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Research articles: This is the most important type of article since it provides new information based on original research. The main text of research articles should be structured with Introduction, Material and Method, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for research articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and

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Editorial comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Invited review articles: Invited reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. The invited reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Invited Review Articles.

Case reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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Research Article	3500	250 (Structured)	50	6	7 or tatal of 15 images
Invited Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	2	10 or total of 20 images
Letter to the Editor	500	No abstract	5	1	1

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All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

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Book section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR,

editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a single author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or technical report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study KidneyInt: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktivitelerive Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. SağlıkBilimleriEnstitüsü, DoktoraTezi. 2007.

Manuscripts accepted for publication, not published yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub ahead of print articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. DiagnIntervRadiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts published in electronic format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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THE INFLUENCE OF GROWTH HORMONE TREATMENT ON INSULIN SENSITIVITY IN CHILDREN AND ADOLESCENTS

ÇOCUK VE ADOLESANLARDA BÜYÜME HORMONU TEDAVİSİNİN İNSÜLİN DUYARLILIĞI ÜZERİNE ETKİSİ

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ABSTRACT

Objective: It has been reported that long-term growth hormone (GH) treatment may impair insulin sensitivity, hepatic glucose production, and insulin-dependent glucose utilization. In our study, we examined the effects of GH treatment on insulin sensitivity in patients with GH deficiency after one year treatment.

Materials and Methods: Fifty-nine patients (22 female, 37 male) with GH deficiency who received GH therapy were included in this study. Anthropometric measurements and pubertal examination of the patients were done. Fasting plasma glucose (FPG), fasting plasma insulin (FPI), HbA1c levels were measured and oral glucose tolerance test (OGTT) (1.75 g/kg, max. 75 g) was performed before and one year after treatment. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and Matsuda indices were calculated.

Result: The mean age of the patients at the start of GH treatment was 11.6±2.6 years old. The height standard deviation score (SDS) of the patients was -2.5±0.7, and the body mass index (BMI) SDS was -0.2±1.2. After one year, height SDS was -1.8±1.0 and BMI SDS was similar compared to baseline measurements. No difference was found between the initial and first-year pubertal stages of the patients. At the end of the first year, FPG and HbA1c levels did not change. When baseline and the first year results were compared, FPI, peak insulin, and total in-

ÖZET

Amaç: Uzun dönem büyüme hormonu (BH) tedavisinin insülin duyarlılığını azaltabileceği, karaciğerde glukoz üretimi ve insülin bağımlı glukoz kullanımını bozabileceği bildirilmektedir. Çalışmamızda bir yıllık BH tedavisinin insülin duyarlılığı üzerine etkilerini incelemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya BH eksikliği tanısı ile BH kullanan 59 hasta (22 kız, 37 erkek) dahil edildi. Antropometrik ölçümler ve puberte muayeneleri yapıldı. Tedavi öncesi ve tedavi sonrası birinci yılda plazma açlık glukoz (PAG), plazma açlık insülin (PAİ), HbA1c düzeyleri ölçüldü ve oral glukoz tolerans testi (OGTT) (1,75 g/kg maks 75 g) yapıldı. İnsülin Direncinin Homeostatik Modeli Değerlendirmesi (HOMA-IR) ve Matsuda indeksleri hesaplandı.

Bulgular: Tedavi öncesi hastaların ortalama yaşı (ort±SD) 11,6±2,6 yıl idi. Hastaların ortalama boy standart deviasyon skoru (SDS) değeri -2,5±0,7, vücut kitle indeksi (VKİ) -0,2±1,2 idi. Tedavi sonrası birinci yılda boy SDS -1,8±1,0, VKİ SDS başlangıç değerleri ile benzer idi. Tedavi öncesi ve sonrasında puberte evresi benzerdi. Birinci yıl sonunda PAG ve HbA1c düzeylerinde değişiklik saptanmadı. Tedavi öncesi ve tedavi sonrası karşılaştırıldığında, birinci yılda PAİ, zirve insülin ve toplam insülin düzeyleri anlamlı olarak daha yüksek idi (p=0,037; p=0,05; p=0,017). Matsuda indeks anlamlı olarak düşük saptandı (p=0,009). Tedavi

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sulin were significantly higher at the first year (p=0.037; p=0.05; p=0.017), and the Matsuda index was found to be significantly lower (p=0.009). While HOMA-IR was higher in the first year, the difference was not significant.

Conclusion: We observed that short-term GH treatment caused a decrease in insulin sensitivity, but did not reach disease-causing levels. It is important to monitor children receiving GH treatment for insulin resistance. We recommend further measurements of FPI and FPG, and performing OGTT to evaluate the degree of deterioration of glucose metabolism in risky patients.

Keywords: Growth hormone, glucose metabolism, insulin resistance, oral glucose tolerance test

sonrası HOMA-IR daha yüksek olmasına rağmen istatistiksel olarak anlamlı fark bulunmadı.

Sonuç: Çalışmamızın sonucunda, kısa dönem BH tedavisinin insülin duyarlılığında azalmaya sebep olduğunu ancak yine de hastalığa sebep olacak seviyelere ulaşmadığı sonucuna vardık. BH tedavisi alan hastaları insülin direnci açısından izlemek önemlidir. İzlem sırasında PAG ve PAİ ölçümü ve riskli hastalarda glukoz metabolizmasındaki bozulmaları belirlemek için OGTT yapılmasını önermekteyiz.

Anahtar Kelimeler: Büyüme hormonu, glukoz metabolizması, insülin direnci, oral glukoz tolerans testi

INTRODUCTION

Growth hormone (GH) has metabolic benefits on lipid profiles and body proportions and has favorable effects on bone metabolism. However, the influence of GH on glucose homeostasis is complex. It is known that GH has a direct negative effect on insulin sensitivity, and an indirect positive effect through insulin growth factor 1 (IGF-1), which has an insulin mimetic, glucose-lowering effect (1). The relationship between the GH/IGF-1 axis and insulin has not been clearly established yet.

The lipolytic effect of GH in the visceral and subcutaneous adipose tissue causes an increase in free fatty acids (FFA) (2). Increased FFA in circulation inhibits insulin receptor substrate-1 and phosphoinositide-3-kinase activation in skeletal muscle and the liver and impairs insulin mediated glucose uptake by skeletal muscle and induces insulin resistance (3). In addition, GH stimulates glucose production via glycogenolysis and gluconeogenesis in the liver and kidney (4,5).

Insulin growth factor 1 and insulin receptors have similar properties, and they can bind to their own receptor with great affinity and each other's receptor weakly. IGF-1 may cause hypoglycemia with a possible mechanism of stimulating glucose uptake by skeletal muscle and decreasing gluconeogenesis through insulin receptors and/or IGF-1 receptor activation which is shown *in vivo* studies (6,7).

In adults GH deficiency is associated with increased cardiovascular risk, increased abdominal obesity and hyperlipidemia, which may be a consequence of decreased IGF-1 levels. GH therapy seems to protect adults from hyperlipidemia and hypertension, however, careful monitoring of glucose metabolism is recommended (8,9). Moreover, the prevalence of diabetes is reported to be high in acromegalic patients who are known to have excess GH (5). Similarly, GH-treated children were reported to have an increased incidence of type 2 diabetes, and monitoring glucose metabolism in GH-treated patients who have an increased risk of diabetes is recommended (10,11). Studies in children and adolescents are limited in this issue and if insulin resistance will develop, it remains unknown in what year of treatment it will come out. We planned this study accordingly and we aimed to evaluate the effects of GH on glucose metabolism by comparing oral glucose tolerance test (OGTT) responses, before and one year after treatment in patients with idiopathic GH deficiency (GHD).

MATERIALS and METHODS

The study population included patients who were diagnosed with idiopathic GHD and received GH treatment. The study was designed as an observational study performed retrospectively, and the data was collected from patient files. The patients had short stature due to idiopathic GHD. Idiopathic GHD was diagnosed in children who had low growth velocity, with stimulated GH levels below 10 mg/L on GH stimulation tests (GHST), normal cranial and hypophysial magnetic resonance imaging, no other pituitary hormone deficiencies and no underlying reason for GHD (12,13). For GHST, clonidine (0.15 mg/m^2 per oral) and L-dopa (10 mg/kg per oral) tests were used. For each test, blood samples for GH levels were drawn at the baseline, 30, 60, 90, and 120 minutes. Peak GH values less than 10 mg/L were accepted as a low GH response (14,15).

