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Editorial

Dear Colleagues,

We are very pleased to present the December issue of “The Medical Journal of Bakırkoy”.

Looking back to the past 12 months; we struggled with a huge pandemic, which unfortunately caused the loss of our loved ones as well as our colleagues. We would like to pay tribute to all those healthcare professionals, who lost their lives in this battle.

These days, one more time, remind us and the whole world how important our profession is for the societies live in.

As this difficult year comes to an end, we hope you will enjoy reading our last issue. I wish you a happy, healthy and “normal” 2021.

Prof. Dr. Esra Şevketoğlu
Chief Editor

Original Article

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Medical Journal of Bakirkoy

Assessment of Bone Metabolism and Bone Mineral Density in Children with Helicobacter *pylori* Infection

*Helicobacter **pylori** Enfeksiyonu Olan Çocuklarda Kemik Metabolizması ve Kemik Mineral Dansitesinin Değerlendirilmesi*

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ABSTRACT

Objective: *Gastrointestinal system diseases may have negative impact on bone metabolism. Bone metabolism and bone mineral density in children with Helicobacter pylori (H. pylori) infection were evaluated in this study.*
Method: *A total of 100 children (mean age: 13.69±2.44 years, M/F:0.66) with chronic gastritis were divided into two groups according to the presence of H. pylori infection and tested for biochemical parameters such as calcium, phosphorus, magnesium, alkaline phosphatase, parathyroid hormone and vitamin D. Bone mineral density was measured at lumbar spine in all of the patients by dual-energy x-ray absorptiometry (DXA).*
Results: *Forty-eight of 72 patients with H. pylori and 16 of 28 patients without H. pylori had low vitamin D levels (p=0.35). The other biochemical parameters were within normal limits in both groups. Bone mineral density was measured as -0.16±2.25 g/cm^2 in H. pylori-positive patients and as -0.08±2.62 g/cm^2 in H. pylori-negative patients (p=0.87). Only 2 patients with H. pylori and 1 without H. pylori had BMD z scores below -2.5 (p=1.00).*
Conclusion: *No significant difference was observed in biochemical parameters of bone metabolism and bone mineral density between H.pylori-positive and -negative children.*

Keywords: *children, bone mineral density, calcium, H.pylori, vitamin d*

ÖZ

Amaç: *Gastrointestinal sistemi tutan hastalıklar kemik metabolizması üzerine negatif etki gösterebilir. Bu çalışmada Helicobacter pylori enfeksiyonu olan çocuklarda kemik metabolizması ve kemik mineral dansitesi değerlendirilmiştir.*
Yöntem: *1-18 yaş arası kronik gastriti olan 100 çocuk hasta (ort yaş:13.69±2.44 yıl, E/K:0.66) Helicobacter pylori enfeksiyonuna göre iki gruba ayrıldı. Hastalar kalsiyum, fosfor, magnezyum, alkalenfosfataz, paratiroid hormon ve D vitamini düzeyleri gibi biyokimyasal parametreler açısından test edildi. Kemik mineral dansitesidual x-ışınıabsorbsiyometri (DXA) tekniği ile lomber omurgada ölçüldü.*
Bulgular: *72 Helicobacter pylori enfeksiyonu olan hastanın 48'inde ve 28 Helicobacter pylori enfeksiyonu olmayan hastanın 16'ında D vitamini düzeyi düşük saptandı (p=0.35). Diğer biyokimyasal parametreler her iki grupta da normal tespit edildi. Kemik mineral dansitesi Helicobacter pylori enfeksiyonu olan hastalarda 0.16±2.25 g/cm^2 ve olmayanlarda -0.08±2.62 g/cm^2 ölçüldü (p=0.87). Helicobacter pylori enfeksiyonu olan 2 hastada ve olmayan 1 hastada kemik mineral dansitesi z skoru -2.5 değerinin altında saptandı (p=1.00).*
Sonuç: *Kemik metabolimasının biyokimyasal parametreleri ve kemik mineral dansitesi açısından Helicobacter pylori enfeksiyonu olan ve olmayan çocuklar arasında anlamlı fark saptanmadı.*

Anahtar kelimeler: *çocuk, kemik mineral dansitesi, kalsiyum, H.pylori, d vitamini*

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INTRODUCTION

Helicobacter pylori (H.pylori) infection, one of the most common gastrointestinal infections worldwide, colonizes human gastric mucosa during early childhood persisting throughout life and may lead to chronic gastritis, gastric mucosal atrophy, peptic ulcer, and gastric cancer. H. pylori infection triggers or aggravates a systemic inflammatory response which affects not only the digestive tract, but may also involve extraintestinal tissues and/or organs [1]. The proposed mechanisms that have been suggested to explain the extra-intestinal manifestations are: atrophic gastritis, enhancement in vascular permeability during the gastric infection, the release of inflammatory mediators, systemic immune response and molecular mimicry [1].

In childhood, osteoporosis is generally secondary to chronic diseases such as intestinal inflammatory disease, cystic fibrosis, hepatobiliary disease and anorexia nervosa which interfere with the reabsorption of nutrients, arthritis due to immobility, thyroid disorders, hormonal factors or complication of treatments [2,3].

There are limited data regarding the association between H.pylori infection and osteoporosis in children and adults.In the present study, we aimed to evaluate bone metabolism and bone mineral density (BMD) in children with chronic gastritis and determine its association with H.pylori infection.

MATERIAL and METHODS

A total of 100 children who referred for endoscopy with dyspeptic symptoms (mostly recurrent abdominal pain) suggestive of organic disease and followed as chronic gastritis between 2014 and 2016 at division of pediatric gastroenterology were evaluated prospectively. Exclusion criteria were treatment with antisecretory, antimicrobial, or anti-inflammatory medication for the 3 months preceding the endoscopy.The patients with previous H.pylori eradication and who had diseases that affect bone metabolism such as inflammatory bowel disease, malignancies, chronic kidney disease, diabetes mellitus,hypo/hyperthyroidism, hypo/hyperparathyroid disorders, hypogonadism, malignancies, anorexia nervosa, gastrointestinal disorders with malabsorption, collagen diseases,and were given current or previous treatment with glucocorticoids, thyroid/parathyroid drugs, anticonvulsants, vitamin D, calcium and bisphosphonate were also excluded.The control group was not selected from healthy children because bone mineral measurements would not be ethical in healthy children.Informed consents were taken from all of the parents before procedures.

Diagnosis of H.pylori infection was based on at least two of the three methods; histological examination, culture and rapid urease test. From indicated number of patients, biopsy specimens were systematically taken from the duodenum (n=2), gastric antrum (n=2), and gastric body (n=2). A modified Giemsa stain was used for identification of H. pylori, and gastritis was evaluated according to the updated Sydney scoring system. H. pylori density was scored by using visual analogue scales described in the updated Sydney scoring system on a four-point scale (0, normal/absent; 1,mild; 2, moderate; and 3, marked) [4].

The levels of calcium, phosphorus, magnesium, parathyroid hormone (PTH) and total alkaline phosphatase (ALP) were studied with a Roche/Hitachi Modular PP automated clinical chemistry analyzer (Roche Diagnostics GmbH, Mannheim, Germany). 25-hydroxy vitamin D (25-OH-D) was measured by liquid chromatography–mass spectrometry (LC-MS/MS).

According to Lawson Wilkins Pediatric Endocrine Society Drug and Therapeutics Committee vitamin D status was defined as follows: 25(OH) vitamin D < 20 ng/mL, hypovitaminosis D ; 5–20 ng/ mL, vitamin D insufficiency,<15 ng/ mL, vitamin D deficiency and <5ng/mL, severe vitamin D deficiency [5].

Body mass index (BMI) was calculated as body weight (kg) divided by the square of body height in meters (kg/m^2). Overweight is defined as a BMI at or above the 85th percentile and below the 95th percentile for children and teens of the same age and sex. Obesity is defined as a BMI at or above the 95th percentile and underweight as BMI less than the 5th percentile.

Bone mineral density (BMD) of the lumbar vertebrae 2-4 (L2-4) was measured by dual-energy x-ray absorptiometry (DXA) using a Discovery A (HOLOGIC, Bedford, Massachusetts, USA) densitometer BMD between -1 and -2.5 SD was defined as osteopenia and if BMD <-2.5SD as osteoporosis [6].

This study was performed in accordance with the principles of Declaration of Helsinki.The study was approved by hospital ethics committee (09.17. 2019/1349).

Statistical Analysis

Statistical analysis were performed using the NCSS (NumberCruncher Statistical System) 2007&PASS 2008 Statistical Software (Utah, U.S.A). All results were expressed as the mean ± SD. Statistical comparisons were made using the unpaired Student's t tests. The analysis was conducted using Fisher's exact test and chi-square test to analyze qualitative variables. A value of $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the patients was 13.69±2.44 years (range 8-17years) and male:female ratio was 0.66. The patients were admitted with the complaint of abdominal pain (80%) , inactive (27%), mild (15%) and moderate (58%) chronic gastritis. Only two of H. pylori-positive patients had obesity, whereas none of the patients had malnutrition. The demographic and clinical characteristics of the patients are presented in Table 1.

Table 1. The clinical characteristics of the patients.

Age, y, mean ± SD	13.69±2.44
Gender (M/F)	0.66 (40/60)
Duration of disease, y, mean ± SD	1.86±1.31
Clinical presentation	
Abdominal pain	80 (80%)
Flatulans	64 (64%)
Nausea	60 (60%)
Regurgitation	49 (49%)
Endoscopic findings	
Erosive oesophagitis	100 (100%)
Nodular gastritis	26 (26%)
Duodenal ulcer	11 (11%)
Eosinophilic oesophagitis	1 (1%)
Polyp	1 (1%)
Type of chronic gastritis	
Inactive	27 (27%)
Mild	15 (15%)
Moderate	58 (58%)
H.pyloridensity	
0 (normal, no bacteria)	28 (28%)
1 (mild)	21 (21%)
2 (moderate)	27 (27%)
3 (marked)	24 (24%)

Forty-eight patients out of 72 patients with and 16 of 28 patients without H. pylori had low vitamin D levels (p=0.35). Thirteen H. pylori-positive patients and 9 H. pylori-negative patients had vitamin D insufficiency,whereas 9 H. pylori-positive patients and 2 H. pylori-negative patients had severe vitamin D deficiency (Table 2).

Table 2. It showes comparison of preopertive and postoperative patients' VAS. A statistically significant decline in pain control was detected in both groups.

	H.pylori-positive patients (n=72)	H.pylori-negative patients (n=28)	P
Age	13.64±2.53	13.82±2.35	0.74
Gender (male/female)	0.56 (26/46)	1.0 (14/14)	0.25
Height (cm)	154.6±16.6	152.3±9.2	0.49
Z score for height corrected for age and sex	0.68±0.93	0.49±1.04	0.9
Weight(kg)	55±22.32	52.65±19.5	0.62
Z score for weight corrected for age and sex	1.29±1.05	0.93±1.1	0.84
Body mass index (kg/m²)	25.39±5.53	24.56±3.58	0.46
Laboratory findings			
ALP (U/L)	168.79±81.8	161.78±78.4	0.69
Calcium (mg/dL)	9.47±0.36	9.5±0.41	0.71
Phosphorus (mg/dL)	4.17±0.46	4.37±0.59	0.07
Magnesium (mg/dL)	2.01±0.30	1.95±0.18	0.32
PTH (pg/mL)	48.91±23.4	43.36±16	0.25
25-OH-D (ng/mL)	16.07±9.53	19.68±8.51	0.08
<5	3.6±0.9 (n=9)	2.5±0.7 (n=2)	0.15
5-15	9.9±2.6 (n=26)	9.6±2.4 (n=5)	0.81
15-20	16.7±1.4 (n=13)	17.5±1.9 (n=9)	0.26
≥ 20	27.3±6.3 (n=24)	27±5.2 (n=12)	0.88
Ferritin (ng/ml)	24.74±10	26.22±12.8	0.54
Vitamin B12 (pg/mL)	267.38±95	26.22±12.8	0.56
Folic acid (ng/mL)	7.96±2.1	7.75±1.9	0.64
Bone mineral density (g/cm²)	-0.16±2.25	-0.08±2.62	0.87
< -2.5	-10±9.89 (n=2)	-13 (n=1)	1.00
<-1 and>-2.5	-1.37±0.35 (n=19)	-1.22±0.17 (n=4)	0.35

ALP: alkaline phosphatase
PTH= parathormone
25-OH-D= 25-hydroxyvitamin D
P<0.05 is statistically significant

There were no significant differences in terms of other biochemical parameters and in mean BMD z scores between H. pylori-positive and H. pylori-negative children (p> 0.05) (Table 2). Only 2 (2.7%) H. Pylori-positive and 1(3.5%) H. pylori negative patient had BMD z scores below -2.5 (p=1.00). Nineteen (26.3%) H. pylori –positive and 4 (14.2%) H. pylori –negative patients had osteopenia (p=0.35). Significant difference was observed between patients with and without osteopenia/osteoporosis regarding only the grade of chronic inflammation according to Sydney classification (Table 3).

Table 3. The comparison of patients with osteopenia/osteoporosis and without osteopenia/osteoporosis according to Sydney classification .

	Patients with osteopenia/ osteoporosis (n=3)	Patients without osteopenia/ osteoporosis (n=3)	p
Chronic inflammation			
0 (normal)	-	27	0.56
1 (mild)	-	17	1.00
2 (moderate)	-	40	0.27
3 (severe)	3	10	0.001
Atrophy			
0 (normal)	3	97	1.00
1 (mild)	-	-	
2 (moderate)	-	-	
3 (severe)	-	-	
Neutrophil activity			
0 (normal)	-	-	
1 (mild)	-	31	0.07
2 (moderate)	-	30	0.55
3 (severe)	3	36	0.05
Intestinal metaplasia			
0 (normal)	3	97	1.00
1 (mild)	-	-	
2 (moderate)	-	-	
3 (severe)	-	-	
Density of H.pylori			
0 (normal)	-	28	0.55
1 (mild)	-	21	1.00
2 (moderate)	-	27	0.54
3 (severe)	3	21	0.01

P<0.05 is statistically significant

DISCUSSION

It has been proposed that gastrointestinal disorders, particularly those associated with malabsorption and maldigestion (celiac disease, postgastrectomy, peptic ulcers and atrophic gastritis, pancreatic insufficiency); inflammatory bowel diseases (Crohn's disease and ulcerative colitis) may have negative impact on bone metabolism leading to osteoporosis [3,7-9].

H. pylori causes chronic gastritis and induces both humoral and cellular complex and local (in the gastric mucosa) and systemic immune responses [8,10]). Systemic inflammatory cytokines related to H. pylori infection such as tumor necrosis factor- (TNF-) α and interleukin-1 stimulating osteoblasts to produce cytokines activating osteoclasts and interleukin-6 promoting osteoclast precursor cell differentiation are all associated with bone destruction [2,9,11]. The studies evaluating the local cytokine profile in children have shown that H. pylori infection induces production of proinflammatory cytokines and a Th1 response, similar to studies in adults [12]. In our study, all of three patients with osteopenia/osteoporosis had severe chronic inflammation as detected in histopathological examination.

It has been reported that inflammatory response also provokes reduced levels of osteocalcine, insulin-dependent growth factors (IGF-1) and their transportation proteins and these interleukins also exacerbate catabolism and induce anorexia, reducing the ingestion of nutrients such as calcium and vitamin D which play a crucial role in bone metabolism [2].

Another mechanism postulated is that impaired gastric acidification (gastric mucosal atrophy and hypo-, and achlorhydria) related to H. pylori infection might induce malabsorption of calcium and alter bone architecture [9,13-18]. Asaoka et al.[8] reported that endoscopic gastric mucosal atrophy tended to correlate with osteoporosis and suggested that the decrease of dissolution of calcium salts caused by the decrease in gastric acid secretion in atrophic gastritis may also result in the malabsorption of calcium.

Osteoporosis is defined by the World Health Organization as a systemic metabolic bone disease, characterized by reduced bone mass and deterioration of bone tissue microarchitecture with increased bone fragility and susceptibility to fractures. There is also reduced bone mass in osteopenia, but without involvement of microarchitecture [2,6]. While several studies

reported an association between H. pylori infection and osteoporosis [8,19,20], some of them suggested that H. pylori infection would not to be a risk factor for decreased BMD [10,18]. There are studies determining immune response and cytokines in children with gastritis [12], but the studies evaluating association between H.pylori infection and osteoporosis in children are limited [10]. Ozdem et al.[10] found that H.pylori infection was not accompanied by significant alterations in biochemical markers of bone metabolism in children.In our study, osteoporosis was observed in two of our patients with H. pylori, osteopenia in 19 and hypovitaminosis D in 48 (severe deficiency in 9) patients, but the differences were not significant when compared with H. pylori-negative patients.One of H. pylori-positive patients with osteoporosis, whereas 17 patients with osteopenia had low vitamin D levels.

H.pylori causes vitamin B 12 malabsorption and only a minimum concentration of vitamin B12 is needed for the proliferation of osteoblasts [10]. Although a significant reduction in serum vitamin B 12 levels in H.pylori-positive children compared to H.pylori-negative ones was observed in the study of Ozdem et al.[10], no changes were detected in markers of bone metabolism. They concluded that vitamin B12 levels in H.pylori-positive children may still be far above the minimum levels required for normal osteoblastic proliferation. Vitamin B12 levels were within normal limits in our patients.

Shih H-M et al.[16] reported that early eradication of H. pylori is associated with a relatively lower incidence of osteoporosis when compared with the late eradication group with chronic H. pylori infection, Although Asaoka et al.[20] stated that H. pylori infection is a risk factor for osteoporosis, they did not correlate the success of H.pylori eradication with the risk of osteoporosis [20]. Two of our patients with H. pylori who had osteoporosis and obesity and 19 who had osteopenia were reevaluated one month after eradication treatment, but no improvement was seen in their BMDs and they were referred to the department of pediatric endocrinology.

Limitation of this study is that the markers of bone formation include bone-specific alkaline phosphatase and osteocalcine could not be assessed due to inavailabilitiy of required test kits in our hospital.

In conclusion, considering the shorter duration of H. pylori infection in children, in this study any significant association was not found between H. pylori-positive and H. pylori-negative children in terms of markers of bone metabolism. Early eradication of H. pylori is important for preventing elevation of inflammatory cytokines due to chronic inflammation which causes osteoporosis. As delayed diagnosis may increase the risk of adult osteoporosis, further larger-scale studies are needed for determining whether routine screening of markers of bone metabolism and BMD is necessary in children with H. pylori.

Ethics Committee Approval: İstanbul Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee approval was received (17/09/2019; 1349).
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Informed Consent: Informed consent was obtained from all individual participants included in the study.

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Original Article

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Medical Journal of Bakirkoy

Our 2-Year Real-Life Outcomes in Patients Who Received Ranibizumab Treatment for Diabetic Macular Edema (DME)

Gerçek Yaşam Klinik Uygulama Ortamlarında İki Yıl Takip Edilen Diyabetik Makula Ödemli (DMÖ) Gözlerde Tedavi Sonuçları

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ABSTRACT

Objective: *To assess the real-life performance and clinical outcomes in patients with diabetic macular edema (DME).*
Method: *The chart records were retrospectively evaluated for 42 eyes of 42 patients with DME, who were followed for two years between October 2013 and October 2016 at the Retina Unit. The patients were treated using intravitreal ranibizumab (0.5 mg/0.05 ml) for two years.*
Results: *The Early Treatment of Diabetic Retinopathy Study (ETDRS) letter score indicated BCVA values of 71.1±22.4 letters at baseline, 74.1±19.1 letters at the sixth month, 76.2±16.2 letters at the first year, and 76.1±21.2 letters at the end of the second year. BCVA at the sixth month and first and second years were not significantly different from the baseline value (p=0.172, p=0.051, p=0.108). The mean CFT were 407.4±140.0 µm at the baseline, 375.5±141.5 µm at the 6th month, 357.0±129.1 µm at the 1st year, and 313.8±108.9 µm at the end of 2nd year. The change in mean CFT compared to the baseline value was not statistically significant at the 6th month, but were statistically significant at the 1st and the 2nd years (p=0.082, p=0.040, and p=0.000, respectively).The mean numbers of injections and follow-ups at the end of the second year were 3.7±2.5 and 9.1±3.1, respectively.*
Conclusion: *The BCVA did not change significantly compared to baseline. The BCVA eye scores improved by 15 or more letters, in agreement with findings of other multi-center studies. However, the eyes with a BCVA loss of 15 or more letters showed a significant difference, which might reflect the smaller number of injections given in the present study compared to the other studies.*

Keywords: *Diabetic macular edema, ranibizumab, real-life outcome*

ÖZ

Amaç: *Diabetik makula ödemi (DMÖ) nedeniyle retina birimimizce iki yıl takip ve tedavi altında tutulan olgularda gerçek yaşam performansı ve klinik sonuçlarının ortaya çıkarılması ve benzer çok merkezli başlıca randomize çalışmalardaki sonuçlarla kıyaslanmasıdır.*
Yöntem: *Ekim 2013-Ekim 2016 tarihleri arasında Göz Kliniği Retina biriminde DMÖ nedeniyle takip ve tedavisi gerçekleştirilen, intravitreal ranibizumab 0.5 mg/0.05 ml tedavisi uygulanan ve 2 yıl boyunca takipte kalan 42 hastaya ait 42 gözün dosya kayıtları retrospektif olarak incelendi ve parametreleri değerlendirildi.*
Bulgular: *ETDRS harf skorlamasına göre ilgili gözlerde EİDGK, enjeksiyon öncesi ortalama 71.1±22.4 harf, tedavi sonrası 6. ayda 74.1±19.1 harf, 1. yılda 76.2±16.2 harf, 2. yılın sonunda 76.1±21.2 harf olarak gerçekleşti. Altıncı ay, 1. yıl ve 2. yılın sonunda görme keskinlikleri başlangıç görme keskinliğine göre anlamlı bir değişim göstermemiştir. (p=0.172, p=0.051, p=0.108). Santral foveal kalınlıkla (SFK) ilgili olarak ortalama değerler başlangıçta 407,4±140.0 µm, 6.ayda 375.5±141.5 µm, 1. yılda 357.0±129.1 µm ve 2. yılın sonunda 313.8±108.9 µm idi. Başlangıç değeri ile karşılaştırıldığında SFK'daki değişim 6.ayda istatistiksel olarak anlamlı değil iken, 1. ve 2. yıl değerlerinde istatistiksel olarak anlamlıydı (p=0.082, p=0.040, ve p=0.000). Bunun yanında ortalama enjeksiyon sayımız 2. yılın sonunda 3.7±2.5, takip sayımız 9.1±3.1 olarak gerçekleşmiştir.*
Sonuç: *İkinci yılın sonunda görme keskinlikleri başlangıç görme keskinliğine göre anlamlı bir değişim göstermemiş iken,15 veya daha fazla harf kazanma oranı diğer çok merkezli çalışmalarla benzer oranda, 15 veya daha fazla harf kaybı oranımız ise diğer çalışmalara göre daha yüksek bulunmuştur. Bu sonuçta başlıca faktörün diğer çalışmalara göre düşük kalan enjeksiyon sayısı olduğu değerlendirilmiştir.*

Anahtar kelimeler: *Diabetik maküla ödemi, ranibizumab, gerçek yaşam sonuçları*

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INTRODUCTION

Diabetic macular edema (DME) is the leading cause of vision loss in patients with diabetes mellitus (DM) and it adversely affects quality of life [1-4]. If left untreated, DME can cause loss of visual acuity of more than two lines after two years [5]. The World Health Organization (WHO) predicts that patients with DME in Europe will likely increase in number from the 33 million reported in 2000 to 48 million by 2030, along with a similar increase in the prevalence of DME-related vision problems [6].

The cause of DME is a pathological increase in retinal vascular permeability [7], mediated primarily by the cytokine vascular endothelial growth factor (VEGF). Intraocular VEGF levels and DME show an association [8,9], suggesting that the blockage of VEGF signaling may serve to restore retinal anatomy [10,11], while also reversing vision loss due to macular edema [12].

One currently used anti-VEGF drug is ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland), a humanized monoclonal antibody Fab fragment that selectively binds to and inhibits all known active isoforms of VEGF-A. Ranibizumab was formulated especially for ocular use and is widely used at doses of 0.5mg/0.05 ml in more than 100 countries for the treatment of age-related macular degeneration (AMD), DME-related visual impairment, and macular edema due to retinal vein obstruction [13].

The aim of the present study was to assess the real-life performance and clinical outcomes of ranibizumab use in patients with DME. Our patients were followed in our retina unit for two years and we compared our results with those from similar randomized multicenterstudies.

MATERIAL and METHODS

The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the institutional ethical review board (Approval number: 2017/69). Informed consent was obtained from all individual participants included in the study.

Hospital records of 42 eyes of 42 patients with DME were retrospectively evaluated. All ipatients included in the study were treated between October 2013 and October 2016 with intravitreal ranibizumab (0.5 mg/0.05 ml) applications, and followed up for 2 years. The main inclusion criteria were clinically significant macular edema (CSME) according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) classification, the absence of previous anti-VEGF treatments administered anywhere else, and the absence of any other ocular pathology that may cause vision loss. When both eyes were involved, the eye with the worse BCVA was selected in a one patient–one eye approach. Eyes that had previously undergone focal (grid) laser or panretinal laser photocoagulation (PRP) or underwent cataract surgery during the two years of follow-up were not excluded from the study. Application of PRP for severe non-proliferative (NPDR) or proliferative (PDR) diabetic retinopathy was also not an exclusion criterion. Major exclusion criteria in this study were history of uveitis, thromboembolic events or uncontrolled glaucoma in the affected eyes (intraocular pressure [IOP] >30 mmHg), the presence of vitreomacular traction (VMT), and uncontrolled hypertension.

The eyes were evaluated using color fundus photos and fundus fluorescein angiography images (FFA) (Kowa VX-10İ, Kowa Company Ltd. Tokyo, Japan). The central foveal thickness (CFT) was obtained with the MM5 protocol using optic coherence tomography (OCT) (RTVue Optovue Inc., Fremont, California, USA).

BCVA scores were obtained from hospital records and registered in data form following conversion to the ETDRS letter score. Intraocular pressure (IOP) measurements and biomicroscopic anterior segment and dilated fundus examination findings were all recorded in data form after reviewing the charts. In addition to primary outcome parameters, such as baseline, 6th (±1) month, 1st (±2 months) year, and 2nd (±2 months) year Best Corrected Visual Acuity (BCVA) and CFT, other parameters evaluated included the time between the first visit to FFA assessment (diagnosis-treatment decision), the completion time for the first three loading doses, the total number of injections, and the number of follow-up visits achieved in real-life conditions.

Before the treatment, the patients were informed in detail about the possible outcomes and side effects of intravitreal ranibizumab 0.5 mg, and provided written/oral consent. The patients received three monthly load-

ing doses of ranibizumab and then the eyes with DME were followed up at 4- to 6-week intervals. The ranibizumab injections were continued monthly until BCVA improved and/or CFT thinning were stabilized (change in BCVA <5 letters and change in SFT <10% from the last measurement). Cases with a decrease in BCVA (change ≥5 letters) and a ≥10% increase in CFT received a repeat injection. Focal laser therapy was applied to patients who were detected to have a leaking microaneurysm of 500 µm outside the foveola at baseline or at any follow-up visits, and PRP was applied to cases with severe NPDR and PDR. No specific protocol was adopted for the application of laser procedures at earlier or later timeframes.

The descriptive statistics included the mean, standard deviation, the lowest and the highest values, frequency, and ratio. The Kolmogorov-Smirnov test was used to assess the normality of the data distribution, and the Wilcoxon test was used for the assessment of dependent quantitative data. A value of P <0.05 was accepted as statistically significant. SPSS 22.0 (SPSS Inc. Chicago, USA) software was used for the statistical analyses.

RESULTS

In this study, 42 eyes of 42 patients were analyzed. Sixteen patients were males, 26 were females, and the mean age of all patients was 61.6±10.3 years. The mean duration of the DM diagnosis was 16.5±7.8 (2–33) years. The mean time interval from the first visit to the FFA imaging (which is mandatory for social security agency reimbursement) was 62.3±41.4 days. The patients received a mean number of 2.3±1.4 injections in the first year and 1.4±1.6 injections in the second year. The mean total number of injections at the end of the second year was 3.7±2.5. The mean number of follow-up visits in the first year was 5.1±2.1 and 4.0±1.8 at the end of the second year. The total number of follow-up visits at the end of the second year was 9.1±3.1, and the mean number of weeks to complete three loading doses was 40.4±25.1 weeks.

During the two-year follow-up period, 17 patients received only focal laser photocoagulation, 6 patients only PRP, and 5 patients both focal laser and PRP treatments. Only 10 patients (24%) had never previously received laser treatment at any time at any other center. During the two-year follow-up period, 3 patients had cataract surgery.

According to the ETDRS letter score, the mean BCVA for the eyes of concern was 71.1±22.4 letters at baseline, 74.1±19.1 letters at sixth month, 76.2 ± 16.2 letters at the first year, and 76.1±21.2 letters at the end of the second year. Compared with the baseline value, no significant difference was detected in visual acuity at the sixth month, first year, or second year (P=0.172, P =0.051, and P=0.108, respectively). The changes in BCVA are summarized in Table 1.

Table 1. Changes in the BCVA according to the ETDRS chart (letters)

	Q1-Q3	Med	Mean±Sd.	p
Baseline	50-89	77	71.1±22.4	
6th Month	59-89	80	74.1±19.1	0.172[w]
1st Year	64-89	83	76.2±16.2	0.051[w]
2nd Year	65-92	80	76.1±21.2	0.108[w]

[w]: Wilcoxon test
Med: Median
Q1-Q3: interquertile range
Sd: standard deviation
BCVA: Best corrected visual acuity

The number of eyes with a loss of 15 letters or more was 3 (7.1%) at the first year and 6 (14.2%) at the second year. Similarly, the number of eyes with an improvement of 15 letters or more was 12 (28.6%) at the first year and 13 (31%) at the end of second year.

The OCT measurements revealed a mean CFT of 407.4±140.0 at the baseline, 375.5±141.5 µm at the sixth month, 357.0±129.1 µm at the first year, and 313.8±108.9 µm at the end of the second year. The change in mean CFT compared to the baseline value was not statistically significant at the sixth month, but the differences were statistically significant relative to baseline at the first and the second years (P=0.082, P =0.040, and P=0.000, respectively). The changes in CFT are summarized in Table 2.

Table 2. Change in central foveal thickness (CFT) (µm)

	Q1-Q3	Med	Mean±Sd.	p
Baseline	302-465	372	407.4±140.0	
6th Month	302-465	334	375.5±141.5	0.082[w]
1st Year	302-465	336	357.0±129.1	0.082[w]
2nd Year	302-465	272	313.8±108.9	0.000[w]

[w]: Wilcoxon test
Med: Median
Q1-Q3: interquertile range
Sd: standard deviation
BCVA: Best corrected visual acuity

DISCUSSION

Ranibizumab is a humanized monoclonal antibody FAB fragment specifically designed for ocular use to selectively bind to and inhibit all known active isoforms of VEGF-A [13]. VEGF is the most significant factor that increases vascular permeability and leads to neovascularization in retinal diseases. VEGF also serves as a chemoattractant for macrophages and monocytes, and these cells play additional roles in increases in vascular permeability by producing proinflammatory molecules [14].

The ETDRS study for eyes with clinically significant macular edema (CSME) revealed a risk of loss of 15 or more letters at the end of the third year, but this risk was decreased by approximately 50% in a focal laser arm versus observation only. (24% vs. 12%) [15]. However, many known risks of laser treatment, including limited visual outcomes, collateral damage secondary to expansion of laser scars, occurrence of focal localized scotoma, impairment of color vision, permanent damage to the retinal pigment epithelium (RPE) and photoreceptors, secondary choroidal neovascularization (CNV), and RPE fibrous metaplasia, have prompted a serious search for other treatment options [16,17]. One of the first alternative treatments was the use of intravitreal corticosteroids. These drugs halt the destruction of the blood-retina barrier and lower the permeability by inhibiting VEGF and due to their anti-inflammatory effects [18]. Intravitreally administered steroids are efficacious for the treatment of DME, but they also cause complications that can include retinal detachment, intravitreal hemorrhage, increased IOP, development of cataract, pseudoendophthalmitis, and endophthalmitis (0.87%) [19]. Therefore, the current treatment for DME is predominantly focused on the suppression of VEGF-related effects.

The patients in the extended 24-month period of the multicenter, randomized, pilot RESTORE trial showed a mean letter gain of +7.9 letters after 24 months in the ranibizumab-only group and +6.7 letters in the ranibizumab-plus-laser-therapy group. The mean number of injections at the end of 2 years was 11.2 injections in both ranibizumab groups. The decreases in mean CFT were 140 µm vs. 133 µm [20]. Similarly, the RISE and RIDE trials, which were phase 3 trials for ranibizumab, showed visual gains of +11.9 and +12 letters, respectively, in the monthly 0.5 mg ranibizumab treatment arms, whereas the decreases in mean CFT at the end of 24 months were 253 µm and 270 µm, respectively [12]. The READ-2 trial compared ranibizumab and focal/grid laser treatments both head-to-head and in combination. The first group received 0.5 mg intravitreal ranibizumab at the first, third, and fifth months. The second group received focal/grid laser treatment at the baseline, with the treatment repeated at the third month, if necessary. The third group received the combination of 0.5 mg ranibizumab and focal/grid laser combination at the baseline, and the same treatment was repeated at the third month, if necessary. After the sixth month, the ranibizumab treatment was repeated in all groups when treatment was necessary. At the end of the two-year follow-up, the mean letter gain was +7.7 letters in the first, +5.1 letters in the second, and +6.8 letters in the third group, and the change from baseline was statistically significant for all three groups. At the end of the second year, the mean CFTs were 340 µm, 286 µm, and 258 µm, respectively. The mean number of injections in the groups were 9.3, 4.4, and 2.9, respectively. However, the visual outcomes in the second and third groups at the end of the second year were not significantly different from those of the first group. This finding suggests that the use of a focal or grid laser may significantly decrease the requirement for injections without compromising the visual acuity gain. In a relevant study, the greatest increase in visual gain was observed in the injection-only group [21]. The outcomes in our study are comparable with those of the second and the third groups of the READ-2 study with respect to the presence of a laser combination and the number of injections required.

The two-year extension of the independent, multicenter DRCR.net trial assessed 642 eyes of 526 patients in the following 4 groups: a sham injection plus laser, ranibizumab plus early laser (within a week), ranibizumab plus late laser (at the 24th week or later), and triamcinolone plus early laser (within a week). After 24 months of follow-up, the letter gains were +7 ± 13 letters in the ranibizumab-plus-early-laser group, +9 ±14 letters in the ranibizumab-plus-late-laser group, +2 ±19 letters in the triamcinolone-plus-laser group, and +3 ± 15 letters in the laser-only group. In the ranibizumab-plus-early-laser and ranibizumab-plus-late-laser groups, the median numbers of injections were 8 and 9 in the first year and 2 and 3 in the second year, respectively. At the end of second year, the visual outcomes were

similar in the ranibizumab-plus-early-laser and the ranibizumab-plus-late-laser groups; the results were significantly superior to those of the sham-injection-plus-laser and triamcinolone-plus-early-laser groups. Despite a significant difference in visual outcomes, the change in the CFT from baseline to the end of the second year was -145±141 µm in the sham-injection-plus-laser group, -126±162 µm in the ranibizumab-plus-early-laser group, -148±127 µm in the ranibizumab-plus-late-laser group, and -128±137 µm in the triamcinolone-plus-early-laser group. No significant differences were detected among the groups [22]. The letter gains reported for the ranibizumab-plus-early-laser group in protocol I of the DRCR.net study were also similar to the values obtained in our study.

Both gains and losses in visual acuity have been reported previously. For example, 39.2% of the eyes in the 0.5 mg ranibizumab group of the RISE trial gained 15 or more letters, whereas 45.7% of the eyes in the 0.5 mg ranibizumab group of the RIDE trial gained 15 or more letters. In a 2-year extension of DRCR.net protocol I trial, 29% of the eyes in the 0.5 mg ranibizumab-plus-early-laser group, 28% of the eyes in the 0.5 mg ranibizumab-plus-late-laser group, and 18% of the eyes in the sham-injection-plus-laser group gained 15 or more letters. These values agreed with our data. Indeed, 31% of the eyes gained 15 or more letters. The visual losses of 15 or more letters were detected in 2.4% of the eyes in the 0.5 mg ranibizumab group of the RISE trial and 3.9% of the eyes in the 0.5 mg ranibizumab group of the RIDE trial. In the two-year extension of DRCR.net trial, the corresponding rates of visual loss were 4% in the 0.5 mg ranibizumab-plus-early-laser group, 2% in the 0.5 mg ranibizumab-plus-late-laser group, and 10% in the sham-injection-plus-laser group, whereas our rate was 14.2% in the present study.

A multicenter, 2-year study from Portugal, which evaluated the real-life outcomes of ranibizumab, revealed a median number of 4 injections in the first year and 5 injections at the end of the second year. The baseline mean BCVA was 60 letters, which increased to 65 letters at the end of the second year. At that time, 21.4% of the eyes gained 15 or more letters, while 8.6% of the eyes lost 15 or more letters. The baseline median CFT was 443 µm, which decreased to 325.5 µm at the end of the second year [23].

In our study, the percentage of the patients who gained 15 or more letters was similar to the percentages reported in the previous trials, whereas our percentage of patients who lost 15 or more letters was higher than the relevant data reported previously. Our protocol was most similar to the the protocol used in combined laser-plus-ranibizumab groups analyzed in previous multicenter trials. When the clinical workload permitted, we also applied focal laser photocoagulation to the eyes with extrafoveally located edema and microaneurysms. However, the timing of the laser applications in our study was distributed between the early and late periods. Evaluation at the end of the 24-month follow-up demonstrated a median gain of +5.0±16.8 letters with intravitreal ranibizumab injection; however, the result was not statistically significant. This may be due to the high percentage of patients who lost 15 or more letters in our study. Our mean number of injections by the end of second year was 3.7±2.5, which was lower than that of the other trials. This may explain the reason for the high frequency of cases that lost 15 or more letters in visual acuity tests.

