin needle aspiration can be used for the diagnos that cannot defined by ultrasonography [5-7]. In our case, we were prefered ultrasonography as diagnosing method. No additional imaging method was needed.

Lipomas's treatment is total excision [1]. Although

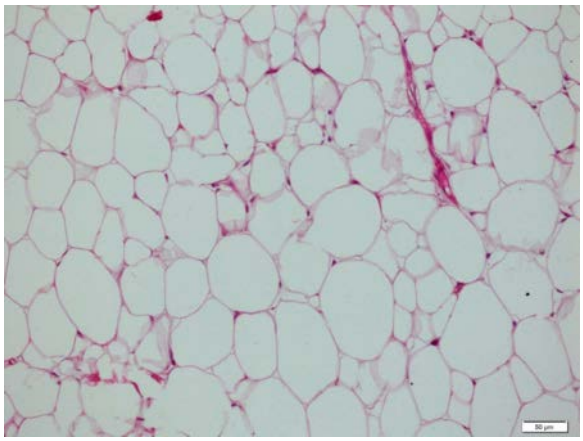

Figure 2. The light microscopic appearance of the lesion (hematoxylin-eosin stain, ×200).

total excision is the most commonly used method, liposuction has been used in some studies [6]. In our case, total excision was performed for treatment. Both preoperative and histopathological diagnosis was benign giant lipoma. The patient's follow-ups continue regularly and there isn't any recurrence.

CONCLUSION

Congenital malignant tumors should be firstly considered in soft tissue masses in childhood. However, we believe that lipomas should be kept in mind. Diagnosis and treatment methods should be selected according the clinic and to the location of the mass. It should not be forgotten that the patients are children.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

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

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The European Research Journal 2019;5(2):421-423 CASE REPORT

Ischemic stroke due to minor head trauma in a child: a case report

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ABSTRACT

Head trauma usually causes hemorrhage, but in children ischemia of basal ganglia may develop. Traumatic stroke occasionally develops after dissection of brain vessels, leading to disseminated cerebral embolism. Stretching forces in cerebral intraparenchymal arteries can cause vascular damage followed by an occluding thrombus. An 18-month-old girl presented to our emergency department with the complaint of head trauma after falling down while playing. Her parents recognized the weakness of her left site extremity after 6 hours after the event. After initial physical examination and further imaging studies brain magnetic resonance imaging (MRI) showed an infarct affecting the caudate nucleus in the right cerebral hemisphere. In childhood, ischemic stroke due to mild head trauma is an exceedingly rare event and may be overlooked in emergency medicine practice. We aimed to emphasize that mild head trauma may cause critical situations such as acute infarct in children.

Keywords: cerebral infarction, head trauma, traumatic stroke

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Trauma can cause many vascular complications. Recognition of childhood stroke is difficult and in children under 18 months is a frequently skipped diagnosis. It is caused by vasospasm of the lenticulostriat arteries in childhood which are disrupted by head injury [1]. Ischemic stroke is an important clinical problem in childhood affecting around 5/100.000 children each year. Although detailed investigation usually reveals risk factors for stroke in the majority of affected children, there is a small group of whom no risk factors can identified. In head injuries the connection between the underlying brain injury and neurological symptoms are usually obvious, and the severity of trauma correlates with the clinical symptoms. Minor head injuries are common accidents and usually cause no severe complications [2]. We present an 18-month girl with hemiparesis due to a post-traumatic infarction in the territory of the right lenticulostriat artery.

CASE PRESENTATION

An 18 month-old girl was referred to our observation following a head injury involving the left zygomatic region. She fell while running onto a thinly carpeted floor. The child did not lose consciousness and had no history of seizures. After 6 hours her parents recognized the weakness in her left arm and leg. Clinical examination confirmed a left hemiparesis