Patients with idiopathic short stature and patients who have known syndromes like Turner syndrome, Prader-Willi syndrome etc., who have chronic disorders, use drugs other than GH, those born as small for gestational age (SGA) and who have a first-degree relative with diabetes were excluded from the study.

Anthropometric measurements were done by the same auxologist. Height was measured using a Harpenden stadiometer (nearest 0.1 mm) which was calibrated at intervals (Holtain Ltd., Crymych, UK). Weight was measured using a digital electronic scale (nearest 0.1 kg). Standard deviation score (SDS) calculations of height, weight, and body mass index (BMI) were done according to the national data of the measurements (16). Marshall and Tanner's staging was used to evaluate puberty (17,18). GH treatment was started subcutaneously daily before bedtime and all patients completed one year of treatment.

Each subject underwent an OGTT to assess insulin sensitivity and glucose tolerance. GH treatment was initiated in patients with a standard dose and individually adjusted according to maintain IGF-1 levels in normal ranges. OGTT, HbA1c, and c-peptide levels were measured before the start of GH treatment and one year after treatment. Each test was performed after 8 hours of overnight fasting. Immediately before the test, samples for fasting plasma insulin (FPI), fasting plasma glucose (FPG), c-peptide, and HbA1c were drawn. Each subject was given 1.75 g/kg oral glucose (max 75 g, 4g/1mL dilution with water) and then samples for insulin and glucose were taken at the baseline and 30, 60, 90, and 120 minutes after the glucose intake.

Glucose was measured by using standard laboratory methods. Insulin was measured with a chemiluminescent immunoassay. HbA1c was measured by ion-exchange high-performance liquid chromatography and the concentrations for insulin and IGF-1 were tested by using IMMULITE 2000 Xpi Analyzer (Siemens, India).

American Diabetes Association criteria were used to classify the glucose metabolism disorders. Diabetes was diagnosed with FPG higher than 126 mg/dL or 120-min glucose higher than 200 mg/dL or HbA1c ³6.5%. Glucose intolerance was defined as FPG levels between 100-126 mg/dL and/or 120 min glucose level of 140-200 mg/dL. FPI levels of ³15 mU/mL in prepubertal and ³20 mU/mL in pubertal children and insulin levels higher than 75 mU/mL at 120 min and total insulin above 300 mU/mL were considered as insulin resistance (19,20).

To estimate insulin sensitivity and total insulin, the homeostasis model assessment insulin resistance index (HOMA-IR), and Matsuda index were calculated from the results of OGTT. The Matsuda index was calculated before and one year after GH treatment based on the formula as described by Matsuda and DeFronzo (21): $10.000/\sqrt{FPG\ (mg/dL)} \times FPI\ (mU/mL) \times Glucose_{mean}\ (mg/dL) \times Insulin_{mean}\ (mU/mL)$. HOMA-IR was calculated as the Matthews formula FPI (mU/mL) x FPG (mg/dL)/405 (22).

The study was performed with the written informed consent of parents. The study protocol was approved by the local ethics committee of Istanbul University, Istanbul Faculty of Medicine (Date: 02.10.2020, No: 24) and conducted according to the Helsinki Declaration's ethical statement.

Table 1: Clinical and biochemical findings of patients

	Baseline mean±SD (median; ranges)	1st year mean±SD (median; ranges)	p value
Age, year	11.6±2.6 (12.2; 5.3-15.3)	13.1±2.5 (13.3; 6.6-17.3)	**<0.001**
Weight SDS	-1.4±1.1 (-1.5; -3.7-1.1)	-1.1±1.3 (-1.6; -3.1-2.1)	**<0.001**
Height SDS	-2.5±0.7 (-2.4; -4.3—1.2)	-1.8±1.0 (-1.9; -4.5-1.4)	**<0.001**
BMI SDS	-0.2±1.2 (-0.2; -2.2-2.2)	-0.2±1.3 (-0.5; -2.7-3.2)	0.964
Prepubertal n(%) **Pubertal n(%)**	16 (27.1) 43 (72.9)	11 (18.6) 48 (81.4)	0.380
IGF1 SDS	-1.0±1.1 (-1.0; -2.9-3.7)	-0.02±1.3 (-0.1;-2.1-3.9)	**<0.001**
OGTT			
FPG mg/dL	80.4±10.0 (80; 61-109)	82.1±9.1 (82; 60.1-110)	0.168
FPI mU/mL	13.6±7.9 (11.4; 2.3-36.2)	15.9±11.1 (14.2; 3.9-73)	**0.037**
2nd h glucose mg/dL	114.5±19.5 (111; 80-168)	114.4±24.0 (114; 72-226)	0.702
2nd h insulin mU/mL	71.8±51.9 (55.3; 16.1-288)	82.8±56.2 (73.7; 2.2-316)	**0.05**
Peak insulin mU/mL	107.1±68.5 (89.5;24.4-332)	126.2±77.1 (120.5;17.2-464)	**0.012**
Total insulin mU/mL	323.5±200.2 (278;34.9-914)	377.8±235.1 (341.4;26.5-1540)	**0.017**
c-peptide ng/mL	2.2±0.8 (2.2; 0.7-4.2)	2.3±0.9 (2.0; 1.0-4.9)	0.166
HbA1c %	5.3±0.3 (5.3; 4.6-6.0)	5.4±0.4 (5.5; 4.1-5.9)	0.126
HOMA-IR	2.7±1.6 (2.3; 0.3-8.0)	3.2±2.5 (2.7; 0.3-16.1)	0.064
Matsuda index	5.8±5.6 (4.2; 1.4-36.6)	5.6±8.2 (3.0; 0.6-56.1)	**0.009**

SD: Standard deviation score, BMI: Body mass index, IGF1: Insulin growth factor 1, OGTT: Oral glucose tolerance test, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HOMA-IR: Homeostasis model assessment insulin resistance

Statistical analysis

Statistical analyses were made using the Statistical Package for Social Sciences (SPSS) program for Windows 22.0. The Shapiro-Wilk test was used to determine the distribution of variables. Results were presented as mean±SD and categorical variables were expressed as numbers or percentages, where appropriate. Comparisons of continuous variables between groups were performed with the Wilcoxon sign rank test for paired samples and those of categorical variables with the Fisher's exact test. Correlation analysis between groups was analyzed using Spearman's test. p-value <0.05 was accepted as statistically significant.

RESULTS

A total of 59 patients consisting of 22 females (37.3%) and 37 males (62.7%) participated in our study. The mean age of the patients at presentation was 11.6±2.6 years old (females 10.2±1.9 years old, males 12.5±2.6 years old). The clinical and biochemical characteristics of the patients are presented in Table 1. All patients were born at an appropriate weight according to gestational age. The mean height SDS was -2.5±0.7, weight SDS was -1.4±1.1, and BMI SDS was -0.2±1.2. When the puberty stage was classified according to five subgroups, statistical evaluation could not be done because some of the puberty groups were too small for evaluation. Therefore, we compared prepubertal patients with pubertal ones. At presentation 27.1% of the patients were prepubertal and 72.9% of the patients were pubertal. The baseline IGF-1 SDS was -1.0±1.1. The peak GH level of GHST was (mean±SD) 5.5±2.6 mg/L and (median; min-max) 6.0; 0.2-9.9 mg/L. Before treatment, FPG, FPI, HbA1c, and c-peptide levels were in normal ranges. HOMA-IR was 2.7±1.6 and Matsuda index was 5.8±5.6. As expected, after one year of treatment weight and height SDS improved significantly. However, no marked change was noted in BMI SDS. After one year 18.6% of the patients were prepubertal and 81.4% were pubertal and there was no significant difference between the initial and the first-year puberty stages of the patients (p=0.380). After GH treatment we noticed a significant increase in IGF-1 levels, however, it was still in normal ranges (p<0.001). At the end of the first year, FPG, HbA1c, and c-peptide levels were in normal ranges and did not change significantly in comparison to baseline values. First-year FPI was 15.9±11.1mU/mL, peak insulin level was 126.2±77.1mU/mL, total insulin level was 377.8±235.1mU/mL, and Matsuda index was 5.6±8.2. When the initial and the first-year results were compared, FPI, peak insulin, and total insulin levels were significantly increased after GH treatment (p=0.037; p=0.05; p=0.017); The Matsuda index was found to be significantly lower (p=0.009). Although first-year HOMA-IR levels (3.2±2.5) were higher than pretreatment levels (2.7±1.6), no differences were found between HOMA-IR levels among patients (p=0.064). FPG and 120 min glucose levels were within normal ranges before and after treatment and we did not detect type 2 diabetes in our patients.