Conclusion

In summary, the accumulating trial data reporting real-life outcomes of DME treatments will greatly aid in the comparisons of the effectiveness of treatment protocols. The pharmaceutical industry may also accelerate its efforts in the field of drug formulations and treatment regimens by taking real-life outcomes into account. The development of customized treatment and follow-up protocols may also be proposed. Thus, patient motivation may be increased, and the goal of less frequent follow-ups/injections in low-risk patients and more frequent follow-ups/injections in high-risk patients may be achieved.

Ethics Committee Approval: Bakirköy Dr. Sadi Konuk Training And Research Hospital Clinical Studies Ethics Committee approval was received (29/5/2017; 2017-04-16).
Conflict of Interest: No conflict of interest was declared by the authors.
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Informed Consent: Written consent was obtained from all patients participating in the study.

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Evaluation of Patients with an Initial Diagnosis of Chorea: Sydenham Chorea and Differential Diagnoses

Kore Ön Tanılı Hastaların Değerlendirilmesi: Sydenham Koresi ve Ayırıcı Tanılar

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ABSTRACT

Objective: *Our aim is to evaluate patients being referred with an initial diagnosis of chorea according to their clinical, laboratory features and final diagnoses while emphasizing cardiological findings of patients with Sydenham chorea.*
Method: *Children aged 4-18 years who were referred to Okmeydanı Research and Training Hospital Pediatric Neurology department with an initial diagnosis of acute, subacute chorea between January 2017-January 2020 were retrospectively included. Chronic chorea and diseases associated with chronic chorea were excluded from the study . Data concerning clinical, laboratory features, cardiological findings, etiologies, treatments, recurrence rates and follow-ups of patients were recorded. Descriptive statistical analysis were performed using SPSS 21.0.*
Results: *Fifteen patients has been referred with the initial diagnosis of chorea. Mean age of the patients was 11.5±2.2 years. Ten (67%) patients were females, 5 (33%) patients were male. After admission, 8 (54%) patients were diagnosed with Sydenham chorea, and 2 (13%) patients with recurrent Sydenham chorea. During physical examination, 5 (33%) patients did not have chorea, and 3 cases had tic disorder. Out of 8 patients with new diagnosis of Sydenham chorea, 3 (37.5%) patients had subclinical carditis, and 5 (62.5%) patients clinical carditis. Chorea had been treated with one of haloperidol/biperiden, valproic acid and prednisolon options. The treatment of 6 patients attending regular follow-up visits was stopped 2-6 months later. Chorea of two patients recurred during our follow-up, and one of our newly diagnosed Sydenham chorea patients had been recognized as antiphospholipid antibody syndrome after recurrence.*
Conclusion: *Sydenham chorea is the most common cause of acquired chorea in childhood. Most of the time it is self limiting. Differential diagnosis of chorea must be kept in mind especially when there is a recurrence.*

Keywords: *Antiphospholipid antibody syndrome, carditis, chorea, haloperidol, Sydenham chorea*

ÖZ

Amaç: *Amacımız; kore ön tanısıyla yönlendirilen hastaların klinik ve laboratuvar özelliklerini, son tanılarını, Sydenham kore tanılı hastaların ise kardiyolojik bulgularını vurgulayarak değerlendirmektir.*
Yöntem: *Çalışmaya Okmeydanı Eğitim ve Araştırma Hastanesi Çocuk Nöroloji Polikliniği'ne Ocak 2017 - Ocak 2020 tarihleri arasında akut, subakut kore ön tanısı ile yönlendirilen 4-18 yaş arası hastalar retrospektif olarak dâhil edildi. Kronik kore ve kronik kore ile ilişkili hastalıklar çalışmadan dışlandı. Hastaların klinik ve laboratuvar özellikleri, kardiyolojik bulguları, etiyolojileri, tedavileri, rekürrens oranları ve izlemleri ile ilgili bilgiler kaydedildi. Tanımlayıcı istatistiksel analizler SPSS 21.0 kullanılarak yapıldı.*
Bulgular: *Toplam 15 hasta çocuk nöroloji polikliniğine kore ön tanısıyla yönlendirilmişti. Hastaların başvuru yaşı 11,5±2,2 yıl idi. On (%67) hasta kız, 5 (%33) hasta erkek idi. Başvurudan sonra 8 (%54) hastaya Sydenham koresi, 2 (%13) hastaya rekürren Sydenham koresi tanıları kondu. Muayenede 5 (%33) hastada kore saptanmadı, üç hasta tik bozukluğu olarak değerlendirildi. Yeni Sydenham koresi tanısı konulan 8 hastadan, 3 (%37,5) hastada subklinik kardit, 5 (%62,5) hastada klinik kardit vardı. Kore haloperidol/biperiden, valproik asit, prednizolon seçeneklerinden biri ile tedavi edildi. Düzenli takibe gelen 6 hastanın tedavisi 2-6 ay süre sonunda kesildi. İzlemimizde rekürrens iki hastada oldu, ilk atak Sydenham koresi olan bir hasta rekürrens sonrası antifosfolipid antikor sendromu tanısı aldı.*
Sonuç: *Çocukluk çağında Sydenham koresi edinilmiş korenin en sık nedenidir. Genellikle kendi kendini sınırlar. Kore ayırıcı tanısı özellikle de rekürrens olduğunda akla getirilmelidir.*

Anahtar kelimeler: *Antifosfolipit antikor sendromu, haloperidol, kardit, kore, Sydenham kore*

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INTRODUCTION

Chorea is a hyperkinetic movement disorder consisting of dance-like involuntary movements that travel from one part of the body to another [1]. Traditionally, chorea has been classified as primary and secondary chorea. The term "primary" is used to refer to idiopathic or genetic chorea, while "secondary" indicates that the chorea is the result of an underlying disorder. Although there are other structural, autoimmune, metabolic, and drug/toxin–induced etiologies of chorea, the most common type of childhood-onset chorea is Sydenham chorea, described in 1686 by Thomas Sydenham as a specific movement disorder. Although he wrote about his patient population in detail, he did not note its association with rheumatic fever [2]. In 1810, Etienne Michel Bouteille recognized the association between Sydenham chorea and rheumatic fever in four of his patients [2].The type of chorea known as Sydenham chorea is a major criteria for acute rheumatic fever (ARF) among all risk groups of patients according to the revised Jones criteria in 2015 [3]. Carditis is the most common and feared manifestation of ARF as it results in permanent sequelae. In a study by Demirören et al., carditis diagnosed by echocardiography was accompanied by Sydenham chorea in 70.5% of 61 patients [4].

Every hyperkinetic disorder, acute or subacute, is first presumed to be chorea by physicians so as to ensure a prompt diagnosis of ARF to prevent further damage to cardiac structures. However, it should be ascertained that the movement disorder is really chorea, followed by identification of the etiology. Although Sydenham chorea is the most common type of chorea, other etiologies are also possible. In the present study, we have evaluated symptoms, medical history, laboratory tests, cardiological findings, final diagnosis, treatment, and follow-up results in patients with an initial diagnosis of chorea.

MATERIAL and METHOD

Patients aged 4-18 years who were referred to the pediatric neurology department of Okmeydanı Research and Training Hospital with an initial diagnosis of chorea between January 2017 and January 2020 were retrospectively evaluated. Children with presumed acute and subacute chorea who were referred by a pediatrician or primary physician were included in the study. Patients with chronic chorea and diseases that lead to chronic chorea- like Huntington disease and choreoathetoid cerebral palsy were excluded from the disease. Chorea is a disorder characterized by continuous movements variable in speed, unpredictable in timing and direction, and flowing or jerky in appearance [5]. A detailed history was taken from all referred patients, who also underwent a physical examination in the pediatric neurology outpatient department to determine if they really had chorea.

Cardiac evaluation was performed by a pediatric cardiologist, and all patients underwent electrocardiography and echocardiography. A Hewlett-Packard Sonos 1000 system ultrasonic imager was used for echocardiographic assessments. Appropriate transducers of 2.5, 3.5, and 5 MHz were used to define the cardiac structures. The echocardiographies were obtained with the patient in the standard precordial positions, and the diagnostic criteria of Gewitz et al. were used for the echocardiographic diagnosis of rheumatic disease [3]. The clinical diagnosis of carditis in an index attack of ARF is based on the presence of significant murmurs suggestive of mitral and/or aortic regurgitation or pericardial rub, or an unexplained cardiomegaly with congenital heart failure [6]. Subclinical carditis refers exclusively to the circumstance in which classic auscultatory findings of valvular dysfunction are either not present or not recognized by the diagnosing clinician, but echocardiography/Doppler studies reveal mitral or aortic valvulitis [3]. Carditis was treated with prednisolon when there was active inflammation with CRP and/or elevated sedimentation and moderate/severe valvular insufficiency and/or heart failure. Prednisolon treatment was ceased in 4-6 weeks. Arthritis was treated with ibuprofen sodium. Sodium and water restriction and enalapril and/or furosemid was used when there was evidence of volume load and heart failure [7]. Secondary prophylaxis was performed every 21 days with intramuscular penicillin G benzathine (1.2 million units for patients weighing 27 kg or more and 600,000 units for those weighing less than 27 kg) starting from the day of diagnosis in patients with ARF to eradicate group A carriage and to start the first dose of prophylaxis.

Patient data including sex, age at presentation, duration of chorea until admission, duration of follow-up, complaints, bodily distribution, and severity of chorea, presence of tonsillitis within the last two months, final diagnosis, anti- streptolysin O titer, sedimentation rate, serum C-reactive protein levels, throat culture results, cardiological findings, treatment of patient, side effects of drugs, and recurrence rates were recorded from the medical files of patients. Chorea was classified according to localization (hemichorea, or movements affecting one side of the body; generalized movements affecting the whole body) and severity of the symptoms (mild, moderate, and severe). The severity of symptoms was determined by how much they interfered with dressing and other activities of daily living as well as school activities such as writing. Symptoms are described as mild when there are minimal movements; moderate chorea results in obvious inconvenience but does not interfere with self care; and severe chorea refers to movements that prevent the patient from performing daily activities meaning the patient requires assistance [8]. It is characterized by increased levels of antistreptolysin O titer (>200 IU/ml), eriyhrocyte sedimentation rate (>30 mm/h), and C-reactive protein (CRP) (>15 mg/L) [3]. Recurrence is described by Korn-Lubetzki et al. [9] as the development of new signs lasting more than 24 h and separated by a minimum of two months from the previous attack [9]. At the time of recurrence, patients were assessed for rheumatic fever activity as well.

Statistical analysis

Statistical analyses were performed with SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA). Descriptive statistical analysis (mean, standard deviation, median, frequency, percentage, minimum, maximum) were also performed.

RESULTS

Fifteen patients were referred to the pediatric neurology department with chorea as an initial diagnosis. The mean age of patients was 11.5±2.2 years. Ten patients (67%) were female and five (38%) were male. Patients were followed up for a mean period of 5.47±5.75 months; the minimum, maximum, and median follow-up periods were one month, 21 months, and three months, respectively. The symptoms of every patient are described in detail in Table 1. Symptom duration was 2-150 days with a median period of seven days. Antistreptolysin O titer results were available for 12 patients; one of them had normal levels, and the other 11 patients had levels ranging between 286, and 1500 IU/ml with a median of 550 IU/ml. Erithrocyte sedimentation rate was available for 11 patients, which ranged between 4, and 67 mm/h with a median of 14 mm/h.C-reactive protein for 12 patients ranged between 0.22, and 17 mg/L with a median of 2.2 mg/L. Out of seven patients for whom a throat culture was performed, in only one patient Group A β hemolytic streptococcous was grown. Cranial MRI was performed in seven patients out of 15, all with normal results.Twelve patients had cardiological findings; the most common cardiological pathology was mitral valve insufficiency, and the second most common one was aortic insufficiency. Seven patients had two valve involvements at the same time. Three patients had normal echocardiographic findings, one of whom had been diagnosed with Sydenham chorea two months before admission to our instituition and was using carbamazepine. This patient had not any symptoms of chorea at the time of admission.

Final diagnoses, of the patients were Sydenham chorea in 8 (54%), and recurrent Sydenham chorea in 2 (13%) patients. Five (33%) patients did not manifest symptoms of chorea during a physical examination. Two patients had a previous diagnosis of Sydenham chorea but were admitted with nonspecific symptoms not related to their previous diagnosis of Sydenham chorea. Three patients were diagnosed with tic disorder, the disease state of one of them had deteriorated after fluoxetin and metilphenidate use. All patients diagnosed with Sydenham chorea and recurrent Sydenham chorea and one patient with cardiac findings compatible with acute rheumatic fever without chorea were started on secondary prophylaxis. The patient who presented with severe hemichorea with a sedimentation rate of 67 mm/h was found to have moderate mitral, and mild aortic insufficiency. This patient with clinical carditis, chorea, and laboratory signs showing ongoing inflammation, was started on prednisolon (1.6 mg/kg/day), and the chorea resolved after treatment with steroids as well. Another patient had been treated with oral prednisolon for four months before the presentation of chorea due to an

Table 1. Detailed clinical features of patients with chorea as an initial diagnosis.

G	Age (yrs)	Complaints	Complaint Duration	Medical History	Chorea severity	Generalized chorea or hemichorea	History of Tonsillitis	ASO/ESR IU/ml/ mm/sa	Echocardiographic Findings	Treatment Chorea treatment	Final diagnosis + Major Criteria	Recurrence
F	10	Behaviour changes, no complaint of abnormal movement	45	Rubeola infection in childhood	Mild	Generalized	3 months ago, she did not finish the antibiotics	286/14	Mild mitral insufficiency Mitral valve prolapsus	Secondary Prophylaxis Valproic acid	Sydenham chorea + Subclinical carditis	-
F	12	Abnormal movements in arms and gait abnormality	7	Epilepsy on VPA	Mild	Generalized	Unknown	741/8	Mild mitral insufficiency Mitral valve prolapsus	Secondary Prophylaxis Haloperidol Biperiden	Sydenham chorea + Subclinical carditis	-
F	11	Involuntary continous movements	7	ARF diagnosis 4 months ago treated with prednisolon	Moderate	Generalized	Unknown	341/7	Mitral insufficiency (mild) Aort insufficiency (Min.)	Secondary Prophylaxis Valproic acid Haloperidol Biperiden Prednisolon	Sydenham chorea + Subclinical carditis	-
F	11	Left side weakness	90	-	Moderate	Hemichorea	Unknown	1500/14	Mitral insufficiency (mild – interm.) Aort insufficiency (Mild)	Secondary Prophylaxis Haloperidol Biperiden	Sydenham chorea + Clinical carditis	-
F	9	Gait abnormality	3	Could not learn how to read	Severe	Hemichorea	Unknown	1015/37	Mitral insufficiency (interm.- signif.)	Secondary Prophylaxis Haloperidol Biperiden	Sydenham chorea + Clinical carditis	-
F	12	Swelling in left ankle and unvoluntary movements in left side	3	Left jugulary vein thrombosis and thrombocytopenia	Moderate	Hemichorea	Present but exact time is unknown	100/37	Mitral insufficiency (mild - interm.)	Secondary Prophylaxis Haloperidol Biperiden Ibuprofen	Sydenham chorea + Arthritis + Clinical carditis	Yes After recurrence diagnsed with antiphospholipid antibody syndrome
F	8	Abnormal movements, shortness of breath, fatigue, exercise intolerance	7	-	Severe	Hemichorea	10 days ago upper throat infection	1189/67	Mitral insufficiency (interm.) Aort insufficiency (mild)	Secondary Prophylaxis Oral prednisolon	Sydenham chorea + Clinical carditis	-
F	12	Continous movement of left hand	2	-	Mild	Hemichorea	Unknown	977/8	Mitral insufficiency (mild/interm.)	Secondary Prophylaxis Haloperidol Biperiden	Sydenham chorea + Clinical carditis	-
M	12	No complaint, admitted for followup	-	Sydenham chorea diagnosis 9 months ago	No chorea on physical examination	Unknown (Her mother started his medication again at recurrence herself during followup)	Unknown	-	Mitral insufficiency (mild – interm.) Aort insufficiency (Mild)	Secondary Prophylaxis Valproic acid	Recurrent Sydenham chorea	Yes
F	12	Dance like movements in extremities	150	Sydenham Chorea diagnosis 2,5 years ago	Moderate	Generalized	Unknown	637/11	Mitral insufficiency (mild) Aort insufficiency (Min.)	Secondary Prophylaxis Haloperidol Biperiden	Recurrent Sydenham chorea	-
F	11	Hand shaking	15	Sydenham chorea diagnosis 2 months ago and on carbamazepine	No chorea on physical examination	No chorea on physical examination	Unknown	463/20	Normal	Already on secondary prophylaxis	Sydenham chorea unrelated symptoms	-
M	11	Abnormal movements	60	Sydenham chorea diagnosis 3 years ago	No chorea on physical examination	No chorea on physical examination	Unknown	-	Mitral insufficiency (mild) Aort insufficiency (Mild)	Already on secondary prophylaxis	Sydenham chorea unrelated symptoms	-
M	18	No complaint, admitted for followup	-	6 years ago dance like movements in left arm and leg	No chorea on physical examination	No chorea on physical examination	Unknown	368/4	Normal	-	Tic disorder	-
M	13	Abnormal movements	2	-	No chorea on physical examination	No chorea on physical examination	Unknown	-	Normal	-	Tic disorder	-
M	10	Anger, not wanting to go to school, tics	2	Tics for the last 2 years	No chorea on physical examination	No chorea on physical examination	Unknown	462/-	Mitral insufficiency Tricuspid insufficiency	Secondary Prophylaxis	Tic disorder, deteriorati-on after fluoxetin and metilphenidate	-

ARF:Acute rheumatic fever;ASO:Antistreptolysin O;F:Female;G:Gender;Interm:Intermediate;M:Male;Sed:Sedimentation;VPA:Valproic acid;yrs:years

diagnosis of ARF with clinical carditis and active inflammatory laboratory signs at that time. These two patients were treated with enalapril/furosemide and enalapril consecutively. Of the eight patients with a new diagnosis of Sydenham chorea, three patients (37.5%) had subclinical, and five patients (62.5%) clinical carditis.

Six patients were started on haloperidol (doses ranging between 0.015–0.125 mg/kg/day), and all of them were treated with biperiden in addition to prevent dystonic reactions. For three patients, valproic acid was the first choice for chorea treatment; and these patients were treated with doses of 15, 20, and 22 mg/kg/day, respectively. One patient who had been diagnosed as ARF four months previously did not respond to valproic acid nor later to haloperidol/biperiden. Therefore, she was started on oral prednisolon with a dose of 1 mg/kg/day, and her chorea diminished. Five patients responded completely to treatment, and five patients showed a partial improvement. Only one patient using haloperidol with a total dose of 5 mg (0.125 mg/kg/day) plus a total dose of 1 mg of biperiden experienced tremors as a sign of parkinsonism as an adverse effect of haloperidol. When the patient stopped taking haloperidol, tremors of the patient disappeared. No other patient had any side effects with any other treatment. Six patients who were attending their pediatric neurology appointments regularly had their treatment stopped after 2–6 months without any symptomatology of chorea No patient had persistent chorea.

Recurrence occurred in two patients during our follow-up, although they stated that they did not delay secondary prophylaxis. One patient had a recurrence after he had been admitted without any symptoms for the purpose of follow-up after using valproic acid and had been been later followed up after ceasing treatment prescribed for his chorea. His mother started his medication again, and when he was admitted, he had no chorea. The other patient was diagnosed with Sydenham chorea at her first admission, which had recurred during her follow-up period. In her past medical history she had left jugular vein thrombosis and ongoing thrombocytopenia. When the etiology of her recurrence was investigated, her anticardiolipin Ig G and lupus anticoagulant levels were found to be increased. She was diagnosed with antiphospholipid antibody syndrome.Detailed clinical features of patients with presumed chorea are described in Table 1.

DISCUSSION

Chorea classically results from disturbances in the caudate nucleus or putamen. Occasionally, the pathology can involve thalamic/subthalamic region. Because of the vulnerability of the basal ganglia and its wide connections, the differential diagnostic spectrum of chorea is very large [10-12]. In the present study, ten patients out of 15 with an initial diagnosis of chorea had Sydenham chorea, and two of these were recurrences. In a Italian study evaluating hyperkinetic movement disorders in a pediatric emergency department, tics were the most common cause of admission (44.5%) followed by tremors (21.1%) and chorea (13.7%) [13]; Sydenham chorea was the only form of chorea identified. As there is no specific biological marker in patients with Sydenham chorea, the diagnosis of Sydenham chorea is based on clinical evaluation and the exclusion of other causes of the chorea [14,15]. We diagnosed three patients with a tic disorder who had been initially thought to have chorea. Sydenham chorea must be differentiated from other hyperkinetic movement disorders like athetosis, ballism, chorea, dystonia, myoclonus, steropathy, tics, and tremor.

Sydenham chorea begins several weeks to months after a GAS infection. Although two major manifestations, or one major and two minor manifestations, with evidence of a preceding GAS infection are necessary for the diagnosis of ARF, chorea is an exception to this as chorea may be the only manifestation of ARF at the time of its presentation [3]. The onset of symptoms is usually insidious in the beginning with gradually progressive clumsiness and behaviour changes slowly increasing in frequency, and severity. Later, the choreic movements become more obvious and typically more generalized [16]. Most commonly, changes include emotional lability and aggression, impulsivity, and obsessive- compulsive behaviour [16,17]. Behavioural changes may dominate the clinical picture more than a movement disorder;one of our patients had symptoms for almost 45 days without any complaint of involuntary movement. Hemichorea is also possible—almost

half of our patients with chorea had hemichorea. Gurkas et al. reported hemichorea in37.8% of their 90 patients, and Demirören et al. reported hemochorea in 20% of 65 patients [4,15]. Hemichorea can present with weakness; in one of our patients, this was the only complaint. Neuroimaging may be necessary when hemichorea is evident as structural basal ganglia etiologies like stroke, moyamoya disease, and vascular malformations can cause hemichorea [18,19]. Five of our chorea patients underwent cranial MRI with normal results.

Antiphospholipid antibody syndrome is one of the differential diagnoses of Sydenham chorea [18]. This chorea is most commonly unilateral, appears in a single episode, and regresses spontaneously or with medication [20]. The chorea associated with antiphospholipid antibodies has been reported to recur in 25–30% of patients [21]. Valvulopathies are also reported to be common in antiphospholipid antibody syndrome, with features making it surprisingly similar to Sydenham chorea [20,22]. After one of our patients had a recurrence compliant with secondary prophylaxis, she was tested positively for antiphospholipid antibody syndrome. She also had mild/intermediate mitral insufficiency. Although recurrences are possible without any delays in secondary prophylaxis, [23] Gurkas et al. found that the risk factors for recurrence included the irregular use of antibiotic prophylaxis, failure to achieve remission within six months, and prolongation of symptoms for more than one year [15].

The treatment of chorea falls into three categories: terminating exposure to the causative agent, symptomatic treatment, and treatment of the underlying etiology [18]. Although the pathophysiology of Sydenham chorea is still unclear, the cross-reactivity of streptococcal antibodies with the basal ganglia and the brain cross-reactive epitopes of streptococcal M proteins are blamed in patients with Sydenham chorea [24,25]. As there is no permanent structural disability, the natural course of the disease is that it continues with a waxing and waning quality for 2-6 months until it finally resolves [8,16,26]. Therefore, most of the time, mild Sydenham chorea may not necessitate symptomatic treatment, however, we treated all our patients like some physicians, even mild ones [15,27]. If the chorea is moderate to severe, and gait is affected, treatment may be more warranted. We preferred haloperidol for most of our patients as it is a very effective treatment. Although haloperidol which is a typical antipsychotic, have side effects of dystonic reaction, somnolence, tardive dyskinesia, and parkinsonism; biperiden is used to correct these extrapyramidal side effects of haloperidol [28]. As patients with Sydenham chorea are thought to be more vulnerable to the extrapyramidal side effects of typical antipsychotics than patients with other causes of chorea, [29] a low dose of biperiden has been given simultaneously to patients with haloperidol in the present study. We had one patient with the side effect of parkinsonism without any dystonia who was taking haloperidol at a dose higher than our regular use. Other treatment options are valproic acid or carbamazepine [30]. Anti-inflammatory/immunomodulatory therapies (e.g., glucocorticoids, IVIG) are restricted to patients with severe chorea who have failed other modes of treatment [31].

The widespread use of echocardiography has provided a way to diagnose carditis even in the absence of overt clinical findings, defined as subclinical carditis; the 2015 revision of the Jones criteria emphasizes the era of Doppler echocardiography [3]. Clinical carditis occurred in 37.5% of our patients with a new diagnosis of ARF who had Sydenham chorea as a major criteria; while the rest of our patients had subclinical carditis. In the literature subclinical carditis has been reported in 0%-53% patients with ARF [32]. With regard to patients specifically with Sydenham chorea, clinical and subclinical carditis has been reported in 31% and 50% of patients, respectively [33]. Anti-inflammatory treatment of carditis has been traditionally performed to prevent permanent sequelae; however, the 2003 Cochrane systematic review of clinical trials found that neither aspirin nor anti-inflammatory corticosteroid treatment improved cardiac outcomes at one year after diagnosis [34]. In 2015, the same group reported that in clinical trials, little benefit was shown from the use of anti-inflammatory treatments for carditis [35]. In Turkey, ARF is the most common cause of valvular heart disease [36]. In the present study, we preferred to treat patients with carditis showing inflammation with corticosteroids as many physicians have done [37] with the hope of preventing a major cause of morbidity and mortality in the young population.

Although its retrospective nature, small number of patients, and short duration of follow-up were limitations of our study. Besides, we reported from a single center and from a relatively short duration of time with detailed patient features.

Conclusion

While investigating Sydenham chorea as the most common cause of pediatric chorea, we retrospectively evaluated patients with an initial diagnosis of chorea in the present study. Giving more importance to cardiac findings, laboratory test results were also analyzed. The differential diagnosis of chorea should be kept in mind in patients diagnosed with Sydenham chorea, especially when there is a recurrence. Hemichorea should not be missed, as weakness in one side may be present rather than a movement disorder. Haloperidol is still an important treatment option for Sydenham chorea, although it has significant side effects, particularly with high doses. Recognizing Sydenham chorea, a disease once thought to have disappeared in the modern world, is significant in the diagnosis of acute rheumatic fever. Conduction of further prospective studies examining its incidence, host factors, chorea-specific treatments, preventive strategies, and outcomes in children with Sydenham chorea is required.

Ethics Committee Approval: This study was approved by the ethical committee of Health Sciences University Okmeydanı Research and Training (31.03.2020 / 112).

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Original Article

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The Overall Distribution of ABO and Rh (D) Groups in The Most Populous City Istanbul as Representing the Complex Ethnicity of Turkey

Türkiye'nin Karmaşık Etnik Kökenini Temsil Eden İstanbul'da ABO ve Rh (D) Gruplarının Dağılımı

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ABSTRACT

Objective: *In humans, 38 different critical blood type classification systems are currently recognized. They differ in frequencies in distinct populations. It is aimed to visualize ABO and Rh(D) groups distribution in Istanbul as having the largest community in Turkey.*
Method: *Volunteered blood donor's data on the automation system were screened retrospectively. Blood donation acceptance criteria were based on the guidelines prepared by the Ministry of Health. ABO and Rh(D) groups were analyzed using column agglutination/gel centrifugation methods.*
Results: *The study covered six years' data between the dates of January 2014 and December 2019, including 136,231 donors. The majority of the donors were found to have blood group A with a frequency of 41.88%(n=57,059). The second most common blood group was group O, and had a frequency of 34.92%(n=47,576). The blood group B (n=20,790;15.26%) and group AB (n=10,806;7.93%) were found to be the rare encountered blood groups. Among the Rh(D) group, 85.02% of the donors were Rh(D) positive.*
Conclusion: *In transfusion medicine, ABO and Rh(D) groups' compatibility is mandatory. According to the monthly and or annual blood products requirement, there are some suggested quantities of blood units to be available at blood centres. Determining the frequency of blood group distribution of populations will help to coordinate the ratio of blood groups to be storaged. The Turkish genetic makeup is a fascinating mixture of European and Asian DNA, necessitates to find out the countries' specific ABO and Rh(D) groups ratio. We compared our results with the previously reported studies performed in different cities of Turkey and the world around. Thus, our research as giving the overall distribution of ABO and Rh(D) groups from the largest city of Turkey reflecting the general ethnic background of the country, would help to the establishment of a databank of ABO and Rh(D) group's ratio.*

Keywords: *ABO, Rh, blood group, blood donor, Turkey, Istanbul*

ÖZ

Amaç: *İnsanda 38 farklı kan grubu sistemi tanımlanmıştır. Kan grupları farklı popülasyonlarda farklı sıklık gösterir. Çalışmamızda Türkiye'nin en fazla nüfusa sahip ili İstanbul'da ABO ve Rh (D) gruplarının dağılımını belirleyerek Türkiye'yi temsilen kan grubu dağılımını öngörmek hedeflenmektedir.*
Yöntem: *Gönüllü kan bağışçılarının verileri hastane kan merkezi otomasyon sisteminden geriye dönük olarak tarandı. Kan bağışçısı kabulü Sağlık Bakanlığı tarafından hazırlanan kılavuzlar doğrultusunda yapılmıştır. ABO ve Rh (D) grubu tayini kolon aglütinasyon / jel santrifügasyon yöntemi kullanılarak analiz edildi.*
Bulgular: *Çalışma Ocak 2014 ve Aralık 2019 tarihleri arasında 6 yıllık dönemde kan merkezine başvuran 136.231 kan bağışçısını kapsamaktadır. Kan bağışçılarının çoğu A kan grubu % 41.88 (n = 57.059) oranında bulundu. İkinci en yaygın olarak O kan grubu idi, % 34.92 (n = 47.576) sıklıkta izlendi. B kan grubu (n = 20.790; % 15.26) ve AB grubu (n = 10.806; % 7.93) nadir görülen kan grupları olarak bulundu. Kan bağışçılarının % 85.02'si Rh (D) pozitifti.*
Sonuç: *Transfüzyon tıbbında ABO ve Rh (D) gruplarının uyumluluğu zorunludur. Aylık ve / veya yıllık kan ürünleri ihtiyacına göre, kan merkezlerinde önerilen bazı miktarlarda kan stoğu bulundurulur. Popülasyonların kan grubu dağılım sıklığının belirlenmesi, depolanacak kan gruplarının miktarının koordine edilmesine yardımcı olacaktır. Türkiye'de yaşayanların genetik yapısı, Avrupa ve Asya DNA'sının bir karışımıdır. Sonuçlarımızı, Türkiye'nin ve dünyanın farklı bölgelerinden farklı şehirlerde daha önce bildirilmiş çalışmalarla karşılaştırdık. ABO ve Rh (D) gruplarının ülkenin genel etnik kökenini yansıtan Türkiye'nin en büyük kentinden toplam dağılımını sağlamaya yönelik çalışmamız, ABO ve Rh (D) grubu dağılımı konusunda ülke veri bankasının oluşturulmasına yardımcı olacaktır.*

Anahtar kelimeler: *ABO, Rh, kan grubu, kan bağışı, Türkiye, İstanbul*

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INTRODUCTION

Erythrocyte blood group antigens are polymorphic, carbohydrate, or protein molecules located on the outer membrane of erythrocytes that transmit from generation to generation. These antigenic structures are also found in some cells other than erythrocytes, such as saliva, serum, tear, urine, and similar body secretions [1].

At the beginning of the twentieth century, Karl Landsteiner pointed out that the serum of certain people agglutinates the blood group system of ABO [2]. Later, his colleague Alexander S. Wiener described the Rh blood group system. The presence of one, both, or none of the A and B antigens in erythrocytes, constituted the ABO blood group system. The associated anti-A and anti-B antibodies are usually IgM antibodies, produced in the first years of life by sensitization to environmental substances such as food, bacteria, and viruses [2].

The five antigens D, C, c, E, are the most essential Rh blood group system antigens. An individual is typically described as Rh-positive when the Rh (D) antigen does exist on erythrocytes. In contrast, someone who lacks the Rh (D) antigen is referred to as Rh-negative [2]. The Rh (D) antigen is extremely immunogenic, and in the condition of exposure, IgG type anti-D develops [3].

The blood group systems are essential in many clinical aspects. ABO and Rh (D) blood group system must be investigated before transfusions, stem cell, and solid organ transplantations for safety. Besides that, there are some relationships between some blood groups and diseases [4].

The variations in the distribution of four distinct ABO blood groups, A, B, AB, and O, are worldwide [5-7]. The frequency of the three alleles of the ABO gene has been estimated in various populations. For example, blood group O is the most common blood type in Hispanic donors (a group of Mexican donors, Puerto Ricans, and Cubans) with a ratio of 57 percent [2]. Again, North American Indian and black donors had the highest proportions of blood group O i.e. 55%, and 50%, respectively [2,6].

The Turkish genetic background is a complex mixture of European and Asian DNAs [8]. Istanbul, with the largest population in the country,may reflect the broad ethnic diversity in Turkey.

In our study, it was aimed to identify the frequency of ABO and Rh (D) blood groups among blood donors. Our secondary goal was to find out whether there is a difference from previously reported studies, regarding mostly from restricted regions of the country and world around.

MATERIAL and METHODS

Volunteered blood donors admitting to our hospital Blood Center, were screened retrospectively. The study was conducted based on the data retrieved from the hospital automation system available between 01.01.2014 - 31.12. 2019.

Blood donation was accepted according to the National Blood and Blood Products Guide (2011) and the National Blood and Blood Components Preparation, Usage and Quality Assurance Guide (2016) prepared by the Ministry of Health [9, 10].

ABO and Rh (D) groups were analyzed using column agglutination/gel centrifugation methods (Ortho BioVue System, Ortho Clinical Diagnostics, Inc, Johnson&Johnson Company, Raritan, NJ, USA; Across, Dia Pro A.Ş, Gebze, Kocaeli, Turkey).

All donors gave their written consent with blood donor registration, information, and inquiry form and blood donor consent form.

Descriptive statistical methods determined the distribution of blood groups.

RESULTS

Data of 136,231 blood donors were screened. Most of the donors (93.27%) were male, as depicted in Figure 1.

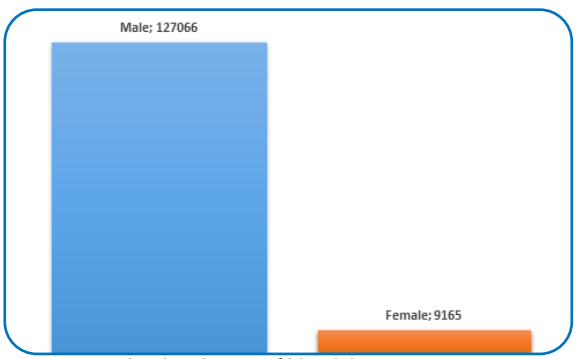

Figure 1. Gender distribution of blood donors.

More than half of blood donors were between the ages of 25 and 55 (Table 1).

Table 1. Distribution of blood donors by age and gender.

Age group (years)	Total (%)	Female (%)	Male (%)	M/F ratio
18-24	5.05	0.58	4.48	7.07
25-34	33.23	2.22	31.01	13.94
35-44	35.86	1.92	33.94	17.63
45-54	21.12	1.39	19.73	14.18
55-64	4.51	0.54	3.97	7.35
>65	0.22	0.01	0.21	15.00
Total		6.67	93.33	13.99

The majority of donors were found to be group A with a frequency of 41.88% (n=57,059). The second much common blood group was group O and had a distribution frequency of 34.92% (n=47,576). The blood group B (n= 20,790; 15.26%) and group AB (n=10,806; 7.93%) were proved to be more seldom encountered blood groups.

Among the Rh blood group, the majority of donors (n=115,819; 85.02%) were Rh (D) positive (Table 2).

Table 2. Distribution frequencies of ABO and Rh (D) among voluntary or referred donors in our blood centre.

Blood group	A	O	B	AB
n (%)	57.059 (41.88)	47.576 (34.92)	20.790 (15.26)	10.806 (7.93)
Rh positive	49.519 (36.35)	39.644 (29.10)	17.350 (12.74)	9.306 (6.83)

The distribution frequency of Rh positivity in ABO blood groups are given in Table 3.

Table 3. Distribution of Rh factor frequency with ABO blood groups.

	A		O		B		AB	
	Rh+	Rh-	Rh+	Rh-	Rh+	Rh-	Rh+	Rh-
n.	49.519	7.540	39.644	7.932	17.350	3.440	9.306	1.500
%	87	13	83	17	83	17	86	14

Distribution of blood groups , according to the gender of the donors is given in Figures 2a and 2b.

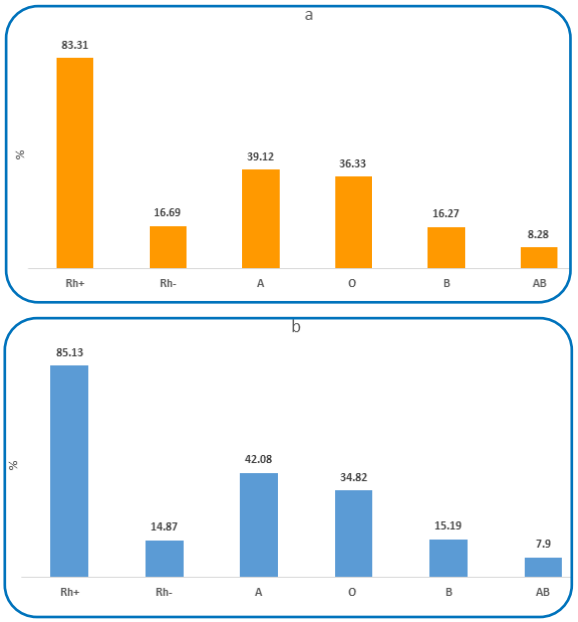

Figure 2. Percentage distribution of ABO Rh groups by gender a. Female donors, b. Male donors.