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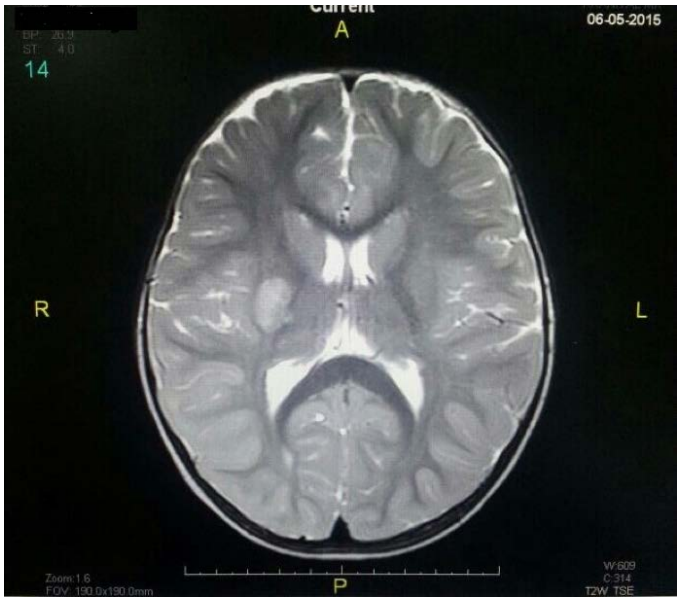

Figure 1. Magnetic resonance imaging (T2 sequence) shows a sharply demarcated high signal intensity lesion.

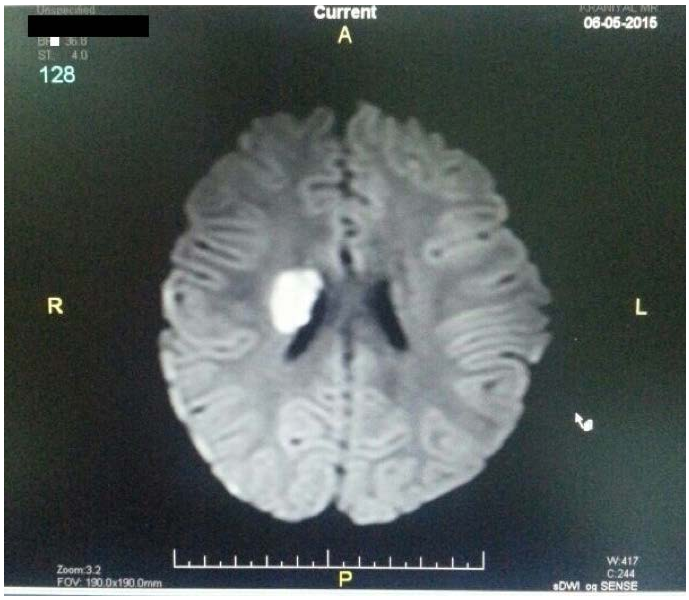

Figure 2. Magnetic resonance imaging (Flair sequence) shows a sharply demarcated high signal intensity lesion.

with 3/5 muscle tone and positive Babinski reflex on left site. Immediately cerebral CT and extremity X-ray showed no abnormalities. Further imaging studies were obtained to find the etiology of hemiparesis. Brain MRI showed an infarct affecting the caudate nucleus and corona radiata in the right cerebral hemisphere. Diffusion-weighted images showed a sharply demarcated high signal intensity lesion in a similar area on T2 weighted and fluid-attenuated inversion recovery sequences images (Figures 1 and 2). In brain MR angiography normal blood flow pattern has been determined. There was no additional finding in her blood count and coagulation parameters. She admitted to pediatric neurology service for anticoagulant therapy and follow-up. Cardiological and immunological tests were in normal range but in her genetic tests Factor V (G1691A, Leiden) and MTHFR (A1298C), mutations were positive. Conservative therapy resulted in symptomatic improvements and the patient discharged with a hemiparesis on the nineteenth day of her admission.

DISCUSSION

Whether ischemic stroke related to minor head trauma is seen in 5/100,000 children each year, it is an important diagnosis [1]. Children are particularly vulnerable to, stretching and shearing forces effects on the vessels because of the high moment of brain meninges. This leads to a traumatic endothelial intimal lesion, followed by fibrin accumulation, leukocyte reaction, and a formation of a white thrombus occluding the lumen. The obstruction causes ischemia of cerebral parenchyma with clinical symptoms after a symptomless latency period [2]. Common conditions predisposing to stroke include embolism associated with congenital or acquired heart disease, or arterial malformations as in the Ehler Danlos syndrome, and fibromuscular dysplasia. Further risk factors are sickle cell disease, dehydration, meningitis, varicella infection, homocystinuria and hemolytic uremic syndrome [3]. It is mandatory to exclude all possible secondary causes before classifying a cerebral infarction in children as idiopathic. Therefore CT scan, brain MRI with diffusion weighted imaging, angio MRI, carotid doppler imaging, echocardiogram and complete blood workup should be performed.