DISCUSSION

In our study, we investigated the changes in glucose metabolism and insulin levels in patients with GH deficiency who received GH treatment. The GH effect was confirmed to maintain a positive response by the increase in height and IGF-1 SDS. In our patients, we found significantly higher insulin levels when compared to the levels at the start of therapy. Insulin levels and insulin indices revealed a decrease in insulin sensitivity and increased insulin resistance. However, we did not have any patients who developed diabetes in the follow-up and we did not observe a change in glucose levels.

GH treatment has been used since the 1990s for GH deficiency. Since then, there has been an increasing number of studies related to the effects and side effects of GH. Adults with GH deficiency have an increased risk of atherosclerosis, insulin resistance, deterioration in lipid profile, and increased risk for cardiovascular mortality (8,23). GH therapy provides an increase in muscle strength, lean mass, bone mineral density, and benefits for lipid metabolism. The risks of cerebrovascular disease and insulin resistance constitute the main limitations of GH therapy in adulthood (9).

Glucose intolerance following impaired insulin sensitivity and increased insulin resistance raises concerns about the possibility of developing diabetes during GH treatment in the long term. GH has an important role in glucose homeostasis and insulin metabolism, but the data about the metabolic effects of GH therapy in childhood is controversial. Some studies showed deterioration in insulin sensitivity with pubertal development and ageing progress (24,25). Moreover, GH treatment seems to be associated with impaired insulin sensitivity in the short term, and long-term studies suggested that this initial negative effect was temporary (26). However, Cutfield et al. reported the results of an international pharmacoepidemiological survey which indicates an increased incidence of diabetes mellitus and glucose intolerance in children and adolescents who receive GH therapy and have a predisposal factor for diabetes (10). This acceleration in diabetes development may be reversible after discontinuation of treatment or dose reduction. Lutski et al. found no difference in diabetes incidence among patients with idiopathic GH deficiency and those who were born with SGA and received GH therapy during childhood when compared with the healthy population (27). However, they advised checking glucose levels closely during and after treatment, especially for individuals with diabetes risk factors such as a family history of diabetes, obesity, and Turner syn-

drome. GH therapy in children with SGA seems to be safe in terms of carbohydrate metabolism. Because no adverse effect was detected in glucose metabolism of SGA children during 260 weeks of GH treatment and in another long follow-up study, glucose metabolism was found to be normal at the end of six years in short SGA children (28,29).

Most studies have demonstrated an increase in insulin levels and HOMA-IR and normal glucose levels after one year of treatment of GH in prepubertal and pubertal children with GH deficiency. Our first-year results are in line with the reported data. We summarized the studies investigating the one-year effects of GH therapy on glucose metabolism in Table 2 (30-37).

According to the results of long-term studies, GH treatment is well tolerated after a three year follow-up and does not impair glucose metabolism, although it causes an increase in insulin levels. This increase in insulin levels started after one year of treatment and did not increase in the following years (35). A six year follow-up study showed the safety of GH treatment on glucose metabolism in GH-deficient children and they attributed the increased insulin secretion to the fact that GH causes a positive influence on beta cell capacity (38). Another study revealed a significant worsening in insulin sensitivity after four years of GH treatment in GH deficient children, while glucose and HbA1c levels were normal (31). Some long-term studies have shown hyperglycemia and insulin resistance under GH therapy. Glucose intolerance has been found in children who consume a high amount of simple carbohydrates and who have bad dietary habits. They suggest evaluating the diets of children carefully because these effects are possibly reversible with appropriate diet and may not require discontinuation of treatment (39).

In a recent study in an animal model, although an increase in endogenous GH and a concomittant increase in IGF-1 and insulin were detected, insulin sensitivity remained normal and glucose tolerance improved under GH therapy. The increase in insulin levels without systemic insulin resistance in the body was thought to be a result of increased beta cell mass or function (40).

In pubertal children, a physiological increase in insulin secretion and decreased insulin sensitivity is a known condition (41). It is difficult to estimate the role of puberty in the changes in glucose homeostasis during GH therapy. Pubertal children who are treated with GH may have an increased risk for glucose intolerance. However, in our study increased insulin levels were detected both in pubertal and prepubertal children. Furthermore, the changes in insulin levels cannot be attributed to body weight, since BMI SDS did not change significantly during the treatment. Besides, the increased insulin levels may be a result of increased beta cell compensatory capacity that develops secondary to GH-mediated inhibition of glucose uptake in the muscles and liver.

The main limitation of the present study is to assess insulin resistance and beta cell function with OGTT. The hyperinsulinemic-euglycemic clamp is the gold standard procedure, However, today, it is rarely used due to its impracticality in clinical practice. Another limitation of our study was that there were very few patients in puberty subgroups. Therefore, the effects of puberty on insulin resistance could not be clearly evaluated.

Table 2: Effects of one year recombinant human GH treatment on glucose metabolism in children and adolescents with GH deficiency

Reference	n	Age	FPG (mg/dL)	FPI (μU/mL)	HOMA-IR	Findings
30	30	8.6±3.4	97.5±8.5	12.3±7.6	2.99±0.21	FPG↑, FPI↑, HOMA-IR↑
31	118	10.7±3.5	83.4±8.3	5.7 (2.8-9.5)	1.18 (0.54-2.07)	FPG↑
32	16	8.9 (3.4-14.7)	82 (68-85)	4.2 (0.27-14.3)	1.1 (0.45-2.12	FPG↑, FPI↑
33	34	11.6±2.6	86.9±6.2	17.5±11.3	3.7±2.4	FPG↔, FPI↑, HOMA-IR↑
34	73	10.5±2.8	4.9±0.5	9±6.1	2±1.4	FPG↔, FPI↔, HOMA-IR↑
35	101	10.4 (7.7-12.5)	82 (76-88)	7.9 (4.9-13.6)	1.16 (0.72-1.72)	FPI↑, HOMA-IR↑
36	30	9.3±0.5	85±1.8	7.7±1.2	1.7±0.4	FPG↔, FPI↑, HOMA-IR↑
37	30	9.84±1.48	85.1±7.7	10.6±8.9	1.6±0.62	FPG↔, FPI↔, HOMA-IR↑
This study	59	13.1±2.5	82.1±9.1	15.9±11.1	3.2±2.5	FPG↔, FPI↑, HOMA-IR↔

FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HOMA-IR: Homeostasis model assessment insulin resistance, ↔: No change in the values at the end of the study,↑: Increase in the values at the end of the study. The age of the patients was presented in mean±SD or range.

CONCLUSION

After one year of GH treatment, we demonstrated an increase in insulin resistance. However, this increase did not reach pathological levels. According to our results before starting GH treatment, checking FPI, FPG and HbA1c and in case of suspicious findings performing OGTT is a practical, easily applicable, and reliable method for evaluation of insulin resistance and glucose metabolism until new biomarkers are developed for this purpose in the following years. Our results do not exclude the possible development of glucose intolerance with long-term use of GH treatment and we suggest performing OGTT annually while using GH in children at risk and detecting metabolically affected children. Following up with patients after treatment discontinuation is important since insulin resistance can be reversible. In addition, studies with larger numbers of patients are needed to investigate the effects of puberty in children receiving GH treatment.