DISCUSSION

The gene determining the human ABO blood groups is located on chromosome 9 (9q34.1), and the product is called glycosyltransferase [5]. The gene has three primary alleles for blood groups A, B, and O. Each of the alleles contributes to different gene products. The alleles are inherited from parents which define the ABO blood antigens in different individuals and so in different populations [5].

Blood types of human beings may belong to ancient genetic indicators developing over several million years. However, it was assumed that the blood groups of three primary human races namely blood group A in Europe, B in Asia, and finally O in South America might point to eventual migration and race-mixing [5]. There are other theories. One of them put forward that blood groups A and B originated from a fundamental group of blood O. The second theory based on the assumption that the original blood group is AB and other blood groups A, B, and O emerged from this blood type due to various mutations [5].

Beyond genetic mutations, natural selection against environmental factors may also play in varied blood group distribution in different populations [5].

Determining the blood group distribution frequency of populations is primarily required for preparing a critical stock in blood centers. Another scientific issue is the

relationship of some disorders with blood groups, which may provide academic and epidemiological data. Indeed several studies are showing this correlation. The low risk of having heart disease in people with type O blood is an example. [1,11].

Intricate distribution patterns of ABO and Rh (D) groups around the world correlate with the assumption of the complicated evolutionary history of humanity. In general, the A blood allele is somewhat more common than the B group. The majority of the people in the world have Rh-positive blood type [12].

Studies are evaluating the relationship between blood groups and ethnicity from different countries [6,7,13] (Table 4). It is noteworthy that the blood group O in the American continent is with a frequency of 45% and above, and this rate reaches 50% in Native Americans and African Americans. Hispanic people also have mostly O blood type. The data from England, the country of the primary source of immigrants to the American continent, and from Germany, which could be used as a representative of Caucasians, showed that the distribution frequency of the blood group O is approximately 40% [12].

Table 4. Distribution of ABO and Rh blood groups in different countries around the world

Country	A (%)	O (%)	B (%)	AB (%)	Rh (%)	
Asia (China) [7]	30.50	30.40	29.40	9.70	**Rh+:**	98.98
					Rh-:	1.02
America reflecting Indians[6]	35.00	54.60	7.90	2.50	**Rh+:**	90.30
					Rh-:	9.70
America reflecting Caucasians[6]	39.70	45.20	10.90	4.10	**Rh+:**	82.70
					Rh-:	17.30
America reflecting Africans[6]	25.80	50.20	19.70	4.30	**Rh+:**	92.90
					Rh-:	17.10
England[14]	42	47	8	3	**Rh+:**	85.00
					Rh-:	15.00
Germany[15]	42.00	42.80	11.00	4.20	**Rh+:**	85.00
					Rh-:	15.00

Table 5. ABO and Rh blood group distribution reported from different regions of Turkey.

Region, city	Investigator	Study Group (n)	A (%)	O (%)	B (%)	AB (%)	Rh+ (%)	Rh- (%)	Publication Year
Turkey	Akbay T[18]	9,931	42.84	32.67	16.46	8.03	88.54	11.46	1989
Istanbul	Eren C[17]	123,900	43.82	33.79	15.21	7.16	87.31	12.69	2019
Istanbul	Salduz ZIY[16]	6,041	43.44	33.02	15.00	8.54	85.95	14.05	2015
Sanliurfa	Zerin M[19]	28,994	36.38	34.69	21.25	7.68	90.79	9.21	2004
Sivas	Dogan E[20]	99,207	43.80	31.80	16.40	8.00	87.00	13.00	2015
Sakarya	Cekdemir E[21]	13,116	44.30	35.70	12.50	7.50	84.90	15.10	2018
Thrace	Yaprak M[22]	6,777	45.95	31.05	16.54	6.46	87.66	12.34	1993
Diyarbakir	Temiz H[23]	206,673	40.81	33.66	18.53	6.98	89.17	10.82	2008
Diyarbakir	Arac E[24]	127,091	39.69	33.62	18.63	8.06	88.44	11.56	2019
Balıkesir	Alpdemir M[25]	128,862	42.70	30.70	18.20	8.40	89.00	11	2014
Cukurova, Adana	Yildiz SM[26]	136,038	38.90	37.10	17.00	6.90	89.90	10.10	2016
Denizli	Balci YI[27]	64,840	42.60	33.30	16.80	7.40	89.90	10.10	2010
Eastern Black Sea, Rize	Ozkasap S[28]	38,329	44.07	44.07	9.26	2.60	83.70	16.30	2013
Van	Akin G[29]	6,982	39.99	28.26	17.09	14.66	89.49	10.51	2005
Eastern Anatolia, Van	Dilek I[30]	33,193	43.80	30.80	16.20	9.20	85.00	15.00	2006
Van	Ciftci IH[31]	18,308	45.05	30.65	16.14	8.16	90.37	9.63	2004
Eastern Anatolia, Van	Ekinci O[32]	108,368	44.00	31.20	16.20	8.60	87.70	12.30	2019
Kayseri	Torun YA[33]	86,797	44.00	33.30	16.20	6.50	88.20	11.80	2012
Erzurum	Kocak AO[34]	27,587	46.11	31.62	14.77	7.50	86.01	13.99	2017
Yozgat	Kader C[35]	5,257	44.30	31.70	15.90	8.10	88.00	12.00	2014
Malatya	Kuku I[36]	65,277	41.21	37.23	14.99	6.56	89.30	10.70	2004
Gaziantep	Coskun Y[37]	33,317	40.01	35.09	18.10	6.80	81.90	9.10	1990
Malatya	Genc M[38]	2,500	39.32	41.28	13.36	6.04	89.04	10.96	1997
Istanbul (Our Study)	**Yanasik M**	**136,231**	**41.88**	**34.92**	**15.26**	**7.93**	**85.02**	**14.98**	

Turkey is a country of a mixture of different ethnic groups [8]. However, giving an overall distribution rate for ethnicity is not possible since from 1965 the ethnicity is not interrogated in the country. Istanbul is Turkey's most populous city. The diversity of Istanbul population reflects the ethnic heterogeneity of Turkey.

In two previously performed studies concerning the distribution of blood groups in Istanbul, Salduz et al. [16] and Eren [17] demonstrated that blood group A is the most encountered blood group in contrast to the American continent and/or the European population. Our study conducted with a greater number of individuals confirms that blood group A has the highest prevalence in Istanbul. (Table 5)

We evaluated all of the published Turkish studies regarding the distribution frequencies of ABO and Rh (D) blood groups. (Table 5). It was striking that in the population from a restricted region of the Anatolian cities, the frequency of blood group A was less than 40 percent [19,24,26,29,38]. Distribution pattern of blood groups in the population of these cities mainly reflects the geopolitical evolution in this region. Another remarkable result came from the Black Sea region [28], where the frequency of blood group O was more than 40% similar to the Caucasian and American population [6], which also points to a genetic mixture of the country.

In conclusion, the emergence and evolution of blood groups in humans have not been clearly elucidated yet. The ethnic colouration changed over time in Turkey related to a mass immigration problem in the past century, resulting in population displacement and marriages within different ethnic groups. This issue also creates some basis for local differences in the distribution frequency of blood groups among different regions.

Knowing the frequency of the ABO and the Rh blood type in the country, and also in cities with complex ethnical populations will make it easier to manage blood and blood product storage and to plan the donor acquisition programs. We believe that our study will contribute to our country's blood group database and world literature.

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Evaluation of the Depression, Anxiety Levels and Attitudes of Mothers of Children with Celiac Disease

Çölyak Hastalığı Olan Çocukların Annelerinin Depresyon, Kaygı Düzeyleri ve Tutumlarının Değerlendirilmesi

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ABSTRACT

Objective: *In celiac disease, a gluten-free diet is required for lifelong. Difficulties experienced by children with celiac disease can also negatively affect caregivers. The aim of this study is to evaluate the anxiety and depression of mothers having a child with celiac disease, and evaluate mothers' attitude towards their children.*
Method: *Thirty-six children with celiac disease, their mothers, and 36 healthy controls were included in the study. The Parent Attitude Research Instrument, State–Trait Anxiety Inventory, and the Beck Depression Inventory were completed by all mothers.*
Results: *The mothers of children with celiac disease had significantly higher scores in depression and state-trait anxiety than the mothers of the healthy children. Mothers of children with celiac disease had significantly higher scores in the attitude of over-parenting, authoritarian attitude and attitude of hostility and rejection than the mothers of healthy children.*
Conclusion: *This study revealed that having a child with celiac disease might have negative effects on mothers and their attitudes towards their children. Because of psychopathologic risks appropriate psychologic support should be provided for mothers.*

Keywords: *Çölyak hastalığı, çocuklar, annelerin tutumu, psikolojik durum*

ÖZ

Amaç: *Çölyak hastalığında ömür boyu glutensiz diyet gerekmektedir. Çölyak hastalığı olan çocukların yaşadığı zorluklar, bakım veren kişileri de olumsuz etkileyebilir. Bu çalışmanın amacı, çölyak hastası çocuğu olan annelerin kaygı ve depresyonunu değerlendirmek ve annelerin çocuklarına karşı tutumunu değerlendirmektir.*
Yöntem: *Otuzaltı çölyak hastası çocuk ve annesi ile 36 sağlıklı çocuk ve annesi çalışmaya dahil edildi. Aile hayatı ve çocuk yetiştirme tutumları ölçeği, durumluk sürekli kaygı envanteri ve Beck Depresyon envanteri tüm anneler tarafından doldurduldu.*
Bulgular: *Çölyak hastası çocukların annelerinin, depresyon ve kaygı düzeyleri, sağlıklı çocukların annelerine göre anlamlı yüksek saptandı. Aile hayatı çocuk yetiştirme tutum ölçeğinde, aşırı annelik, gereken ilgiyi gösterme, baskı ve disiplin alt boyutlarında, sağlıklı çocukların annelerine göre anlamlı oranda yüksek puan bulundu.*
Sonuç: *Bu çalışma çölyak hastalığının çölyaklı çocukların annelerinin yaşamları ve çocuklarına karşı tutumlarını olumsuz yönde etkileyebileceğini gösterdi. Çölyak hastalığı olan çocukların annelerinde psikopatolojik risk görülebileceğinden, annelere uygun psikososyal destek verilmelidir.*

Anahtar kelimeler: *Celiac disease, children, mothers' attitude, psychological state*

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INTRODUCTION

Celiac disease (CD) is a chronic disease caused by immunologic and environmental factors, primarily affecting small intestines and is usually observed in genetically sensitive people [1,2]. Abdominal pain-distention, diarrhea, vomiting, failure to thrive and constipation can be noticed in childhood, while short stature, puberty latency, aphthous stomatitis, refractory iron deficiency anemia, osteoporosis and dyspeptic complaints can appear during childhood and adolescence. Nowadays, the only treatment for celiac disease is a lifelong gluten-free diet [3,4].

During the course of chronic disease and the treatment process, both the children and their parents encounter many short- and long-term troubles [5-7]. Parents who have children with chronic illnesses may also more frequently develop mental problems. Taking care of a child with a chronic illness requires more effort when compared to taking care of a healthy child [8-10]. Overall, the literature suggests that the adaption to illness following diagnosis seems to be related to personal and familial characteristics [11,12].

There isn't sufficient data in the literature specifically examining maternal experiences of childhood celiac disease. The aim of the present study is to investigate how having a child with CD affects the anxiety, depression levels, and attitudes of mothers.

MATERIAL and METHODS

Study Population:
Children between the ages of 4-18, who were diagnosed with celiac disease (CD) according to the European Society for Paediatric Gastroenterology Hepatology and Nutrition diagnosis criteria [2], and their mothers were included in the study. Children with some other chronic disease and/or CD diagnosis with less than six months were excluded from the study.

Study participants were evaluated in detail with regard to the duration of gluten-free diet (GFD), compliance to the GFD and the factors that affect the compliance to the GFD. GFD compliance was evaluated according to the patients' and the mothers' verbal responses.

After the participants in the CD group were selected, a control group was formed. The healthy children with similar demographic features and their mothers were enrolled. They were selected randomly from the general pediatric outpatient clinic. The children and their mothers without any chronic complaints, chronic disease and psychiatric diagnosis were included in the control group. The sociodemographic data of mothers and children were recorded. Written informed consent was obtained from all mothers and their children who agreed to participate in the study.

This study was conducted in conformity to the Helsinki Declaration and approved by our local research ethics committee (04/08/2015; 20478486-184).

Child and Family Assessment Tools

Beck Depression Inventory (BDI):
The BDI measures physical, emotional, and cognitive symptoms noted during depression. In this study, this survey was completed by mothers and aimed to rate depressive symptoms in these respondents. Developed by Beck and colleagues in 1961 [13] this scale is a self-asessment inventory covering 21 symptom categories. The scores for each item vary from zero to three points. High total scores indicate a greater severity of depression. The validity and reliability study for this scale in Turkey was undertaken by Hisli [14].

State-Trait Anxiety Inventory (STAI):
The STAI is typically used to investigate anxiety levels. In this study, it was completed by mothers and aimed to understand anxiety symptoms in these individuals. Developed by Spielberger and colleagues in 1970 [15], the state anxiety scale measures how a person feels under certain conditions, at a certain point of time; while the trait anxiety scale evaluates how a person feels independently of the state and conditions they are in. The scores for each item vary from one point (not at all) to four points (very much). Higher scores indicate a higher level of anxiety, while lower points indicate a lower level of anxiety. The inventory was translated into Turkish and adapted in 1977 by Oner [14].

Parental Attitude Research Instrument (PARI):
To evaluate parental attitudes towards child-rearing,

the PARI scale was used. It was completed by mothers in the present study and sought to rate the child rearing attitudes of parents. The scale was developed in 1958 by Schaefer and Bell [16] and includes 60 items and five subscales. The answers given by mothers are stratified as follows: overprotective mother, democratic attitude, recognition of equality, rejecting the role of being a housewife, marital conflict and incompatibility, and strict discipline and pressure. It is a four-point Likert-type scale. All items are rated with a directly scored grade, except for items 2, 29, and 44. For each factor dimension, the scores are summed separately. An increase in points for all categories except "democratic attitude" indicates the presence of negative parental attitudes. The scale was adapted by Oner to Turkish in 1978 [14].

Statistical Analysis:

In this research, numeric variables were presented as means±standard deviations and categorical variables were presented as numbers and percentages. The distribution of the data was evaluated using the Kolmogorov-Smirnov method. Since the data demonstrated normal distribution, the chi-square test was used for categorical data, and a t-test for parametric data. Pearson correlation analysis was used to determine the relationships between continuous variables. A bidirectional hypothesis was established for the research and the results were evaluated within 95% confidence intervals, level of significance was established as $p<0.05$.

A sample size of 33 participants (per group) was determined to be necessary, based on a power of 80% and an effect size(d)=0.70 of $\alpha^2=0.05$.

Table 1. Socio-demographic features of study group.

	Celiac group n (%)	Healthy group n (%)	P
Gender			
Male	13 (36)	11 (30)	0.694
Female	23 (64)	25 (70)	
Employment status of the mothers			
Housewife	23 (64)	15 (42)	0.059
Worker	13 (36)	21 (58)	
Family structure			
Extended family	7 (19.4)	4 (11.1)	0.326
Nuclear family	29 (80.6)	32 (88.9)	

RESULTS

Thirty-six children with CD with a mean age of 12.0±3.6 years and 36 healthy children with a mean age of 11.6±3.4 years were recruited for this study (p=0.617). Five children with CD diagnosis with less than six months were not included. Sociodemographic features of the study group are shown Table 1. Twenty-one (58.3%) children with CD were accepted as non- adherent to GFD. The factors that may contribute to a difficulty in staying on a GFD were found to be unavailability of gluten-free foods at schools and restaurants (83.3%), difficulty in finding a variety of gluten-free foods for sale (61.1%), the bad taste of gluten-free foods (19.4%), lack of information on packages about gluten (47.2%), and giving up following the diet due to having no complaints and/or feeling healthy (27.8%).

The results of the BDI, STAI, and PARI surveys are shown in Table 2. The total scores of BDI and STAI scores indicating mothers' psychological symptoms were found to be statistically significantly higher in mothers of children with CD versus those in the control group, suggesting that mental complaints are more common in mothers of children with CD.

Table 2. Scores of Beck Depression Inventory, State and Trait Anxiety Inventory and Parental Attitude Research Instrument filled by mothers in the groups.

	Celiac group Mean±SD	Healthy group Mean±SD	P*
Beck depression inventory	9.79±8.56	4.74±6.18	0.007
State anxiety inventory	39.11±9.90	33.85±9.17	0.025
Trait anxiety inventory	43.84±9.68	38.54±8.24	0.018
Parental attitude research instrument			
Attitude of over-parenting	46.00±7.65	35.57±9.50	0.0001
Democratic attitudes	27.37±4.15	28.42±3.44	0.251
Attitude of hostility and rejection	31.57±8.25	27.60±7.30	0.037
Marital discordance	14.40±4.20	12.85±3.85	0.115
Authoritarian attitude	36.48±7.19	26.71±7.51	0.0001

**t test was applied. CD = celiac disease; SD = standard deviation.*

Regarding mean scores obtained in PARI survey a statistically significant intergroup difference was observed for excessive motherhood, rejecting the role of being a housewife, and strict discipline,.

The relationships between BDI, STAI, and PARI scores and the duration of illness were assessed without any significant correlation.

There was no significant difference regarding the BDI, STAI and PARI scores between patients who were and were not compliant with a GFD.

DISCUSSION

This study indicates that when it comes to maternal psychological well-being and mother's attitudes towards their own children, there were significant differences between the mothers of children with CD and mothers of healthy children. We found that the mothers of children with CD had significantly higher levels of depression, anxiety, excessive motherhood, rejecting the role of being a housewife, and strict discipline according to their mean scores.

Both children with chronic disease and their parents encounter many troubles besides the onset of such a disease and the process of treatment. A child's chronic illness may also influence parents' psychological adjustment. Many factors are likely to affect this situation such as the symptoms of the disease, frequent doctor visits, treatment processes, socioeconomic problems, adaptation to a certain diet, and inability to find an appropriate food for the diet. These reasons can cause distinction between studies. The study conducted in Turkey revealed no significant difference regarding anxiety and depression levels [17]. Another study conducted in Italy, parents of children with CD had higher parental stress than parents of healthy children [18]. In a study of children with CD and their parents, parents expressed different views and difficulties concerning the symptoms of the disease, the process of getting a diagnosis, regarding regulating the diet, difficulties experienced at school and the social environment regarding the diet, the supply of food appropriate for the diet, economic concerns and the difficulties might be faced in the future [19]. Another study reports that the parents of children with CD who complied with a prescribed diet had less concerns regarding the health of their children but higher concerns about the negative effects that the disease may have on the future of their children [20]. Previous studies showed that the well-being of the child is influenced by the psychosocial problems of their parents [21]. Parental psychosocial problems may have an effect on the physical health of the child with a chronic illness, in addition to influencing the psychosocial functioning of the child. Bartlett et al. have shown that the child's adherence to therapy is influenced by maternal depression [22]. Therefore, the mental assessment of parents is important.

Numerous studies have identified the importance of parenting behaviors to the well-being of children with chronic physical conditions [23]. The frequent observation of anxiety and depression symptoms in mothers may affect family functions and attitudes towards children. We found that mothers of children with CD had more problems in the subscale of the overparenting, attitude of hostility and rejection, and strict discipline categories of the PARI. Overparenting involves issues such as extreme control, intervention, asking the child to be dependent, the mother being extremely self-sacrificing and believing that the child should also acknowledge that. The mother showing an attitude of hostility and rejection is tense, worried, and angry. Oppression and discipline involves acts such as forcing certain rules on the child and believing in the absolute domination of the parents [24]. Studies have suggested that parents of children with chronic illnesses are overprotective, have less close and positive relations with their children, and that the severity of the chronic illness leads to more frequent protecting and controlling behaviors in the parents [25-27]. The more efficient parenthood helps to decrease behavioral problems of children. Behavioral adaptations increase in frequency when the child's and the family's quality of life rises and the worries of parents lessen [11].

Our study has some limitations that need to be acknowledged. The accuracy of our findings may not be reflected by the small sample size. Larger-scale studies comparing different chronic diseases (diabetes mellitus type 1) are needed to strengthen and increase meaningfulness of the study. This study included mothers without known psychiatric illness. However, the fact that the psychiatric evaluations of the mothers were not known in the period before children were diagnosed with CD was another limitation of the study. Additionally, data collection from other countries may help to identify whether any cultural differences affect childrens' behaviours, adherence rate for the GFD, contrubuting factors to maintain the GFD, and parental attitudes.

Conclusion

The mothers have a major influence on the well-being and adjustment of their children, and play an important role in adaptation of their child to living with an illness. In the literature, there is a gap specifically when it comes to examining maternal attitudes towards children with CD. Thus, the results of our study is precious for the literature. In addition, determining psychological conditions such as anxiety and depression in the mothers of children with CD who require special diet and care is important for the management of the disease. Consequently the children with CD and their mothers should be provided with psychological assessment and support during diagnosis and follow-up.

Ethics Committee Approval: Celal Bayar University Clinical Research Ethics Committee approval was received (08/04/2015; 20478486-184).

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

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Comparıson of the Effects of On-Pump and Off-Pump Techniques on the Quality of Life in Coronary Artery Bypass Surgery

Koroner Arter Baypas Cerrahisinde On-Pump ve Off-Pump Tekniklerinin Yaşam Kalitesi Üzerine Etkisinin Karşılaştırılması

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ABSTRACT

Objective: *In this study, we aimed to compare the effects between on-pump and off-pump coronary artery bypass surgery on the effect of quality of life.*
Methods: *Fifty patients who underwent isolated coronary artery bypass (CABG) between 01.08.2012 - 31.01.2013 were divided into two equal groups (group 1: off-pump CABG; group 2: on-pump CABG). The quality of life of all patients was evaluated using the SF-36 questionnaire in the postoperative first week and first month (8 basic parameters in SF-36 questionnaire form: Physical function, pain, physical role, mental health, emotional role, social function, fitness / fatigue, general health)*
Results: *One week after CABG surgery, physical function, physical role, social function and emotional role were significantly better in group 1 than group 2 (p <0.05). There was no statistically significant difference between the two groups in terms of quality of life, one month after CABG surgery (p> 0.05). Physical function was significantly better in female gender one week after CABG (p <0.05). There was no difference between the two genders in terms of quality of life after one month (p> 0.05).*
Conclusion: *We think that CABG performed off-pump in order to avoid from negative effects of cardiopulmonary bypass has no significant effect on the quality of life of the patients in the postoperative period. Nevertheless, in order to get a clearer idea on this issue, we think that large series studies should be conducted with a higher number of patients.*

Keywords: *coronary artery bypass surgery, life quality, SF-36 form*

ÖZ

Amaç: *Bu çalışmada çalışan kalpte yapılan koroner arter bypass (off-pump) ile kardiyopulmoner bypass altında yapılan koroner arter baypasın (on-pump) yaşam kalitesi üzerine etkisini karşılaştırmayı amaçladık.*
Metod: *Bu çalışmada 01.08.2012 - 31.01.2013 tarihleri arasında izole koroner arter bypas (KABG) yapılan 50 hasta, iki eşit gruba ayrılarak çalışmaya alındı (grup 1: off-pump KABG; grup 2: on-pump KABG). Grupların yaşam kalitesi SF-36 anket formu kullanılarak KABG ameliyatından 1 hafta ve 1 ay sonra değerlendirildi (SF-36 anket formunda ki 8 temel parametre: Fiziksel fonksiyon, ağrı, fiziksel rol, mental sağlık, emosyonel rol, sosyal fonksiyon, zindelik/yorgunluk, genel sağlık).*
Bulgular: *KABG ameliyatından 1 hafta sonra grup 1'de fiziksel fonksiyon, fiziksel rol, sosyal fonksiyon ve emosyonel rol grup 2'den anlamlı olarak daha iyiydi (p<0.05). 1 ay sonra yaşam kaliteleri açısından iki grup arasında istatistiksel olarak fark bulunmadı (p>0.05). KABG'den 1 hafta sonra fiziksel fonksiyon kadın cinsiyetinde anlamlı olarak daha iyiydi (p<0.05). 1 ay sonra yaşam kalitesi açısından iki cinsiyet arasında fark bulunmadı (p>0.05).*
Sonuç: *Kardiyopulmoner baypas'ın olumsuz etkilerinden kaçınmak için çalışan kalpte yapılan koroner arter baypasın postoperatif dönemde hastaların yaşam kalitelerinin iyileşmesinde anlamlı bir katkısının olmadığını düşünüyoruz. Yine de bu konuda daha net fikir elde edebilmek için hasta sayısının çok daha fazla olduğu geniş serili çalışmaların yapılması gerektiğini düşünüyoruz.*

Anahtar kelimeler: *Koroner arter baypas cerrahisi, yaşam kalitesi, SF-36 formu*

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INTRODUCTION

Coronary artery disease (CAD) is one of the important diseases affecting the quality of life and one of the most preferred treatment methods is coronary artery bypass (CABG) surgery [1]. Currently, coronary bypass surgeries are still commonly performed with traditional sternotomy by using cardiopulmonary bypass (on-pump) or with the beating heart technique without using cardiopulmonary bypass (off-pump).

On-pump CABG has become the preferred treatment method for patients with multiple vascular diseases. On-pump CABG is both safe and effective. However, the use of cardiopulmonary bypass causes many undesirable side effects [2]. This affects the quality of life after the operation.

In recent years, off-pump CABG has been the focus of attention. The aim of off-pump CABG is to refrain from cardiopulmonary bypass completely and to avoid the side effects it will cause [3]. This surgical technique is thought to improve the postoperative quality of life of the patients.

Although there are many publications in the literature comparing off-pump and on-pump CABG methods in terms of mortality and morbidity, there are few studies comparing these two surgical techniques in terms of quality of life. In this study, we aimed to prospectively compare the effects of on-pump CABG and off-pump CABG surgery on quality of life.

MATERIAL and METHODS

Approval was obtained from Uludağ University Medical Research Ethics Committee for our study (approval number: 2012-17/6). Fifty patients who underwent isolated CABG operations in Uludağ University Medical Faculty Cardiovascular Surgery Clinic between 01.08.2012-31.01.2013 were included in the study.

Literate and ambulatory patients under 80 years of age who had ejection fraction over 30%, without valve disease, and underwent elective coronary bypass surgery were included in this study. Illiterate nonambulatory patients older than 80 years of age with an additional valvular disease, and an ejection fraction of less than 30%, who were urgently operated were excluded from the study. Patients were divided into 2 groups, as those undergoing off-pump (n=25:Group 1) or on-pump CABG (n=25: Group 2)

The quality of life of the patients was evaluated by using the SF-36 questionnaire in the first postoperative week and the first postoperative month. SF-36, also known as Short Form 36, is a quality of life questionnaire developed by the Rand Corporation in 1992 [4]. The reliability and validity studies of the Turkish version of SF-36 were conducted by Koçyigit, et al. [5]. The SF-36 test also provides important information on patients undergoing cardiac surgery [6]. The SF-36 evaluates the person's quality of life with eight sub-parameters:

- Physical function (10 question)
- Pain (2 question)
- Physical role (4 question)
- Mental health (5 question)
- Emotional role (3 question)
- Social function (2 question)
- Fitness/fatigue (4 question)
- General health (5 question)

SF-36 scale provides self-assessment. The scores range from 0 to 100, separately for each subscale. The higher the scores, the higher the quality of life.

Statistical Analysis

In the statistical analysis of the data, the SF-36 scale scores were expressed as median (minimum-maximum) values. Scale reliability was examined with the Cronbach alpha coefficient. In the intergroup comparisons of subscale total scores, the differences in the scores obtained at the end of the first month relative to the scores of the first week were calculated and the difference scores obtained were compared using the Mann-Whitney test. The Wilcoxon rank sum test was used for within-group comparisons. Analyses of the study were made using the SPSS 20.0 program and $p < 0.05$ was considered statistically significant.

RESULTS

Fifty patients were included in the study. Nine female and 16 male patients underwent on-pump CABG surgery in Group 1 and 3 female and 22 male patients in Group 2 had off-pump CABG surgery.
No statisticaly significant difference was present between both groups in terms of comorbidity and age ($p > 0.05$).

In Group 1, one week after surgery, physical function, physical role, social function and emotional role were significantly better than in Group 2 (p <0.05). There was no significant difference between the two groups in terms of pain, general health, mental health and fitness / fatigue (p> 0.05) (Table-1 and Figure-1).

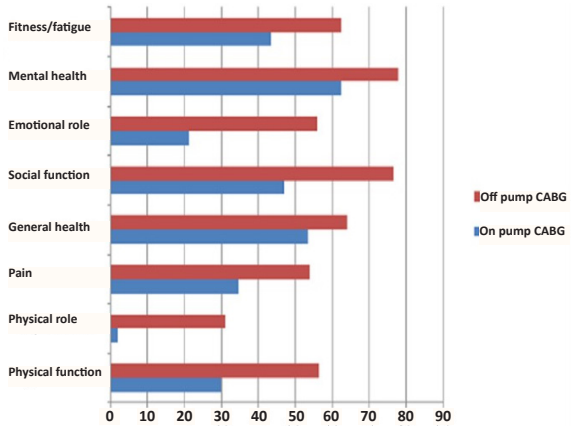

Figure 1. Comparison of the quality of life of the off-pump CABG group and the on-pump CABG group one week after surgery.

In Group 1, one month after surgery, physical role was significantly better than in Group 2 (p <0.05). There was no significant difference between the two groups in terms of social function, emotional role, mental health, fitness / fatigue, physical function, pain and general health (Table-1).

In the first postoperative week, the female gender was significantly better than men in terms of physical function regardless of the surgical technique used (p <0.05). There was no significant difference between men and women in terms of physical role, pain and general health, social function, emotional role, mental health and fitness / fatigue (p> 0.05). Regardless of the surgical technique used, there was no significant difference between men and women in terms of quality of life in the first postoperative first month (p> 0.05).

DISCUSSION

In our study, although the quality of life of the group with off-pump CABG surgery was better than that of the group with on-pump CABG surgery in the first postoperative week, there was no difference between the two techniques in terms of quality of life of the patients in the first postoperative month.

In the study conducted by Immer et al. with 504 patients (on-pump CABG, n=438 and off-pump CABG, n=66) using the SF-36 form, off-pump CABG patients were significantly better than on-pump CABG patients in physical role/function and emotional role/function after an average of 10.8 months. In this study, it was found that emotional role/function decreased significantly in off-pump CABG patients and physical and emotional role/function in on-pump CABG patients compared to the normal population [7].

Table 1. Comparison of the quality of life between groups one month and one week after coronary bypass surgery.

	Group 2			Group 1				
	1.week	1.month	Point difference	1.week	1.month	Point difference	p^1	p^2
Social function	45 (10-100)	70 (12.50-100)	22.50 (-42.50-60)	67.50 (22.50-100)	90 (20-100)	10 (-80-65)	0.014	0.131
Emotional role	33.33 (0-66.67)	0 (0-0)	-33.33 (-66.67-0)	33.33 (0-100)	0 (0-100)	-33.33 (-100-33.33)	0.008	0.084
Mental health	72 (16-92)	80 (20-96)	4 (-20-76)	76 (28 -100)	84 (20-92)	8 (-60-64)	0.325	0.521
Fitness/ Fatigue	45 (5-85)	65 (20-90)	15 (-35-60)	60 (20-95)	75 (15-90)	15 (-50-65)	0.073	0.992
Physical function	20 (0-60)	55 (10-90)	30 (0-70)	45 (0-70)	75 (30-90)	25 (-5-80)	0.003	0.876
Physical role	0 (0-75)	0 (0-0)	0 (-75-0)	0 (0-100)	0 (0-100)	0 (-100 -100)	0.011	0.024
Pain	32.5 (0-100)	77.50 (0-100)	22.50 (-10-90)	55 (10-100)	87.50 (20-100)	22.50 (-70-90)	0.061	0.545
General health	60 (10-100)	65 (10-95)	5 (-30-45)	60 (30-100)	80 (50-100)	15 (-20-50)	0.695	0.073

p^1: Comparison of scale scores obtained at the end of the first week between groups
p^2: First month as a result of taking the differences of the scale scores obtained at the end of the first week scores comparison of calculated difference scores.

In the study conducted by Kapetanakis et al. with 191 patients (off-pump CABG, n=116 and on-pump CABG, n=75) using the SF-36 form, there was no difference in terms of quality of life 6 months after on-pump and off-pump CABG. The expected quality of life in patients with multi-vessel coronary artery disease and hypertension was similarly worse in both groups. Six months after CABG, physical component scores of quality of life increased in diabetic patients [8]).

In a study conducted by Lindsay et al. in Scotland, the SF-36 questionnaire was applied to 214 patients about 4 weeks before and one year after CABG surgery, and it was determined that there was a significant improvement in the physical role, but less in the physical role of the SF-36 scores of patients who were clinically well postoperatively, [6]. Differently, we divided the patients into on-pump and off-pump groups in our study. We did not evaluate the preoperative quality of life with the SF-36 form. When we looked at the difference in one-month and one-week quality of life scores within the on-pump CABG and off-pump CABG groups, we found that the quality of life increased in both surgical techniques.

In the study conducted by Angelini GD, et al., no difference was found between the groups in terms of mortality, morbidity and quality of life due to cardiac causes 6 to 8 years after on-pump CABG and off-pump CABG [9]. In the study by Ascione R et al. involving 328 patients (on-pump CABG, n=159 and off-pump CABG, n=169), general and disease-specific quality of life after two to four years postoperatively was similar in both groups [10].

In our study, similar to the above studies, it was found that there was no significant difference between off-pump and on-pump CABG one month after surgery in terms of other subscales of quality of life, except for physical role. In our study, unlike these studies, physical function, social function, physical role, emotional role were significantly better one week after the operation in off-pump CABG than in on-pump CABG.

In the study by Herlitz et al., in which they evaluated the quality of life of patients who underwent CABG, they stated that the 3 factors that negatively affect the quality of life 5 years after CABG were female gender, diabetes and chronic obstructive pulmonary disease [11]. In our study, regardless of the surgical technique, one week after CABG, physical function was better in the female gender group than in men and one month later, no significant difference was found in the quality of life subscales in both gender groups.

Conclusion

As a result, although there was a more significant increase in the quality of life of the patients one week after off-pump CABG compared to on-pump CABG, no significant difference was found after one month. One week after CABG, it was determined that physical function was significantly better in women than in men, while there was no significant difference in quality of life in terms of gender after one month. We think that off-pump CABG performed to avoid the negative effects of cardiopulmonary bypass does not significantly contribute to the improvement of the patient's quality of life in the postoperative period. Nevertheless, we think that large-series studies with a much higher number of patients should be conducted in order to obtain a clearer idea on this subject.

Ethics Committee Approval: Approval was obtained from Uludağ University Medical Research Ethics Committee for our study (approval number: 2012-17 / 6)

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

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Informed Consent: Written consent was obtained from all patients participating in the study.

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Original Article

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Endoscopy-Assisted Laparoscopic Resection for Gastric Submucosal Tumors Located Within 5 cm Away from The Esophagogastric Junction; Combined Surgery at Difficult Localization

Özofagogastrik Bileşkeye 5 cm Yakınlıkta Yerleşen Mide Submukozal Tümörlerde Endoskopi Destekli Laparoskopik Rezeksiyon; Zor Lokalizasyonda Kombine Cerrahi

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ABSTRACT

Objective: *Removal of the lesion with safe surgical margins is often sufficient including GISTs. Endoscopic resections can become challenging or impossible if the tumor is located near esophagogastric junction. Performing gastrectomy for these mostly benign lesions will also be a rather overtreatment method in most cases.Therefore, alternative minimal invasive resection techniques and their reliability should be evaluated.*
The aim of this study is to evaluate the efficacy and safety of endoscopy-assisted laparoscopic transgastric resection method in proximally located submucosal tumors.
Method: *Transgastric combined endoscopic and laparoscopic surgery (CELS) using an intragastric port was performed in one patient and transgastric CELS with gastrotomy was performed in six patients who had tumor located near esophagogastric junction at Ankara City Hospital between February 2019 and February 2020.*
Results: *Three male, and 4 female patients with an average age of 45.8 years (range 25-70) were included in the study. In five of the cases, four ports and Nathanson retractor were used for liver retraction. Three ports were used in one patient, and the stomach was suspended with traction suture. In one patient, 5 ports were used. The average operation time was 88 minutes (range 59-140 min). While gastrostomy line was closed with linear stapler in two patients, laparoscopic suturing method was used in the remaining patients. Intraoperative complication was not seen in any patient.*
Conclusion: *We are in the opinion that the laparoscopic transgastric resection approach for submucosal tumors close to the gastroesophageal junction, is a feasible and safe method, when used in combination with endoscopic guidance.*

Keywords: *Esophagogastric junction, gastric submucosal tumors, transgastric combined endoscopic and laparoscopic surgery.*

ÖZ

Amaç: *Submukozal tümor güvenli cerrahi sınırlar ile lezyonun çıkarılması genellikle GIST'ler dahil olmak üzere yeterlidir. Endoskopik rezeksiyonlar, tümör özofagogastrik bileşkenin yakınında bulunduğunda zor veya imkansız hale gelebilir. Çoğunlukla iyi huylu bu lezyonlar için gastrektomi yapmak gereğinden fazla bir tedavi yöntemi olacaktır, bu nedenle alternatif minimal invaziv rezeksiyon teknikleri ve bunların güvenilirliği değerlendirilmelidir. Bu çalışmanın amacı, proksimal yerleşimli submukozal tümörlerde endoskopi yardımlı laparoskopik transgastrik rezeksiyon yönteminin etkinliğini ve güvenliğini değerlendirmektir.*
Yöntem: *Şubat 2019 - Şubat 2020 tarihleri arasında Ankara Şehir Hastanesi'nde özofagogastrik bileşke yakınında submukozal tümörü olan hastalardan 1'ine intragastrik port ile transgastrik kombine endoskopik ve laparoskopik cerrahi (CELS), diğer 6 hastaya gastrotomi ile Transgastrik CELS uygulandı.*
Bulgular: *Yaş ortalaması 45,8 yıl (25-70 aralığında) olan 3 erkek ve 4 kadın hasta çalışmaya dahil edildi. Vakaların beşinde, karaciğer retraksiyonu için dört port ve nathanson retraktörü kullanıldı. Bir hastada üç port kullanıldı ve mide traksiyon sütürü ile askıya alındı. Bir hastada 5 port kullanıldı. Ortalama operasyon süresi 88 dakika (dağılım 59-140 dakika) idi. İki hastada gastrostomi hattı lineer stapler ile kapatılırken, kalan hastalarda laparoskopik olarak sütütrasyon sağlandı. Hiçbir hastada intraoperatif komplikasyon görülmedi.*
Sonuç: *Gastroözofageal bileşkeye yakın submukozal tümörler için laparoskopik transgastrik rezeksiyon yaklaşımının endoskopi ile birlikte kullanıldığında uygulanabilir ve güvenli bir yöntem olduğu kanaatindeyiz.*

Anahtar kelimeler: *Özofagogastrik bileşke, mide submukozal tümörler, transgastrik kombine endoskopik ve laparoskopik cerrahi.*

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INTRODUCTION

With the increasing use of upper gastrointestinal endoscopy, the incidence of tumors detected incidentally in the stomach has increased gradually. Some of these tumors are gastric submucosal tumors and have a wide range from ectopic pancreatic tissue to gastrointestinal stromal tumors (GISTs). Since these tumors are located under a normal mucosa, it is not possible to differentiate them endoscopically. However, these tumors can be distinguished from each other by immunohistochemical evaluation and pathological examination [1] but bite biopsy often does not give reliable results. Although most of these tumors have benign behavior and asymptomatic, it should be remembered that some of them may be malignant like some GISTs and leiomyosarcoms. Therefore, some algorithms have been proposed regarding the management of these tumors. While these algorithms state that asymptomatic lesions smaller than 2 cm can be followed endoscopically, they suggest that biopsy-proven GISTs should be removed regardless of size [2]. Resection is also recommended for symptomatic lesions, lesions bigger than 2 cm or those showing potential for malignancy during follow-up.