Prothrombotic polymorphisms, such as the substitution of arginine with glutamine at amino acid residue 506 in coagulation factor V (factor V Leiden [FVL]) and a G-to-A transition at position 20210 of the 39 untranslated region of the factor II gene (FII G20210A), have been found to be the most common risk factors for venous thromboembolism [3-5]. Increased prevalence of FVL was observed in some

reports on pediatric arterial thromboses and stroke [6, 7] but many other studies have no similar outcomes. Similarly, the association between FII G20210A and childhood stroke is controversial [7, 8]. In addition, the homozygous state for the C-to-T transition at nucleotide 677 (C677T) polymorphism of 5,10-methylenetetrahydrofolate reductase (MTHFR) gene was not found to be a risk factor for stroke in children [6-8].

Mild head injuries may cause cerebral infarction at the internal capsule due to mechanical vasospasm or thrombosis of the perforating vessels, although ischemic symptoms are not so severe and tend to disappear in the early period by conservative therapy. Rapid reversal or attenuation of neurological symptoms may be attributed to the resolution of vasospasm [4, 5].

In general practise minor head travma is a comman cause of emergency admissions. Most cases have no clinical sign or symptoms for acute brain injury. Presence of pathologic findings on physical examination traumatic hemorrhage is the expected result.

CONCLUSION

Emergency physicians must be aware of lenticulostriat infarction as a rare complication of mild trauma in young children and early diagnosis can prevent possible permanent neurological damage.

Informed consent

Written informed consent was obtained from the patient's family for publication of this case report and any accompanying images.

Conflict of interest

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

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The European Research Journal 2019;5(2):424-427 CASE REPORT

Coronary artery bypass grafting in a renal transplant patient: case report

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ABSTRACT

The patients with end-stage renal disease have an increased risk of atherosclerosis and the probability of cardiovascular diseases. Due to the use of immunosuppressive agents, the patients having renal graft carry an additional risk of atherosclerosis or endocarditis. A 67-year-old male patient with a history of renal transplantation was referred to our hospital with a severe chest pain and dyspnea. After diagnosing severe ischemic coronary artery disease by coronary angiography, the patient underwent a successful operation of a single vessel coronary artery bypass grafting (CABG) in beating heart. Up to 20% of post-renal transplantation mortality is attributed to cardiovascular diseases. Graft rejection, the need of hemodialysis, perioperative infection are some of the major complications for renal transplant patients undergoing CABG surgery. Off-pump CABG (OPCABG) surgery is a less invasive technique in comparison with CABG with cardiopulmonary bypass (CPB), and protects the patient from negative effects of CPB such as complement system activation, inflammatory mediator secretion, thrombocytopenia, clotting disorders. We recommend to prefer OPCABG and have preoperative prophylaxis in order to avoid both perioperative infection and renal graft rejection in renal transplant patients undergoing CABG surgery.

Keywords: Coronary artery bypass grafting, renal transplant, cardiopulmonary bypass, beating heart, immunosuppressive treatment

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Owing to renal transplantation, patients with end-stage renal disease have improved a remarkable survey and a better life quality. However, these patients have an increased risk of atherosclerosis and cardiovascular diseases due to the use of immunosuppressive agents [1-4]. Renal transplant patients undergoing coronary artery bypass grafting (CABG) also are under the risk of higher rates of postoperative complications such as graft rejection, infection or impairment of renal function.

CASE PRESENTATION

A 67-year-old male patient with a history of renal transplantation in 2008 was referred to our hospital with a severe chest pain and dyspnea aggravating by effort. The angina got over with resting and 5 mg of sublingual isosorbid dinitrat. Functional capacity was class III (New York Heart Association (NYHA) classification, 2011). The patient used prednisolone 10 mg 1x1 (Oral), Tacrolimus 1000 mcg 1x2 (Oral), and