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RESEARCH / ARAŞTIRMA
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COURSE OF PAPILLARY THYROID CARCINOMA DIAGNOSED IN CHILDHOOD AND ADOLESCENCE AND FOLLOWED THROUGH ADULTHOOD: EXPERIENCE FROM A TERTIARY REFERRAL CENTER*

ÇOCUKLUK VE ADÖLESAN DÖNEMDE TANI KONULAN ERİŞKİNLİK DÖNEMİ BOYUNCA TAKİP EDİLEN PAPİLLER TİROİD KARSİNOMUNUN SEYRİ: BİR ÜÇÜNCÜ BASAMAK MERKEZ DENEYİMİ*

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ABSTRACT

Objective: Differentiated thyroid cancer accounts for 1.5% of all pediatric malignancies. Papillary thyroid cancer (PTC) is the most common subtype and is associated with more advanced disease at diagnosis compared to adults. This study aimed to identify long-term outcomes of pediatric PTC.

Material and Method: Records of 30 patients with PTC diagnosed in childhood and adolescence and followed up at the Istanbul Faculty of Medicine were reviewed retrospectively.

Result: The mean age of 30 patients (21 females, 9 males) at diagnosis was 14.7±2.3 years. The mean duration of follow-up was 10.6±3.8 years. The patients underwent total thyroidectomy

ÖZET

Amaç: Diferansiye tiroid kanseri, tüm pediatrik malignitelerin %1,5'ini oluşturur. Papiller tiroid kanseri (PTK) en sık görülen alt tiptir ve tanı anında hastalık evresi erişkinlere kıyasla daha ileridir. Bu çalışmanın amacı, pediatrik PTK'nin uzun vadeli sonuçlarını değerlendirmekti.

Gereç ve Yöntem: İstanbul Tıp Fakültesi'nde takip edilen çocukluk ve adölesan döneminde PTK tanısı konulan 30 hastanın retrospektif olarak verileri incelendi.

Bulgular: Otuz hastanın (21 kadın, 9 erkek) tanı anındaki ortalama yaşı 14,7±2,3 idi. Ortalama takip süresi 10,6±3,8 yıldı. Dokuz hastaya total tiroidektomi, dokuz hastaya santral lenf nodu di-

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(n=9), total thyroidectomy with central lymph node dissection (n=9), or total thyroidectomy with central and lateral lymph node dissection (n=12). The mean tumor diameter was 1.6±1.5 cm and was microcarcinoma in 12 of the patients. There were five patients with T2 and two patients with T3 disease. At diagnosis, half of the patients had lymph node metastasis to the neck or upper mediastinum (N1a=5, N1b=10), and two also had lung metastasis. Post-operative radioactive iodine (RAI) treatment was administered to 22 patients, the median cumulative dose was 150 mCi (range 50 to 1100)]. Sixteen patients had excellent responses following single (n=13) or multiple (2 for persistent and 1 for recurring disease after 8.3 years) RAI administrations. The remaining three patients had structural incomplete and three had indeterminate responses.

Conclusion: Although PTC presented at a more advanced stage in childhood and adolescence, the response to treatment was fairly good with appropriate management.

Keywords: Papillary thyroid cancer, thyroid, pediatric, radioactive iodine

seksiyonu ile total tiroidektomi, 12 hastaya ise santral ve lateral lenf nodu diseksiyonu ile total tiroidektomi uygulandı. Ortalama tümör çapı 1,6±1,5 cm idi ve 12 hastada mikrokarsinom saptandı. T2 hastalığı olan beş hasta ve T3 hastalığı olan iki hasta vardı. Tanı sırasında hastaların yarısında boyun veya üst mediastende lenf nodu metastazı (N1a=5, N1b=10), iki hastada da ayrıca akciğer metastazı vardı. Ameliyat sonrası 22 hastaya radyoaktif iyot (RAI) tedavisi uygulandı, ortanca kümülatif doz 150 mCi (aralık 50-1100) idi. Hastaların 13'ü tekli doz, 3'ü (2 hasta persistan hastalık, 1 hasta 8,3 yıl sonra gelişen nüks hastalık nedeniyle) çoklu doz RAI uygulamasının ardından mükemmel yanıt verdi. Kalan üç hastada yapısal inkomplet ve üç hastada indetermine yanıt alındı.

Sonuç: PTK çocukluk ve ergenlik döneminde daha ileri evrede ortaya çıksa da uygun hastalık yönetimiyle tedaviye yanıt oldukça iyiydi.

Anahtar Kelimeler: Papiller tiroid kanseri, tiroid, pediatrik, radyoaktif iyot

INTRODUCTION

Thyroid cancer is an uncommon malignancy in childhood and adolescence; however, it is the most common endocrine cancer in this age group (1). Between 1973 and 2013, the annual incidence rate of pediatric thyroid cancer was reported as 0.6/100 000, but it is increasing worldwide (2,3). The most common type of thyroid cancer is papillary thyroid cancer (PTC) which accounts for approximately 86.0% of pediatric thyroid malignancy. Follicular thyroid cancer and medullary thyroid cancer constitute 8-9.0% and 4.0% of the remaining cases, respectively (2). Exposure to radiation increases thyroid cancer risk. Although the majority of thyroid cancer in children is sporadic, having a family history is one of the most important risk factors for the development of thyroid cancer. Syndromes such as familial adenomatous polyposis, PTEN (phosphatase and tensin homolog) hamartoma tumor syndrome, Carney complex type 1, McCune-Albright, multiple endocrine neoplasia type 2 A, Peutz-Jeghers, DICER1, and Werner syndrome are associated with non-medullary thyroid cancer (4,5).

At the time of diagnosis, children with PTC tend to present with more advanced disease and have larger tumors compared to adults. Regional lymph nodes and distant metastases are more common. The lung is the most common distant metastasis site of PTC (6,7). Therefore, all patients with PTC should be evaluated by a comprehensive neck USG preoperatively, and a fine-needle aspiration biopsy should be performed if there is a suspicious lateral cervical lymph node to optimize the surgical procedure. Total thyroidectomy is the procedure of choice for the majority of patients. Additionally, if there is evidence of metastasis, lateral neck lymph node dissection is also recommended. After surgery, radioactive iodine (RAI) therapy must be considered according to American Thyroid Association (ATA) risk stratification to treat persistent disease or to decrease the risk of recurrence. RAI is not indicated in patients with the low-risk PTC category, TSH suppressive-levothyroxine treatment is recommended for this group of patients (8).

Despite these features, the limited available data suggest that children with thyroid cancer generally have an excellent prognosis with appropriate management (9,10). This study aimed to assess the long-term oncological outcomes of pediatric PTC.

MATERIAL and METHODS

We retrospectively screened available medical records of patients who had PTC diagnosed in childhood and adolescence and followed up in the Istanbul Faculty of Medicine between 1980 and 2023.

Clinical characteristics of patients, age at diagnosis, gender, risk factors (such as radiation exposure, family history), surgical procedure, pathological findings (tumor diameter, histological type, microscopic subtype, invasion, lymph node metastasis), tumor stage, postoperative evaluation, and radioiodine treatment, presence of persistent disease or recurrence at follow-up, time to recurrence, the number of patients underwent reoperation, total RAI dose administered, presence of postoperative complications (recurrent nerve palsy and permanent hypoparathyroidism), duration of follow-up and oncological outcomes were evaluated.

PTC staging was made according to the American Joint Committee on Cancer/Tumor, Node, Metastasis (TNM) staging system (AJCC 8th.edition) (11).

The dose of administered activities of RAI was as follows: 30-100 mCi for tumors limited to the thyroid; 150 mCi for tumors that invaded the tissues surrounding the thyroid capsule and/or with metastasis to the neck or mediastinal lymph nodes; 175-200 mCi for distant metastases. In younger children, dose adjustments were made on a per kg basis using doses for a standard 70 kg person as a reference point.

An excellent response is defined as the absence of clinical, biochemical, or structural evidence of disease after RAI therapy.