Gastric submucosal tumors grow inside the gastric wall and rarely cause lymph node metastasis. Therefore, removal of the lesion with safe surgical margins is often sufficient including GISTs [3]. In addition to endoscopic resection techniques, various techniques have been described where the tumor needs to be surgically removed. Gastrectomy, gastric wedge resection (exogastric), transgastric resection or transluminal (intragastric) resection are some of these techniques [4]. One of these surgical techniques can be selected for the patient depending on the location and size of the tumor and these resections can be performed by open or laparoscopic method. However, the known advantages of the laparoscopic method have been accepted by many surgeons, so it is more preferable today [5].

In tumors located in the proximal region of the stomach (cardia, fundus) resection can be a bit challenging. Wide resections may cause stenosis due to the presence of the esophagogastric junction and thus pose a risk. Endoscopic resections can become challenging or impossible even if endoscopy can be confronted with a tumor mostly in retroflection position. Performing gastrectomy for these mostly benign lesions will also be a rather brutal treatment method in most cases. Therefore, alternative minimal invasive resection techniques and their reliability should be evaluated.

The aim of this study is to evaluate the efficacy and safety of endoscopy-assisted laparoscopic transgastric resection method in proximally located submucosal tumors.

MATERIAL and METHODS

A retrospective review of all patients undergoing endoscopy- assisted laparoscopic surgery for gastric submucosal tumors located near esophagogastric junction at Ankara City Hospital between February 2019 and February 2020 was performed. All consecutive cases were identifed using the prospectively maintained surgical database. Patient, operative, and tumor characteristics were obtained via chart review. Operative notes and preoperative imaging modaliites were also reviewed. Since it is a retrospective evaluation, only operation consent was obtained from the patients before the procedure.

All patients were diagnosed by endoscopy and after that computed tomography (CT) and endosonographic ultrasound (EUS) were performed for differential diagnosis. The surgical decision was made as stated above, in accordance with the recommendations of the guidelines. The patient's own decision was also taken into consideration.

Endoscopy and laparoscopy teams worked together in the operating room and all cases were operated by the same surgical team. Transgastric resection was performed either through a gastrostomy incision or using intragastric ports;

Combined endoscopic and laparoscopic transgastric surgery (CELS) using intragastric ports: First, the abdomen was entered using the Hasson technique, and a 10 mm port was inserted through the umbilicus. The stomach was inflated with the endoscope and one 12 mm- and two 5 mm- ports were inserted into the abdomen to provide an endoscopic image of the larger curvature. Using an extra 5 mm port, jejunum was clamped from the distal to Treitz ligament with non-crushing forceps and thus preventing air leakage into

the intestines. A total of five ports were used. Gastrotomy was performed with cautery, then stomach was hung on the abdominal wall with 3/0 silk sutures and the ports inserted directly into the stomach. Stomach was then explored with 5 mm camera. The mass located in the proximal part was detected using endoscopic guidance, suspended with laparoscopic forceps, then resected with white cartridge endo-GIA stapler (Endocutter 60 staple, white cartridge;Ethicon Endo-Surgery) and the specimen removed with an endoscopic mesh basket. Port sites on the stomach were closed with 3/0 PDS and 3/0 prolene (Figure 1).

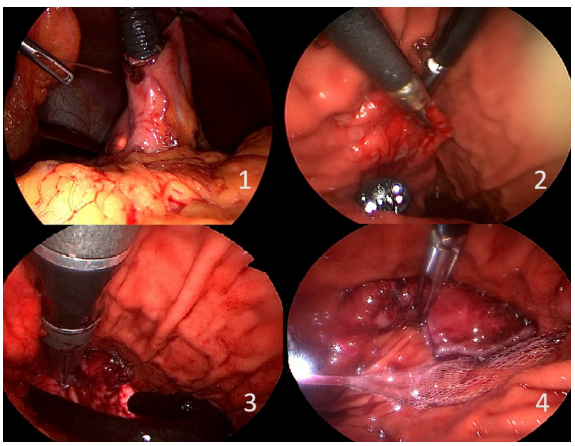

Figure 1. Transgastric combined endoscopic and laparoscopic surgery (CELS) with intragastric port (1-intragastric port placement and traction of the stomach to the abdominal wall with a suture; 2- The mass located in the proximal part is detected by endoscope guidance and hung with laparoscopic forceps; 3- Mass resected with white cartridge laparoscopic stapler ; 4- The specimen removed with an endoscopic mesh basket)

Transgastric CELS with gastrotomy: A 12 mm port was inserted from the left side of the umbilicus with the Hasson technique.

A 5 mm port was inserted from the upper right and a 10 mm port from the upper left quadrant. In one case, the stomach was hung on the abdominal wall with traction suture. In subsequent cases, the subcostal 5mm assistant port and the subxiphoid Nathanson retractor were used. The stomach was examined by endoscope and the mass in the cardia was detected and the gastrotomy line identified. Stomach was opened anteriorly with cautery or ligasure from the proximal corpus. The mass on the cardia was tractioned with forceps and resected with white cartridge endo-GIA stapler. The gastrotomy line was closed with green endo-gia stapler (Endocutter 60 staple, green cartridge; Ethicon Endo-Surgery) in the first two cases. Subsequent cases were closed with double layer sutures.

All tumors were processed and analyzed by the same pathologist. Stromal tumors were routinely subjected to immunohistochemical analysis to distinguish leiomyoma and GIST (CD117, CD34, smooth muscle actin, desmin, S-100, and MIB-1/Ki-67). Tumors were evaluated for histologic features, size, grade, and surgical margins (Figure 2).

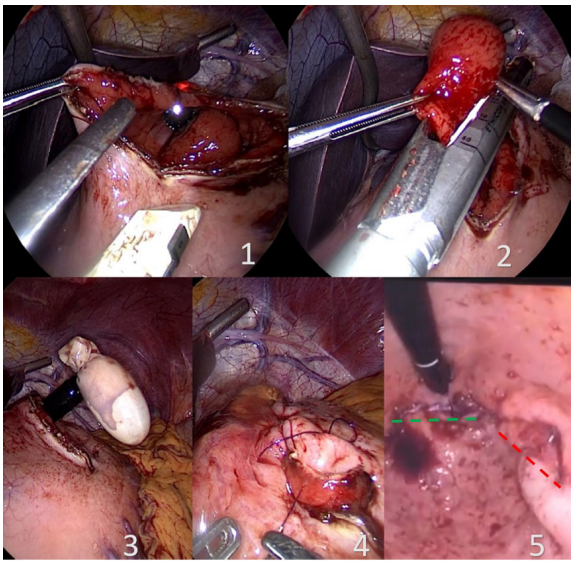

Figure 2. Transgastric CELS with gastrotomy (1- Stomach is opened anteriorly with cautery or ligasure from the proximal corpus; 2- The mass on the cardia is tractioned with forceps and resected with white cartridge laparoscopic stapler; 3- After the specimen was put in the finger of the glove, it was removed with endoscopy by holding it with snare; 4- The gastrotomy line was closed with double layer sutures; 5- Endoscopic visualition of the resection margine (green dotted line) and visualization of the gastrostomy line (red dotted line)

RESULTS

Three male and 4 female patients with an average age of 45.8 years (range 25-70) were included in the study. Three of the cases described dysphagia-like symptoms, while one had epigastric pain. One patient was detected while investigating the etiology of anemia. In the other two patients, the lesion was detected incidentally. Only three patients had preoperative comorbidities (hypertension, chronic obstructive pulmonary disease, coronary artery disease). None of the patients had a previous history of abdominal surgery.

All submucousal lesions were detected with gastroscopy. EUS was performed to six of the patients preoperatively and only three patients underwent CT examination. All of the tumors were in the localization less than

3 cm from the esophagogastric junction. This distance was evaluated during endoscopy. Gastroscopies were performed by an endoscopist specialized in endoscopic surgical resection, and after evaluation of the lesion by EUS or CT, lesions that were not considered suitable for endoscopic resection were directed to surgery.

All patients underwent endoscopy-assisted laparoscopic transgastric resection and no conversion to open surgery was required. In six cases, gastrostomy incision was used for transgastric resection, while in one patient, resection was performed using intragastric ports. In five of the cases, four ports and a Nathanson retractor were used for liver retraction. While three ports were used in one patient, the stomach was suspended with traction suture. In one patient, 5 ports were used. The average operation time was 88 minutes (range 59-140 min). While gastrostomy line was closed with linear stapler in two patients, laparoscopic hand sewing method was used in the remaining patients. No patient had intraoperative complications. Only three patients had a drain left at the end of the operation.

Enhanced recovery after surgery (ERAS) protocols was applied to all patients. Permanent nasogastric and urinary catheters were not used in any patient. Drains were withdrawn on the first or second postoperative day. Liquid meal was started on the postoperative first day and its amount was gradually increased. Pneumonia was observed in only one patient. Apart from this, no complication was observed in any of the patients. The average length of hospital stay was 4.8 days (range 4-8 days). Pathological diagnosis was leiomyomas in five of the patients, while the diagnosis was reported as GIST in two patients. The average tumor diameter was 26 mm (range 10-37mm). The surgical margin is safe in all patients.

Table 1 shows clinical characteristics, preoperative assessment, operative and postoperative data of all patients.

DISCUSSION

With the widespread use of endoscopy and endosonography the number of gastric lesions detected has also increased [6]. The issue of which of these masses is of clinical importance, which lesions can be followed and should be removed has been the framework of many studies. The result of these studies is that lesions smaller than 2 cm and asymptomatic can be followed and the other tumors or biopsy-proven GISTs must be

Table 1. Clinical characteristics, preoperative assessment, operative and postoperative data of all patients.

Patient's no:	1	2	3	4	5	6	7
Age (year)	25	47	60	43	24	52	70
Gender	Male	Female	Male	Female	Female	Female	Male
Comorbidities	None	None	COPD	CAD	None	None	COPD
Symptom	Dysphagia	Dysphagia	Dysphagia	None	Epigastric pain	None	Anemia
Pre-op EUS	None	M.propria	M.propria	M.propria	M.mucosa	M.propria	M.mucosa
EUS tumor size (mm)	None	30x15	20x15	24x20	21x6.2	10	35
CT tumor size (mm)	30x20	30x23	None	None	20x14	None	30
Operation time (min)	140	105	77	95	59	65	75
Port number	5	3 + gastric traction suture	4+nathanson	4+nathanson	4+nathanson	4+nathanson	4+nathanson
Closure of gastrostomy	Suture	Stapler	Stapler	Suture	Suture	Suture	Suture
Drain	1	1	1	None	None	None	None
Convertion	None	None	None	None	None	None	None
Diet	ERAS	ERAS	ERAS	ERAS	ERAS	ERAS	ERAS
Complication	None	None	Pneumonia	None	None	None	None
Length of stay (days)	5	4	8	4	5	4	4
Pathology	Leiomyom 28x21 mm	Leiomyom 32x17 mm	Leiomyom 25x18 mm	Leiomyom 30x25 mm	Leiomyom 20x15 mm	GIST 10x6 mm	GIST 37x25 mm

removed, regardless of their size [7]. Often the patient's symptoms, endoscopy, endoscopic biopsy, EUS and CT evaluation will help to make this decision. Sometimes, in the presence of a followable lesion, the patient's own will may affect this decision.

There are several methods that can be performed in patients who have decided to undergo surgery, and thanks to the developments in minimally invasive surgery in recent years, most of these methods are now performed laparoscopically. Since these lesions are mostly benign and rarely require lymph dissection, it is sufficient to remove them with safe surgical margins [8]. Basically, the size and location of the lesion is effective in deciding the surgical method to be performed. However, removal of lesions close to the upper or lower gastric sphincters with limited resection can be challenging due to the risk of disruption and narrowing of the sphincter [9]. Therefore, in such tumors, it is very important not to disrupt the anatomy of the sphincter, and to perform resection without compromising oncological principles by resection of minimal gastric tissue.

We mostly prefer endoscopic resection options for these types of lesions. However, in tumors close to the gastroesophageal junction, it is not possible to work in a straight position, and the endoscope often remains retroflexed, making the procedure very difficult. Therefore, although the procedure is endoscopically initiated in all tumors close to the junction, the laparoscopic surgery team is ready to intervene and is included in the procedure when necessary. In such cases, we prefer endoscopy-assisted laparoscopic surgery because we believe that it has some advantages, especially in tumors close to the gastroesophageal junction [10].

The low number of cases in our study is a disadvantage, but even these cases have shown us the following;

- Endoscopy is very useful both in localizing the tumor and in maintaining the integrity of gastroesophageal junction during resection with staples and should be used throughout the procedure.
- This option is especially useful in submucosal tumors with an intragastric growth pattern. It is not suitable for exophytic tumors that can be resected with stapler and gastric wedge resection.
- We completed our first case using intragastric ports. However, after locating ports on stromach, we fixed the large curvature with traction sutures on the abdominal wall because of the absence of a balloon trocar. To prevent bowel dilatation with endoscopic insufflation, we had to enter another port to clamp the jejunum distal to the Treitz. The duodenum balloon catheter used in the study performed by Tagaya et al. [11] can be considered as an alternative to the jejunal clamp to prevent gas insufflation into the intestines. We believe that materials such as duodenum balloon catheter and balloon trocar in addition to conventional laparoscopic instruments, may be difficult to insert through intragastric ports.for the resection of intragastric lesions.
- While our first operation was intragastric resection, one of the biggest reasons for continuing with transgastric resection later was the fact that our intragastric port application was much more challenging than the transgastric resection due to the ports entered along the major curvature and limitations of left subcostal marjin and the difficulty of triangulation, which is the main working principle of laparoscopy. Because of intragastric port entry points and trocar angles are perpendicular, suturing of gastric port locations was also more difficult than transgastric procedure.
- Transgastric resection provided wider point of view and easier visualization of the mass in our cases. Although the number of cases is not high, the case that we performed intragastrically lasted 140 minutes, but the longest duration was 105 minutes for the cases we performed transgastric resection, and it was still shorter than our intragastric resection time. In the study of Tagaya et al. [11] the mean operation time was 168 ± 33.1 minutes.
- For the closure of anterior gastrotomy, although we used stapler in two cases, we closed anterior gastrotomy with a double layer suture in other five patients because of the need for clip-suture procedures in the stapler line due to bleeding. R0 resection margin was achieved in all patients and there was no capsule injury or deterioration of mass integrity. Although these masses can also be removed by enucleation, high recurrence rates have been reported for GIST with this method [12].

Bedard et al. [13] suggested that stenosis may result after resection with stapler, due to excess tissue loss in the gastro-esophageal junction and proposed repair via

cutting and suture and bougie tube techniques [13]. However, in our study, dysphagia was not observed in any patient during postoperative and control follow-ups. Also, during resection with staples, the endoscope acts as a bougie tube by passing the gastroesophageal junction and staying in the stomach. Villano et al. stated in their study that resection is very difficult or impossible in patients with an endophytic (intragastric) growth pattern using a standard laparoscopic approach, and this can be overcome by creating an intragastric port [14]. We think that tumor localization can be determined with transgastric approach by performing it under endoscopic guidance. In other words, we use the endoscope for tumor localization and also as a bougie tube.

We also think that the transgastric approach has some advantages over the intragastric approach. First of all no sutures or balloon trocars are needed to hang the stomach on the abdominal wall. Secondly, triangulation, which is the working principle of laparoscopy, is easier in the transgastric approach. Thirdly, intragastric approach is a challenging approach due to staying at upright angles during port closure of the intra-gastric port entrance with staples or sutures, whereas in the transgastric approach, the gastrotomy line is sutured more easily.

Although it was thought that gastric fluid might cause abdominal contamination in the transgastric approach, none of our patients had a clinical manifestations of an intra-abdominal infection that required use of an imaging method or intervention. Except for one of our patients with pneumonia, antibiotherapy was not required. We started liquid food for all of our patients at the postoperative 4th hour. In pathological examination, R0 resection margin was achieved in all of our patients. We did not use postoperative nasogastric drainage or urinary catheter in any of our patients.

Conclusion

We strongly suggest laparoscopic transgastric resection approach for submucosal tumors close to the gastroesophageal junction, because it is a feasible and safe method, when used in combination with endoscopic guidance.

Ethics Committee Approval: This Study is designed retrospectively, so Ethics Committee Approval was not taken.

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

Funding: No funding was used for this study.

Informed Consent: This manuscript is a retrospective study.

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Original Article

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Association Between Depression and Cardiometabolic Risk Factors in Adolescents with Obesity[§]

Aşırı Ağırlıklı ve Şişman Ergenlerde Depresyon ve Kardiyometabolik Risk Etmenlerinin İlişkisi

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ABSTRACT

Objective: *The aim of this study was to examine whether the presence of depression in overweight or obese adolescents increases the likelihood of cardiometabolic risk factors.*
Method: *We performed a retrospective cross-sectional analysis of the data obtained from overweight or obese, adolescents aged 11-18 years, who were evaluated in our clinic from January 2012 to December 2015. Depression was evaluated by "Children's Depression Inventory". Hypertension, dyslipidemia, hyperinsulinemia, hyperglycemia and insulin resistance were defined as cardiometabolic risk factors. The degree of obesity was calculated as the body mass index standard deviation score.*
Results: *Among 283 adolescents who were included in the study, 75 (26.5%) were overweight, and 208 (73.5%) were obese. The mean age was 14.02±1.67 years and 168 (59.4%) subjects were girls. The mean body mass index standard deviation score was 2.36±0.62, The mean Children's Depression Inventory score was 12.72±6.5, and 47 (16.6%) of the participants were in depression. Depression was more frequently detected in females than in males (p=0.047). Body mass index standard deviation score was in positive correlation with Children's Depression Inventory scores (r=0.123, p= 0.038). In univariate analyses, hyperinsulinemia was found to be 2.3 times more frequent in depressed group than in nondepressed group (p=0.026). In logistic regression analysis this relation disappeared.*
Conclusion: *We showed that severity of depression increased, as the degree of obesity increased, but we could not find any clear relationship between depression and cardiometabolic risk factors in overweight or obese adolescents.*

Keywords: *Adolescents, cardiometabolic risk factors, degree of obesity, depression*

ÖZ

Amaç: *Bu çalışmanın amacı aşırı ağırlıklı ya da şişman ergenlerde depresyon varlığının kardiyometabolik risk etmenlerini artırıp artırmadığını incelemektir.*
Yöntem: *Ocak 2012 - Aralık 2015 tarihleri arasında kliniğimizde değerlendirilen, 11-18 yaş arası aşırı ağırlıklı ya da şişmanergenlerin verilerinin geriye dönük kesitsel çözümlemesi yapıldı. Depresyon, "Çocuklar için Depresyon Ölçeği" ile değerlendirildi. Hipertansiyon, dislipidemi, hiperinsülinemi, hiperglisemi ve insülin direnci kardiyometabolik risk etmenleri olarak tanımlandı. Şişmanlık derecesi, beden kitle indeksi standart sapma skoru olarak hesaplandı.*
Bulgular: *Çalışmaya alınan 283 ergenden 75'i (% 26.5) aşırı ağırlıklı, 208'i (% 73.5) şişmandı. Olguların yaş ortalaması 14.02 ± 1.67 yıldı ve 168'i (% 59.4) kızdı. Beden kitle indeksi standart sapma skoru ortalama değeri 2.36 ± 0.62, Çocuklar için Depresyon Ölçeği ortalama puanı 12.72 ± 6.5 idi ve katılımcıların 47'sinde (% 16.6) depresyon saptandı. Depresyon sıklığı kızlarda erkeklerden daha yüksek saptandı (p = 0.047). Beden kitle indeksi standart sapma skoru ile Çocuklar için Depresyon Ölçeği puanları arasında aynı yönlü anlamlı ilişki saptandı (r=0.123, p = 0.038). Tek değişkenli çözümlemelerde depresyonu olanlarda hiperinsülinemi, depresyonu olmayanlara gören 2.3 kat daha sık bulundu (p = 0.026). Lojistik regresyon çözümlemesinde bu ilişki kayboldu.*
Sonuç: *Şişmanlığın derecesi arttıkça depresyonun şiddetinin arttığını gösterdik, ancak aşırı ağırlıklı ya da şişman ergenlerde depresyon ve kardiyometabolik risk etmenleri arasında bir ilişki bulamadık.*

Anahtar Kelimeler: *Ergenler, kardiyometabolik risk etmenleri, şişmanlığın derecesi, depresyon*

[§]This study, "Association between depression and cardiometabolic risk factors in overweight and obese Turkish adolescents" was presented as oral presentation at 9th Europaediatrics Congress 2019, Dublin, Ireland.

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INTRODUCTION

The prevalence of adolescent obesity and depression is increasing, and these conditions are currently recognized as major public health concerns [1]. According to the data of the World Health Organization, the prevalence of overweightness and obesity increased to a great extent from 4% in 1975 to 18% in 2016 in children and adolescents aged between 5 and 19 years [2]. It was shown that cardio metabolic risk factors, such as hypertension, insulin resistance, and dyslipidemia are more prevalent among children and adolescents with obesity compared to their normal -weight peers [3]. It has also been shown that there is a strong association between obesity and some mental health disorders such as depression and anxiety [4,5]. In overweight or obese children and adolescents the prevalence of depression was reported to be 10.4% in a previous study, and the prevalence of depressive symptoms has been reported to be 21.73% in a recent meta-analysis [5,6].

A bi-directional relationship was established between obesity and depression in adolescents [1]. It was displayed that adolescents with depression had a 70% higher risk of becoming obese. On the other hand, obese adolescents had a 40% greater risk of being depressed [1]. The association was found to be stronger for the depression causing obesity compared to the obesity causing depression [1]. In a review focused specifically on shared biological pathways that may influence the bi-directional association between depression and obesity, it was considered that genetic factors, changes in certain homeostatic regulatory systems (hypothalamic-pituitary-adrenal axis [HPA], immuno-inflammatory activation, neuroendocrine regulators of energy metabolism and microbiome) and brain circuits that combine homeostatic and mood regulatory responses, might have an impact on this relationship [4]. Insulin and dysregulation of leptin are also considered as factors that may represent a mediating mechanism in the obesity-depression relationship [4]. Psychological and behavioral factors may also influence this relationship. For example, disordered eating attitutes and behaviours were found to be associated with both depression and obesity [7,8].

The association of depression with cardiovascular risk factors has also been widely recognized in both children and adults [9,10]. A scientific statement from the American Heart Association indicated that major depressive disorder and bipolar disorder were tier II moderate risk factors for accelerated atherosclerosis and early cardiovascular disease in young individuals [10]. However, young individuals with major depressive disorder and bipolar disorder who have more than one risk factor (obesity, hypertension, smoking, suboptimal physical activity) should be considered tier I high-risk group and implementation of more aggressive interventions are needed for this group [10]. In the light of the literature, the aim of this study was to examine whether the presence of depression in overweight or obese adolescents increased the likelihood of cardiometabolic risk factors.

MATERIAL and METHODS

We obtained retrospective data from medical records of overweight or obese adolescents aged between 11 to 18 years who attended our Medical Faculty Adolescent outpatient clinic from January 2012 to December 2015, in order to evaluate the association between depression and cardiometabolic risk factors. In our adolescent outpatient clinic, we routinely calculate the body mass index (BMI) of the patients irrespective of their admission complaints, and if we determined that the patient was overweight/obese, we evaluated him/her for the cardiometabolic risk factors that might be associated with obesity. The included patients were either admitted to our clinic for weight management or for an acute transient health problem and were found to be overweight/obese in routine evaluation. Between January 2012 to December 2015, four different studies with overweight/obese adolescents were conducted in our clinic. For this study, the cases in those four studies were retrospectively screened and those evaluated with Children's Depression Inventory (CDI) were included in this study [8,11-13]. Pubertal patients who met the criteria for definition of overweightness/obesity established by Cole et al. [14] according to age and gender and had been evaluated with CDI were included in this study. Patients with any chronic disease (except for being overweight/obese and having overweightness/obesity associated complications such as hypertension, disordered glucose metabolism and dyslipidemia) and endogenous obesity of any etiology (such as hypothyroidism, etc.) were excluded from the study. Pubertal staging was performed in accordance with the Tanner staging sys-

tem [15]. Testicular volume was evaluated using the Prader orchidometer in boys and recorded. Telarche in girls and a testicular volume of 4 mL in boys were considered as puberty [15]. Age, gender, weight, height, blood pressure, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, fasting blood glucose and insulin levels of the adolescents were recorded from the patients' files.

Weight status was classified on the basis of measured height and weight obtained at the time of physical examination and BMI was calculated using the following formula: BMI= weight/height^2(kg/m^2) [2]. Patients with BMIs between 85th-95th persentiles were accepted as overweight and BMI values above 95th percentile as obese. [14,16] The degree of obesity was calculated as the body mass index standard deviation score (BMI-SDS) by using age and gender specific to Turkish BMI percentiles which were generated by using lambda, mu, sigma (LMS) method, to standardize degree of obesity [14,17]. The LMS method provides a way of obtaining normalized growth centile standards which simplifies this assessment of growth standards and summarixes the data in terms of three smooth age- specific curves called L (lambda), M (mu), and S (sigma) [14].

Hypertension, dyslipidemia, hyperinsulinemia, hyperglycemia and insulin resistance were defined as cardiometabolic risk factors. We used standard cut-off values for levels of fasting blood glucose (> 100 mg/dl), total cholesterol (≥200 mg/dl), HDL cholesterol (<40 mg/dl), LDL cholesterol (≥ 130 mg/dl) and triglycerides (≥ 130 mg/dl) to define abnormal values [18]. Homeostasis model assessment of insulin resistance was calculated using the equation: HOMA-IR=fasting insulin (µU/mL)x fasting glucose(mg/dL)/405 [19,20]. Fasting insulin levels above 30 µU/mL were accepted as cut-off levels for hyperinsulinemia and the HOMA-IR cut-off point for diagnosis of insulin resistance was accepted as 3.16 [19,20]. Seated blood pressure (BP) was measured after the adolescent had been resting quietly for 10 minutes using auscultator method. We used standardized blood pressure tables in which abnormal BP values were defined as those above the 95th percentile [21].

Depression was evaluated by the Children's Depression Inventory (CDI): This inventory is comprised of 27 items which can be applied to children aged between 6 and 17 years. Its Turkish version has a high internal consistency (Cronbach α= 0.77) [22]. The participants are asked to choose the option that is most appropriate for their condition during the last two weeks. Each item is scored as 0, 1 or 2 according to symptom severity. The highest score is 54. The recommended cut-off point is 19. The subjects who scored higher than 19 in CDI, were referred to a psychiatrist for clinical evaluation and treatment for depression.

Statistical Analyses

The Statistical Package for Social Sciences (SPSS) version 21.0 statistical package was used for statistical analyses. The data were assessed for normality using visual and analytic methods. Continuous variables were expressed as mean±standard deviation and categorical variables as percentages. Correlation analysis was planned if a cardiometabolic risk factor was found to be associated with CDI score in univariate analysis to evaluate whether this risk factor was also associated with BMI-SDS. Chi-square test was used to compare categorical variables. In the assessment of the relationship between CDI score, BMI-SDS and other cardiometabolic risk factors, Pearson's correlation test was used. Logistic regression analyzes were conducted to determine the factors which were independently associated with depression. Variables with a p value <0.25 in univariate analyses were accepted as independent variables. The enter method was used in the logistic regression model.

RESULTS

Among 283 adolescents with a BMI at the 85th percentile or higher; 75 (26.5%) were overweight, and 208 (73.5%) were obese. The mean age was 14.02±1.67 years and 168 (59.4%) of the subjects were girls. The mean BMI value was found to be 30.13±3.71 kg/m^2 and the mean BMI-SDS value was 2.36±0.62 kg/m^2. The mean CDI score was 12.72±6.5, and 47 (16.6%) of the parcipitans had CDI scores higher than 19.

The depression frequency was found to be higher in females compared to males (p=0.047). Depression was observed in 20.2% of overweight and obese female, and in 11.3%. of male adolescents. It was determined that being female increased the risk of depression 1.9 times among overweight and obese adolescents (Table 1). Any significant difference was not found in depres-

Table 1. Differences in gender, body mass indexes and cardiometabolic risk factors between depressed and nondepressed groups.

Variables		CDI scores				P value*	Odds ratios (OR)	95% confidence intervals	
		<19		≥19					
		n	%	n	%			Lower	Upper
Gender	Female	134	79.8	34	20.2	**0.047**	**1.991**	**0.999**	**3.965**
	Male	102	88,7	13	11.3				
BMI (kg/m²)	Overweight	66	88	9	12	0.211	1.639	0.751	1.916
	Obese	170	81.7	38	18.3				
Hypertension (mm/hg)	Yes	51	85	9	15	0.726	0.868	0.393	1.916
	No	182	83.1	37	16.9				
Total cholesterol (mg/dl)	High	195	81.9	43	18.1	0.302	0.567	0.190	2.334
	Normal	32	88.9	4	11.1				
HDL- cholesterol (mg/dl)	Low	184	83.3	37	16.7	0.843	1.081	0.501	2.334
	Normal	46	82.1	10	17.9				
LDL- cholesterol (mg/dl)	High	206	82.7	43	17.3	0.311	0.532	0.154	1.834
	Normal	27	90	3	10				
Triglyceride (mg/dl)	High	172	82.3	37	17.7	0.481	0.762	0.357	1.625
	Normal	61	85.9	10	14.1				
Fasting blood glucose (mg/dl)	High	33	80.5	8	19.5	0.589	1.262	0.542	2.938
	Normal	203	83.9	39	16.1				
Insulin (µU/mL)	High	30	71.4	12	28.6	**0.026**	**2.33**	**1.091**	**4.982**
	Normal	204	85.4	35	14.6				
HOMA-IR	High	155	82.9	32	17.1	0.807	1.087	0.556	2.126
	Normal	79	84	15	16				

**chi-square test, CDI: Children's depression inventory, HOMA-IR: homeostatic model assessment of insulin resistance ,BMI: body mass index*

sion frequency between overweight and obese groups. The frequency of hypertension, dyslipidemia and insulin resistance was not significantly different between depressed and nondepressed groups. Hyperinsulinemia was found to be more frequent in the depressed group compared to the nondepressed group (p=0.026). Among overweight and obese adolescents with and without hyperinsulinemia, the rates of depression were 28.6%, and 14.6%. , respectively.The frequency of hyperinsulinemia was found to be 2.3 times higher in patients with depression compared to those without (Table 1).

Using Pearson's correlation test, the BMI-SDS had positive correlation with CDI scores and insulin levels (r, p= 0.123, 0.038; 0.341, and 0.0001, respectively). The correlations between CDI scores and BMI-SDS and cardiometabolic risk factors are given in Table 2.

In logistic regression analysis, no factors were found to be independently associated with depression (Table 3).

Table 2.Relationship between depression scores, degree of obesity and cardiometabolic risk factors (Pearson's correlation test).

CDI scores	Whole group		Female		Male	
	r	p	r	p	r	p
Age	.047	.431	.049	.530	.027	.773
SDS-BMI	.123	.038	.108	.165	.050	.596
SBP(mmHg)	-.095	.112	-.060	.445	-.113	.231
DBP(mmHg)	.031	.610	.045	.570	.039	.683
Total cholesterol (mg/dl)	-.061	.314	-.090	.253	-.050	.606
HDL- cholesterol (mg/dl)	-.069	.251	-.050	.526	-.160	.091
LDL- cholesterol (mg/dl)	-.009	.875	.003	.966	-.034	.717
Triglyceride (mg/dl)	-.058	.336	-.030	.701	-.103	.276
Fasting blood glucose (mg/dl)	-.044	.462	-.049	.531	-.023	.808
Insulin (µU/mL)		.103	.084	.083	.286	.140
HOMA-IR	.105	.080	.112	.286	.078	.409

CDI: Children's depression inventory
DBP: diastolic blood pressure
HOMA-IR: homeostatic model assessment of insulin resistance
SDS-BMI: body mass index standard deviation
SBP: systolic blood pressure

Table 3. Associations between depression and gender, obesity and hyperinsulinemia (depression was the dependent variable in logistic regression analysis).

Variables	Beta	Significance	Odds ratios	95% confidence intervals	
				Lower	Upper
Female	0.700	0.051	2.014	0.996	4.074
Obesity	0.454	0.276	1.575	0.696	3.560
Hyperinsulinemia	0.651	0.108	1.918	0.867	4.242

Gender (1=male vs 2=female), degree of obesity (1=overweight vs 2=obese) and hyperinsulinemia (no=0 vs yes=1) were the independently associated variables with depression

DISCUSSION

In our study, we found that the severity of depression increased, as the degree of obesity increased, and the frequency of depression was 16.6% in overweight or obese Turkish adolescents. Similar to our results, it was shown that higher BMI levels were associated with depressive symptoms in young individuals and this association was shown to be mediated by body image perception in one study [23]. Also in another study, it was found that depression was associated with more severe obesity in young individuals who were seeking treatment for obesity [24]. In a recent review, it has been reported that the prevalence of depression in obese children and adolescents was found to range between 1.8% and 63.7% in different studies, and the overall prevalence of depression among obese children and adolescents was 10.4% [6]. In our study, the frequency of depression was found to be higher in female adolescents compared to male adolescents. However, it cannot be concluded that female gender increases the frequency of depression to a greater extent compared to overweight or obese male adolescents, though we found a p value of <0.05, because the confidence interval included 1. This result may be related to the small sample size of our study. In the literature, there are some studies indicating that obes female adolescents were more likely to develop depression compared to their male counterparts [1,25,26]. This condition may be related to the complex developmental processes that female adolescents confront during puberty [1,27].

In the literature, it was shown that there is a relationship between depression and obesity [4-8]. Both depression and obesity were reported to be associated with an increase in cardiometabolic risk factors both in adolescents and adults [3,9,10]. Plausible biological mechanisms exist between depression and cardiometabolic risk factors, however, these mechansims are still not well understood. In some studies, it was suggested that alterations in the HPA axis might play an important role in the pathophysiology of depression and cardiometabolic disease and most of the studies in this topic evaluated adults [4,28-30]. A large percentage of subjects with depression have autonomic imbalance which is characterized by increased sympathetic activation and abnormal HPA activity [4,28]. Moreover, activation of the HPA axis leads to increased secretion of corticotrophin-releasing factor which results in excess cortisol secretion [30,31]. Cortisol is known to be a counter-regulatory hormone which is associated with type 2 diabetes, insulin resistance, dyslipidemia, and hypertension [29,30]. As cortisol levels were not evaluated in our study, we cannot draw conclusion about the effects of cortisol level on cardiometabolic risk factors in depressed adolescents.

In this study, in univariate analysis hyperinsulinemia was found to be more frequent in the depressed group compared to the nondepressed group. However, in logistic regression analysis, this relationship disappeared. When we analyzed the relationships between CDI scores, insulin levels and BMI-SDS by using Pearson's correlation test, and we found that there were significant correlations between the CDI scores, insulin levels and BMI-SDS. For this reason, hyperinsulinemia was considered an outcome of obesity rather than depression. Gross et al. [9] demonstrated that depression was

associated with HDL-cholesterol, triglycerides, and metabolic syndrome cluster score in children and adolescents aged between 8 and 18 years across a wide range of BMIs (normal weight to severe obesity). However, these relationships were not significant when body fat percentage was controlled. In that study, it was interpreted that the correlation between depression and cardiovascular disease risk factors might be emerging at least during childhood, but excess adiposity rather than depression might play a greater role in exacerbating the risk [9]. Our results might be speculated to support Gross et al.'s [9] study, as the association between depression and hyperinsulinemia was not significant after controlling for degree of obesity in logistic regression analysis.

We examined a range of cardiometabolic risk factors in this study; however, our study has certain methodologic limitations. Firstly, the cross-sectional retrospective design did not allow us to examine the causes of depression and the effects of depression on future health of the participants. Secondly, there may be other factors including family background (single or separated parents, siblings, socio-economic status), sleep disorders, tobacco use, disordered eating attitudes, inadequate physical activity that were not examined in this study [10,32,33]. Thirdly, depression was assessed by self-reports of the study participants only, so the diagnosis of depression might be under/overdiagnosed.