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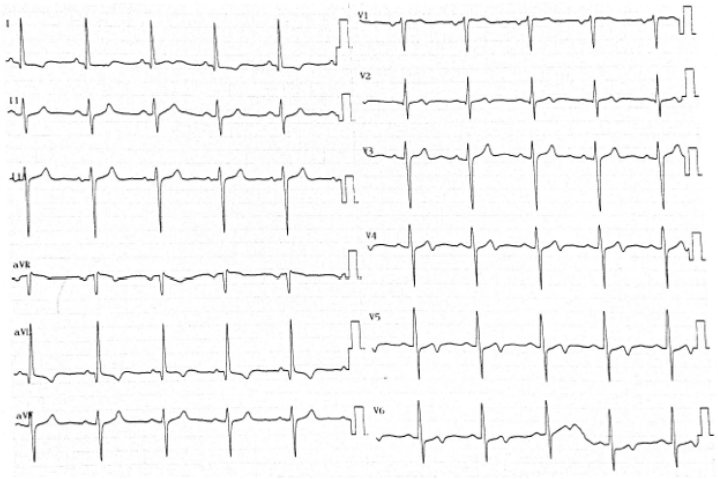

Figure 1. Electrocardiogram of the patient.

Mycophenolate 500 mg 1x2 (Oral) since 2008.

On the physical examination; systemic arterial pressure was measured 129/71 mmHg, and heart beat was rhythmic and 74/min. Two old scar tissues of previously opened and non-functional arteriovenous fistulas on the proximal and distal anterior parts of left forearm were observed. Cardiac and pulmonary auscultation was non-specific.

Preoperative blood urea nitrogen (BUN) and creatinine were 15 mg/dL and 1.09 mg/dL. Other hematologic data were normal as well. Electrocardiogram showed biphasic T waves in V4-6 derivations (Figure 1). On the transthoracic echocardiography ejection fraction was 55%. On the percutaneous coronary angiography 95% occlusion was observed in the proximal part of the left anterior descending artery (LAD) and without any serious occlusive disease in other coronary arteries (Figure 2).

The patient was hospitalized in a single bad room and Ertapenem 1000 mg 1x1 (IV) was ordered in order to have a prophylaxis due to immunosuppressive therapy. Immunosuppressive therapy was organized as in Table 1. The patient underwent a successful CABG in beating heart, left internal mammarian artery (LIMA) was anastomosed to LAD. Oral treatment of prednisolone was ordered as intravenous form with the highest dose in the operation day and the dose decreased day by day until the postoperative sixth day. On the postoperative seventh day oral prednisolone was started again. The patient was discharged without any complication on the postoperative tenth day. BUN and creatinine levels at discharge were 18 mg/dL and 1.12 mg/dL.

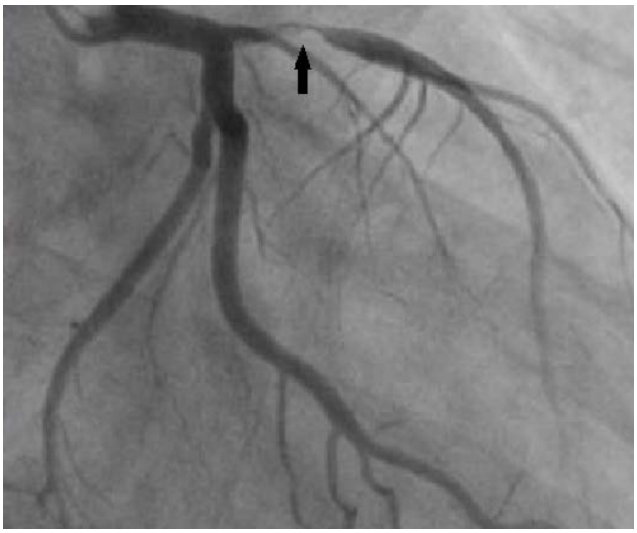

Figure 2. Coronary angiogram shows the LAD lesion (arrow). LAD = left anterior descending coronary artery.

Table 1. Immunosuppressive drugs management during operational process

Time	Prednisolone	Tacrolimus	Mycophenolate
Preoperative 06:00	250 mg (IV)	1000 mg 1x2 (Oral)	500 mg 1x2 (Oral)
Postoperative Day 1	125 mg (IV)	1000 mg 08:00	500 mg 10:00
		1000 mg 20:00	500 mg 22:00
Postoperative Day 2	100 mg (IV)	1000 mg 08:00	500 mg 10:00
		1000 mg 20:00	500 mg 22:00
Postoperative Day 3	80 mg (IV)	1000 mg 08:00	500 mg 10:00
		1000 mg 20:00	500 mg 22:00
Postoperative Day 4	60 mg (IV)	1000 mg 08:00	500 mg 10:00
		1000 mg 20:00	500 mg 22:00
Postoperative Day 5	40 mg (IV)	1000 mg 08:00	500 mg 10:00
		1000 mg 20:00	500 mg 22:00
Postoperative Day 6	20 mg (IV)	1000 mg 08:00	500 mg 10:00
		1000 mg 20:00	500 mg 22:00
Postoperative Day 7	10 mg (Oral)	1000 mg 08:00	500 mg 10:00
		1000 mg 20:00	500 mg 22:00