BRAF mutation analysis was performed in thyroid tumor specimens and by using the QIAamp DNA tissue kit (Qiagen, Hilden, Germany) for genomic DNA preparation. The mutation was determined by pyrosequencing using the Qiagen PyroMark Q24 pyrosequencer (Qiagen, Venlo, Netherlands).

The Ethics Committee of the Istanbul Faculty of Medicine approved the study protocol (Date 28.04.2023, No: 09). The written informed consent was waived because of the nature of this retrospective study. For the statistical analyses, SPSS version 21.0 was used. Continuous and categorical variables were represented by mean±standard deviation, and frequency/percentage values, respectively. Categorical variables were compared with the chi-square test. The independent sample t-test was used to compare the baseline laboratory data.

RESULTS

The cohort included all patients who were transitioned from the pediatric to the adult endocrinology department and therefore who were followed up at the same tertiary center throughout the the entire process. In this study, a total of 30 patients were evaluated. The mean age at diagnosis was 14.7±2.3 years (range, 7 to 18). There were 21 females (70.0%) and 9 males (30.0%). The female-to-male ratio was 2.3:1. Among the patients, five had a history of radiation exposure to the neck and the mean duration from radiation exposure to the diagnosis of PTC was 7.2±2.4 years (range, 5 to 11). Only one patient had a family history of PTC (Figure 1). Ultrasound imaging was performed because of neck swelling in 18 patients, hypothyroidism in eight patients, and a history of lymphoma in two patients. The mean nodule size was 1.5±1.3 cm. According to Bethesda Classification fine-needle aspiration biopsy findings were as follows: Bethesda II category: 6.6% (n=2), Bethesda III category: 6.6% (n=2), Bethesda IV category: 10.0% (n=3), Bethesda V category: 26.6% (n=8), and Bethesda VI category: 46.6% (n=14). All of the patients underwent total thyroidectomy. Total thyroidectomy was combined with central lymph node dissection in 30.0% of the patients (n=9), and central and lateral lymph node dissection in 40.0% (n=12).

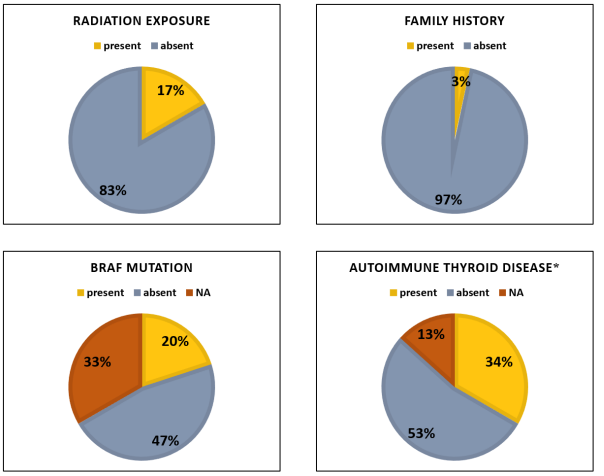

Figure 1: Presence of risk factors for papillary thyroid cancer. * Controversial risk factor

The tumor was bilateral in 43.3% of the patients, was located in the left lobe in 30.0%, in the right lobe in 20.0%, and in the isthmus region in 3.3%. The mean tumor size was 1.6±1.5 cm (range, 0.1 to 6), and the tumor was microcarcinoma (maximum diameter of 1 cm or less) in 12 of the patients. Histopathological subtype was available in 29 patients, and distribution was as follows; follicular variant in 13, classic variant in nine, encapsulated follicular variant in three, tall cell variant in one, macrofollicular variant in one, hobnail variant in one, diffuse sclerosing variant in one. The tumor was multicentric in 19 patients (63.3%). Histopathological examination revealed chronic lymphocytic thyroiditis in 10 patients. BRAF mutation could be analyzed in 20 patients and was detected in 30.0% of them (Table 1).

Most of the patients presented with a T1 disease (T1a, n=12; T1b, n=9; T2, n=5; T3, n=2). At diagnosis, half of the patients had lymph node metastases to the neck or upper mediastinum. Five patients had metastases to the central lymph nodes (N1a), and ten patients had metastases to the lateral lymph nodes (N1b). Seven of the patients with N1b had multicentric disease and vascular invasion, and six had lymphatic invasion. Lung metastases were detected in two patients (6.7%).

There was no difference between the metastasic and non-metastatic groups in terms of age at diagnosis and nodule size (p=0.68 and p=0.264 respectively). There was no association between the BRAF mutation and metastatic disease (p=0.051). However, radiation exposure was significantly higher in the non-metastatic group (p=0.014)

The mean duration of follow-up was 10.6±3.8 years. Eight low-risk patients still in remission were treated with only TSH-suppressive levothyroxine. Post-operative RAI treatment was administered to 22 patients [median number of administration was one (range 1-7), and the median cumu-

Table 1: Stage at diagnosis, treatment modalities and response to therapy

Patients	Gender	Age at diagnosis	BRAF	pT	pN	pM	No. of surgery	No. of RAI therapy	Total RAI dose	Persistent/ Recurrent disease	Response to therapy (Surgery and RAI)	Response to therapy (Only surgery)
Case 1	M	12.4	NA	T1a	N0	M0	1	-	-	-		Remission
Case 2	F	13.5	Positive	T2	N1b	M0	2	2	200	Recurrent	Excellent	
Case 3	F	15.7	Negative	T2	N0	M0	2	2	300	Persistent	Structural incomplete	
Case 4	F	16.3	NA	T1a	N0	M0	1	-	-	-		Remission
Case 5	F	13.7	Negative	T3a	N1b	M0	2	1	150	-	Excellent	
Case 6	F	13.6	NA		N1b	M0	4	4	750	-	Excellent	
Case 7	F	14.5	Positive	T1b	N1b	M0	1	1	150	-	Excellent	
Case 8	F	12.7	Negative	T1b	N0	M0	2	1	50	-	Excellent	
Case 9	F	15.6	Positive	T2	N1a	M0	1	1	150	-	Indeterminate	
Case 10	M	15.6	NA	T1b	N1b	M0	1	1	150	-	Excellent	
Case 11	F	15.8	Negative	T1b	N0	M0	1	1	100	-	Excellent	
Case 12	M	11.6	NA	T2	N1b	M1	1	5	605	-	Excellent	
Case 13	F	16.8	Negative	T1a	N0	M0	1	-	-	-		Remission
Case 14	M	17.7	Negative	T1a	N0	M0	1	-	-	-		Remission
Case 15	F	14.6	NA	T1b	N0	M0	1	1	100	-	Excellent	
Case 16	F	16.9	Negative	T1a	N0	M0	1	1	100	-	Excellent	
Case 17	F	15.2	NA	T1a	N0	M0	1	-	-	-		Remission
Case 18	F	14.7	Negative	T1a	N0	M0	1	-	-	-		Remission
Case 19	F	14.4	NA	T1b	N1b	M0	4	3	450	Persistent	Structural incomplete	
Case 20	F	7.3	Negative	T2	N1a	M0	1	1	50	-	Excellent	
Case 21	F	14.5	Positive	T1b	N1b	M0	5	3	450	Persistent	Indeterminate	
Case 22	F	17.5	Positive	T1a	N0	M0	1	-	-	-		Remission
Case 23	M	10.7	NA	T1a	N0	M0	1	1	50	-	Excellent	
Case 24	F	17.3	Negative	T1b	N0	M0	1	1	150	-	Excellent	
Case 25	F	15	Negative	T1a	N1a	M0	1	1	75	-	Excellent	
Case 26	M	18	Negative	T1a	N0	MO	1	-	-	-		Remission
Case 27	M	17.3	Negative	T1b	N1a	M0	1	1	150	-	Excellent	
Case 28	M	12.8	Positive	T1a	N1a	M0	1	1	150	-	Excellent	
Case 29	M	15.2	Negative	T3a	N1b	M0	3	2	250	Persistent	Structural incomplete	
Case 30	F	14	NA	NA	N1b	M1	4	7	1100	Persistent	Indeterminate	

pTNM: Pathological Tumor-Node-Metastasis, RAI: Radioactive Iodine, No. of surgery: Number of surgery, No. of RAI therapy: Number of radioactive iodine therapy NA: Not available

lative dose was 150 mCi (range 50 to 1100)]. Sixteen patients had excellent response following single (n=13) or multiple (2 for persistent and 1 for recurring disease after 100 months) RAI administrations. The remaining three patients had structural incomplete and three had indeterminate response. Data regarding the clinical characteristics and the follow-ups of the patients are summarized in Table 1.