In conclusion, adolescents with both depression and obesity might have a greater risk for future morbidity and mortality compared to adolescents who are only depressed or only obese. However the relationship between depression and cardiometabolic risk factors in overweight or obese adolescents remain elusive. Therefore, all adolescents should be screened for both obesity and mood disorders periodically, and especially overweight or obese adolescents should be followed up closely in terms of depression.

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Retrospective Analysis of Peripheral T-Cell Lymphoma Patients: Single Center 'Real-Life' Experience

Çevresel T-Hücreli Lenfoma Hastalarının Geriye Dönük Değerlendirmesi: Tek Merkez 'Gerçek-Yaşam' Deneyimi

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ABSTRACT

Peripheral T-cell lymhomas (PTCLs) represent a heterogeous group of diseases, with poor long-term outcomes excluding ALK+ anaplastic large cell lymphoma (ALCL).
We represent data of our retrospective analysis of 62 consecutive PTCL cases diagnosed since 2002. Median observation time was 16 months. The overall response rate to first line treatment was 53 percent. Data related to median progression- free survival and overall survival times could not be obtained for ALK+ALCL group whereas median progression- free survival and overall survival times for ALK-negative ALCL group were 1 and 18 months, respectively.
Disease progression was frequently observed histologically in ALK-negative group. For ALK-negative ALCL, advanced stage disease was defined as the presence of serum albumin <3.4 g/dl, serum total protein ≤6.2 g/dl, high serum LDH, and serum ferritin >200 ng/ml, presence of B symptoms, and extranodal involvement of more than one site. Risk factors associated with death were serum albumin <3.4 g/dl, serum total protein ≤6.2 g/dl, serum ferritin over 200 ng/ml, and bone marrow involvement at the time of diagnosis.
During follow-up 39 patients (64%) died. Most common reasons were progressive disease and infections. Four patients developed secondary malignancies.
Our study is a reflection of the 'real-life'. Three patients died due to disease progression shortly after diagnosis without providing treatment due to aggressiveness of the disease. Alternatives to CHOP-based chemotherapies should be found for the ALK + non-anaplastic large cell lymphoma group.

Keywords: *T cell lymphoma, Anaplastic lymphoma kinase, ALK positive, ALK negative*

ÖZ

Çevresel T hücreli lenfomalar heterojen bir hastalık grubu olup, ALK+ anaplastik büyük hücreli lenfoma dışında uzun dönem sonuçları kötüdür. Merkezimizde 2002 senesinden beri tanı alıp takip olmuş 62 ardışık çevresel T hücreli lenfoma hastamızın verilerini sunmaktayız. Ortanca takip süremiz 16 aydır.
İlk seri tedaviye genel yanıt oranı %53'dür. Ortanca progresyonsuz ve genel sağkalım sürelerine ALK+ anaplastik büyük hücreli lenfoma grubunda ulaşılamamıştır. ALK negative grupta ise ortanca progresyonsuz ve genel sağkalım süreleri sırasıyla 1 ve 18 ay olarak tespit edilmiştir. Hastalık progresyonu sıklıkla histolojik olarak ALK negatif grupta gözlenmiştir. ALK negative anaplastik büyük hücreli lenfomada ileri evre hastalık, serum albumin <3,4 g/dl, serum total protein ≤6.2g/dl, serum ferritin >200 ng/ml olması, yüksek serum LDH düzeyi, B semptomları olması ve birden fazla ekstranodal tutulum bölgesi olması, progresyonla ilişkili risk faktörleri olarak tanımlanmıştır. Ölüm ile ilişkili risk faktörleri ise serum albumin <3.4 g/dl, serum total protein ≤6.2 g/dl, serum ferritin >200 ng/ml ve tanı anında kemik iliğinin tutulu olması olarak belirlenmiştir.
Takipte 39 hasta (%64) vefat etmiştir. En sık neden ise hastalığın ilerlemesi ve enfeksiyonlardır. Dört hastada ise ikincil malinite gelişmiştir. Çalışmamış, 'gerçek yaşam'ın bir yansımasıdır. Üç hasta, tanıdan kısa süre sonra tedavi dahi verilemeden, hastalığın agresifliği neticesinde kaybedilmiştir. ALK+ anaplastik büyük hücreli lenfoma dışı grupta CHOP tabanlı kemoterapilere alternatif bulunması gereklidir.

Anahtar kelimeler: *T hücreli lenfoma, anaplastik lenfoma kinaz, ALK pozitif, ALK negatif*

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INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) represent a heterogeneous group of lymphoproliferative disorders derived from mature T cells and usually characterized by an aggressive clinical course. Although their incidence rates vary according to geographic location and ethnic origin of the population PTCLs are uncommon in general which contributes to limited experience bringing several challenges in diagnosis and also standardization of treatment [1]. These neoplasms can be grouped according to their usual presentation into disseminated diseases (leukaemias), predominantly extra-nodal or cutaneous, or predominantly nodal lymphomas.

Multiple subtypes represent distinct clinicopathologic entities or prognoses. The most common subtype is PTCL-not otherwise specified (PTCL-NOS-26%), followed by angiommunoblastic TCL (AITCL-19%), Anaplastic Lymphoma Kinase (ALK) -positive anaplastic large cell lymphoma (ALCL) (7%), ALK -negative ALCL (6%) and, enteropathy- associated TCL (EATCL-<5%) [2]. CHOP-type chemotherapy has been the mainstay of therapy. However they have poor outcomes with a 3-year survival rate of approximately 30% with the notable exception of ALK-positive ALCL. Compared to ALK- negative PTCLs, ALK- positive group was reported to have better 5-year failure- free survival (FFS) (60% vs 36%, p=0.015) and OS (70% vs 46%, p=0.016). The survival rates were worse than ALK- negative ALCL for PTCL-NOS and AITCL [3]. Although addition of etoposide to CHOP regimen was associated with increased response rates and better PFS, it had no contribution to OS [4]. Additionally, no clear survival advantage of consolidative autologous hematopoietic stem cell transplantation (HSCT) could be shown [5].

The parameters such as advanced age, increased serum LDH levels, poor performance status, extranodal disease, decreased platelet counts, increased Ki67 score and many other serum biomarkers were analyzed to estimate the survival of PTCL patients and to refine the poor prognostic group. The International Prognostic Index (IPI) [6], the prognostic index for PTCL-NOS [7], prognostic index of International T Cell Lymphoma Project [8], the T cell score [9] and NCCN-IPI [10] are used to stratify prognostic risk parameters and estimate survival. Gene expression profile studies showed that DUSP-22 rearranged ALK- negative ALCL patients have OS rates similar to ALK positive ALCL patients [11]. Additionally, high expression of GATA3 in PTCL-NOS was significantly associated with worse OS [12].

For relapsed/refractory PTCL patients the second- line treatment may consists of single agents brentuximab vedotin for CD30 positive disease, pralatrexate [13], lenalidomide [14], romidepsin [15], belinostat [16] or combination regimen with intention to proceed to autologous [17] or allogeneic [18] HSCT. However, the optimal recommendation could not be defined.

Herein, we report our single center data for PTCL patients. We hope documentation center's experience with survival data related to this rare disorder group with a poor outcome in general may provide guidance for novel therapy replacing traditional strategies.

MATERIAL and METHODS

From 2002 to 2019, patients diagnosed with PTCL and managed at our institution were retrospectively analyzed. Primary cutaneous T- cell lymphomas and nasal NK/T -cell lymphomas were not included in the analysis.

All pathology specimens were assessed by our pathology department. The stratification of cases was made according to 2008 World Health Organization classification of lymphoid neoplasms [19].

The evaluation of treatment response was realized with CT or PET/CT. OS was defined as the time from initial diagnosis to death or latest follow-up. PFS was defined as the time from initial diagnosis to progression or relapse or death due to progressive disease.

Our study was approved by Istanbul University Istanbul Medical Faculty ethics committee (2019/1044), and conducted according to the principles of Declaration of Helsinki.

Statistical Analysis

Categorical variables were compared using Pearson's chi- square test. Multivariate analysis was done using a stepwise Cox proportional hazard model. The survival estimates were calculated with Kaplan-Meier method. STATA/SE11.1 was used for the statistical analysis.

RESULTS

Population characteristics

There were 62 eligible patients. The median age was 54 years (range 20-82). Although not statistically significant, ALK+ ALCL patients were younger with a median age of 32 years, compared to the rest of the cohort having a median age of 55 years. Seventy-four percent of the patients was male. The patients were distributed according to the histological type of the disease as follows: PTCL-NOS (n=17: 27%), AITL (n=13: 21%), ALCL (n=21: 34%), HSTCL (n=4), EATCL (n=4) and NK/T cell lymphoma (n=3). Among 21 ALCL patients, 9 were ALK-positive. Forty-three patients presented with advanced stage disease (Ann-Arbor stage III-IV). Most commonly involved extranodal sites were bone marrow, spleen, liver and gastrointestinal tract. Patient characteristics are summarized in Table 1. The median follow-up time was 16 months (range:1-156).

Survival Analysis Of The Entire Cohort

The median PFS and OS rates were 8 months (95% CI: 0.37-0.61) and 20 (95% CI: 0.36-0.61) months for the entire cohort, respectively. Five-year PFS rates was 19% (95% CI: 0.07-0.35) whereas OS rate was 26% (95% CI: 0.14-0.39).

The ALK+ ALCL patients had significantly better survival rates compared to the rest of the cohort. The data for the median PFS and OS were not reached for ALK+ALCL group though they were less than 2 (95%CI: 0.33-0.60) and 18 (95% CI: 0.35-0.62) months for the rest of the cohort, respectively.

Five-year PFS rates were 66% (95% CI: 0.16-0.91) for ALK+ALCL whereas 19% (95% CI: 0.09-0.32) for non-ALK+ groups. Five -year OS rates were 75% (95%CI: 0.31-0.93) for ALK+ALCL group and 18% (95% CI: 0.07-0.32) for the rest of the cohort. The survival curves according to histology are presented in Figure 1.

Treatment Strategy

Three patients (1 PTCL-NOS, 1 EATCL, 1 NK/T cell lymphoma) died without having chance to be treated, due

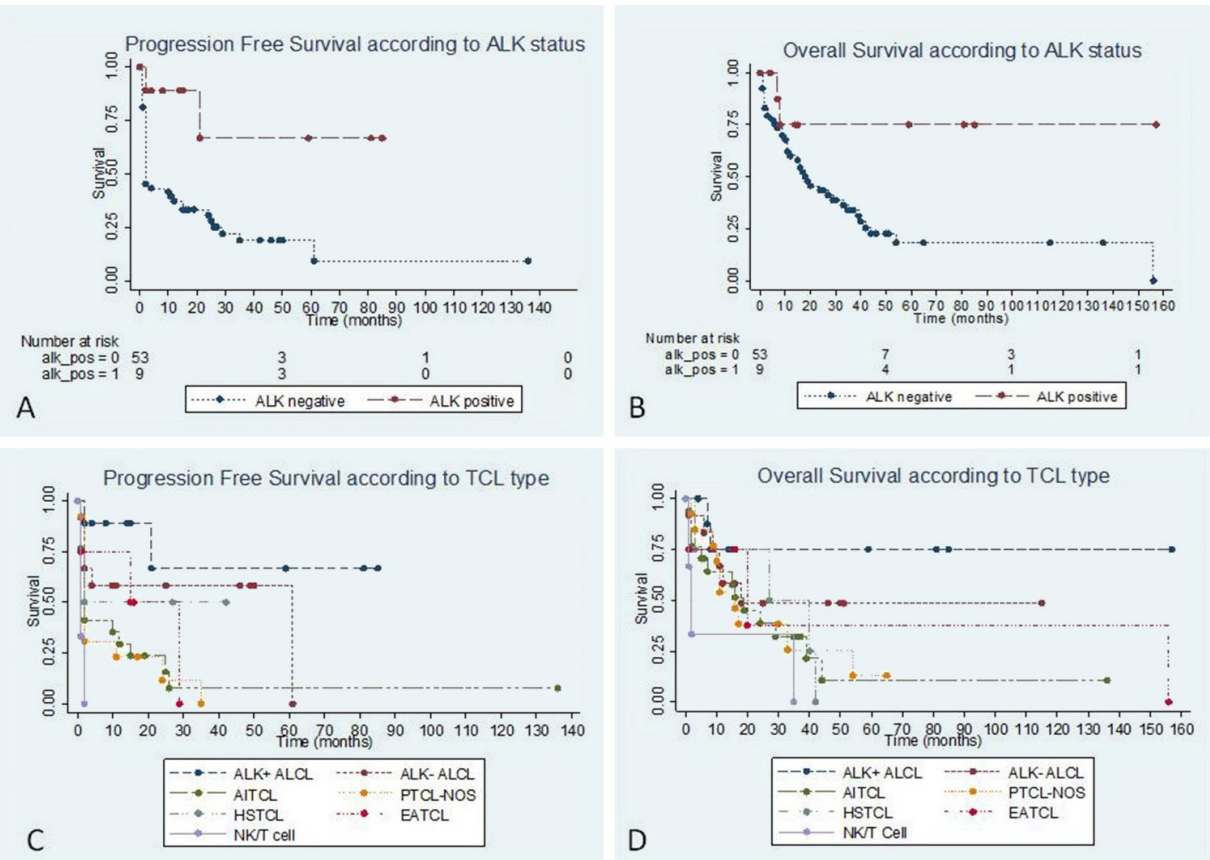

Figure 1. Kaplan-Meier Survival Curves – Progression free survival and overall-survival according to ALK status (A&B) and T cell lymphoma type (C&D)

to rapid progression of the disease. One patient with HSTCL underwent splenectomy which established the diagnosis and the patient received steroid treatment. One patient with PTCL-NOS had a poor ECOG performance status and could only be given steroids.

The remaining 56 patients received mainly (n=46). CHOP-based chemotherapy. One patient initially was diagnosed as having HL and received ABVD as first- line treatment . Re-evaluation of the case revealed the diagnosis of PTCL-NOS. In five patients, radiotherapy was added to the treatment.

The ORR to first line treatment was 52%, including CR in 23 (40%) and PRs in 7 (12%) cases.

Regardless of the treatment arm, the CR rate was significantly higher in ALK+ALCL than in other groups (77% of the patients achieved CR). The ORR was 67% for ALK-ALCL, whereas it was lower for PTCL-NOS (47%) and AITCL (31%) groups (Table 1)

As treatment for relapsed and refractory patients the treatment agent was chosen taking into account the toxicity of previous treatment and patients' performance status. Gemcitabine- based regimens, brentuximab vedotin (BV), bendamustine, pralatrexate and lenalidomide were the preferred regimens for further treatment of these cases.

Survival Analysis of Patients Who Had Objective Response to Initial Treatment

Median PFS and OS for responders to the first- line treatment were 29 (95% CI: 0.31-0.73) and 136 months, respectively. The 5-year OS (52%: 95% CI: 0.29-0.71) and PFS rates (48%: 95% CI: 0.25-0.68) were as indicated.

Patients Who Had SCT

Among 30 responders to the first- line treatment, 10 patients underwent autologous SCT upfront as consolidation. For this group 5-year OS (75% :95% CI: 0.31-0.93) and PFS rates (63% :95% CI: 0.23-0.86) were as indicated. Patients who had consolidative auto-SCT had better 5-year OS rates compared to those having chemotherapy alone (75% vs 41%; p=NS).

Nine patients had autologous SCT following salvage treatments. Five patients responded to auto-SCT (4 CR and 1 PR). The median OS was 20 months (95% CI: 0.16-0.79), and PFS was less than 2 months (95% CI: 0.08-0.62).

Four patients underwent allo-SCT (1 AITCL, 1 PTCL-NOS, 1 HSTCL, 1 ALK-ALCL). Two of them had previous auto-SCT. Three of them died due to progressive disease (n=1) and infectious complications (n=2).

One patient with ALK-ALCL relapsed at the fifth year of auto-SCT. This patient achieved CR with reuse of CHOEP but experienced a second relapse and underwent allo-SCT after salvage BV&GDP treatment. He is still alive with complete response at the 115th month of follow-up.

Risk Factors

Progression was frequently associated with T cell-lymphomas having other than ALK+ALCL (p=0.004) histology. For ALK- ALCL, advanced stage disease (p=0.000), serum albumin <3.4 g/dl (p=0.013), serum total protein ≤6.2g/dl (p=0.032), high serum lactate dehydrogenase level (LDH) (p=0.042), serum ferritin > 200 ng/ml (p=0.006), presence of B symptoms (p=0.03), and extranodal involvement of more than one site (p=0.021) at the time of diagnosis were associated with progression. In addition, hemoglobin level less than 10 gr/dl (p=0.061) and bone marrow involvement at the time of diagnosis (p=0.103) tend to be more frequently-though not statistically significantly- associated with progressive disease. In the multivariate analysis, high serum LDH and extranodal involvement involving more than one organ were found to be significant. For ALK+ALCL, none of the risk factors was associated with progressive disease.

In the univariate analysis, T cell lymphoma type other than ALK+ALCL was associated with death (p=0.006). For ALK -positive group, none of our criteria was associated with poor OS.

For ALK- negative group, serum albumin <3.4 g/dl(p=0.001), serum total protein ≤6.2 g/dl (p=0.032), serum ferritin >200 ng/ml (p=0.031), bone marrow involvement (p=0.020) at the time of diagnosis were associated with death. In the multivariate analysis, only bone marrow involvement was associated with poor survival. Although not statistically significant, high serum lactate dehydrogenase (LDH) (p=0.085) and

Table 2. It showes comparison of preopertive and postoperative patients' VAS. A statistically significant decline in pain control was detected in both groups.

	All patients (n=62)	ALK+ALCL (n=9)	PTCL, NOS (n=17)	AITCL (n=13)	ALK- ALCL (n=12)	Hepatosplenic T cell lymphoma (n=4)	Enteropathy ass. T cell lymphoma (n=4)	NK/T cell lymphoma (n=3)
Age, median (range)	54 (20-82)	32 (20-66)	62 (28-73)	65 (30-82)	52.5 (24-79)	58 (26-64)	52.5 (35-58)	43 (32-47)
Male vs Female	46 vs 16	9 vs 0	11 vs 6	8 vs 5	8 vs 4	4 vs 0	3 vs 1	3 vs 0
B symptoms								
present	37	4	10	8	4	3	4	3
absent	19	5	5	3	6	1	0	0
Stage								
I-II	13	3	3	1	3	1	1	1
III-IV	43	6	11	12	8	2	2	2
Bone marrow involvement								
present	19	2	6	2	2	4	0	2
absent	37	7	8	9	8	0	4	1
Extranodal involvement								
0 - 1	37	8	8	9	7	2	2	1
≥2	17	1	6	1	3	2	2	2
ECOG Performance Score								
0 - 1	43	9	23	20	5	2	2	2
≥2	18	0	5	3	6	2	2	1
Serum LDH								
Normal	18	6	7	7	6	0	2	1
>ULN	29	3	8	6	4	4	1	2
Serum albumin								
<3.4 g/dl	23	3	5	7	4	2	1	1
≥3.4 g/dl	28	6	8	4	5	2	2	1
Serum total protein								
≤6.2 g/dl	17	1	2	7	2	1	3	1
>6.2 g/dl	26	8	7	3	6	2		1
Serum ferritin								
<200 ng/ml	9	1	2	2	2	1	3	1
≥200 ng/ml	29	6	7	6	5			2
Hemoglobin								
<10 g/dl	20	1	5	5	3	3	2	1
≥10g/dl	36	8	8	10	7	1	1	2
Platelets								
≥150.000/mm^3	40	8	9	11	7	2	2	1
<150.000/mm^3	16	0	6	2	3	2	1	2
Absolute neutrophil count								
≤6500/mm^3	36	3	1	5	5	3	1	2
>6500/mm^3	19	5	14	8	5	0	2	1
Response to first line treatment available for	**n=57**	**n=8**	**n=16**	**n=13**	**n=12**	**c**	**n=3**	**n=2**
Complete response	23	7	5	3	6	0	2	0
Partial response	7	0	3	1	2	1	0	0
Stable disease	2	0	1	1	0	0	0	0
Progressive disease	25	1	7	8	4	2	1	2
IPI Score available for	**n=55**	**n=9**	**n=13**	**n=13**	**n=11**	**n=4**	**n=3**	**n=3**
0&1	19	6	5	3	3	0	1	1
2&3	28	2	5	9	6	3	1	2
4&5	9	1	3	1	2	1	1	0
NCCN-IPI Score available for	**n=56**	**n=9**	**n=13**	**n=13**	**n=11**	**n=4**	**n=3**	**n=3**
0&1	5	1	1	1	1	1	1	1
2&3	26	8	5	5	5	3	1	2
4&5	22	0	5	7	4	0	1	0
≥6	3	0	2	0	1	0	0	0
PIT score available for	**n=53**	**n=9**	**n=14**	**n=11**	**n=9**	**n=4**	**n=3**	**n=3**
0	13	4	3	2	2	0	1	1
1	15	4	5	2	3	0	1	0
2	13	0	2	6	2	1	1	1
3&4	12	1	4	1	2	3	0	1
ITCLP score available for	**n=56**	**n=8**	**n=16**	**n=13**	**n=10**	**n=4**	**n=3**	**n=3**
0	20	7	5	4	2	1	0	1
1	22	1	6	6	4	1	3	1
2	12	0	4	2	4	1	0	1
3	3	0	1	1	0	1	0	0
T cell score available for	**n=53**	**n=9**	**n=12**	**n=13**	**n=10**	**n=3**	**n=3**	**n=3**
0	3	1	1	0	2	1	0	0
1&2	36	7	8	9	7	2	2	2
3&4	14	1	3	2	1	0	1	1

ECOG PS: Eastern Co-operative Oncology Group performance score
LDH: Lactate Dehydrogenase
ULN: Upper limit of normal
IPI: International Prognostic Index
PIT: Prognostic Index for PTCL-U
NCCN-IPI: National Comprehensive Cancer Network International Prognostic Index
ITCLP: International T Cell Lymphoma Project

presence of B symptoms (p=0.066) were more frequently detected in patients with poor OS.

As expected, response to first- line treatment was statistically significantly associated with decreased progression (p=0.000) and death (p=0.000) rates. The International Prognostic Index (IPI) (p=0.007), the National Comprehensive Cancer Network (NCCN)-IPI (p=0.03) were effective in discriminating progressive cases in ALK- negative, but not in ALK- positive group. The NCCN-IPI (p=0.035) was effective to predict deaths in ALK- negative group.

Deaths& Secondary Malignancies

Forty-one patients (66%) died during the follow-up period. Most common etiologies were progressive disease and infections.

Four patients developed secondary malignancies including esophageal squamous cell cancer in 1 EATCL; myelodysplastic syndrome in 1 HSTCL 1 HL in 1 PTCL and multiple myeloma in 1 PTCL patient . None of them had radiotherapy history and the median follow-up time was 73 months (range: 27-156 months).

DISCUSSION

PTCLs are less responsive to conventional anthracycline- based regimens. Savage et al. reported that the ORR with anthracycline-based treatment was 73% for PTCL, with 3-year PFS and OS rates of 32% and 52%, respectively. Compared to ALK- negative PTCLs, ALK-positive group was reported to have better 5-year FFS (60% vs 36%, p=0.015) and OS (70% vs 46%, p=0.016) rates [3]. In the Japanese experience, 5-year PFS and OS rates for PTCL-NOS were 28% and 35%, respectively. The 5-year OS rate was almost 60% for patients consolidated with auto-SCT (20).With a median OS of 1.59 years, the 4-year OS rate was 34% in the Australian cohort [21]. In our cohort, the ORR to the first- line treatment was 52%. Five-year PFS, and OS rates were 19% , and 26%, respectively. Five-year PFS rates were 66% and 19% for ALK+ALCL and non-ALK+ groups, respectively. Similarly, 5-year OS rate was 75% for ALK+ALCL group and 18% for the rest of the cohort.

The place for SCT as consolidation treatment is for PTCLs still debatable. Reimer et al reported that 66% of PTCL patients were able to proceed to SCT consolidation. All 55 patients kept their response following transplantation and the 3-year OS and PFS rates were 48% and 36%, respectively [22]. CHOEP followed by high dose therapy and SCT was reported to be effective for ALK-negative PTCL patients, with 5-year PFS and OS rates of 44% and 51%, respectively [23]. Better OS rates were also reported in a Japanese cohort [20]. In our cohort, patients who had consolidative auto-SCT had better OS rates (75% vs 41%; p=NS). On the other hand, auto-SCT following salvage treatment did not improve the outcome.

To predict the prognosis in PTCLs, variable risk factors were defined elsewhere [6-10] and many efforts were made for amelioration [20,21,24]. In our study, there were no risk factor associated with OS and PFS in ALK+ ALCL patients. For ALK- negative group, IPI [1], NCCN-IPI [10] scores were able to discriminate risk groups to predict PFS and, NCCN-IPI was able to discriminate risk groups to predict OS. We, with this study observed that high stage disease, serum albumin <3.4g/dl, serum total protein ≤6.2g/dl, high serum LDH, serum ferritin > 200 ng/ml, presence of B symptoms, and extranodal involvement of more than one site at the time of diagnosis were associated with disease progression in ALK -negative patients in the univariate analysis. Serum albumin <3.4g/dl, serum total protein ≤6.2g/dl, serum ferritin > 200 ng/ml, bone marrow involvement at the time of diagnosis were associated with death. In the multivariate analysis, high serum LDH and extranodal involvement of more than one organ were found to be significant to predict progression, whereas only bone marrow involvement was associated with death.

Our study showed a secondary malignancy risk which is not a well-known entity for PTCL. Thus, in patients with extended follow-up, evolving secondary malignancies should be kept in mind.

One of our patients was initially diagnosed as having HL however, PTCL-NOS was defined in the re-evaluation emphasizing the still challenging complexity of the PTCLs.

The survival rates in our study were lower compared to literature, which may be due to exclusion of 'untreated' patients in the majority of the studies. Our study is a reflection of the 'real-life'. The experience with 3 patients, who died due to disease progression after diagnosis without receiving treatment, point out aggressiveness of the disease and we observed also CHOP- based regimen for PTCLs other than ALK- positive ALCLs needs to be replaced by another treatment modality. Although the low number of patients is a

limitation of our study, it is a single- center study and PTCLs are rare types among NHLs.

A recently published study has suggested that patients receiving novel agents have superior outcomes compared to cases who received chemotherapy-based treatments [25]. However, newer agents are still being searched for the optimal treatment to be given. Although DUSP22 was defined as a favorable prognostic factor for ALK- negative group [11], advances in molecular research could not still compare this group to other types of NHL, which may be seen in scarce number of PTCL patients and multi-center comprehensive organizations should be realized . More effective prognostic indices are needed to better stratify PTCL patients, to define the subgroup which might have advantage of SCT consolidation so as to be able to suppress the disease early in its nature.

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Informed Consent: Informed consent was taken from all the participants.

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Original Article

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Medical Journal of Bakirkoy

The Utility of the Callosal/Supratentorial-Supracallosal Area Ratio to Evaluate Corpus Callosum Morphometry in Children

Çocuklarda Kallosal/Supratentoryal-Suprakallosal Alan Oranının Korpus Kallosum Morfometrisini Değerlendirmede Yararlılığı

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ABSTRACT

Objective: *To perform morphometric analysis of corpus callosum (CC) by using callosal area (CA), supratentorial-supracallosal area (SSA) and CA/SSA parameters in a healthy pediatric population and to investigate changes according to age and gender.*
Method: *Method: This retrospective study included a total of 313 children (154 boys, 159 girls) aged between 3-17 years. The cases were divided into three groups according to age: 3-6 years (Group 1) (pre-school), 7-12 years (Group 2) (preadolescent) and 13-17 years (Group 3) (adolescent). CA and SSA were measured on the mid-sagittal plane on T1-weighted images. CA/SSA index was calculated. Differences in age, CA, SSA, and ratio parameters among the gender groups were compared using the Mann-Whitney U or the t-test.*
Results: *Median values of CA (p= 0.002), mean values of SSA (p=0.001) and CA/SSA ratios (p= 0.04) were significantly higher in boys compared to girls. The median CA and mean CA/SSA ratios in Group 3 were significantly higher than Groups 1 and 2 (p= 0.001). Mean CA/SSA ratio values of boys and girls in Age Group 3 were significantly higher than Group 1 (p= 0.001) and significantly higher than Age Group 2 in girls. There were highly significant positive correlations of age with CA (p=0.001, r=0.47), SSA (p=0.028, r=0.12) and CA/SSA ratio (p=0.001, r=042). There was a highly significant and positive correlation between CA and SSA (p=0.001, r=0.25) and CA/SSA ratio (p=0.001, r=0.87).*
Conclusion: *CA, SSA, and CA/ SSA ratio values in children are affected by age and gender. These parameters can be used as reference values for the diagnosis of congenital and acquired pathologies affecting the corpus callosum.*

Keywords: *Corpus callosum, morphometry, children, magnetic resonance imaging*

ÖZ

Amaç: *Sağlıklı bir pediyatrik popülasyonda kallozal alan (KA), supratentoryal-suprakallosal alan (SSA) ve KA / SSA parametrelerini kullanarak korpus kallozum (KK)'un morfometrik analizini yapmak ve yaş ve cinsiyete göre değişimi araştırmak.*
Yöntem: *Bu retrospektif çalışma, 3-17, 154 erkek ve 159 kız arasında toplam 313 çocuğu kapsamaktadır. Olgular yaşa göre üç gruba ayrıldı: 3-6 yaş (Grup 1) (okul öncesi), 7-12 yaş (Grup 2) (preadolesan) ve 13-17 yaş (Grup 3) (ergen). KA ve SSA, T1 ağırlıklı görüntülerde sagittal düzlemde ölçüldü. KA / SSA indeksi hesaplandı. Cinsiyet grupları arasındaki yaş, KA, SSA ve oran parametrelerindeki farklılıklar ''Mann-Whitney U'' veya t testi kullanılarak karşılaştırıldı.*
Bulgular: *Ortalama medyum (çeyrekler arası aralık) değerleri KA (p=0,002) ve ortalama SSA değerleri (p=0,001) ve KA / SSA oranları (p=0,04) erkeklerde kızlara göre anlamlı olarak daha yüksekti. Grup 3'teki ortanca KA ve ortalama KA / SSA oranları grup 1 ve 2'den anlamlı olarak yüksekti (p=0,001). Grub 3'deki kız ve erkeklerin ortalama KA / SSA oranı değerleri Grup 1'den anlamlı olarak yüksek (p=0,001) ve kızlarda yaş grubu 2'den anlamlı olarak daha yüksekti. KA (p=0,001, r=0,47), SSA (p=0,028, r=0,12) ve KA / SSA oranı (p=0,001, r=0,42) ile yaş arasında anlamlı pozitif korelasyon vardı. KA ile SSA (p=0,001, r=0,25) ve KA / SSA oranı (p=0,001, r=0,87) arasında yüksek derecede anlamlı pozitif korelasyon vardı*
Sonuç: *Çocuklarda KA, SSA ve KA / SSA oranı değerleri yaş ve cinsiyetten etkilenmektedir. KK'u etkileyen konjenital ve edinilmiş patolojilerin tanısında referans değerler olarak kullanılabilir.*

Anahtar kelimeler: *Korpus kallozum, morfometri, çocuklar, manyetik rezonans görüntüleme*

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INTRODUCTION

The corpus callosum (CC) is a commissural structure consisting of nerve fibers that provide the connection between the cortical and subcortical neurons of the two cerebral hemispheres [1]. This white matter structure, consisting of at least 200-300 million fibers, is critical for the transfer of sensory, motor and cognitive information [2]. The CC anatomically consists of four parts: rostrum, genu, body and splenium. While other parts of the CC develop in the intrauterine 8th to 20 th weeks, the rostrum develops 18-20 weeks after postconceptional age [3]. The main determinant of CC size is the degree of myelination of the fibers. There is rapid growth within the first 1-4 years after birth and can continue until the third decade of life [4].

In recent years, many morphometry studies have been published investigating the relationship between the appearance of clinical signs of various developmental disorders and pathological conditions and the morphology of the CC [5-7]. Different pathological processes such as mental disorders, dyslexia, autism, speech dysfunction, seizure, and Alzheimer's disease were shown to cause changes in the morphology of the CC [8-10]. Different measurement methods and studies published have shown that the shape and dimensions of the CC can vary according to age, gender, size of the brain and societies [11,12]. In one of these methods, Erdoğan N, et al. reported a morphometric index defined by the proportion of callosal area (CA) and supratentorial-supracallosal areas (SSAs) [13]. The described index was used in the adult population and reported to be a reliable tool in the morphometric analysis of the CC for the evaluation of conditions such as developmental deficiency (hypogenesis) or widespread loss of white matter [13]. However, there are not enough scientific studies about the use of this index in childhood.

This study aims to perform morphometric analysis of CC and investigate its change by age and gender using CA, SSA and CA/SSA parameters in healthy pediatric and adolescent populations.

MATERIAL and METHODS

Study Design and Subject Selection

This study was approved by the local ethics committee and the study was carried out in accordance with the principles of Helsinki Declaration. Since the study was conducted retrospectively, "informed consent" was not received from the parents. No personal information about the cases was given and the radiological images were presented anonymously. In this retrospective study conducted in a single center between January-May 2020, the brain MRI of a total of 313 cases including 154 boys and 159 girls aged 3-17 years, were examined.

The MR imaging examinations were performed in children presenting with findings possibly associated with cerebral pathology including for example, headache, seizures, myoclonia, dizziness, balance disorders, abnormal visual findings, deafness, precocious puberty, facial palsy, scalp midline mass or cyst without any cerebral abnormality. Children with metabolic or neuropsychological disorders, cerebral mass, cerebral malformation, trauma, cranial hematoma or hypoxic injury, intracranial hemorrhage, edema, hydrocephalus, cranial malformation, cerebral atrophy and multiple extracerebral malformations, any pathologic cranial findings, premature birth, and insufficient image quality were excluded from the study. The cases were divided into three groups according to age: 3-6 years (Group 1) (preschool), 7-12 years (Group 2) (preadolescent) and 13-17 years (Group 3) (adolescent).

MRI Technique and Image Analysis

The MRI examination was performed using a 1.5-T imager (Siemens Magnetom Aera; Siemens AG Healthcare Sector, Erlangen, Germany) with a standard head coil. From the survey scans, T1-weighted (T1-W) mid-sagittal sections through the anterior and posterior commissures and axial sections through the third ventricle were obtained for measurements. Parameters for T1-W images were as follows: FOV: 230 mm, matrix: 256 x 256, slice thickness: 5 mm, interslice gap: 1 mm, NEX: 2- 3, TR/ TE: 562/ 14 msec. FLAIR sequence was obtained to exclude cases where pathological signal changes might occur.

Evaluation of MRI was performed by a pediatric radiologist with more than 8 years of pediatric neuroradiology experience. Firstly, the section showing the CC and SSA parenchyma in midsagittal T1-W images was selected for evaluation. The borders of the CA and SSA were drawn free-hand separately (Figure 1 a, b). During the drawing, special attention was paid to the lines

passing through the boundary of the dura and calvarium in order not to affect the results of cortical gray matter changes. The calculation of the area was done automatically by the device. The index was calculated by proportioning the resulting field values.

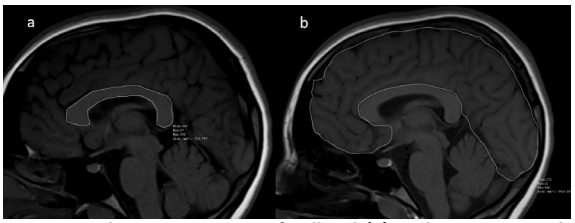
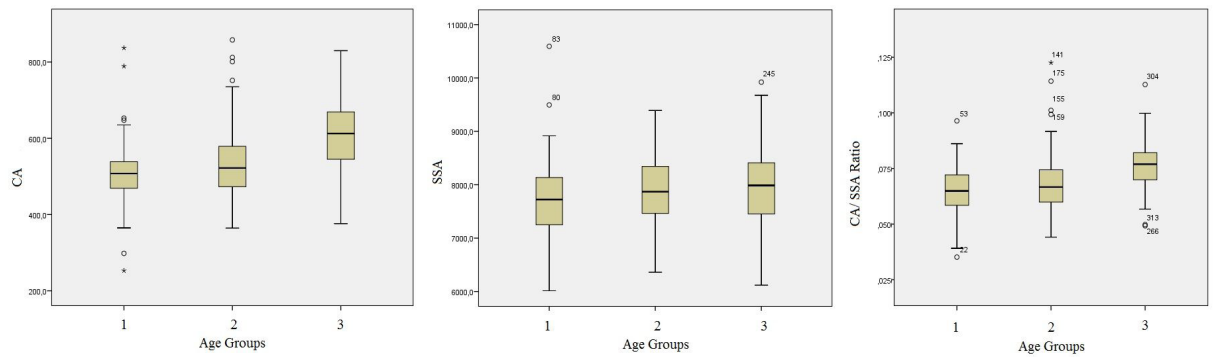


Figure 1 a, b. Measurement of callosal (a) and supratentorial-supracallosal (b) area in mid-sagittal plane on T1-weighted MR images

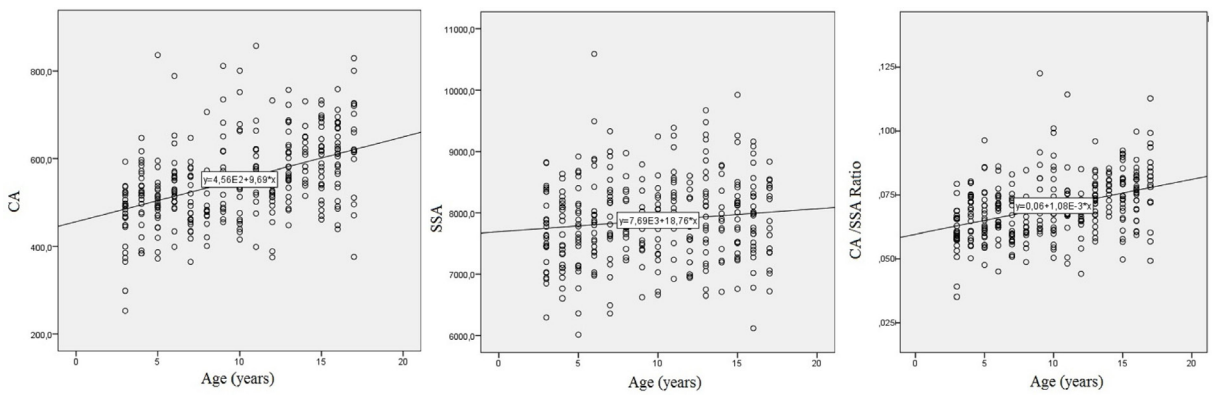
Statistical Analysis

All data were processed in Microsoft Office Excel and transferred to SPSS (version 21.0, IBM Corp.) for statistical analysis. The distribution of the data was assessed with the Kolmogorov-Smirnov test paying attention to skewness and kurtosis. Descriptive statistics of the data were expressed as mean ± standard deviation or median with interquartile range (IQR). Differences in age, CA, SSA, and ratio parameters among the gender groups were compared using the Mann-Whitney U or the t-test. Differences in age, CA, SSA, and ratio parameters among the three age groups were compared using the Kruskal-Wallis or ANOVA test. A comparison between two age groups was assessed using the Mann-Whitney U or the t-test. Correlation analysis of the age, CA, SSA, and ratio parameters were tested with Spearman's correlation analysis. Box-plot graphics demonstrating CA, SSA, and CA/SSA ratio by age groups were plotted (Graphic 1).