DISCUSSION

Renal transplant patients have many risk factors for coronary artery disease due to the nature of end-stage renal disease and immunosuppressive drugs [1-3] Up to 20%of post-renal transplantation mortality is attributed to cardiovascular diseases such as acute coronary syndrome (ACS) [3].

In a renal transplant patient referring to a medical center with ACS, percutaneous coronary intervention (PCI) has a low success rate due to the calcification of the coronary arteries, which is a common problem of end-stage renal disease [5, 6]. CABG is usually a better treatment solution for these patients.

The rejection of the renal graft and renal dysfunction, the need of hemodialysis, perioperative infection are some of the major complications for renal transplant patients undergoing CABG surgery. Performing CABG with cardiopulmonary bypass (CPB) has additional risk factors due to its effects such as inflammatory activation, volume overload, increased blood concentration of immunosuppressant [7, 8] and perfusion pressure, low urine output [7-9]. Because of that, in renal transplant patients undergoing CABG with CPB, addition of mannitol and human albumin in hemofilter and prime solution, and less preparation of prime solution, and decreased transfusion of blood products may help avoiding the negative effects of CPB.

Off-pump coronary artery bypass grafting (OPCABG) surgery is a less invasive technique in comparison with CABG with CPB, and protects the patient from negative effects of CPB as mentioned before. In a renal transplant patient, aortic calcification is severe and use of CPB may be difficult. That's why; performing CABG surgery in a renal transplant patient in off-pump technique would be a better option.

Perioperative infection is another serious complication for renal transplant patients undergoing CABG due to immunosuppressive treatment. Because of that, hospitalizing the patient in a private room and ordering a wide-spectrum antibiotic would be helpful for prophylaxis.

The rejection of the renal graft and renal dysfunction are major critic problems. In order to minimize these fatal complications, we prefer to order the oral corticosteroid treatment as intravenous form starting from the operation day with the highest dose as 250 mg of prednisolone until the postoperative sixth day with the lowest dose of 20 mg. On the postoperative seventh day we order the oral standart 10 mg dose of prednisolone.

CONCLUSION

As a result, we recommend to prefer OPCABG and have preoperative prophylaxis in order to avoid both perioperative infection and renal graft rejection in renal transplant patients undergoing CABG surgery.

Authorship declaration

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

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

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

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The European Research Journal 2019;5(2):428-432 CASE REPORT

Foot-ankle involvement of complex regional pain syndrome associated with pregnancy

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ABSTRACT

Complex regional pain syndrome (CRPS) is a condition which develops after a painful incident and characterized by allodynia/hyperalgesia, edema, skin anomalies and anomaly in blood flow and abnormal sudomotor activities independent of the precipitating incident. It is a rare condition in pregnancy and difficult to distinguish from pelvis and lower extremity pains which are inherent in pregnancy. Hips are typically involved, symmetrical involvement of feet and ankles are rarely reported; has a benign course however it is important to diagnose and treat due to fracture risk. Herein, we have presented a 28-year-old patient who came to us in week 32 of her pregnancy and gave birth in week 36 and diagnosed CRPS with bilateral involvement of foot and ankle.

Keywords: Pregnancy, complex regional pain syndrome, symmetrical foot-ankle involvement

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As well as complex regional pain syndrome (CRPS) can occur idiopathically it usually develops after a painful event such as trauma, fracture, in addition, central nervous system diseases, medications, hemiplegia can cause the situation. Pathophysiology has not been fully elucidated. Central and peripheral mechanisms are influential. It is associated with sympathetic cutaneous vasoconstrictor activity, allodynia/hyperalgesia, edema, impaired skin blood flow and abnormal sudomotor activity. The complex is a chronic painful condition. The diagnosis is made after the other causes of pain and dysfunctioning are eliminated [1, 2].