DISCUSSION

In this study, the clinical features of PTC diagnosed in childhood and adolescence including stage at diagnosis, therapy modalities, response to treatment, and course of the disease were evaluated.

As in similar studies in the literature, our patients were predominantly female (12,13). Specific risk factors for thyroid cancer are ionizing radiation and genetic predisposition (14). There were five patients with a history of radiotherapy and one patient with a family history in our study.

In the literature, it was reported that the presence of autoimmune thyroid disease might be a risk factor for the development of thyroid cancer (15). However, in the study of Anil et al, it was found that Hashimoto's thyroiditis was not a risk factor for thyroid cancer in patients with thyroid nodules (16). On the pathological examination, histopathological characteristics of non-tumor thyroid tissues were available in 26 patients, and autoimmune thyroid disease was detected in 10 of them (38.4%, n:10/26). No other identified risk factors were detected for the remaining patients.

Children with PTC tend to have bilateral and more advanced disease at presentation compared with adults. Hay et al., reported the presence of regional lymph node metastases at initial surgery in 75.0% of patients (7). It was detected in 50.0% of the patients in our study. In the study of Cherella et al., bilateral disease was reported in 41.0% of the patients, and similarly, it was detected in 43.3% of the patients in our study (17). Total thyroidectomy is recommended as the first surgical procedure due to the risk of bilateral disease. After surgery, RAI treatment should be considered according to risk assessment (8).

Despite more advanced disease at presentation, the prognosis of PTC in children is excellent, and the survival rate is better than in adults (7). In our study, an excellent response was obtained in 16 of 22 patients who received RAI therapy. One of the patients with lung metastases (case 12) had an excellent response after repeated RAI therapies (total dose of 605 mCi). In the study of van de Berg et al., it was reported that the recurrence rate was 19.0% and the median duration of follow-up was 11.3 years (10). In our study, recurrence occurred in only one patient and the time from the initial surgery to recurrence was 8.3 years. The patient had lymph node metastasis at the time of diagnosis, and multicentricity and vascular invasion were present in the microscopic examination.

BRAF mutations are associated with lymph node metastases and advanced-stage at presentation (18). However, in the study of Poyrazoğlu et al., it was stated that BRAFV600E mutation was found in 25% of patients, and no relation was found between BRAFV600E mutation and lymph node or pulmonary metastasis at diagnosis (19). In the study of Senyurek et al., it was found that the locoregional recurrence rate was higher in BRAFV600E positive patients than in negative patients nevertheless BRAFV600E mutation had no role in the achievement of the excellent response to treatment (20). Six of our patients had BRAF mutations. Five of the 6 patients with BRAF mutations had lymph node metastases at the time of diagnosis, and one of them recurred during follow-up. However, no association between the BRAF mutation and metastatic disease was found.

Patients with a history of radiation exposure were diagnosed before the development of metastasis and these patients had smaller nodules (the mean nodule diameter 1.2±1.1 cm) at the time of diagnosis. This result may be related to the closer follow-up of the patients due to the risk of radiation exposure.

Postoperative complications developed in 12 patients; recurrent nerve palsy in one of them and permanent hypoparathyroidism in 11 patients. According to the literature, the risk of second primary cancer increases in children who receive RAI (21). Second primary cancer did not occur in our patients who received RAI, but the duration of follow-up might be short to assess.

The limitation of the study is the number of patients, but a small sample size is an unavoidable limitation in rare diseases like pediatric thyroid cancer.

CONCLUSION

In conclusion, pediatric PTC, the most common endocrine cancer in childhood and adolescence, had a tendency to present at a more advanced stage, but the response to treatment was fairly good with appropriate management.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date 28.04.2023, No: 09).

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EVALUATION OF MONOCYTE TO HIGH-DENSITY LIPOPROTEIN CHOLESTEROL RATIO AS A PREDICTIVE MARKER OF DIABETES MELLITUS SEVERITY IN OLDER PATIENTS

MONOSİT/YÜKSEK YOĞUNLUKLU LİPOPROTEİN KOLESTEROL ORANININ YAŞLI HASTALARDA DİYABETİN ŞİDDETİNİN PREDİKTİF BİR BELİRTECİ OLARAK DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: Diabetes mellitus (DM) is a disease characterized by chronic hyperglycemia and inflammation, the frequency of which increases with age. The monocyte to high-density lipoprotein cholesterol ratio (MHR) is a recently emerging inflammatory biomarker associated with various diseases. We aimed to investigate the utility of the MHR as a clinically useful inflammation-based marker in determining the severity of DM in older patients.

Material and Method: We designed our study in a retrospective, cross-sectional structure. The participants were assessed for eligibility from the population aged over 60 years of diabetic patients who were admitted to the Istanbul Medipol University Hospital endocrinology outpatient clinic between September 1st 2022, and March 1st, 2023. Data were collected from electronic medical records. Age, gender, and laboratory findings were recorded.

Result: Overall, 148 older participants (70 females, 78 males, mean age 69.17±5.74 years) were included in the analysis. MHR, white blood cell, neutrophil, lymphocyte, and monocyte counts were higher, while high-density lipoprotein cholesterol (HDL-C) levels were lower in patients with inadequate glycemic control (HbA1c≥7%) (p<0.001, for both of them). There was a moderately

ÖZET

Amaç: Diabetes mellitus (DM), sıklığı yaşla birlikte artan, kronik hiperglisemi ve inflamasyon ile karakterize bir hastalıktır. Monosit/yüksek yoğunluklu lipoprotein kolesterol oranı (MHR), çeşitli hastalıklarla ilişkili, son zamanlarda ortaya çıkan inflamatuar bir biyobelirteçtir. Yaşlı hastalarda DM'nin ciddiyetini belirlemede inflamasyona dayalı bir belirteç olan MHR'nin kullanımının faydasını araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmamızı retrospektif, kesitsel bir yapıda tasarladık. Araştırmanın populasyonu oluşturmak için, 01 Eylül 2022 - 01 Mart 2023 tarihleri arasında İstanbul Medipol Üniversitesi Hastanesi endokrinoloji polikliniğine başvuran 60 yaş üstü diyabetik hastalar uygunluk açısından değerlendirildi. Veriler elektronik tıbbi kayıtlardan toplandı. Yaş, cinsiyet ve laboratuvar bulguları kaydedildi.

Bulgular: Toplam 148 yaşlı katılımcı (70 kadın, 78 erkek, ortalama yaş 69,17±5,74 yıl) analize dahil edildi. Yetersiz glisemik kontrolü olan hastalarda (HbA1c ≥%7) MHR, lökosit, nötrofil, lenfosit, monosit sayıları daha yüksek iken, yüksek yoğunluklu lipoprotein kolesterol (HDL-C) düzeyleri daha düşük saptandı (p<0,001, her ikisi için de). HbA1c ve MHR arasında orta derecede güçlü bir korelasyon vardı (r=0,611, p<0,001). Düşük HDL-K ((OR=0,88, (%95

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strong correlation between HbA1c and MHR (r=0.611, p<0.001). Lower HDL-C ((OR=0.88, (95% CI:0.82–0.94), p< 0.001) (Model 1)) and higher MHR ((OR:1.45, 95% CI:1.27-1.65, p<0.001) (Model 4)) were independently associated with increased HbA1c.

Conclusion: HDL-C and MHR were independent factors in predicting an increased HbA1c in older diabetic patients. Lower HDL-C levels had a more significant role in the severity of predicting increased HbA1c compared to the monocyte counts.