The scattered dot graph was plotted for correlation of age with the CA, SSA, and CA/SSA ratio parameters (Graphic 2). Regression equations were obtained with linear regression analysis. Variables were studied at the 95% confidence interval, and p- values below 0.05 were considered statistically significant.



Graphic 1. Spearman's correlation analysis. Box-plot graphics demonstrating CA, SSA, and CA/SSA ratio by age groups



Graphic 2. The scattered dot graph. Correlation of age with the CA, SSA, and CA/SSA ratio parameters

Table 1.Descriptive statistics of age, CA, SSA and ratio parameters by gender groups

Parameter	Descriptive statistics		p
	Mean±Std. Dev. / Median (IQR)		
	Girls (n: 159)	Boys (n:153)	
Age (years)	10 (6-15)	10 (5-13)	0.58'
CA (mm^2)	524 (469.7-580)	559 (493-641)	0.002'
SSA (mm^2)	7734.75 ± 628.3	8018.4 ±732.1	0.001*
CA / SSA Ratio	0.069±0.011	0.071 ± 0.013	0.04*

*P-values by the Mann-Whitney U' and t-test**
Bold p-values represent statistically significant results
IQR: Interquartile range

RESULTS

Descriptive statistics for age, CA, SSA, and CA/SSA ratio parameters in gender and age groups are given in Tables 1 and 2. No significant difference was found among the median ages of the males (10 [5-13]) years) and females (10 [6-15]) years) (p=0.58). Median (interquartile range) values of CA (p= 0.002), and mean values of SSA (p=0.001) and CA/SSA ratios (p=0.04) were significantly higher in boys compared to girls. There were statistically significant differences in median CA and mean CA/SSA ratios among age groups. The median CA and mean CA/SSA ratios in Group 3 were signifi-

Table 2. Descriptive statistics of age, CA, SSA, and CA / SSA ratio parameters by age groups

	Group 1	Group 2	Group 3	p	
	3-6 years (n:100) Mean± Std. Dev./Median (IQR)	7-12 years (n:104) Mean±Std. Dev. / Median (IQR)	13-17 years (n:109) Mean±Std. Dev. / Median (IQR)		
Age (years)	4 (3-5)	9 (8-11)	15 (14-16)	0.001*	1 vs 2: 0.001' 1 vs 3: 0.001' 2 vs 3: 0.001'
CA (mm^2)	507.65 (468.57-538.82)	522 (472-579.5)	612.6 (543.9-670.2)	0.001*	1 vs 2: 0.09' 1 vs 3: 0.001' 2 vs 3: 0.001'
SSA (mm^2)	7745.6 ± 704.3	7901.8 ± 650.5	7966.92 ± 712.36	0.062§	-
CA / SSA Ratio	0.065 ± 0.01	0.068 ± 0.013	0.076 ± 0.01	0.001§	1 vs2: 0.17''

P-values by the Kruskal Wallis and Mann-Whitney U' or ANOVA§ and t-test''*
Bold p-values represent statistically significant results

Table 3. Comparison of mean/ median values of age, CA, SSA and CA / SSA ratio parameters in boys and girls by age groups

		Age groups			p	
		Group 1 3-6 years (n:50) Mean ±Std. Dev/ Median (IQR)	Group 2 7-12 years (n:52) Mean±Std. Dev/ Median (IQR)	Group 3 13-17 years (n:57) Mean±Std. Dev/ Median (IQR)		
Age (years)	Girls	5 (4-6)	9 (7-11)	15 (14-16)	0.001	1 vs 2: 0.001'' 1 vs 3: 0.001'' 2 vs 3: 0.001''
	Boys	4(3-5)	9.5(8-11)	15(13-16)	0.001	1 vs 2: 0.001'' 1 vs 3: 0.001'' 2 vs 3: 0.001''
CA (mm^2)	Girls	510.15 (460.7-533.5)	492.65 (455-557.1)	582.1 (534.4-624.7)	0.001	1 vs 2: 0.84'' 1 vs 3:0.001'' 2 vs 3: 0.001''
	Boys	506.75 (474.6- 571.25)	540.5 (494-610.5)	631.6 (851-684.5)	0.001	1 vs 2: 0.07'' 1 vs 3:0.001'' 2 vs 3: 0.001''
SSA (mm^2)	Girls	7599.14±542.15	7845.71±663.8	7752.48±653.56	0.13*	-
	Boys	7892.06 ±815.21	7957.93±638.4	8203.9±712.5	0.08*	
CA / SSA Ratio	Girls	0.065±0.008	0.065±0.01	0.075±0.01	0.001*	1 vs 2: 0.99‡ 1 vs 3: 0.001‡ 2 vs 3: 0.001‡
	Boys	0.066±0.01	0.072±0.015	0.077±0.01	0.001*	1 vs 2: 0.054‡ 1 vs 3: 0.001‡ 2 vs 3: 0.092‡

P-values by the Kruskal Wallis and Mann-Whitney U' or ANOVA§ and t-test''*
Bold p-values represent statistically significant results

cantly higher than Groups 1 and 2 (p=0.001). No significant differences were found in median CA and mean CA/SSA ratios in Age Groups 1 and 2. No significant differences were found in mean SSA values among age groups (p=0.062).

Because of significant differences among gender groups, we assessed the descriptive statistics and comparisons among age groups paying attention to the genders in each age group. Descriptive statistics of the age, CA, SSA, and CA/SSA ratio parameters in boys and girls by Age Group are given in Table 3. The median values of CA in both boys and girls in Age Group 3 were significantly higher than age groups 1 and 2 (p=0.001). However, there were no significant differences in median CA values of boys and girls between Age Groups 1 and 2. There were no significant differences in mean SSA values of boys and girls among the age groups. Mean CA/SSA ratio values of boys and girls in Age Group 3 were significantly higher than Age Group 1 (p=0.001) and significantly higher than Age Group 2 for girls. No significant difference was found in CA/SSA ratios of boys and girls between age groups 1 and 2.

Correlation of age, CA, SSA and CA/SSA ratio parameters along with linear regression equations are given in Table 4. There were highly significant positive correlations of age with CA (p=0.001, r=0.47), SSA (p=0.028, r=0.12) and CA/SSA ratio (p=0.001, r=0.42). There were highly significant moderate positive correlations among CA with SSA (p= 0.001, r= 0.25) and CA/SSA ratio (p= 0.001, r= 0.87). Age-dependent regression equations were as follows: "CA (mm^2) = 456 + 9.69 x Age (years)", "SSA (mm^2) = 7693+ 18.76 x Age (years)", and "CA/ SSA ratio=0.06+1.08/1000x Age (years)". The CA-dependent regression equation for SSA was "SSA (mm^2) = 6740 + 2.07x CA (mm^2)".

Table 4. Correlation of age, CA, SSA and CA/SSA ratio parameters along with linear regression equations

	p	r	Regression equations
Age- CA	0.001	0.47	CA (mm^2)= 456+ 9.69 X Age (years)
Age- SSA	0.028	0.12	SSA (mm^2) =7693+18.76 X Age (years)
Age- CA/SSA ratio	0.001	0.42	CA/SSA ratio =0.06 + 1.08/1000 x Age (years)
CA-SSA	0.001	0.25	SSA (mm^2) =6740 + 2.07 X CA (mm^2)

DISCUSSION

Corpus callosum (CC) is the main commissural structure that connects both cerebral hemispheres, and many factors may affect its morphology including developmental anomalies, myelination disorders, and degenerative, ischemic or traumatic axon losses. It affects development in association with demographic differences such as age, gender, right or left-handed dominance, and ethnic group [12-14]. In a recent study of the Turkish population with 436 adult cases, thickness and vertical length measurements were made in different sections of the CC and it was reported that there could be gender differences for all parameters [12]. In a study conducted in Iran, in which morphometric analyses were used based on the measurements of frontal occipital pole of the brain, longitudinal size of the brain - the genus of CC, the occipital pole of the brain - the splenium of CC and the point from the posterior point of the front of CC to the poster length, parameters were higher in males than females [14]. WHA Ng et al. reported that the CC was thicker in Chinese boys than girls [15]. In two different studies using CA, SSA and CA/SSA ratio parameters in the adult population, these parameters differed according to gender and were shown to be higher in males [11,13]. In this study, CA, SSA, and CA/SSA ratio parameters were used for the first time in children and they were higher in boys in all age groups. The results were similar to previous morphometric measurements. These results may have occurred due to developmental and hormonal differences in children. In terms of providing reference data for morphometric studies, these data should be supported with future biochemical and hormonal data.

There are important differences in brain development during adolescence. White matter development is affected by sex hormones such as testosterone. The corpus callosum, the largest white matter structure in the brain, changes structurally in the pubertal period when hormonal changes occur [16]. Chavarria MC et al. reported the increase in callosal thickness progressed during adolescence in children and adolescents. In the same study, they stated that callosal parts were affected differently by pubertal growth [17]. In a morphometric analysis of the CC performed up to 15 years after birth, it has been reported that callosal length and thickness increase with age [18]. The parameters used in this study (CA, SSA, and CA/SSA ratio) increased with

age and the highest values appeared in the adolescent period. The change with age was similar to measurements made with different parameters in previous years. However, since this study had a retrospective nature, real hormone levels could not be measured; therefore, a possible relationship between hormone levels and parameters could not be revealed. Diffusion tensor imaging (DTI) and fiber monitoring techniques allowed the CC to be separated into bands corresponding to functional units. DTI-based fiber tractography can help to show whether callosal effects are associated with cortical changes in adolescence [5]. DTI studies, along with hormonal tests in the future, will help to clarify the relationships and the underlying mechanisms between pubertal status and neurodevelopment.

There are important limitations in our study. The first is the low number of patients and that cases younger than three years old were excluded from the study. Second, since it was performed retrospectively, data about height, weight, BMI, hormone values and ethnic origin of the cases could not be obtained. Thirdly, intra-observer and inter-observer comparisons could not be made since the evaluations were made by only one observer. Finally, clinical and laboratory data used to support the fact that subjects are healthy were provided only from the electronic archive system. We cannot completely exclude potential underlying pathological changes that involve the brain parenchyma.

Conclusion

In conclusion, CA, SSA and CA/ SSA ratio parameters provide important contributions to the morphometric evaluation of CC in children. The depicted values vary according to age and gender. It can be used as reference values for the diagnosis of various congenital and acquired pathologies affecting the CC. Future studies will contribute to the understanding of callosal development by using hormonal tests and other radiological methods.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of Selcuk University (08.01.2020, 06/2020)

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Informed Consent: Written informed consent could not be obtained due to the retrospective nature of the study.

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Original Article

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Medical Journal of Bakirkoy

Comparison of Immigrants and Turkish Patients Hospitalized in the ICU with the Diagnosis of Gastrointestinal Cancer in Terms of Malnutrition and Its Effects on Mortality

Yoğun Bakım Ünitesinde Gastrointestinal Kanser ile Yatan Hastalarda Malnutrisyon ve Mortalite Üzerindeki Etkileri Açısından Göçmen ve Türk Hastaların Karşılaştırılması

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ABSTRACT

Objective: *The aim of this study was to compare the effects of malnutrition on mortality in immigrants and Turkish patients hospitalized in our ICU with the indication of gastrointestinal cancer.*
Method: *This study was performed as a prospective observational study. One-hundered and three (41.3%) patients were Turkish and 146 (58.7%) were immigrants (all Syrian). Age, body mass index (BMI), duration of hospitalization, albumin value, and 30-day and 6-month mortality rates were evaluated. Also, the following assessment tools were calculated: Subjective Global Assessment (SGA), Nutrition risk screening-2002 (NRS), Charlson Comorbidity Index (CCI) Acute Physiology and Chronic Health Evaluation (APACHE) II and III.*
Results:*In total, 150 (60.2%) patients had moderate (SGA B), while 71 (28.5%) patients had severe malnutrition (SGA C). The frequency of SGA C in the immigrants was significantly higher than Turkish ciitzens (p=0.004). The overall mortality rate in our study was 36.9%. No significant difference was found between Turkish citizens and immigrants in terms of overall mortality (p=0.592). Albumin value, APACHE II, APACHE III, CCI and NRS scores were significantly higher in those that died within 30 days. The APACHE 3 score was the most successful tool in predicting 30-day mortality according to ROC analyses.*
Conclusion: *This study revealed that malnutrition is a significant problem for both immigrants and Turkish citizens hospitalized in the ICU. Although there are tools specific for malnutrition assessment, APACHE III score was found to have the highest likelihood to predict mortality.*

Keywords: *Malnutrition, immigrants, subjective global assessment, mortality*

ÖZ

Amaç: *Bu çalışmanın amacı, mide bağırsak kanseri nedeniyle yoğun bakım ünitemize yatırılan göçmen ve Türk hastalarda malnütrisyonun mortalite üzerindeki etkilerini karşılaştırmaktır.*
Yöntem: *Bu çalışma ileriye dönük gözlemsel çalışma olarak yapıldı. Hastaları 103'ü Türk (% 41,3), 146'sı (% 58,7) göçmendi (Tümü Suriyeli). Yaş, vücut kitle indeksi (VKİ), hastanede kalış süresi, albümin değeri ve 30 günlük ve 6 aylık mortalite değerlendirildi. Ayrıca, aşağıdaki değerlendirme skorlamaları hesaplandı: Subjektif Global Değerlendirme (SGA), Nütrisyon Risk Değerlendirmesi-2002 (NRS), Charlson Komorbidite İndeksi (CCI) Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi (APACHE) II ve III.*
Bulgular: *Toplamda 150 (% 60,2) hastada orta düzeyde yetersiz beslenme (SGA B) varken 71 (% 28,5) hastada şiddetli beslenme bozukluğu (SGA C) vardı. Göçmenlerde SGA C sıklığı Türk vatandaşlarına göre anlamlı olarak daha yüksekti (p = 0,004). Çalışmamızdaki genel ölüm oranı% 36,9'du. Genel ölüm oranları açısından Türk vatandaşları ve göçmenler arasında anlamlı bir fark bulunmadı (p = 0.592). 30 gün içinde ölenlerde albümin değeri, APACHE II, APACHE III, CCI ve NRS skorları anlamlı olarak yüksekti. APACHE 3 skoru, ROC analizlerine göre 30 günlük mortaliteyi tahmin etmede en başarılı olanıydı.*
Sonuç: *Bu çalışma yetersiz beslenmenin hem göçmenler hem de yoğun bakım ünitesinde yatan Türk vatandaşları için önemli bir sorun olduğunu ortaya koymuştur. Yetersiz beslenme değerlendirmesi için özel araçlar olmasına rağmen, APACHE III skorunun mortaliteyi tahmin etme olasılığının en yüksek olduğu bulunmuştur.*

Anahtar kelimeler: *Malnütrisyon, göçmenler, subjektif global değerlendirme, mortalite*

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INTRODUCTION

In recent years, the war in Syria has led to the spread of large immigrant groups to many countries including Turkey. When people migrate, the first requirements are the most basic human needs, such as nutrition and health care. Immigrants have often faced several problems, the most important of them being nutritional deficiency in areas where they migrate to take refuge [1,2].

Although malnutrition has been shown to disproportionately affect children, it can also be seen in adults, especially in the elderly, and may cause significant health problems [3,4]. In general, malnutrition in adults is associated with a decrease in general functional status and reduced bone mass, immune dysfunction, delayed postoperative recovery, higher hospitalization and readmission rates, and increased mortality [5,6].
In disadvantaged groups such as refugees or immigrants, the impact of malnutrition on overall health is more pronounced [7]. Malnutrition in immigrants and refugees should be viewed not only as a health issue, but also as a serious lack of access to basic human rights. Although there are many studies on the effect and frequency of malnutrition in child immigrants, very few studies have assessed its impact on the adult age group [8-10].

The aim of the present study is to compare hospitalized adult immigrants and Turkish patients with gastrointestinal cancer in intensive care units (ICU) in terms of malnutrition and its effects on mortality.

MATERIAL and METHODS

Patients

This is a prospective study including 249 patients, who were hospitalized at our intensive care unit (ICU) between October 2017 – December 2018. All subjects had a diagnosis of colorectal or non-colorectal gastrointestinal cancer and were consulted to the Department of Nutrition and Dietetics at xxxxxxx hospital/medical faculty with suspect malnutrition. All subjects were followed for six months (the first follow up visit was scheduled one month after discharge). Hundred and three (41.3%) patients were Turkish citizens and 146 (58.7%) were immigrants. All the immigrants were Syrians. Inclusion criteria were as follows: having a gastrointestinal cancer (colorectal or non-colorectal), being consulted to our nutrition team due to a suspicion for malnutrition, accepting to participate in the study by providing written informed consent, and not being an alcohol or drug abuser. Exclusion criteria were as follows: being younger than 18 years of age, having any diagnosis other than colorectal or non-colorectal gastrointestinal cancer and refusing to participate in the study or withdrawing at any time.

Ethics

Measurements

Age, body mass index (BMI), duration of hospitalization, albumin value and mortality (30-day and 6-month) were evaluated in all patients. Mortality was assessed as intra-hospital and overall mortality at both 30 days and 6 months. In addition, the screening tools explained below were used to assess malnutrition and mortality. All screening tools were applied under the supervision of two researchers from the Department of Nutrition and Dietetics.

Subjective Global Assessment

Subjective Global Assessment (SGA) is an assessment consisting of history of weight loss and dietary intake, gastrointestinal symptoms, functional capacity, metabolic requirement and physical examination. After scoring, patients were classified into three groups (A, B and C) as follows: well-fed: Group A, moderate malnutrition: Group B, severe malnutrition: Group C.

Nutrition Risk Screening-2002

Nutrition risk screening-2002 (NRS) was developed in 2002 by Kondrup et al. [11]. It is comprised of a 2-step screening process, the first 'initial screening' assesses the presence of the following: BMI value below 20.5 kg/m2, weight loss within the last 3 months, reduction in dietary intake within the last week, and being hospitalized in an intensive care unit. If none of these conditions are met, the patient is considered 'low risk' for malnutrition; however, if any of these four conditions are met, then the 'final screening' step (comprised of 3 questions about nutritional status, disease severity and age). Nutritional status and disease severity are scored from 0 to 3 points, while age is scored with regard to being younger or older than 70 years (0 and 1 point, respectively). The risk of malnutrition according to the final score was assessed as follows: low risk: 0–3 pts; at risk, 4 pts, and 'high risk 5-7 pts.

Acute Physiology and Chronic Health Evaluation

Acute Physiology and Chronic Health Evaluation (APACHE) II was developed by Knaus et al.[12] in 1985 and is the most widely used scoring system for the

evaluation of survival. It consists of three parts: acute physiology score, age and chronic health assessment. The range of the APACHE II score is from 0 to 71 points. As the total score increases, the estimated mortality rate also increases.

The APACHE III scoring system is a renewed and updated version of the APACHE II system [13]. Simply put, the diagnoses of primary disease section used in APACHE II are expanded and the clinic at which the patient is receiving care (intensive care, emergency room, ward etc.) is included in the assessment. The score range of the APACHE III is from 0 to 299 points, with higher scores indicating worse prognosis.

Charlson Comorbidity Index

Charlson Comorbidity Index (CCI) was developed by Charlson et al. [14]. In this scale, diseases that correlate with 1-year mortality are evaluated and scores are given according to patients' relative risks.

Statistical Analysis

The IBM SPSS Statistics software v21.0 (SPSS Inc., Chicago, IL) was used for all data analyses. Descriptive data were presented as numbers (n), percentages (%), mean ± standard deviation and median (range). The Kolmogorov- Smirnov test with Lilliefors correction was used to evaluate the normality of distribution of quantitative variables. Continuous variables were compared using the Students t-test or Mann-Whitney U test, depending on normality of distribution. Categorical variables were compared using Pearson's chi-square test or Fisher's Exact test. Receiver operating characteristics (ROC) analysis was used to determine the effectiveness of screening tools (APACHE II, III, CCI and NRS) in predicting mortality. Logistic regression model was used to identify significant independent predictors of mortality. P<0.05 was accepted as the level of statistical significance.

RESULTS

The study group consisted of 249 patients (135 males, 114 females). The mean age of the study group was 61.3 ± 16.5 years. According to SGA, 150 (60.2%) patients had moderate (SGA B), while 71 (28.5%) patients had severe malnutrition (SGA C). The frequency of SGA C (severe malnutrition) in the immigrant group was significantly higher than Turkish citizens (p=0.004). There were no significant differences between Turkish citizens and immigrants in terms of age and BMI (p>0.05). The duration of hospitalization was significantly longer in immigrants than in the Turkish citizens (p<0.001).

Serum albumin levels were significantly lower in the immigrants compared to Turkish citizens (p=0.014). APACHE II, APACHE III and CCI scores were significantly higher in the immigrant group compared to Turkish citizens (p<0.001 for all). No significant difference was found between the groups in terms of NRS scores (p=0.653). There was no significant difference between the Turkish citizens and immigrants in terms of intra-hospital 30-day and six-month mortality rates (p=0.571 and p=0.069). Also, 30-day overall mortality rate was significantly higher in Turkish citizens (p=0.045); however, six-month overall mortality rates were similar (p=0.080) (Table 1).

Table 1. Comparison of Turkish nationals and immigrants.

	Turkish nationals	Immigrants	p
Age, mean±SD	64.0±14.6	60.0±17.5	0.052
BMI, mean±SD	25.2±6.0	24.5±7.1	0.374
Hospitalization (day), mean±SD	5.3±6.2	11.4±18.4	0.000
SGA, n (%)			
A	15 (14.6%)	13 (8.9%)	
B	70 (68.0%)	80 (54.8%)	0.004
C	18 (17.5%)	53 (36.3%)	
Albumin, mean±SD	2.9±0.6	2.7±0.6	0.014
APACHE II, mean±SD	12.7±8.6	19.0±6.7	0.000
APCAHE III, mean±SD	35.4±23.9	55.4±34.9	0.000
CCI, mean±SD	3.7±2.8	5.2±2.5	0.000
NRS, mean±SD	3.7±0.9	3.6±0.7	0.653
Last situation, n (%)			
Alive	67 (65.0%)	90 (61.6%)	0.592
Dead	36 (35.0%)	56 (38.4%)	
30-day intra-hospital mortality, n (%)			
(-)	98 (95.1%)	141 (96.6%)	0.571
(+)	5 (4.9%)	5 (3.4%)	
6-month intra-hospital mortality, n (%)			
(-)	80 (77.7%)	98 (67.1%)	0.069
(+)	23 (22.3%)	48 (32.9%)	
30-day all mortality, n (%)			
(-)	91 (88.3%)	139 (95.2%)	0.045
(+)	12 (11.7%)	7 (4.8%)	
6-month all mortality, n (%)			
(-)	79 (76.7%)	97 (66.4%)	0.080
(+)	24 (23.3%)	49 (33.6%)	

BMI: Body Mass Index
SGA: Subjective Global Assessment
APACHE: Acute Physiology and Chronic Health Evaluation,
CCI: Charlson Comorbidity Index,
NRS: Nutrition risk screening

Table 2. It showes comparison of preopertive and postoperative patients' VAS. A statistically significant decline in pain control was detected in both groups.

	Alive at 6 months	Died at 1 to 6 months	p	Alive at 30 days	Died within 30 days	p
Age, mean±SD	60.7±16.5	65.6±16.4	0.214	59,8±16,4	64,1±16,3	0,061
BMI, mean±SD	25.1±6.8	21.2±3.6	0.004	24,5±6,6	25,5±6,7	0,358
Hospitalization (day), mean±SD	8,9±15,3	8,6±11,0	0,878	8,7±17,0	9,4±8,3	0,003
SGA, n (%)						
A	28 (12,2%)	0 (0%)		18 (10,2%)	10 (13,7%)	
B	137(59,6%)	13 (68,4%)	0,271	114 (64,8%)	36 (49,3%)	0,074
C	65 (28,3%)	6 (31,6%)		44 (25,0%)	27 (37,0%)	
Nationality, n (%)						
Turkish nationals	79 (44,9%)	24 (32,9%)	0,080	91 (39,6%)	12 (63,2%)	0,045
Immigrant	97 (55,1%)	49 (67,1%)		139 (60,4%)	7 (36,8%)	
Albumin, mean±SD	2,8±0,6	2,6±0,5	0,362	2,9±0,6	2,5±0,5	0,000
APACHE II, mean±SD	15,1±8,6	18,0±6,1	0,067	13,3±7,1	20,0±9,5	0,000
APCAHE III, mean±SD	46,3±31,6	57,7±39,4	0,175	36,8±24,9	72,5±34,6	0,000
CCI, mean±SD	4,2±2,7	5,4±3,7	0,232	4,0±2,6	5,0±3,0	0,017
NRS, mean±SD	3,6±0,8	3,9±1,0	0,233	3,6±0,8	3,9±0,8	0,007

BMI: Body Mass Index
SGA: Subjective Global Assessment
APACHE: Acute Physiology and Chronic Health Evaluation,
CCI: Charlson Comorbidity Index,
NRS: Nutrition risk screening

The BMIs of patients that died within 6 months were significantly lower than those who survived (p=0.004). There was no significant difference between these groups in terms of other variables. Albumin values, APACHE II, APACHE III, CCI and NRS scores were significantly higher in those that died within 30 days (Table 2).

The APACHE 3 score was the most successful in predicting 30-day mortality according to ROC analysis (Table 3).

Table 3. Predicting 30-day mortality

	Area Under the Curve	95% Confidence Interval	p
APACHE 3	0,840	0,787-0,893	0,000
APACHE 2	0,715	0,644-0,786	0,000
CCI	0,596	0,514-0,677	0,020
NRS	0,592	0,513-0,671	0,026

APACHE: Acute Physiology and Chronic Health Evaluation,
CCI: Charlson Comorbidity Index,
NRS: Nutrition risk screening

Albumin and APACHE 3 scores were found to be successful in predicting 30-day mortality in the multivariate model (Table 4).

Table 4. Fracture levels of patients and the amount of collapse

	Univariate Model			Multivariate Model		
	OR	95% Confidence Interval	p	OR	95% Confidence Interval	p
Albumin	0,272	0,158-0,468	0,000	0,457	0,242-0,864	0,016
APACHE II	1,125	1,076-1,176	0,000			
APCAHE III	1,038	1,027-1,050	0,000	1,037	1,025-1,049	0,000
CCI	1,134	1,026-1,253	0,013			
NRS	1,563	1,115-2,191	0,010			
Hospitalization	1,003	0,986-1,021	0,733			

OR: Odds ratio
APACHE: Acute Physiology and Chronic Health Evaluation,
CCI: Charlson Comorbidity Index,
NRS: Nutrition risk screening

DISCUSSION

In the present study, malnutrition among immigrants and Turkish citizens was evaluated and patients hospitalized in the ICU due to colorectal or non-colorectal gastrointestinal cancers were compared in terms of mortality. Overall, we found malnutrition in 221 (88.7%) patients. Of the patients with malnutrition, 88 (39.8%) were Turkish citizens and 133 (60.2%) were immigrants. In our study, malnutrition was more common in immigrants. The frequency of SGA C (severe malnutrition) was significantly higher in the immigrant group compared to the patients with Turkish nationality. Even though, our results demonstrated that malnutrition rates were unexpectedly high in both immigrants and Turkish citizens, this condition may be associated with the fact that many of these patients had been suffering from gastrointestinal cancers and were receiving different types of treatment. Despite the possibility that disease stage, treatment types and patient characteristics could have contributed to the presence and severity of malnutrition, these data identify malnutrition as a high priority target, especially in hospitalized patients. Similarly, in a study where indigenous and non-indigenous people were compared in terms of malnutrition, the overall frequency of malnutrition was reported to be 41.1%, and malnutrition was more common in the non-Indigenous group [15].

The duration of hospitalization was significantly higher in immigrants than in the Turkish citizens ($p<0.001$). Considering that immigrants were in significantly worse state in terms of malnutrition, it is apparent that this finding is in agreement with a study that reported nutritional status as an independent variable for the length of hospital stay [16]. Therefore, we believe that the presence of malnutrition was the cause of prolonged hospital stay among immigrants in the current study.

The overall mortality rate in our study was 36.9 percent. No significant difference was found between Turkish citizens and immigrants in terms of overall mortality. We determined that the APACHE III score and albumin value were successful in predicting mortality. However, it was concluded that the APACHE 3 score was the most successful predictor of mortality. In a study assessing the health-related needs of Syrian refugees conducted in Turkey, it was concluded that malnutrition has become a major health problem in Turkey because malnutrition had an impact on mortality either directly or indirectly [17]. In an another study by Lim et al. [18], it was reported that malnutrition negatively affected the length of hospital stay, re-admission rates and mortality. Thus, we believe that determining the presence or risk of malnutrition at admission is crucial to predict prognosis of the patient and to prevent associated negative health consequences.

The relatively short follow-up duration (six months) is one of the limitations of the current study, since mortality rates, especially those associated with nutrition, may be only evident at longer term follow-up. Another limitation is the fact that treatments for malnutrition and their results were not assessed in this study; therefore, patients that received direct treatment in this regard may have skewed our results. However, the aim of this study was to assess differences between immigrants and Turkish citizens with regard to malnutrition. Nevertheless, future studies should take into account this characteristic of patients. Finally, we also had no data regarding patient admission to other hospitals during follow-up, which may have affected mortality findings.

Conclusion

This study revealed the presence of high malnutrition and mortality rates in immigrants and Turkish citizens that were hospitalized in the ICU due to gastrointestinal cancers. However, it was found that especially severe malnutrition was more frequent in the immigrant group. In addition, this study showed that the APACHE III score was the most successful tool in predicting mortality. In order to prevent negative health consequences of malnutrition, patients should be evaluated in terms of malnutrition and protected from malnutrition, both during hospitalization and after discharge.

Ethics Committee Approval: The study was approved by Ethics Committee of Non-Interventional Clinical Researches of Adana Metropolitan City Research and Training Hospital (Decision No.355 and Decision Date 19.12.2018).
Conflict of Interest: No conflict of interest was declared by the authors.
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Informed Consent: Informed consent was obtained from all individual participants included in the study.

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Original Article

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The Relation of Uric Acid And MPV Levels And Cognitive Functions In Fibromyalgia

Fibromiyalji Sendromunda Serum Ürik Asit ve Ortalama Trombosit Hacmi Düzeylerinin Bilişsel Fonksiyonla İlişkisi

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ABSTRACT

Objective: *Patients with fibromyalgia syndrome (FMS) have mild cognitive dysfunction. Higher serum uric acid (UA) levels in some diseases are reported to be associated with cognitive impairment. Mean platelet volume (MPV) is an indicator of platelet activation. Activated platelets may play a role in neuroinflammation and cognitive dysfunction. The purpose of this study was to compare cognitive functions of FMS patients and controls and investigate the relation of serum UA and MPV levels with cognitive functions.*
Method: *Fifty-four patients with FMS and 33 healthy controls were enrolled,retrospectively. Evaluations were performed with Visual Analog Scale (VAS), Fibromyalgia Impact Questionnaire (FIQ), Beck Depression Inventory(BDI) and to asses phychological status and cognitive impairment Mini Mental State Examination(MMSE) was used in both groups.*
Results: *Mean VAS and sleep quality of FMS group were significantly higher than the control group ($p<0.05$). Mean MMSE score was statistically significantly lower in the FMS group ($p=0.0001$). There was not statistically significant correlation between serum UA levels and VAS pain/sleep quality, FIQ, BDI and MMSE scores ($p>0.05$). No significant correlation was found between serum MPV levels and VAS pain/ sleep quality, FIQ, BDI and MMSE scores ($p>0.05$) but declined cognitive functions were determined in the FMS group when compared with the control group.*
Conclusion: *Declined cognitive functions were determined in the FMS the FMS group when compared with the control group . Although we did not determine an association of serum uric acid and MPV levels with cognitive functions, larger prospective studies with longer follow up periods are warranted to elucidate the role of these biomarkers in FMS and to determine the factors affecting cognitive functions.*

Keywords: *Fibromyalgia syndrome, cognitive function, uric acid, mean platelet volume*

ÖZ

Amaç: *Çalışmalar Fibromiyalji sendromlu (FMS) hastalarda orta derecede kognitif bozukluk olduğunu göstermiştir. Serum ürik asit (ÜA) düzeyleri ile bazı hastalıklarda bilişsel bozukluklar arasındaki ilişki rapor edilmiştir. Ortalama trombosit hacmi (OTH) trombosit aktivasyonunun bir göstergesidir. Aktive trombositler nöroinflamasyon ve bilişsel işlev bozukluğunda rol oynayabilir. Amaç, FMS hastalarında serum ÜA ve OTH düzeylerinin yanı sıra FMS hastaları ve kontrolleri arasındaki bilişsel işlevleri karşılaştırmak ve FMS hastalarında ÜA, OTH ve bilişsel bozukluk arasındaki ilişkiyi araştırmaktı.*
Yöntem: *54 FMS hastası ve 33 sağlıklı kontrol retrospektif olarak değerlendirildi. Ağrıyı değerlendirmek için Visuel Analog Skala (VAS), fonksiyonel durumu değerlendirmek için Fibromiyalji Etki Anketi (FEA), Mini Mental Test (MMT) ile psikolojik durumu ve bilişsel bozukluğu değerlendirmek için Beck Depresyon Envanteri (BDE) kullanıldı*
Bulgular: *FMS grubunun ortalama VAS ve uyku kalitesi kontrol grubuna göre anlamlı olarak yüksek bulundu ($p <0.05$). Ortalama MMT skoru FMS'de kontrollere göre istatistiksel olarak anlamlı derecede düşüktü ($p = 0.0001$). Serum ÜA düzeyleri ile VAS ağrı / uyku kalitesi, FEA, BDE ve MMT skorları arasında istatistiksel olarak anlamlı bir ilişki saptanmadı ($p> 0.05$). Serum MPV düzeyleri ile VAS ağrı / uyku kalitesi, FEA, BDE ve MMT skorları arasında anlamlı bir ilişki bulunmadı ($p> 0.05$), ancak bilişsel işlevler kontrol olgularına göre azaldı.*
Sonuç: *FMS'de kontrol olgularından daha düşük bilişsel işlevler saptandı. Serum ürik asit ve MPV düzeyleri ile bilişsel işlevler arasında bir ilişki belirlememiş olsak da, bu biyobelirteçlerin FMS'deki rolünü aydınlatmak ve bilişsel işlevleri etkileyen faktörleri belirlemek için daha uzun takip süreleri olan daha geniş prospektif çalışmalar yapılması gerekmektedir.*

Anahtar kelimeler: *Fibromiyalji sendromu, bilişsel fonksiyon, ürik asit, ortalama trombosit hacmi*

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INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic pain syndrome, effecting about 3-6% of population and mainly women [1]. It is mostly characterized by diffuse and generalized musculoskeletal pain; sleep disturbance, fatigue and morning stiffness [2]. Accompanying these symptoms, patients with FMS commonly complain from physical and cognitive impairments [3]. Moreover, recently, significant deficiencies in the daily living functions have been reported in patients with FMS [4]. However, it should also be kept in mind that, FMS patients are generally treated with centrally acting drugs which can also cause cognitive impairments [5].

The role of oxidative stress in cognitive impairment has been shown exactly [6]. Uric acid is a member of antioxidant system with its some properties such as scavenging hydroxyl radicals, and peroxynitrite and stabilizing other antioxidant systems including superoxide dismutase and ascorbic acid [7]. Reduced uric acid levels, as marker of augmented oxidative stress, have been associated with cognitive impairment in some diseases before [8,9]. However, recently, elevated levels of uric acid levels, with its vascular effects, were also associated with decline in cognitive functions [10]. To the best of our knowledge the role of uric acid levels in cognitive functions of patients with FMS has not been investigated before.

Other than oxidative stress, inflammation is also a factor accused in the development of cognitive impairment [11]. Mean platelet volume (MPV) is a marker of activated platelets and has been associated with many inflammatory conditions [12-14]. On the other hand, elevated MPV levels were also reported in patients with Alzheimer disease having cognitive impairments [15].

Factors affecting the cognitive functions of patients with FMS are critically important since this condition may alter the life quality of patients. To the best of our knowledge, data about the cognitive impairments in FMS patients is limited. In this study we aimed to compare the cognitive functions of FMS patients with control cases and to determine the effects of uric acid, as a marker of antioxidant status, and of MPV as a marker of inflammation, on cognitive functions in FMS.