CRPS is classified as type 1 and type 2. In CRPS type 1 there is no specific pathology; in type 2 there is nerve damage that is called causalgia, and it is associated with trauma [3].

CASE PRESENTATION

A 28-year-old patient with 32 weeks of gestation presented to our outpatient clinic for the complaint of gait abnormality with pain, swelling on both ankles and feet. The patient did not have any systemic disease or trauma in the past and had no alcohol use and no smoking in the history. There was no family history of diseases with musculoskeletal involvement. The patient was pregnant for the third time and in previous pregnancies she gave birth to healthy babies after full-term gestations. In this pregnancy there also was no pathology related to the baby.

There was swelling in both ankles especially remarkable in the left ankle, also increased temperature, sweating, and light cyanosis was found during the physical examination, peripheral pulse was

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regular, and there wasn't any neurological deficit. Ankle range of motions (ROMs) were painful during both the active and passive movements and were restricted due to pain. The pain of the foot was increasing when pressure applied and decreased while resting; the patient's ambulation was possible with a wheelchair.

The patient was 32 weeks pregnant when applied to the orthopedic outpatient clinic previously, and ankle strain was considered. For the local treatment, cold application and 5% ibuprofen cream were recommended and Paracetamol 500 mg twice daily were given orally for the pain relief. Routine blood tests were performed at the outpatient clinic to exclude rheumatological diseases. Blood biochemistry, calcium, sedimentation, CRP values were normal; vitamin D was not measured. The patient refused to undergo through the radiological examination. The previous treatment suggested to be continued and rest was recommended. An appointment was set to repeat the examination and checkup. However, the patient did not come to the appointment. During the pregnancy, the patient did not receive any supportive treatment such as supplementary vitamins especially Vitamin D, iron or calcium.

The patient presented in the second week after delivery. The baby was delivered by cesarean-section under general anesthesia in week 36 and was 3200 kg and healthy. The patient could ambulate with the help of two crutches; edema in her feet was partially regressed however ROMs were found to be painful and tender during the examination; an X-ray and routine blood tests were performed again.

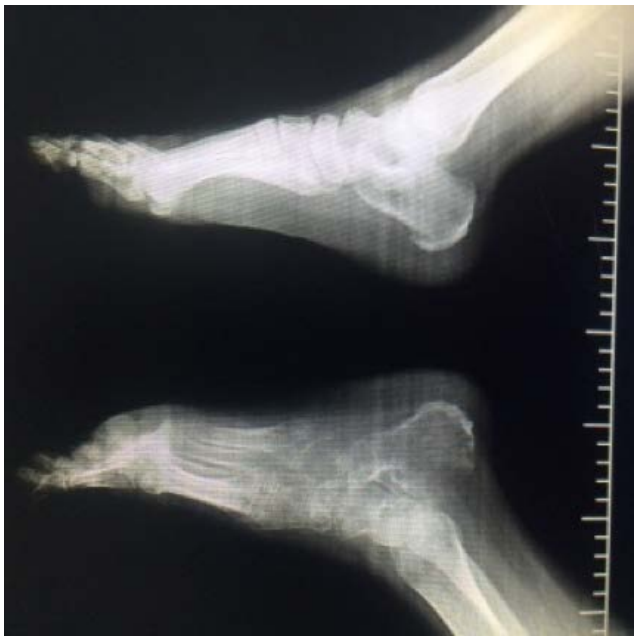

Figure 1. X-ray study shows speckled osteoporosis in the calcaneus and tarsal bones at both ankles.

The following results were found in the laboratory tests: Hemoglobin: 11.9 g/dL (12-18), leukocyte: 10.41 mm^3 (4.60-10.2), alkaline phosphatase: 122 U/L (50-136), cholesterol: 416 mg/dl (0-200), triglyceride: 156 (0-150), CRP: 1.27 mg/dL (0.0-0.8), sedimentation rate: 43 mm/hour (0-15 mm/hour), total calcium: 9.2 mg/dL (8.5-10.5), parathormone: 156 pg/ml (15-65), and vitamin D3: 4.4 ng/mL (11-43). In the X-ray examination of both ankles; speckled osteoporosis was present in the calcaneus and tarsal bones (Figure 1).

MRI imaging could not be performed since the patient was claustrophobic. In the computed tomography, widespread speckled osteoporotic deformation in calcanea areas and thickening in the trabecular area on both feet but predominantly on the left foot were seen (Figure 2).