Keywords: Monocyte to high-density lipoprotein cholesterol ratio, inflammation, diabetes mellitus, HbA1c, older patient

CI:0,82-0,94), p<0,001) (Model 1)) ve yüksek MHR ((OR:1,45, %95 CI:1,27-1,65, p<0,001) (Model 4)) bağımsız olarak yüksek HbA1c değerleri ile ilişkili bulundu.

Sonuç: HDL-c ve MHR, diyabetik yaşlı hastalarda artmış HbA1c' yi öngörmede bağımsız faktörlerdi. Düşük HDL kolesterol düzeyleri, monosit sayılarına kıyasla artmış HbA1c'yi öngörme şiddetinde daha anlamlı bir role sahipti.

Anahtar Kelimeler: Monosit/yüksek yoğunluklu lipoprotein oranı, inflamasyon, diabetes mellitus, HbA1c, yaşlı hasta

INTRODUCTION

As a result of the prolonged average life expectancy worldwide, the world population is aging. As a natural consequence of extending life, comorbidities are increasing rapidly and becoming a challenge for older adults (1). Diabetes mellitus (DM) is a chronic metabolic disorder that threatens human health all over the world, and its frequency increases with age. This insidious disease is characterized by chronic hyperglycemia, multi-organ dysfunction, and systemic complications, the main causes of increased diabetes-related morbidity and mortality rates. The prevalence of DM between 20-79 years of age is estimated to be 10.5% (536.6 million people) in 2021, increasing to 12.2% (783.2 million) in 2045. The highest prevalence of diabetes was between the ages of 75 and 79 (2). It is emerging as a public health problem, especially in developing countries (3). Diabetes is a disease that requires early intervention, not only because it negatively affects public health but also because managing diabetes and its complications is responsible for the significant increase in healthcare costs (4). Inadequate glycemic control is an important factor affecting the health status of the patients, causing mortality (5). Chronic hyperglycemia related to end-stage organ dysfunctions. (6). Therefore, pathological knowledge about factors in the development and homeostasis of the disease is critical for preventing and controlling it.

The pathophysiology of DM is complex and multifactorial. There are non-modifiable risk factors, including aging and genetic predispositions, and modifiable risk factors, such as physical exercise, diet, and smoking, as a determinant of blood glucose regulation (7). However, inflammation is the main pathological event in the development of DM and its associated complications (8). In particular, these inflammatory biomarkers, secreted from adipocytes, are associated with DM incidence and progression, as well as significant complications and cardiovascular events (9, 10).

Diabetes mellitus is a metabolic disorder whose etiopathogenesis is based on chronic inflammation. It has been associated with various peptide hormones synthesized in many tissues, complete blood count parameters, and their ratios. Monocytes interact mainly with platelets and endothelial cells, causing the exacerbation of the inflammatory and pro-thrombotic pathways (11). Furthermore, high-density lipoprotein cholesterol (HDL-C) particles are dynamically modified by altering lipid and protein content, both structurally and functionally, in response to physiological, pathological, and acute inflammatory conditions. Unlike monocytes with inflammatory and pro-oxidant effects, HDL-C protects endothelial cells from inflammation and oxidative stress by controlling monocyte activation and the migration of macrophages. Although HDL-C has an anti-inflammatory effect in healthy individuals, in case of severe inflammation, the components of HDL-C change, turning it into a dysfunctional, pro-inflammatory particle that cannot perform its normal anti-inflammatory, atheroprotective, and anti-oxidative functions (12). Based on this information, researchers have investigated a new marker of systemic inflammatory response, the monocyte to HDL-C ratio (MHR), obtained by dividing the monocyte count by the HDL-C value. Previous studies have demonstrated that both a high monocyte count and a low HDL-C level are associated with inflammation and oxidative stress. MHR is a useful parameter in predicting patients' clinical course and prognosis in various inflammatory and cardiovascular diseases (12-14). However, to our knowledge, no studies have investigated the utility of the MHR as a clinically useful inflammation-based marker in determining the severity of DM in older patients. In light of the current information, this study was planned to explore whether MHR is a predictive marker for assessing the severity of diabetes in the older diabetic patient group.

MATERIALS and METHODS

We designed our study in a retrospective, cross-sectional structure. The participants were assessed for eligibility from the population aged over 60 of previously diagnosed diabetic patients who were admitted to the Istanbul Medipol University Hospital endocrinology outpatient clinic between September 1st 2022, and March 1st

2023. The diagnosis of diabetes mellitus was identified according to the American Diabetes Association criteria: fasting plasma glucose≥126 mg/dL, or randomly plasma glucose≥200 mg/dL with suspected diabetes-related symptoms, or 2nd-hour plasma glucose ≥200 mg/dL with 75 g oral glucose tolerance test, or HbA1C value ≥%6.5. Some exclusion criteria were determined for the study. Patients with a clinical diagnosis of malignancy, inflammatory disease, autoimmune disease, anemia, hematologic disease, severe complications of type 2 diabetes, hepatic and renal failure, steroid usage, and receiving lipid-lowering therapy were excluded. After exclusion, a total of 148 participants were analyzed. Data were collected from electronic medical records. Age, gender, and laboratory finding were recorded. Evaluated venous blood parameters were taken in the morning after all participants had fasted for 8-10 hours. The complete blood count, fasting plasma glucose, and biochemistry parameters, including lipids, were assessed. Given that the current guidelines from the American Diabetes Association and Association of Clinical Endocrinologists recommends an HbA1c level of <7.0% as the treatment goal for older adults with intact cognitive and functional status, we divided into two categories the patients according to HbA1c values (below and above 7%) and examined. MHR was calculated by monocyte counts ($\times 10^9$/l)/HDL-C (mg/dL). Informed consent was obtained from all participants. Ethical committee approval for this study was obtained from the ethics committee of Istanbul Medipol University Hospital (Date: 20.03.2023, No: 265).

Statistical analysis

Statistical Package (SPSS for Windows, version 21.0; IBM Corp. Armonk, NY, USA) was used for data analysis. Descriptive statistics were given as mean and standard deviation (SD) for continuous variables, counts and percentages for categorical variables, and median and Interquartile range (IQR) for do not have normal distribution variables. The chi-square test was performed for categorical variables. The groups were compared by Student's t-test when the data was with a normal distribution and by The Mann–Whitney U-test when the data has a non-normal distribution. A Pearson correlation analysis was performed for Hba1c, age and associated laboratory parameters. Values determined to interpret the correlation's power were, for values of r, 0.00-0.29 is regarded as weak, 0.30-0.69 as moderate, 0.70-0.99 as strong, and 1.00 as a perfect linear relationship. Logistic regression analysis was applied to determine the factors related to the HbA1c level. Values of $p<0.05$ were accepted as statistically significant.

RESULTS

Overall, 148 older participants (70 females, 78 males) were analyzed. The mean age of patients was 69.17±5.74. Patients were divided into groups according to their HbA1c values.

The baseline clinical characteristics and laboratory findings of the patients according to the HbA1c value are given in Table 1. The mean white blood cell (WBC), neutrophil, lymphocyte, and monocyte counts were significantly higher in patients with inadequate glycemic control (HbA1c ≥7%) ($p<0.001$, for both of them). Moreover, the mean eosinophil, basophil, and mean platelet volume (MPV) values significantly differed between groups ($p=0.027$, 0.002, 0.002, 0.015, respectively).

Within the biochemistry parameters, glucose was significantly higher, as expected in patients with inadequate glycemic control ($p<0.001$). HDL levels were lower ($p<0.001$), and creatinine were higher ($p=0.004$) in patients with HbA1c≥7%. Monocyte to HDL-C ratio was higher in patients with the T2DM inadequately controlled ($p<0.001$).

The correlation analysis between HbA1c, MHR, and associated laboratory parameters is given in Table 2. There was a moderate correlation between HbA1c and MHR ($r=0.611$, $p<0.001$), HbA1c and monocyte counts ($r=0.458$, $p<0.001$). A negative correlation was found between Hba1c and HDL-C ($r=-0.624$, $p<0.001$). MHR was correlated with glucose, creatinine, WBC, hemoglobin, neutrophil, lymphocyte, monocyte, basophil, and platelet counts. A negative correlation was found between MHR and HDL-C ($r=-0.868$, $p<0.001$), MHR and total cholesterol ($r=-0.162$, $p=0.049$) levels.