MATERIAL and METHODS

This study was carried out in Bakırkoy Training Hospital Physical Medicine and Rehabilitation Department, between December 2014 and February 2015. Totally 54 premenopausal female patients with FMS diagnosed according to 1990, 2010 and 2013 ACR Physical Medicine and Rehabilitation, retrospectively and 33 volunteer healthy age-matched premenopausal women were enrolled. Exclusion criteria were menopausal status, presence of a systemic disorder including hypertension, diabetes mellitus, hematologic disease, autoimmune diseases, renal failure, liver diseases, steroid and anticoagulant use, infectious, inflammatory and cardiovascular diseases, serious psychiatric disorders involving psychotic symptoms, recent risk of suicide or substance abuse and/or neurological disease, pregnancy and abnormal results of routine examinations. The present study has been approved by Local Ethics Committee.

Demographic and Clinical Information

Patient characteristics, mean disease duration, symptoms accompanying FMS and number of tender points were determined. Age (year), height (cm), weight (kg), body mass index (BMI; calculated as weight in kilograms divided by height in meters squared : kg/m^2) presence of fatigue, morning stiffness, sleep disturbance, morning fatigue, paresthesia, headache, Raynaud's phenomena, irritable bowel syndrome, sicca symptoms, female urethral syndrome, sensation of tissue swelling and dysmenorrhea were all recorded.

Laboratory Findings

Venous blood samples were obtained from the antecubital vein, followed by 12 hours fasting. The tubes were centrifuged at 2000 g for 10 min and then the serum portions of the blood samples were discarded The samples were analyzed within an hour. In all cases, MPV and platelet counts were calculated as part of each complete blood count. Complete blood count was measured using Coulter LH 750 auto-analyser (Beckman Coulter, CA, USA). From the blood tests, parathormon (PTH), thyroid stimulating hormone (TSH) and other biochemical parameters were recorded to rule out other diseases mimicking FMS. These parameters were determined by Beckman Coulter's AU5800 Clinical Chemistry, DXI 800 immunoassay auto-analyser and using commercial kits (Beckman Coulter, CA, USA).

Serum C-reactive protein (CRP) was measured with Siemens BNII nephelometric system (Siemens Healthcare Diagnostics, USA) using reagents and protocols provided by the manufacturer.

Visual Analog Scale (VAS) was used to evaluate pain and sleep quality, and Fibromyalgia Impact Questionnaire (FIQ) wasused to assess functional status of patients. Beck Depression Inventory (BDI) was used to evaluate depressive symptoms and the frequency of cognitive impairment was evaluated with Mini Mental State Examination (MMSE) [16].

VAS is a measurement instrument used to assess pain and sleep quality. It is a 10-cm scale with "no pain" at the beginning and "the worst possible pain" at the other end. Scores are recorded by the patient with a mark on the line according to pain intensity. Sleep quality was also evaluated by a similar scale 10 cm in length, "I have a good sleep" at the beginning and "I have a bad sleep" at the end.

FIQ is an evaluation instrument for FMS. It measures components of health status that are affected by FMS. The total score ranges from 0 to 100 and high scores indicate more severe symptoms [17].

BDI is a 21-item scale most widely used for measuring the symptoms and severity of depression. Each item is scored between 0 and 3, with higher scores indicating more severe disease. Total score is obtained by the sum of the scores and interpreted as follows: 0 – 10: no depression, 11-17: mild depression, 18-23: moderate depression, 24 or above: severe depression [18,19].

MMSE is a 30 –item test that is used for measuring cognitive impairment in clinical and researchs [20,21].

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) was used for the statistical analyses in this study. In evaluation of data, descriptive statistics (mean±standard deviation), together with independent samples t test for normally distributing data, Mann Whitney U test for non-normally distributing data and chi square test for the qualitative analyses, were used. The associations of variables with each other were determined according to Pearson correlation test. The p value <0.05 was regarded as statistically significant. In the comparison of MPV levels between the patient (n = 15) and the control (n=15) groups, it was found that the effect power was 0.719 as a result of the plot study conducted with a total of 30 cases in both groups. As a result of the power analysis performed for 5% error and 80% power, it was determined that the number of cases to be included in the patient and control groups should be 32, with a minimum of 64 in both groups totally.

RESULTS

Totally 54 patients and 33 control cases were included in the study. General characteristics and laboratory data of study participants are summarized in Table 1.

Social characteristics and symptoms of study participants are summarized in Table 2.

There was not any statistically significant difference regarding age, weight, height and BMI, between control and FMS groups (p>0.05). The mean number of children in the FMS group was statistically significantly higher than that of the control group (p=0.0001). There was not a statistically significant difference between both groups for leucocyte, and platelet counts, hemoglobin, MPV, CRP, urea, creatinine uric acid, ALT, AST, ALP, calcium, phosphorus, 25 OH Vitamin D, PTH and TSH levels, (p>0.05). The mean hematocrit levels were statistically significantly lower in the FMS group than control group (p=0.045). On the other hand, sedimentation levels (p=0.03), mean VAS pain and VAS sleep values (p=0.0001), FMS 1990ACR, disseminated pain index, symptom severity scale score, pain localization score, symptom effect score, fibromyalgia syndrome impact q score and Beck depression index were statistically significantly higher in the FMS group compared with the control group (p=0.0001). The mean of MMSE score was statistically significantly lower in the FMS group than control group (p=0.0001).

There was not a statistically significant difference between 2 groups regarding educational level, marital status, job, and smoking status or habitual alcohol use (p>0.05).

Symptoms including fatigue, morning stiffness, sleep disturbances, paresthesia, headache, irritable bowel syndrome, sicca symptoms, female urethral syndrome, sensation of tissue swelling and dysmenorrhea were statistically significantly higher in the FMS group compared with the control group. However, there was not a significant difference between groups regarding the presence of Raynaud's phenomena (p=0.069).

Table 1. General characteristics and laboratory data of study participants.

Characteristics	Control Group (n:33)	FMS Group (n:54)	p
Age (years)	33.7±6.42	35.31±9.12	0.377
Height (cm)	162.55±6.05	162.89±6.32	0.805
Weight (kg)	64.39±12.94	69.17±14.11	0.119
BMI (kg/m²)	24.31±4.27	26.1±5.2	0.101
Number of children	0.73±0.94	2.28±1.7	0.0001
Leucocyte count	6.91±1.31	7.11±1.86	0.597
Hemoglobin	12.69±1.34	12.23±1.08	0.086
Hematocrit	38.04±3.35	36.69±2.76	0.045
Platelet	253.91±50.34	273.58±78.42	0.202
MPV	7.34±0.99	21.95±106.36	0.433
Sedimentation	15.61±10.19	21.94±14.38	0.03
CRP	0.45±0.45	0.53±0.35	0.359
Urea	26.12±6.95	24.83±5.75	0.352
Creatinine	0.6±0.1	0.66±0.3	0.278
Uric acid	3.79±0.94	3.93±0.85	0.477
ALT	17.94±9.39	19.13±7.97	0.529
AST	21.67±9.5	19.22±6.37	0.154
ALP	60.31±16.24	65.77±17.77	0.162
Calcium	9.54±0.37	9.38±1.3	0.490
Phosphor	3.25±0.51	3.47±0.66	0.105
25 OH vitamin D*	18.98±11.46	17.64±12.46	0.689
PTH*	53.54±22.33	41.75±48.45	0.324
TSH	1.49±0.73	1.69±0.91	0.296
VAS pain	20.45±20.93	82.69±18.98	0.0001
VAS sleep	33.94±31.27	76.85±23.68	0.0001
FMS 1990ACR	3.06±3.05	14.07±1.73	0.0001
Disseminated pain index	3.12±3.09	12.59±3.6	0.0001
Symptom severity scale score	2.61±1.68	9±1.44	0.0001
Pain localization score	4.42±4.95	17.39±5.02	0.0001
Symptom effect score	21.64±15.83	61.13±15.38	0.0001
Fibromyalgia syndrome effect score	25.91±16.37	62.91±15.89	0.0001
Beck depression index	8.91±6.98	17.98±9.92	0.0001
Mini-mental score	29.64±0.74	24.72±3.88	0.0001

BMI: Body mass index
MPV:Mean platelet volume
CRP:C reactive protein
ALT: Alanine aminotransferase
AST:Aspartate aminotransferase
PTH: Parathormon
TSH: Thyroid stimulating hormone
VAS: Visual analogue scale

Table 2. Social characteristics and symptoms of study participants

		Control Group (n:33)		FMS Group (n:54)		p
Educational Level	Primary school	16	48.48%	33	61.11%	0.336
	Mid-school	4	12.12%	6	11.11%	
	High school	11	33.33%	10	18.52%	
	University	6	18.18%	5	9.26%	
Marital status	Single	8	24.24%	7	12.96%	0.523
	Married	22	66.67%	43	79.63%	
	Widow	2	6.06%	2	3.70%	
	Divorced	1	3.03%	2	3.70%	
Job	Housewife	22	66.67%	41	75.93%	0.801
	Employee	4	12.12%	5	9.26%	
	Government official	5	15.15%	4	7.41%	
	Profession libérale	1	3.03%	2	3.70%	
	Student	1	3.03%	2	3.70%	
Smoking		6	18.18%	11	20.75%	0.771
Alcohol		2	6.06%	1	1.89%	0.305
Fatigue		23	69.70%	54	100.00%	0.0001
Morning stiffness		11	33.33%	50	92.59%	0.0001
Sleep disturbance		8	24.24%	48	88.89%	0.0001
Morning fatigue		17	51.52%	51	94.44%	0.0001
Paresthesia		2	6.06%	42	77.78%	0.0001
Headache		11	33.33%	47	87.04%	0.0001
Raynaud's phenomena		2	6.06%	11	20.37%	0.069
Irritable bowel syndrome		4	12.12%	17	31.48%	0.041
Sicca symptoms		1	3.03%	14	25.93%	0.006
Female urethral syndrome		0	0.00%	14	25.93%	0.001
Sensation of tissue swelling		7	21.21%	30	55.56%	0.002
Dysmenorrhea		3	9.09%	26	48.15%	0.0001

In the control group, there was not a statistically significant correlation between uric acid or MPV levels and age, VAS pain, VAS sleep, FMS 1990 ACR, disseminated pain index, symptom severity scale score, pain localization score, symptom effect score, fibromyalgia syndrome effect score, Beck depression index and MMSE score (p>0.05). Although there was not a statistically significant correlation between BMI and MPV levels; there was a significant, and positive correlation

between BMI and uric acid levels (r=0,664 p=0.0001).

In the FMS group, there was not a statistically significant correlation between uric acid or MPV levels and age, disease duration, VAS pain, VAS sleep, FMS 1990 ACR, disseminated pain index, symptom severity scale score, symptom effect score, fibromyalgia syndrome impact questionnaire score, Beck depression index and MMSE score (p>0.05). On the other hand, there was a statistically significant, and positive correlation between uric acid and BMI (r=0.454 p=0.001), but a statistically significant, and negative correlation between uric acid and pain localization score (r=-0.349 p=0.011).These findings are summarized in Table 3.

Table 3. Results of correlation analysis of some general characteristic features and laboratory data of study participants with MPV and uric acid levels

		Control Group		FMS Group	
		MPV	Uric acid	MPV	Uric acid
Age	r	-0.165	0.336	0.117	0.066
	p	0.358	0.056	0.399	0.64
BMI	r	-0.091	0.664	0.019	0.454
	p	0.615	0.0001	0.894	0.001
Disease duration	r	.	.	-0.029	-0.123
	p	.	.	0.857	0.443
VAS Pain	r	-0.199	0.134	0.053	0.06
	p	0.268	0.456	0.703	0.674
VAS Sleep	r	-0.07	0.109	0.077	-0.137
	p	0.698	0.544	0.578	0.332
FMS 1990ACR	r	-0.11	0.069	-0.006	-0.011
	p	0.543	0.702	0.965	0.939
Disseminated Pain Index	r	-0.114	-0.188	0.091	-0.217
	p	0.529	0.295	0.512	0.122
Symptom Severity Scale Score	r	-0.035	0.063	0.095	-0.051
	p	0.845	0.726	0.495	0.72
PainLocalization Score	r	-0.054	-0.024	0.1	-0.349
	p	0.764	0.892	0.474	0.011
Symptom Effect Score	r	-0.093	-0.039	0.078	-0.164
	p	0.607	0.828	0.578	0.246
Fibromyalgia Syndrome Effect Score	r	-0.065	-0.189	-0.15	0.115
	p	0.718	0.292	0.279	0.416
Beck Depression Index	r	0.022	0.024	-0.129	0.052
	p	0.903	0.895	0.357	0.719
MMSE Score	r	-0.142	0.029	0.196	0.055
	p	0.429	0.871	0.172	0.709

DISCUSSION

In this study we have evaluated the cognitive functions of patients with FMS and aimed to determine the effects of uric acid and MPV levels on cognitive functions in this group of patients. We have determined that, MMSE results of FMS patients were statistically significantly lower than those of age and gender-matched control cases, displaying a cognitive impairment in this group. We did not determine any correlation between cognitive functions and uric acid or MPV levels in FMS patients. To the best of our knowledge, this is the first study in the literature evaluating the effects of uric acid and MPV levels on cognitive functions of FMS patients.

In the literature, there are some investigations regarding the cognitive impairments in FMS patients but with small patient groups [22]. Although in 2010 ACR criteria, in symptom severity scale, the severity of cognitive functions directly support the diagnosis [23]; the results of studies about the cognitive functions in FMS have failed to arrive 0 at a general consensus. Rodríguez-Andreu J et al compared the MMSE results of FMS patients with controls per diagnosis of neuropathic (NeP) or mixed pain (MP) and reported a slight but statistically significantly lower score in the adjusted MMSE score in FMS group and high frequency of cognitive impairment compared with the population reference value [24]. Leavitt et al especially reported a significant level of cognitive deficit in FMS patients in the absence of rehearsal [25]. Luerding et al studied 20 FMS patients and reported significantly reduced working memory and impaired non-verbal long-term memory when compared with normative data derived from age- and education-matched control groups [26]. Tesio et al reported the presence of impairments of attention, long-term memory, working memory in FMS patients compared with healthy controls based on a self-reported questionnaire [27]. On the other hand, Mohs et al assessed the cognitive functions by Symbol Digit Substitution Test, Trail-Making Test and Verbal Learning and Recall Tests in FMS patients who were under fluoxetine treatment and did not determine any cognitive impairment [28]. In another recent study, FMS patients showed normal performance in executive functioning and decision-making and pain was associated with neuropsychological functioning but anxiety, depression and medications were not [29]. de Melo LF and Da-Silva

SL evaluated the MMSE results of FMS patients with rheumatoid arthritis and systemic lupus erythematosis patients; and did not determine any statistically significant difference regarding the test results among 3 groups. However, the mean MMSE result was 23.07 in FMS group, where the cut-off point was 24, defining a mild impairment [30]. In our study, we have also determined a statistically significant decrease in MMSE scores and a cognitive impairment in FMS patients.

Serum uric acid is an endogenous antioxidant. The association of serum uric acid levels with cognitive impairment has been studied in some diseases. However recent results in literature are conflicting. Cicero et al assessed the cognitive functions of 288 healthy young participants by MMSE and determined a positive association between serum uric acid levels and cognitive dysfunction in young elderly subject. Similarly, Chen et al reported a positive correlation between the degree of cognitive symptoms and serum uric acid levels in patients with essential tremor and Parkinson's disease [31]. On the other hand, high plasma urate levels were associated with slower rate of cognitive decline in mild cognitive impairment in 3 years follow-up of 747 patients [8]. Vannorsdall et al followed 423 cognitively healthy community-dwelling older women for 9 years and reported that higher baseline serum uric acid levels were associated with poorer working memory, but there was no correlation between baseline serum uric acid levels and global cognitive functioning [32]. We also could not determine an association between serum uric acid levels and cognitive functions in FMS patients.

The studies about the association of MPV levels and cognitive functions are also limited in number. Liang et al reported significantly reduced MPV levels as cognitive levels declined and showed that MPV levels were significantly associated with MMSE [33]. Koç et al reported elevated MPV levels in patients with Alzheimer's disease but in that study when the patients were divided into 2 subgroups as having mild or moderate cognitive impairments according to MMSE scores, there was not any statistically significant difference between moderate and the mild groups regarding MPV values [15]. We also could not determine an association between serum MPV levels and cognitive functions. Mild cognitive impairment of FMS patients may be due to low Beck depression scores of these patients relative to control groups.

Nevertheless, small sample size and cross-sectional design are the main limitations of this study. Thus, a direct cause and effect relationship cannot be established.

Conclusion

FMS is a common disease and complaints of FMS patients regarding cognitive impairments are increasing day by day. We have determined declined cognitive functions in FMS patients compared with the control cases. In that aspect, factors affecting the cognitive functions gain importance. Although we could not determine an association of serum uric acid and MPV levels with cognitive functions, larger prospective studies with longer follow- up periods are warranted to elucidate the role of these biomarkers in FMS patients.

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Evaluation of Health-Related Quality of Life and Its Influencing Factors in Pediatric Patients with Voiding Dysfunction

İşeme Bozukluğu Olan Çocuk Hastalarda Yaşam Kalitesi ve Etkileyen Faktörlerin Değerlendirilmesi

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ABSTRACT

Objective: *Health-related quality of life and its influencing factors in pediatric patients with voiding dysfunction and their families were assessed.*
Method: *The patients who were admitted with urinary incontinence for at least 6 months to the clinics of pediatrics and pediatric nephrology were enrolled in the study. The patients were divided into three groups as daytime urinary incontinence (DUI), enuresis and both DUI and enuresis. The Pediatric Quality of Life InventoryTM (PedsQLTM) was administered to patients and mothers.*
Results: *A total of 100 patients with voiding dysfunction admitted with urinary incontinence aged from 5 years to 18 years (mean age: 8.8±2.6) were included in the study. The mean dysfunctional voiding symptom score was 15.5±6.6 in all groups and significantly higher in the group who experienced both DUI and NE (p<0.001). No significant difference was observed in terms of mean PedsQL scores of the children and their mothers between groups with urinary incontinence (65.5±16 and 58.4±13.5, respectively), but a strong positive correlation was detected between them (p<0.001). The mean PedsQL score for the children aged from 8 years to 12 years was significantly lower than the scores for the children aged from 5 to 7 years (p<0.05). The mean PedsQL score for the children aged between 13, and 18 years was not different from the other age groups.*
Conclusion: *The early diagnosis and treatment of patients aged from 8 to 12 years who had the lowest PedsQL score is important. Additionally, the success in the improvement of the quality of life of children with voiding dysfunction requires cooperation with parents.*

Keywords: *Enuresis; incontinence, quality of life, voiding dysfunction*

ÖZ

Amaç: *İşeme bozukluğu olan çocuklarda ve ailelerinde yaşam kalitesinin ve etkileyen faktörlerin incelenmesidir.*
Yöntem: *Pediatri ve pediatrik nefroloji polikliniklerine idrar kaçırma nedeniyle başvuran ve şikayetleri en az 6 aydır devam eden çocuk hastalar çalışmaya alındı. Hastalar gündüz idrar kaçıranlar, gece idrar kaçıranlar ve hem gündüz hem gece idrar kaçıranlar olmak üzere üç gruba ayrıldı. Çocuklar için Yaşam Kalitesi Ölçeği (ÇİYKÖ) çalışmaya katılan tüm çocuklara ve annelerine uygulandı.*
Bulgular: *5-18 yaş arası (ortalama yaş: 8,8±2,6, E:K=0,31) idrar kaçırma yakınması olan 100 çocuk hasta çalışmaya alındı. Ortalama disfonksiyonel işeme semptom skorlaması (DİSS) 15.5±6.6 saptandı. DİSS hem gece hem gündüz kaçıran grupta istatistiksel olarak anlamlı daha yüksek saptandı (p<0.001). Anne ve çocukların yaşam kalitesi skorlarında işeme bozukluğu grupları arasında anlamlı farklılık saptanmadı (58,4±13,5; 65,5±16) fakat kuvvetli pozitif yönde bağıntı saptandı (p<0.001). 8-12 yaş grubunda ortalama ÇİYKÖ skoru 5-7 yaş grubuna oranla istatistiksel olarak anlamlı düşük bulundu (p<0.05). 13-18 yaş grubunun ÇİYKÖ skoru diğer gruplardan farklı değildi.*
Sonuç: *En düşük ÇİYKÖ skoru saptanan 8-12 yaş grubu çocuk hastaların erken tanı ve tedavisi önem taşımaktadır. Ayrıca işeme bozukluğu olan çocukların yaşam kalitelerinin iyileştirilmesindeki başarıda ailelerin katkısı önemlidir.*

Anahtar kelimeler: *Enürezis, idrar kaçırma, yaşam kalitesi, işeme disfonksiyonu*

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INTRODUCTION

Urinary incontinence is a common problem in childhood, and constitutes up to 20% of visits to pediatric and pediatric urology clinics. Voiding disorders are non-organic incontinence and classified as enuresis and daytime urinary incontinence (DUI) affecting school children, most commonly girls. It has been shown that enuresis has important effects on children's emotional, social and psychological status, courage, self-esteem and school success [1-8]. Urinary incontinence negatively affects quality of life of both children and their parents[9] DUI has negative effects on all of the life qualities including social relationships and future expectations of especially school-age children because DUI is a problem persisting every day [10].

The health-related quality of life (HRQOL) measurement refers to the impact of health and illness on an individual's quality of life. The Pediatric Quality of Life InventoryTM (PedsQLTM), firstly developed by Varni et al.[11], is a widely used instrument to measure pediatric HRQOL in children aged 2 to 18 years. It queries physical health, emotional and social functionality [11-13]. The relation between severity of voiding dysfunction and quality of life and parents' attitudes such as anxiety, discomfort and fear are not clearly established [9]. Health related and overall quality of life are useful constructs, and are reduced in children with urınary incontinence based on parental rating. Thus, this study was carried out to assess HRQOL among children with voiding dysfunction and their parents.

MATERIAL and METHODS

One hundred and ten children (5-18 years of age) who were admitted with urinary incontinence to the clinics of pediatrics and division of pediatric nephrology were enrolled in this cross-sectional study. If needed, detailed history, physical examination, ultrasonography and advanced imaging were performed. The patients whose complaints were continuing for at least for 6 months were included in the study.

The patients with psychomotor retardation and organic disorders such as spina bifida, neurogenic bladder, obstructive uropathy, vesicoureteral reflux and chronic renal insufficiency and the patients whose parents refused to give written consent were excluded. Ten patients were excluded because of noncompletion of the questionnaires.

The patients were given a questionnare consisting of 17 questions inquiring demographic characteristics, socio-cultural level of family, level of mother's education, symptoms of incontinence and accompanying signs. Some (11%) of the mothers were illiterate, primary school (69%), high school (12%), and university (2%) graduates. Only the mothers, considered as primary caregivers were enrolled in the study.

The patients were divided into three groups as daytime urinary incontinence (DUI), enuresis and both DUI and enuresis according to International Children's Continence Society (ICCS) criteria [14]. The patients were evaluated in consideration of coexistence of urinary tract infection, constipation and/or fecal incontinence, and any treatment (medical therapy/urotherapy). They received.

The patients were evaluated by means of a questionnaire including urinary incontinence, sudden onset of urination and urgency, urine retention maneuvers, weak and an interrupted urine stream. Voiding diaries and uroflowmetry were used in all of the patients with daytime symptoms. The patients who had daytime incontinence were also regarded as having boveractive bladder and daytime incontinence.

The type and severity of voiding dysfunction was evaluated by the dysfunctional voiding scoring system (DVSS) which includes 13 questions scored between 0 and 35 [15]. The patients who had scores ≥9, regarded as having voiding dysfunction.

The Pediatric Quality of Life InventoryTM (PedsQLTM 4.0) was administered to pediatric patients with voiding dysfunction and their mothers independently using different appropriate forms. The 23-item PedsQL generic core scales encompass physical (eight items), emotional (five items), social (five items), and school functioning (five items) domains [11,12]. Items are reverse scored and linearly transformed to a zero to 100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0) with higher scores. The scoring included: a physical health summary score that represented a physical functioning scale score (8 items), and a psychosocial health summary score that was the sum of the items answered in the emotional,

social, and school functioning scales (15 items). The higher scores indicate better HRQOL. The questionnaires were applied to children aged 5-7 years under the supervision of the doctors and their mothers.

The study protocol was approved by the hospital ethics committee (No:1062, 01/09/2015). Written informed consents were taken from parents.

Statistical Analysis

Statistical analyses was performed using SPSS 15.0 software (SPSS Inc, Chicago,IL,U.S.A.). Results were expressed as numbers and percentages for categorical variables and means ± SD, minimum, maximum for quantitative variables. If the quantitative variables were normally distributed, the analysis was conducted using Student t test when two groups were compared, and one way ANOVA test for the comparison of more than two groups. If the quantitative variables were not normally distributed, Mann -Whitney U test was used between two groups, and Kruskal Wallis test for more than two groups. The analysis of subgroups were done by Mann- Whitney U test and improved with Bonferroni test. P values of <0.05 were considered statistically significant.

RESULTS

A total of 100 patients with urinary incontinence aged from 5 to 18 years (mean age: 8.8±2.6) were included in the study. The demographic characteristics of the patients are shown in Table 1. The patients were divided in three groups according to age as Group 1:5-7 years old (48%), Group 2:8-12 years old (45%), and Group 3:13-18 years old (%7). The patients were divided in three groups according to type of incontinence as Group 1: daytime urinary incontinence (DUI) (16%), Group 2: enuresis(36%), and Group 3: both DUI and enuresis (48%). The mean age of the patients who had both DUI and enuresis was lower than the other two groups (7.8±2.6,p< 0.01).

The mean age of the mothers was 33.8±6.0 years. A decrease was observed in the rate of voiding incontinence as the mothers' educational level increased (p=0.01) (Table 1).

Table 1. Demographic characteristics of participants.

	Total Patients (n=100)	Group 1 (n=16)	Group 2 (n=36)	Group 3 (n=48)	P
Age (year, mean±SD)	8.5±2.6	8.0±2.1	9.7±2.6	7.8±2.6	
Age group (n,%)					
5-7 years	48 (48%)	10 (62.5%)	10 (27.8%)	28 (58.3%)	0.027
8-12 years	45 (45%)	6 (37.5%)	21 (58.3%)	18 (37.5%)	
13-18 years	7 (7%)	0	5 (13.9%)	2 (4.2%)	
Gender (%)					
Female	76 (76%)	14 (87.5%)	27 (75%)	35 (72.9%)	0.489
Male	24 (24%)	2 (12.5%)	9 (25%)	13 (27.1%)	
Types of daytime incontinence (%)					
Overactive bladder	50 (50%)	14 (87.5%)	0	36 (36%)	0.001
Dysfunctional	14 (14%)	2 (12.5%)	0	12 (25%)	
Age of mother (mean±SD, median)	33.8±6.0 (22-50)	32.4±5.5 (25-42)	33.8±6.2 (22-48)	34.2±6.0 (23-50)	0.525
Educational level of mother					
None	11 (11%)	3 (18.8%)	1 (2.8%)	7 (14.6%)	0.010
Primary school	69 (69%)	7 (43.8)	32 (88.9%)	30 (62.5%)	
Secondary school	6 (6%)	3 (18.8%)	1 (2.8%)	2 (4.2%)	
High school	12 (12%)	3 (18.8%)	1 (2.8%)	8 (16.7%)	
University	2 (2%)	0	1 (2.8%)		
Febrile urinary tract	30 (49.2%)	9 (69.2%)	8 (47.1%)	13 (41.9%)	0.250
Infection (%)					
Constipation (%)	34 (34%)	3 (18.8%)	14 (38.9%)	17 (35.4%)	0.353
Fecal incontinence (%)	24 (24%)	8 (50%)	6 (16.7%)	10 (20.8%)	0.027
Treatment given (%)	47 (47%)	8 (50%)	17 (47.2%)	22 (45.8%)	0.959

Group 1: Daytime incontinence
Group 2:Enuresis
Group 3: Daytime incontinence and enuresis
P<0.05 is statistically significant

The DVSS and PedsQL scores of the patients and mothers are shown in Table 2. The mean DVSS was 15.5±6.6 in all groups and significantly higher in the group who experienced both DUI and enuresis (p<0.001). No significant difference was observed in terms of the mean PedsQL score between children and their parents (65.5±16 and 58.4±13.5, respectively)

Table 2. Voiding symptom scores and mean PedsQL scores according to groups

	Total patients (n=100)	Group 1 (n=16)	Group 2 (n=36)	Group 3 (n=48)	p
DVSS (mean±SD, range)	15.5±6.6 (2-31)	12±4.6 (6-22)	11.3±4.9 (2-30)	19.7±5.7 (10-31)	<0.001
Total PedsQLscore (mean±SD, range)					
Patients	65.5±16 (9.8-100)	65.5±16 (30.4-95.7)	67.5±14.6 (39.1-97.2)	64.7±16.7 (9.8-100)	0.619
Mothers	58.4±13.5 (28.3-93.5)	54.7±13.7 (34.8-87)	57.6±13.4 (28.3-84.8)	60.2±13.5 (31.5-93.5)	

DVSS= Dysfunctional voiding symptom score; PedsQL=Pediatric quality of life inventory
Group 1: Daytime incontinence
Group 2:Enuresis
Group 3: Daytime incontinence and enuresis
P<0.05 is statisticaly significant

The comparison of PedsQL scores according to demographic characteristics and accompanying conditions is shown in Table 3. The mean PedsQL score for children aged from 8 years to 12 years was significantly lower than the scores for the children aged from 5 to 7 years (p<0.05). The mean PedsQL score of the patients with febrile urinary tract infection was significantly lower than those without (p<0.05). No difference was detected between PedsQL scores of patients whether they had constipation and/or fecal incontinence, and whether they were given treatment or not (p>0.05).

Table 3. The comparison of demografic characteristics with mean PedsQL scores of the patients

	Total PedsQL scores of the patients		P
	Mean±SD	Median	
Age of the patients			
5-7 years	70.0±14.8	69.6	0.020
8-12 years	60.8±15.5	59.8	
13-18 years	64.6±20.6	57.6	
Gender			
Female	66.1±16.0	65.9	0.473
Male	63.4±16.2	63	
Febrile urinary tract infection			
Present	60.3±18.9	59.7	0.018
Absent	70.3±12.4	69.6	
Constipation			
Present	64.5±17.5	64.7	0.655
Absent	66.0±15.3	67.6	
Fecal incontinence			
Present	60.0±17.6	60.3	0.052
Absent	67.2±15.2	69.6	
Treatment			
Yes	62.4±14.8	60.9	0.073
No	68.2±16.7	69.6	

PedsQL= Pediatric quality of life inventory
P<0.05 is statistically significant

A weak negative correlation was observed between PedsQL scores and the age of patients and mothers (p<0.01,r=0.277 and p<0.05,r=0.204, respectively). A strong positive correlation was observed between PedsQL scores of the patients and parents (p<0.001) (Table 4).

Table 4. The association between mean PedsQLscore of the patients and the age of mother, Voiding symptom score and PedsQLscore of the mothers

	Total PedsQL score of the patients	
	r	P
Age of patients	-0.277	0.005
DVSS	-0.470	0.640
Age of the mothers	-0.204	0.042
Total PedsQL score of the mothers	0.607	<0.001

DVSS= Dysfunctional voiding score; PedsQL= Pediatric quality of life inventory
P<0.05 is statistically significant

DISCUSSION

There are limited number of studies investigating emotional and behavioral changes, and quality of life in patients with voiding dysfunction [4-9]. We evaluated HRQOL and influencing factors in pediatric patients aged 5-18 years who had various voiding dysfunction. Most of the children in our study were in the group of patients who had both DUI and enuresis, and 76% of our patients were female. The mean age of the patients with both DUI and enuresis was lower than the patients who had solely DUI or enuresis (p<0.01). Although PedsQL score of this group was good, symptoms of these children with both DUI and enuresis exerted much more adverse effects such as anxiety and discomfort on parents, and thus may lead to admittance to clinics earlier.

In concordance with the previous studies, the mean age of the patients with only enuresis was higher than

the other two groups [16],which was attributed to the parents' thought that enuresis will resolve spontaneously with time.

The educational level of the mother was considered as a socio-cultural index in many studies. It has been reported that urinary incontinence was more common among families who had low socio-cultural level [8,17]. Similarly, we observed that with increasing level of education of the mother, the rate of incontinence was decreased (p=0.01).

It is important to identify accompanying disorders such as urinary tract infection and constipation in these patients with urinary incontinence since improvement of these conditions affects the treatment success [16,17]. We detected concomitant urinary tract infection in 30% , constipation in 34%, and fecal incontinence in 24% of our patients most commonly in the patients with both DUI and enuresis. Logan BA et al.[18] reported that bladder and bowel dysfunction is frequent and an overlooked problem in children with voiding dysfunction and mentioned that 60% of these patients had at least one psycihosocial factor. In another study[19], it has been reported that 31.1% of 429 children with nocturnal enuresis aged between 5 and 16 years had at least one lower urinary tract symptom (LUTS) and 16.3% of them had a comorbid condition. We did not determine neuropsychiatric disorder in this study. All of the groups, especially the group with DUI had frequently accompanying symptoms, which represents importance of the treatment and its urgency in these children.

The DVSS score was found higher in the patients who experienced both DUI and enuresis in our study. DVSS is an important measurement tool in diagnosis, follow-up, treatment and improvement of voiding dysfuction. DVSS and Pediatric Urinary Incontinence QOL tool (PIN-Q) were performed in pediatric patients aged from 5 to 11 years and a correlation was found between DVSS and PIN-Q scores of the patients and their parents in the study of Thibodeau et al. [9]. In contrast with the previous studies, we found no association between voiding dysfunction symptoms and PedsQL scores.
Compatible with the literature [16,20,21], the results of this study showed low PedsQL scores in children with voiding dysfunction. No significant difference was observed between the mean PedsQL total scores of our groups and their parents. Deshpande et al. [22] reported that quality of life was lower in older children with incontinence, female gender and nonwhite ethnicity and drawn the attention of the clinicians to the fact that urinary incontinence had different effects on children with different age groups and ethnicity.

We also observed a weak correlation between PedsQL scores and age of the patients and their mothers and a strong correlation between PedsQL scores and the parents' quality of life. In various studies, the quality of life has been reported to be similar in children with incontinence and their parents, but no change was observed at diagnosis and during treatment. It has been considered that parents overlooked emotional improvement of their children with DUI, or they still had negative affect [7,10]. Therefore, it is mandatory that quality of life of children and parents must be complementary for raising awareness about voiding dysfunction symptoms at early ages by parents, leading to early diagnosis and treatment.

The limitations of current research include; performing a single measurement instead of multiple measurements for evaluating changes over time, failure to compare these changes with those of the healthy children and being a single center experience with a small number of patients.

In conclusion, urinary incontinence affects social, emotional, and behavioral aspects adversely and lowers the quality of life both of the children and their parents. Early diagnosis of urinary incontinence should motivate patients and also their parents, leading to increased success of the treatment given, especially in the patients aged from 8 to 12 years who had the lowest PedsQL scores in our study. The healthcare professionals should be informed about the effects of enuresis on the quality of life of children and be able to help and alleviate the negative effects of psychological consequences to the child, as well as to the parents.

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Original Article

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The Effectiveness of the Amount of Polymethylmethacrylate Used in the Treatment of Lumbar Osteoporotic Compression Fractures

Lomber Osteoporotik Kompresyon Kırığının Tedavisinde Polimetilmetakrilat Miktarının Etkinliği

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ABSTRACT

Objective: *We aimed to investigate the effectiveness of the amount of polymethylmethacrylate used in pain control and maintenance of long-term vertebra corpus height in patients undergoing percutaneous vertebroplasty due to osteoporotic compression fracture of the lumbar vertebra.*
Method: *A total of 60 patients who underwent unilateral percutaneous vertebroplasty between 2014 and 2019 due to osteoporotic compression fracture of the lumbar vertebrae were included in the study. Patients who received 5 ml and 3 ml cement injection were retrospectively analyzed. Of patients, postoperative visual analogue scale (VAS) score and anterior vertebral height of the patients at 1st-year control were evaluated.*
Results: *In the postoperative period, the mean visual analogue scale score was 2.3±0.46 in the 5 ml injected group and 2.2±0.4 in the 3 ml injected group (p5 ml=0.001, p3 ml= 0.001). There was a statistically significant decline in pain control in both groups. The mean anterior vertebral height loss (AVHL) in the 5 ml injected group was 31.5±0.40%, and 32.6±0.47% in the 3 ml injected group (p5 ml=0.820, p3ml= 0.870). There was no statistically significant alteration in both groups.*
Conclusion: *Our results indicate that the 3 ml polymethylmethacrylate injection during the percutaneous vertebroplasty procedure provides adequate pain control and stabilization in patients with lumbar vertebral osteoporotic fracture. Therefore we think that small amount of polymethylmethacrylate (3 ml) is sufficient to avoid undesirable complications in this patient group.*

Keywords: *Compression fractures, osteoporotic fractures, pain, polymethyl methacrylate, spinal fractures, vertebroplasty, visual analog scale*

ÖZ

Amaç: *Lomber vertebra osteoporotik kompresyon kırığı nedeniyle perkutan vertebroplasti yapılan hastalarda, kullanılan polimetilmetokrilat miktarının ağrı kontrolünde ve uzun dönem vertebra korpus yüksekliğinin korunmasındaki etkinliğini araştırmayı amaçladık.*
Yöntem: *2014 ve 2019 yılları arasında lomber vertebranın osteoporotik kompresyon kırığı nedeniyle uniletaral perkütan vertebroplasti işlemi uyguladığımız toplam 60 hasta çalışmaya dahil edilmiştir. 5 ml ve 3 ml sement enjeksiyonu yapılan hastalar retrospektif olarak incelenmiştir. Hastaların postoperatif VAS skorları ve 1. yıl kontrol anterior vertebra yükseklikleri değerlendirilmiştir.*
Bulgular: *Postoperatif dönemde 5 ml enjeksiyon yapılan grupta ortalama VAS skoru 2,3±0,46 olur iken 3ml enjeksiyon yapılan grupta ortalama VAS skoru 2,2±0,4 idi. (p5 ml=0,001, p3 ml=0,001) Her iki grupta ağrı kontrolünde istatiksel olarak anlamlı bir gerileme tespit edildi. Hastaların ortalama anterior vertebra yükseklik kaybı; 5 ml enjeksiyon yapılan grupta %31,5±0,40 iken 3 ml enjeksiyon yapılan grupta %32,6±0,47 (p5 ml=0,820, p3 ml=0,870) idi. Her iki grupta da istatiksel olarak anlamlı değişim saptanmadı.*
Sonuç: *Sonuçlarımız lomber osteoporotik vertebra fraktürü hastalarında perkütan vertebroplasti işlemi sırasında 3 ml polimetilmetokrilat enjeksiyonunun yeterli ağrı kontrolü ve stabilizasyonu sağladığını göstermektedir. Bu nedenle bu hasta grubunda gereksiz komplikasyonlardan kaçınmak için daha az miktarda (3 ml) polimetilmetokrilat kullanımının yeterli olduğunu düşünmekteyiz.*

Anahtar kelimeler: *Compresyon kırıkları, osteoporotik kırıklar, ağrı, polimetilmetakrilat, spinal kırıklar, vertebroplasti, vizüel analog skalası*

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INTRODUCTION

Pathological vertebral fractures are most commonly seen due to osteoporosis, which leads to bone mineral loss, but can also be seen due to tumor infiltration. Vertebral compression fractures can cause severe pain that restricts the daily activity of the patients. Analgesic treatment, physical therapy, and corset usage are generally unresponsive to the relief of pain seen in patients [1].