Three-phase bone scintigraphy could not be taken hence the patient wanted to breastfeed her baby and did not want to stay away from the baby because of the radioactivity even for a short time. The patient was diagnosed with CRPS type 1 based on the clinical and radiographic findings.

The patient was recommended to rest at home and not to apply pressure on feet. The medical treatment was given appropriately for breastfeeding. Prednisolone 16 mg/day (to be gradually decreased and stopped in two weeks), calcium 1200 mg and vitamin D 1000 IU/day were initiated. Physiotherapy modalities such as contrast bath, in water ultrasound (5 min, 1.5 w/cm^2,), TENS were applied. Passive ROM, active ROM, active-assisted ROM exercises, targeting the ankle were started for the beginning; these exercises were followed by gradual stretching and strengthening, stress loading The patient was recommended to repeat these short-term exercises at home twice a day.

After receiving twenty sessions (for 4 weeks every week-day) the patient started to walk without crutches, pain was regressed, and her complaints were almost entirely gone at the end of the first month.

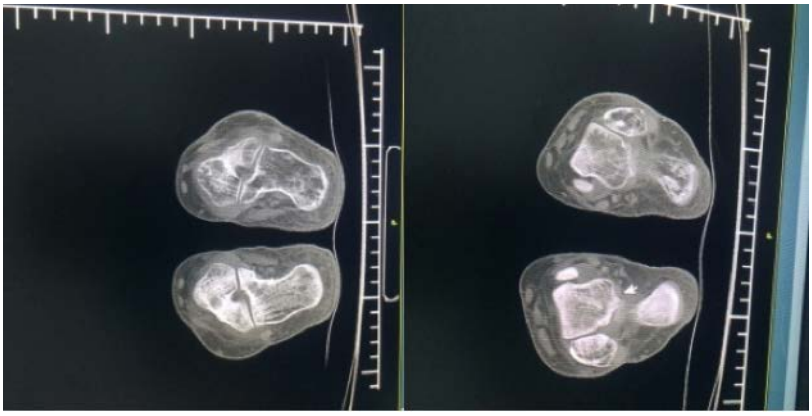

Figure 1. Computed tomographic scan shows widespread speckled osteoporotic deformation in calcanea areas and thickening in the trabecular area on both feet.

DISCUSSION

Nonspecific pain edema and difficulty in walking during in the lower extremity and pelvic region during pregnancy is often confronted due to mechanical and inflammatory causes, and differential diagnosis is difficult and most times a definite diagnosis cannot be made [4]. Among mechanical reasons, ligamentous laxity, sacroiliac joint dysfunction are the frequently encountered pathologies.

Pregnancy induced CRPS is very rare. It was first described by Curtiss and Kincaid [5] in 1959. In 1968 Lequesne [6] described three cases in the same pathology and named them transient osteoporosis or neurotrophic rheumatism, in the further considerations those situations are named as reflex sympathetic dystrophy, algoneurodystrophy and Sudek's atrophy. The most recent terminology change was made in 1993 by the International Association for the Study of Pain (IASP) as 'Complex Regional Pain Syndrome' [7].

In a study structured with disease analysis of nine cases retrospectively and a review of the literature (57 patients and 159 sites of reflex sympathetic dystrophy) by Poncelata *et al*. [8], it was concluded that CRPS in pregnancy was seen in different parts of the body; and the rates were as follows; 88% in hips, 25% in knees and 21% in ankles.

CRPS is frequently seen in the third trimester of pregnancy and the involvement can be bilateral [4, 8, 9]. In our case, there was bilateral involvement of the ankles in the third trimester was accompanied by severe pain, edema, increased temperature, sweating, tenderness and restriction in ROM. Also there was no underlying reason that can cause CRPS therefore the patient was evaluated as CRPS type 1.

CRPS is an entirely clinical situation and diagnosis is made according to the Veldman diagnostic criteria (Table 1) [10].

When seen in pregnancy, CRPS generally follows a benign course and can regress spontaneously so that many cases can heal without being diagnosed however with the diagnosis and treatment regression can occur faster and fracture which is the most common complication can be prevented.

There are various theories about the pathophysiology of CRPS during pregnancy; the pressure on the obturator nerve applied by the baby's head is thought to trigger the autonomic dysfunction, however, this does not provide sufficient evidence for CRPS in the first trimester. The increasing weight of both the mother and the baby during pregnancy and lordosis disrupt the microcirculation of the extremities, hence microtrauma is repetitive, it stimulates autonomic system, spasm occurs in the arterial and precapillary sphincters and the back-flow in capillaries cause passive dilatation; this mechanism is an accepted hypothesis for the occurrence of CRPS; another hypothesis is the unexplained increase in bone turnover and osteoclastic activity [3, 4, 11, 12].

In another theory, the hormonal changes during pregnancy are thought to be the cause, and the postpartum regression of CRPS was shown as the evidence. PTH, 1.25 dihydroxycholecalciferol and calcium balance are claimed to impair. Also in our case, PTH was increased, and serum vitamin D level

Table 1. Veldman diagnostic criteria for CRPS

Criteria 1: Positivity of the four symtomps out of the five criteria below supports the diagnosis.
1- Pain
2- Temperature difference when compared to the other extremity
3- Volume asymmetry when compared to the other extremity
4- Color asymmetry when compared to the other extremity.
5- Limitation in the active joint ROM
Criteria 2: Occurrence or progression of these symptoms during or after exercise
Criteria 3: Symptoms spreading to a wider area after the initiation in the first trauma region.

was significantly decreased; the calcium levels were in normal range [13].

Hypertriglyceridaemia is a condition that can be seen in pregnancy and increases in the third trimester; in the study of Ponceleta *et al*. [8], triglyceride levels of the patients with CRPS were found to be high and in the study conducted by Acquaviva *et al*. [11] on 765 CRPS patient, especially the involvement of the hip joints were reported with the accompanying hypertriglyceridaemia. Additional inflammatory conditions, cellulitis, arthritis, DVT, vascular disorder, bone tumors and other malignities should be considered for the diagnosis; radiography is helpful however hence the use of radiography is limited during the pregnancy period and the condition can only be detected in 3-6 weeks after the onset, MRI is a preferable method for the diagnosis. Similarly, bone scintigraphy cannot be used during pregnancy [4, 14]. After seeing the postpartum X-ray imaging of our patient, the patient was diagnosed with CRPS based on the clinical findings. Speckled osteoporosis was confirmed and no bone fractures were seen in the computed tomography. MRI scanning and scintigraphy could not be performed hence the patient had claustrophobia and did not give consent for the scintigraphic evaluation. The CRPS treatment guideline published in 1998 is based on three principles; rehabilitation, pain management and physiotherapy. Later, in addition to these basic principles, functional rehabilitation has been updated with self-management techniques and new treatments [15, 16].

When CRPS is detected during pregnancy, symptomatic treatment is applied; physiotherapy modalities, pressure-free cold press elevation of the feet, passive and active mobilization exercises can be recommended; postpartum use of calcitonin, beta-blockers, antiepileptics, tricycle antidepressants, NMDA receptor agonists, opioids, tramadol, corticosteroids, griseofulvin, nifedipine, baclofen are in the medical treatment options and if necessary sympathetic blockage can be applied. Calcitonin is not recommended during pregnancy, and the lactation period, IV pamidronate can be given to breastfeeding mothers hence its safe during the breastfeeding period. Pamidronate passes into breast milk in negligible amount, the biological half-life is short and when complexed with calcium it can not be absorbed from the gastrointestinal tract of the baby [12, 14, 17].

For the treatment Prednol, 16 mg/day (to be gradually decreased and stopped in two weeks) and calcium 1200 mg and vitamin D 1000 IU/day were initiated on our patient who wanted to breastfeed her baby. Physiotherapy modalities and exercises were given. One month later, the patient stopped using the crutches and started to walk without aid, and her pain was almost absent.

CRPS should be taken into account for lower extremity pain in pregnancy, although rarely there is a fracture risk, for this reason, it should be treated with early diagnosis. CRPS can also regress with symptomatic treatment during the pregnancy period. Postpartum aggressive treatment can be given but the treatment should be managed cautiously on mothers who want to breastfeed their babies.

CONCLUSION

Pain in the lower extremity often occurs during

pregnancy. CRPS is a rare cause, and when diagnosed the treatment is easy. Symptomatic treatment can prevent a fracture that can occur as a complication. In pregnancy, this diagnosis should be kept in mind to avoid misdiagnosis and malpractice/wrong treatment.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

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

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