As a result of the vertebroplasty procedures performed in vertebral compression fractures, the resolution of the complaints of patients' pain is quite satisfactory. In the series of 100 patients, McGraw and colleagues stated that 97% of the patients had significantly reduced pain in the first 24 hours [2].

Percutaneous vertebroplasty (PV) is a very powerful method to strengthen the vertebra with polymethylmethacrylate in pathological vertebral compression fractures caused by osteoporosis, tumor or trauma [3]. It was first applied in 1987 by Galibert and Deromond in France [4]. Percutaneous vertebroplasty can be achieved unilaterally or bilaterally. Still, no significant difference was found between them [5]. In the unilateral procedures, the polymethylmethacrylate should cross the midline and vertical axis of the vertebral corpus [6]. If the polymethylmethacrylate given remains on one side of the vertebral corpus and does not pass to the other side, it causes curvature of the spine in the future [7].

The most important point for the efficacy of PV is that the polymethylmethacrylate should be injected at an amount sufficient to achieve enough stabilization and pain control. It is reported in the literature that 3-5 ml of cement injection is sufficient in the lumbar and thoracic vertebrae region [8-12]. Therewithal, the most common complication during vertebroplasty is polymethylmethacrylate leakage into the spinal canal or neural foramen. In the series of McKiernan et al., this rate of leakege was 15 percent [13]. Therefore, it is necessary to avoid over-injection of polymethylmethacrylate in order to ensure the effectiveness of vertebroplasty and to avoid possible complications.

In this study, we investigated the patients who underwent percutaneous vertebroplasty for osteoporotic compression fractures of the lumbar spine. We evaluated the productiveness of the amount of polymethylmethacrylate injected on radiological findings and pain control in the postoperative period and long-term follow-up.

MATERIAL and METHODS

Sixty patients, who presented with low back pain between 2014 and 2019 and had a single-level osteoporotic vertebral compression fracture in the lumbar vertebrae detected during magnetic resonance imaging (MRI) and computed tomography (CT) tests, were included in the study. All patients Bone mineral densities (BMDs) of all patients were measured by dual X-ray absorptiometry (DXA). Patients' T-scores were between-2.5 standard deviation (SD) and -3.2 SD. Patient whose preoperative imaging studies, did not reveal bone fragments causing canal occupation, those without neurological deficits detected in neurological examinations and patients whose pain control cannot be achieved despite conservative treatment were included in the study .

Under general anesthesia, and scopy, the patients with compression fractures lying in the prone position, received percutaneous injections of polymethylmethacrylate using special needles inserted unilaterally into the vertebral corpus through the midline of the vertebral corpus, which were advanced up to anterior 1/3 (Ntcem. Spine, Meta Biomed Co., Ltd Osongsaengmyeong, Korea) w (Figure 1).

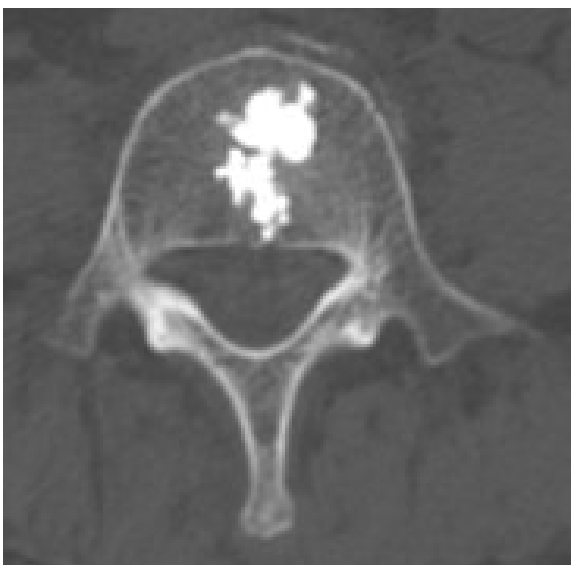

Figure 1. Axial plan CT scan. 3 ml polymethylmethacrylate reached up to middle and anterior 1/3 vertebrae.

Five ml and 3 ml of polymethylmethacrylate were injected into the vertebrae of the patients consecutively. The patients were placed in the supine position for at least 6 hours after the procedure. All patients underwent lumbar CT in the postoperative period and at 1st-year follow-up (Figure 2).

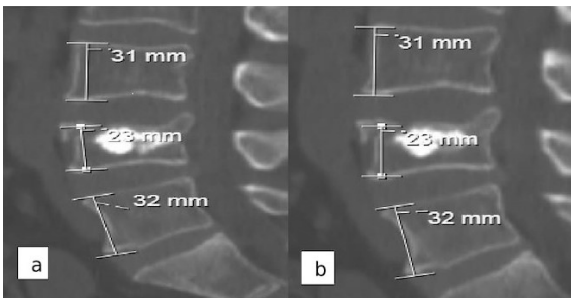

Figure 2. Sagittal plan CT scan of the patient undergoing 3 ml of polymethylmethacrylate;
a) Post-operative 1st day b) 1st-year follow-up

The pain severity of the patients was evaluated using the VAS scores ranging between 0, and 10 points. The height of the vertebrae in the postoperative and 1st-year follow-up was measured using the Picture Archiving and Communication System. The AVHL percentage was calculated by dividing the height of the anterior wall of the fractured vertebra by the average of the anterior wall heights of the adjacent lower and upper vertebrae (Figure 3).

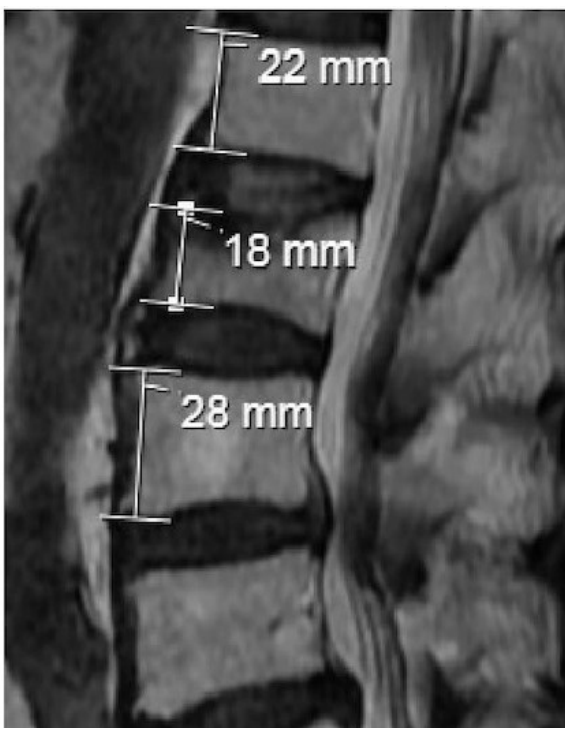

Figure 3. 2nd Lumbar vertebrae with 28% height loss.

This study was performed with clinical data collected from patient files collected retrospectively. This study was approved by the Medical Ethics Committee of Tekirdag Namık Kemal University (2019.229.12.04). All procedures performed in studies involving human participants were conducted under the ethical standards of the institutional and/or national research committee and the Helsinki Declaration of 1964 and subsequent amendments or comparable ethical standards. All permissions were obtained to access the data used in our study. Written informed consent was obtained from all patients.

Descriptive statistics were used to describe continuous variables (mean, standard deviation, minimum, and maximum). The student t-test was used to evaluate VAS value and AVHL among the groups.

RESULTS

Data were analyzed using SPSS ver. 20.0 (SPSS Inc., Chicago, IL, USA). Paired t-test was used to determine the significance of intergroup differences in preoperative and postoperative p values presented as mean and standard deviation. Mann-Whitney U-test was used to determine the significance of differences between groups presented as median with maximum and minimum values. A $p < 0.05$ was considered statistically significant.

Sixty patients with lumbar spine fractures due to osteoporosis were included in the study. 45 patients were female and 15 were male. The mean age of the patients was 67.6 years (SD 3.34, range 61-76). The demographic data of the patients according to subgroups are shown in (Table 1).

Table 1. It showes demographic characteristics of participants.

	3 ml	5 ml	p
Age (years)	67.2±3.09	67.9±3.59	0.444*
Weight (kg)	69.4 ±7.29	71.8±9.45	0.275*
Height (cm)	165.6±6.3	164.8±4.78	0.597*
BMI (kg/m^2) †	25.3±2.16	24.7±2.32	0.338*
Female/Male	23(77%)/7 (23%)	22 (73%)/8 (27%)	

†BMI:Body Mass Index

The mean VAS scores of the patients who received 5 ml and 3 ml polymethylmethacrylate injections during vertebroplasty were calculated as 7.2±0.4 and 7.6±0.56, respectively (p=0.002). The mean VAS score was 2.3±0.46 in the 5 ml injected group one day after the procedure and 2.2±0.4 in the 3ml injected group (p5ml=0.001, p3ml=0.001). A statistically significant decline in pain control was detected in both groups. Early postoperative and 1st year postoperative VAS results were similar in both groups. (Table 2)

Table 2. It showes comparison of preopertive and postoperative patients' VAS. A statistically significant decline in pain control was detected in both groups.

	3 mL	5 mL	p
Pre-op VAS‡	7.6±5.56	7.2±0.4	0.002
Post-op VAS§	2.2±0.4	2.3±0.46	0.379
P	0.001	0.001	

‡ Pre-op VAS: Preoperative visual analogue scale.
§ Post-op VAS: Postoperative visual analogue scale.

The mean AVHLs of the patients who received 5 ml and 3 ml polymethylmethacrylate injections during vertebroplasty procedure was 31.7±4.66% and 32.8±4.9%, respectively (p = 0.377). At 1st-year follow-up, the mean vertebral height loss in the 5 ml injected group was 31.5±0.40% and 32.6±0.47% in the 3ml injected group (p5ml=0.820, p3ml= 0.870). In both groups, no statistically significant change was observed in vertebral height loss at 1st-year follow-up (Table 3).

Table 3. It showes comparison of preoperative and 1 st-year follow-up patients' AVHL values. In both groups, no statistically significant change was observed in AVHL at 1st-year follow-up.

	3 mL	5 mL	P
Pre-op AVHL ‖	32.8±4.91%	31.7±4.66%	0.397
Follow-up AVHL ¶	32.6±4.57%	31.5±4.4%	
P	0.870	0.820	

‖ Pre-op AVHL: Preoperative anterior vertebra height loss.
¶ AVHL: Anterior vertebra height loss.

Mean AVHL measurements according to vertebral levels are shown in Table 4.

While no complication was observed in the 3 ml injected group, it was found that in 3 patients who were treated with 5 ml polymethylmethacrylate, cement leaked into the disc space, anterior part of the vertebral corpus, and into the spinal canal.

Table 4. Fracture levels of patients and the amount of collapse

		preoperative AVHL		1-years follow up AVHL	
		3 ml	5 ml	3 ml	5 ml
L1 (n=19)	n	9	10	9	10
	mean AHVL	34.3%	29.9%	34.1%	29.6%
L2 (n=17)	n	10	7	10	7
	mean AHVL	32.6%	33.3%	32.5%	33.2%
L3 (n=12)	n	4	8	4	8
	mean AHVL	32%	31.4%	32%	31.5%
L4 (n=8)	n	4	4	4	4
	mean AHVL	33.3%	31.8%	32.5%	30.8%
L5 (n=4)	n	3	1	3	1
		29.7%	42%	29.7%	40%

AVHL: anterior ver

DISCUSSION

Percutaneous vertebroplasty was first performed by Galibert and Deromond in France in 1987 [4].

Percutaneous vertebroplasty is most commonly applied to osteoporotic vertebral fractures [14,15]. In osteoporosis, due to low bone mass and deterioration of the microstructure of bone tissue, deformities occur in the vertebra because of trauma. As a result, obvious physical and functional disorders, such as limitation of movement and pain occur [16]. This condition, especially seen in old ages, leads to severe low back pain and limitation of movement. Conservative methods such as analgesic therapy for pain, and corset and bed rest to maintain vertebral height are generally not successful. However, the stabilization surgery performed for the osteoporotic compression fracture increases the length of hospital stay, mortality, and morbidity [17,18].

Vertebroplasty, which was developed as an alternative to stabilization surgery, is a less invasive procedure compared to stabilization and is preferred because it reduces both the operative time and reduces the risk of perioperative complications, as the symptoms disappear quickly and the patients are introduced to their social life early [19,20]. The postop-

erative results of vertebroplasty are fairly pleasing. In a case series of 100 patients with osteoporotic vertebral fractures by McGraw et al., 97% of the patients reported that pain complaints decreased significantly in the first 24 hours and this state of well-being continued for an average follow-up period of 21 months[2]. In another study performed by Perez-Higueraz et al., the VAS score, which was 9.1 before the operation, was reported as 2.1, and 2.2 points at average 72 nd-hour and 2 at the end of fifth-year after the operation [21].

During vertebroplasty, complications may occur, albeit rarely. The most feared complication is systemic embolization through paraspinous veins caused by polymethylmethacrylate during the procedure [22,23]. The most common complication during vertebroplasty procedure is leakage of polymethylmethacrylate into the spinal canal or neural foramen. In the series performed by McKiernan et al., this rate was determined as 15% [13]. Therefore, to ensure adequate strength resistance and pain control and to avoid complications, the amount of cement used during vertebroplasty procedures must be at an optimum level. In the literature, several studies are reporting that 3-5 ml of cementum injection is sufficient for the lumbar vertebra region [9-12]. However, the dose-dependent response between the cement volume applied and the strength resistance and hardness is not fully known [8].

In our 60-case series operated, it was observed that the vertebral heights were preserved in both groups during the 1st-year controls of patients who had received 5 ml or 3 ml polymethylmethacrylate injection. However, in 3 patients who received 5 ml polymethylmethacrylate, it was found that cement escaped to the disc space, anterior part of the vertebral corpus, and towards the spinal canal. For all that, the preoperative mean VAS scores in both groups significantly decreased on postoperative 1st day after the procedure. In addition, no significant change in AHVL height was observed in either group after 1 year of follow-up.

Our results show that 3 ml polymethylmethacrylate injection during percutaneous vertebroplasty procedure provides adequate pain control and stabilization in patients with lumbar osteoporotic vertebral fractures. Therefore, we think that lesser amount (3ml) of polymethylmethacrylate is sufficient to avoid unnecessary complications in this patient group.

Ethics Committee Approval: Tekirdağ Namık Kemal University Clinical Research Ethics Committee approval was received (26/2/2019; 2019.229.12.04).
Conflict of Interest: No conflict of interest was declared by the authors.
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Original Article

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Comparison of Burying the Appendiceal Stump Using Laparoscopic and Open Methods in Complicated Acute Appendicitis

Komplike Akut Apandisitte Laparoskopik ve Açık Yöntemle Güdük Gömmenin Karşılaştırması

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ABSTRACT

Objective: *The choice of laparoscopic technique in the treatment of complicated acute appendicitis (CAA) harbours debatable evidence because of higher rates of surgical complications such as postoperative intraabdominal abscess (POIIA). The aim of this study is to compare postoperative results of appendiceal stump (AS) ligation and its burial into the cecum using laparoscopic or open surgical techniques in patients with CAA.*
Method: *This is a single-center and retrospective analysis of patients with CAA operated between May 2018 and April 2020. AS was intracorporeally knotted with silk and buried in the cecum with a purse-string suture (PSS). The patients were divided into open appendectomy (OA) and laparoscopic appendectomy (LA) groups. Data concerning demographic characteristics, intraoperative variables, hospital stay, surgical complications, morbidities, and postoperative findings were compared.*
Results: *A total of 66 patients including 36 patients (54.54%) underwent LA and 30 patients had OA were enrolled in the study. Partial resection of cecum was performed in one patient in the OA group and two patients in the LA group with the help of a stapler due to cecal floor necrosis. The operative time and duration of hospital stay were significantly shorter in the LA group compared to the OA group. Surgical site infection and POIAA were significantlymore frequent in the OA group (p<0.001).*
Conclusion: *In acute complicated appendicitis, laparoscopic method can be applied as an effective method by closing the appendiceal stump and burying into the cecum with a purse-string suture.*

Keywords: *complicated acute appendicitis, open appendectomy, laparoscopic appendectomy, purse- string suture*

ÖZ

Amaç: *Ameliyat sonrası intraabdominal apse (POIIA) gibi daha yüksek cerrahi komplikasyonlar nedeniyle komplike akut apandisiti (CAA) olan hastalarda laparoskopik yaklaşımın kullanımına ilişkin tartışmalı kanıtlar vardır. Bu çalışmanın amacı, CAA'lı hastalarda laparoskopik veya açık cerrahi teknik kullanılarak apendiks güdüğünün ligasyonu ve çekuma gömülme yönteminin postoperatif sonuçlarını karşılaştırmaktır.*
Yöntem: *2Mayıs 2018'den Nisan 2020'ye kadar ameliyat edilen CAA hastalarının klinik kayıtlarının tek merkezli retrospektif bir analizidir. Apendiks güdük intrakorporeal olarak ipekle düğümlendi ve kese ağzı sütürü (PSS) ile çekuma gömüldü. Hastalar açık apendektomi (OA) ve laparoskopik apendektomi (LA) olarak iki gruba ayrıldı. Demografik veriler, intraoperatif değişkenler, hastanede kalış süreleri, cerrahi komplikasyonlar, morbidite ve ameliyat sonrası bulgular karşılaştırıldı.*
Bulgular: *Çalışmaya 36 LA (% 54,54) ve 30 OA olmak üzere toplam 66 hasta dahil edildi. Çekum taban nekrozu nedeniyle OA grubunda 1, LA grubunda 2 hastaya stapler yardımı ile parsiyel çekum rezeksiyonu yapıldı. LA grubunda ameliyat süresi ve hastanede kalış süresi OA grubuna göre anlamlı olarak daha kısaydı. Cerrahi alan enfeksiyonu ve POIAA OA grubunda LA grubuna göre anlamlı derecede yüksekti (p <0.001).*
Sonuç: *Akut komplike apandisitte laparoskopi, apendiks güdüğünün kapatılması ve çekumun kese ağzı sütürü ile gömülmesiyle güvenli ve etkili bir yöntem olarak uygulanabilir.*

Anahtar kelimeler: *komplike akut apandisit, açık apendektomi, laparoskopik apendektomi, gömme, kese ağzı sütürü*

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INTRODUCTION

Acute appendicitis is seen in 25% of the patients admitted to the emergency department due to abdominal pain [1,2]. Laparoscopic appendectomy has been shown to result in less postoperative pain, reduced hospital stay, better cosmetic results and faster return to normal activities compared to open appendectomy [3-5]. Because of these features, minimally invasive techniques are preferred for surgical surgery. Complicated acute appendicitis (CAA) can be seen in 20-30% of acute appendicitis cases. In the literature, it is a difficult decision to prefer LA in the treatment of complicated appendicitis (CA). However, new studies argue that LA is preferable in CAA [6,7]. LA opponents for complicated appendicitis emphasize fascial perforation and abscess as a relative contraindication to the laparoscopic approach [8].

Postoperative peritonitis, fistula and life-threatening conditions such as sepsis may occur due to ineffective closure of the appendicular stump (AS). For this reason, stump closure is critical during appendectomy surgery. Two techniques have been described for AS closure: as burying the AS after closure or simply closing the stump [9]. While OA can be easily applied using these two techniques, more easily applicable methods have been developed in LA. Different techniques using endo-stapler, endo-loop, metal endo-clip and hem-o-lok clip have been employed to close the stump in LA [10-13]. However, the application of these techniques may not always be possible in complicated appendicitis. If the diameter of the appendix is increased significantly, then necrosis and perforation are close to the base of the appendix, and these techniques may be impossible to apply.

In CAA, OA is also preferred as a safe method for the closure, inversion, and then burying the AS into in the cecum. In our retrospective clinical study, we compared the OA and laparoscopic PSS techniques in CA closure of the AS.

MATERIAL and METHODS

This retrospective study was conducted from February 2017 to November 2019. We analyzed 66 patients with CAA who underwent either open or laparoscopic technique. Ultrasonography and CT were applied to the patients as radiological imaging. CAA was detected using either USG (n=20) or CT (n=46). Surgical techniques were preferred by the surgeon. After surgery, patients were divided into two groups: Group OA (n:30), and Group LA (n:36). Surgical techniques (LA and OA) that the patients would choose were explained to the patients before the surgery. The surgeon informed the patients that the laparoscopic technique can be converted to an open technique and signed their approval.

Data concerning demographic characteristics, C-reactive protein (CRP), white blood cell (WBC) values and comorbidities of the patients were retrieved from the patient files and the computer system. Operation time, hospital stay, postoperative complications and time to enteral feeding were calculated and evaluated.

Ethics Approval

Approval of the Local Ethics Committee was obtained on December 3, 2018 (approval number: BEAH/2018-22).

Surgical Techniques

The operation started after standard general anesthesia. Preoperatively all patients were given 500 mg ciprofloxacin + 500 mg metronidazole iv.

In the first group, the transrectal incision was made at the Mc-Burney point in open appendectomy. After entering the peritoneal cavity, a retractor was inserted into the wound. Mesoappendix was found and tied. AS was held and inverted, and buried in the cecum with a purse- string suture.

In Group 2, a laparoscopic knot-purse-string suture technique was performed. The trocar was entered into the intraperitoneal area and pneumoperitoneum was created. Additional trocars were entered through the appropriate ports. The operating table was tilted to the Trendelenburg position and remained at that position until the end of the surgery. Diagnosis of CA was confirmed by exploration (Figure 1A). The appendix and meso-appendix were separated using 5 mm LigaSure®. The AS was tied with an intracorporeal knot (ICK) using a multifilament non-absorbable suture near the base of the appendix (Figure 1B). Two knots were placed in the first step and one knot in the next step. After the appendix was excised, it was taken out of the abdominal cavity with an endobag. The pelvic area was checked for pus. If there was pus, the area was aspirated. A purse-string suture, which was placed 1 cm away from the stump, was realized using a multifila-

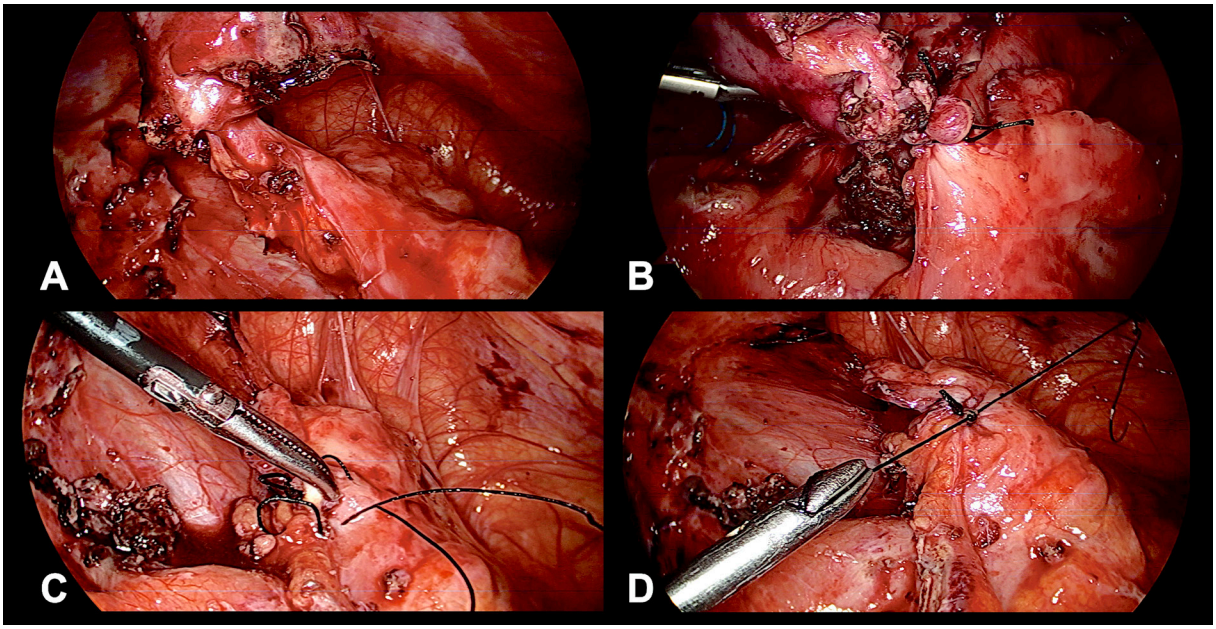

Figure 1A: Intraoperative view The appearance of complicated acute appendicitis. 1B: Intraoperative view: The appendiceal stump was tied close to the base of the appendix with 2/0 silk and an intracorporeal knot. 1C: Intraoperative view: The purse string using atraumatic 3/0 silk thread that will be passed through the 1 cm-thick stump 1D: Intraoperative view the appendiceal stump is inverted and buried in the cecum

ment non-absorbable suture. AS was inverted and buried in the cecum (Figures 1C and D).

All patients, except those with gastrointestinal complaints, started oral intake at the postoperative 4th hour. A nonsteroidal anti-inflammatory agent was used for the treatment of postoperative pain. Patients were followed for four weeks after surgery. Wound infections, conditions of the suture, complications and patients' complaints were recorded.

Statistical Analysis

Descriptive statistics were used to present the demographic characteristics of the study population. Differences between these groups were tested using the Pearson or Fisher's test for categorical variables, and Mann-Whitney U test or independent t-test were used for continuous variables. All analyzes were done using JMP Statistics on the computer. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Sixty-six patients were operated on with the diagnosis of CAA. The laparoscopic technique was applied to 36, and open technique to 30 patients. There was not any significant intergroup difference as for demographic data, levels of CRP and WBC (Table 1).

Table 1. The demographic characteristics, ASA scores, comorbidities and blood values of the patients are shown in the table.

Variables	Group 1 (n:30)	Group 2 (n:36)	Total (n:66)	p value
Age (median (±SD))	37.33 (±17.24)	36.03 (±13.28)	36.62 (±15,10)	0.852
Gender (%)	30 (45)	36 (55)	66 (100)	0.601
Female	9 (30)	13 (36.1)	22 (33.3)	
Male	21 (70)	23 (63.89)	44 (66.67)	
BMI (kg/m²) (median (±SD))	27.44 (±3.57)	27.55 (±5.26)	27.5 (±4.54)	0.918
ASA† classification (n (%))				0.241
I (normal healthy patient)	16 (53.33)	24 (66.67)	40 (60.61)	
II (mild systemic disease)	13 (43.33)	9 (25)	22 (33.33)	
III (severe systemic disease)	1 (3.33)	3 (8.33)	4 (6.06)	
Co-morbidities (n (%))	4 (13.33)	6 (16.67)	10 (15.15)	0.473
Diabetes Mellitus	0 (0)	2 (5.56)	2 (3.03)	
Hypertension	3 (10)	3 (8.33)	6 (9.09)	
Chronic Heart Disease	1 (3.33)	1 (2.78)	2 (3.03)	
WBC‡ (10^3/mm^3) (median (±SD))	15033.33 (±5052)	15208.33 (±3570)	15128.79 (±4273)	0.752
CRP (mg/dl) (mean (±SD))**	10.73 (±4.95)	10.36 (±6.34)	10.53 (±5.71)	0.457

**BMI:Body mass index, †ASA: American Association of Anesthesiology Score, ‡WBC:White blood cell,*
***CRP:C reactive protein*

Diffuse peritonitis was observed in 14 (46.66%) of 30 patients who underwent OA and 21 (58.33%) of 36 patients who had LA without any significant difference between both groups (p: 0.586) (Table 2). The cecum was partially resected with a linear stapler in 3 patients due to cecal necrosis in Groups LA (2/36; 6.56%) and OA (1/30; 3.33%) (Table 2).

Table 2. The operation time, duration of hospital stay, presence of drain, closure of the appendix stump, morbidity of the patients who underwent surgery are shown in the table.

Variables	Group1 (n:30)	Group 2 (n:36)	Totally (n:66)	p value
Operative time (min (±SD))	85.03 (±32.48)	65.67 (±9.88)	74.47 (±24.85)	0.002
Drain insertion (n (%))	27 (90)	22 (61,11)	49 (74,24)	0.008
Hospital Stay (hour (±SD))	156.8 (±101.77)	51 (±31.78)	99.09 (±89.35)	0.001
Conversion	0	0	0	N/A
Appendiceal stump (n (%))				0.876
Ligation and PSS*	29 (96.67)	34 (94.44)	62 (95.46)	
Linear stapler/ End-GIA	1 (3.33)	2 (6.56)	3 (4.54)	
Periperative diagnosis (n (%))				
Peritonitis	14 (46.66)	21 (58.33)	35 (53.03)	0.586
Abscess	16 (53.34)	15 (41.67)	31 (46.97)	
30-day morbidity (n (%))				
SSI†	6 (20)	4 (11.11)	10 (15.15)	0.001
POIAA‡	5 (16.67)	1 (2.78)	6 (9.09)	0.001
PI§	2 (6.67)	2 (5.56)	4 (6.06)	0.120
ASL††	0	0	0	N/A

**PSS; Purse string suture*
†SSI; Surgical site infection
‡POIAA; Postoperative intraabdominal abscess
§PI; Postoperative ileus
††ASL;Appendiceal stump leakage

Operation time was statistically significantly different between the two groups. The mean duration of operation was calculated as 65.67± 9.88 minutes in the Group LA and 85.03±32.48 minutes in the Group OA ($p < 0.001$) (Table 2). There was a significant difference in the mean hospital stays between both groups (156.8 ± 101.77 hours and 51 ± 31.78 hours in the Groups OA and LA, respectively ($p < 0.001$) (Table 2).

A drain was inserted in 90% of the patients in the Group OA and in 61.11% of the patients in the Group LA. Surgical site infection (SSI) occurred in 4 LA (11.11%) and in 6 OA patients (20%) (p: 0.001).

Postoperatively, 6 patients had POIAA (Group OA:, n=5; Group LA, n=1) (p: 0.001)) (Table 2). All patients were primarily treated with a drain inserted under USG guidance.

DISCUSSION

The use of LA in the management of uncomplicated appendicitis was reported in 1980 by Seem et al. It is still a reliable and effective technique since then [3]. Studies have shown that LA is more preferable to OA. Lesser postoperative pain, scarring and faster return to normal life are the most important advantages of LA [2-5]. Morbidity rates increase especially in perforated appendicitis. Surgical treatment of CA is usually associated with greater surgical stress, extended abdominal incision and a longer operative time compared to surgery performed for uncomplicated appendicitis [14-16].

Should the AS be buried after its closure? This remains to be a controversial subject? In particular, two techniques have been described in open appendectomy—that is, the closure and burying of the stump [9,17]. Results from a prospective randomized clinical study performed by Jacops et al. suggested that the AS should be buried in OA due to the possibility of infection, postoperative ileus and cecal fistula [17].

In a meta-analysis comparing closure and burial of the AS in OA, the rates of postoperative fever and wound infection were found to be similar between OA, and LA. When compared as for operative time, postoperative ileus and recovery rate, and closure of the AS, LA was found to be a relatively superior technique [18].

In uncomplicated acute appendicitis, there is a tendency in the literature for the AS to be closed only instead of buying it. Unfortunately, there was insufficient data on complicated appendicitis in another analysis that compared the closure and burial of the AS between both techniques. There is no evidence indicating that burying the AS improves postoperative results, as there are not enough studies on complicated appendicitis. Some studies suggest that postoperative ileus and length of hospital stay may adversely affect out-

comes. However, the scientific quality of these studies is not adequate to effectively stop surgeons from burying the AS [18,19].

In laparoscopic appendectomy, the closure of the AS is the most controversial issue. Although many authors have described AS closure techniques using new technological materials, a common consensus has not been achieved in this regard. In a clinical study by Gomez et al., the authors did not recommend the metal clip technique for AS closure, whereas the metal clip technique is inexpensive and easy to apply. However, they used this technique in cases where the diameter of the appendix is more than 1 cm and in cases of complicated acute appendicitis with perforation and necrosis at the base of the appendix or near the base [20]. In the AS closure, the clip method is presented as a cost-effective, easily applicable and safe technique [10,21,22]. In the study of Delibegovic et al., the authors suggested the use of endo-stapler in cases where the diameter of the inflamed appendix is more than the clip length since the use of the clip cannot provide a safe closure. It is said that the use of an endo-stapler for AS closure is safer than the laparoscopic endo-loop method in terms of preventing intraabdominal abscess formation [21]. Anyway, using endo-loops can reduce the cost of the surgery about 10 times, and also eliminates the risk of creating ileus from staples slipped into the abdomen [11,21,23]. Some studies have also reported that in open appendectomy closure of AS is successfully applied in the laparoscopy technique by ligating AS with a suture, passing it through PSS in the cecum and inverting it into the cecum [24,25]. In our retrospective clinical study, the AS was safely closed using this method, and no stump leak was observed in any of our patients. However, partial resection of cecum was performed in one patient in the OA group with large cecal floor necrosis and in two patients in the LA group with an endo-stapler to protect the ileocecal valve. In both groups, AS closure was successfully performed in cases of perforation or necrosis at or near the base of the appendix. The laparoscopic PSS technique is cheaper than other available techniques, but it requires advanced laparoscopic experience.

In our study, the OA group had significantly longer operation times than the LA group (85 vs. 65.7 minutes, p: 0.002). Other publications report longer or shorter operation times for LA when compared with OA [26,27]. Differences in studies may be related to surgeons' laparoscopic experience.

It is well-known that laparoscopy causes less postoperative adhesions and lower rates of mechanical intestinal obstruction [27]. However, in some studies, publications are indicating that rates of postoperative ileus may be higher in LA [28]. In our study, no difference was found between the LA group and the open group in terms of mechanical intestinal obstruction. We think that postoperative ileus may be caused by CAA that results in widespread peritonitis in both groups.

In most publications related to CAA, there is no clear consensus for categorizing CAA. Perforated appendicitis and peritonitis are the most important criteria for the classification of CAA [26-28]. In the literature, POIAA is more common after LA performed for CAA [26-28]. In a retrospective clinical study of 1516 patients, Horvath et al. stated that the reason why POIAA was significantly at a lower rate in the OA group was that during OA, the appendix was buried in the cecum after the stump was ligated, preventing contamination of the intraperitoneal area [27].The reason for the much greater incidence of POIAA in LA may be the position of the abdomen during the aspiration and leakage of the perforation fluid after removal of the sample. The patients were turned upside down and to the left to standardize the appearance of the operating field. Studies have shown that this position can spread the contamination inside the other quadrants of the abdomen [26-29]. Therefore, additional stump inversion is routinely performed during LA, further reducing endo-bag contamination [29]. Limited irrigation of the operating area is recommended in the Trendelenburg position [26-28]. In our study, POIIA was less common in the LA group compared with the OA group (1 vs. 5 patients, respectively). We think that the reason for our reduced POIIA rate may be due to the burying of the AS in the laparoscopic technique and the aspiration-irrigation performed in the supine position. In the OA group, we think that the perforation fluid in the intraabdominal cavity where cannot be reached through an open incision can lead to abscess formation. Indeed, in our study, subhepatic abscess detected in 4 patients of the OA group supports this assumption. POIIA cavities in both groups were emptied with percutaneous drainage under the guidance of USG.

SSI occurred more frequently in the OA group, but

intergroup difference was not statistically significant. Studies have shown that wound contact and not using endo-bags are among the reasons for the higher SSI rates in the OA group [26-28,30]. The inflamed appendix may have more tissue contact in the OA group. Since there is a smaller incision in LA, the contact is minimal [26-28]. All SSI patients were treated with antibiotherapy.

In randomized clinical trials comparing LA and OA, performed for CAA, a conversion rate of 0-16% to open technique has been reported. In our study, there was no patient in the LA group that required conversion to open technique. However, this technique could not be applied to 2 patients in the LA group due to large necrosis of the cecum floor, and partial resection of the cecum was performed in these patients.

Conclusion

The technique of burying AS applied in the open method can be safely practiced by experienced surgeons using the laparoscopic method in complicated CAA. This technique is effective, safe, and inexpensive.

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Contribution Details

Concept: SF, TD; design: SF, SY; definition of intellectual content: AS; literature search: SF, SA; clinical studies: TD, SF; experimental studies: MK; data analysis: SA; statistical analysis: SF; manuscript preparation: SY, AS; manuscript editing and manuscript review: TD, MK

Ethics Committee Approval: Bakırköy Sadi Konuk Training and Research Hospital Ethics Committee approval was received (3/12/2018; BEAH/2018-22).
Conflict of Interest: No conflict of interest was declared by the authors.
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Informed Consent: Informed consent was obtained from all individual participants included in the study.

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