Moreover, we performed multivariate regression analysis to predict an increased HbA1c in older diabetic patients in Table 3. We found that lower HDL-C was independently associated with increased HbA1c in all models (OR=0.88, (95% CI:0.82–0.94), $p<0.001$) (Model 1), (OR=0.87, (95% CI:0.82–0.93), $p<0.001$) (Model 2), (OR=0.84, (95% CI:0.80–0.89), $p<0.001$) (Model 3). Neutrophil (OR:1.60, 95% CI:1.09-2.33, p:0.017) and lymphocyte (OR:2.47, 95% CI:1.01-6.04, p:0.047) were independently related to predicting factors for an increased HbA1c in older diabetic patients, in Model 3. When MHR was included in the model, only MHR remained to be an independent determinant of predicting an increased HbA1c (OR:1.45, 95% CI:1.27-1.65, $p<0.001$) (Model 4).

DISCUSSION

This study demonstrated a strong association and moderately strong correlation between MHR and HbA1c in older diabetic patients. In other words, older adults with poorly controlled diabetes, revealed a higher MHR than patients with controlled diabetes.

White blood cells (WBC), additionally, leukocyte subtypes were detected to be robustly associated with HbA1c levels. Moreover, monocyte, WBC, neutrophil, lymphocyte, eosinophil, and basophil counts were higher in T2DM

Table 1: The clinical characteristics and laboratory findings of the patients according to the Hba1c value

Characteristics	Hba1c < 7 (n=73)	Hba1c ≥ 7 (n=75)	P value
Age (years), mean±SD	68.86±5.62	69.47±5.79	0.520
Gender, n (%)			
Female	40 (55%)	30 (40%)	
Male	33 (45%)	45 (60%)	0.071
Hemoglobin (g/dL), mean±SD	13.28±1.45	13.70±1.24	0.062
WBC (10^9/L), mean±SD	6.22±1.63	7.78±1.74	**<0.001**
Neutrophil (10^9/L), mean±SD	3.69±1.38	4.71±1.40	**<0.001**
Lymphocyte (10^9/L), mean±SD	1.97±0.48	2.34±0.54	**<0.001**
Monocyte (10^9/L), mean±SD	0.37±0.11	0.53±0.11	**<0.001**
Eosinophil (10^9/L), mean±SD	0.16±0.10	0.20±0.14	**0.027**
Basophil (10^9/L), mean±SD	0.03±0.02	0.04±0.02	**0.002**
Platelet (10^9/L), mean±SD	259.92±61.74	280.55±65.46	0.076
MPV (fL), mean±SD	10.46±1.21	10.02±0.95	**0.015**
Glucose (mg/dL), mean±SD	99.82±23.31	136.72±45.70	**<0.001**
Urea (mg/dL), mean±SD	27.11±8.19	28.44±5.82	0.256
Creatinine (mg/dL), mean±SD	0.75±0.14	0.82±0.14	**0.004**
ALT (U/L), median (IQR 25-75)	17.00 (13.00-25.50)	20.00 (17.00-36.00)	0.052
AST (U/L), median (IQR 25-75)	17.00 (14.00-20.50)	21.00 (16.00-23.00)	0.186
Total Cholesterol (mg/dL), mean±SD	199.64±42.44	197.08±47.24	0.729
HDL-C (mg/dL), mean±SD	50.40±6.89	38.26±8.53	**<0.001**
LDL-C (mg/dL), mean±SD	121.97±36.99	125.41±41.79	0.597
Triglycerides (mg/dL), median (IQR 25-75)	98.00 (65.70-122.00)	102.00 (68.00-170.00)	0.088
MHR, median (IQR 25-75)	6.84 (5.71-8.21)	14.32 (10.70-18.10)	**<0.001**

WBC: White blood count, MPV: Mean Platelet Volume, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HDL-C: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein-cholesterol, MHR: Monocyt-to-HDL cholesterol ratio, SD: Standard deviation, IQR: Interquartile range, Significant p values are bolded. P<0.05 was considered statistically significant

patients with poor glycemic control than in controlled diabetes. In addition, WBC, neutrophil, lymphocyte, and monocyte counts were correlated with increased HbA1c levels. Based on all the scientific data mentioned above, we hypothesized that full blood count parameters indices as a practical way of evaluating diabetes regulation and complication risk in older diabetic patients.

Many of the components in the blood cell are related to the inflammatory process. Circulating monocytes affect platelets and endothelial cells, causing aggravation, thrombosis, and inflammation. In atherosclerosis, low density lipoprotein cholesterol (LDL-C) is captured by macrophages leaving circulating monocytes, thereby forming plaques. The circulating monocytes are decisive in new plaque formation and atherosclerosis progression (11, 15). Therefore, monocytes are essential in managing diabetes and coping with its complications (16). Some studies have highlighted these associations, especially with diabetic micro and macrovascular complications (17-20). HDL-C prevents macrophage migration and LDL-C oxidation and blocks the effects of monocytes. HDL-C promotes Cholesterol efflux from macrophages, inactivates vascular adhesion in endothelial cells, and prevents the development of atherosclerosis; thus, it has an anti-inflammatory effect (21). In our study, HDL-C levels were lower and negatively correlated in our diabetic patients with inappropriate glycemic control. Higher monocyte counts and lower HDL-C levels are signs of inflammation. Moreover, it is well-known that diabetes is a part of inflammation (22).

MHR is a novel and valuable inflammatory biomarker with a routine blood test. MHR has been identified as a reliable marker for cardiovascular diseases (23). In patients with diabetic nephropathy, MHR was found to be a convenient predictive biomarker by detecting simple blood tests (13, 14). Chen WJ et al. suggested that a higher

Table 2: Correlation analysis between Hba1c, MHR and associated laboratory parameters

	Hba1c		MHR	
	r	p	r	p
Age	0.007	0.936	0.141	0.087
Glucose	**0.634**	**<0.001**	**0.469**	**<0.001**
Urea	0.149	0.070	0.043	0.607
Creatinine	**0.229**	**0.005**	**0.277**	**0.001**
ALT	0.066	0.428	0.002	0.979
AST	0.146	0.076	0.013	0.871
Total Cholesterol	-0.088	0.288	**-0.162**	**0.049**
Triglycerides	0.114	0.167	0.061	0.463
HDL-C	**-0.624**	**<0.001**	**-0.868**	**<0.001**
LDL-C	-0.067	0.419	-0.115	0.164
WBC	**0.298**	**<0.001**	**0.478**	**<0.001**
Hemoglobin	0.047	0.569	**0.194**	**0.018**
Neutrophil	**0.228**	**0.005**	**0.392**	**<0.001**
Lymphocyte	**0.290**	**<0.001**	**0.350**	**<0.001**
Monocyte	**0.458**	**<0.001**	**0.891**	**<0.001**
Eosinophil	0.098	0.234	0.102	0.216
Basophil	0.136	0.099	**0.217**	**0.008**
Platelet	0.082	0.321	**0.209**	**0.011**
MPV	**-0.191**	**0.020**	**-0.268**	**0.001**
MHR	**0.611**	**<0.001**	-	-

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein-cholesterol, Wbc: White blood count, MPV: Mean Platelet Volume, MHR: Monocyt-to-HDL cholesterol ratio. Significant p values are bolded. P<0.05 was considered statistically significant

MHR value is influential in prescribing the existence and progression of carotid atherosclerosis in diabetic patients (24). A study found that WBC, neutrophil, and lymphocyte counts were higher in diabetic patients with inadequate control and correlated with cardio-metabolic risk factors (25). You S et al. revealed that MHR was associated with an increased risk of disability or death at discharge in patients with acute cerebrovascular events (26). Another study found MHR to significantly predict high thrombus burden in patients with acute coronary syndrome (27). MHR represents independent variables for predicting patients with cardiovascular risk factors such as diabetes mellitus, hypertension, dyslipidemia, and older age (28).

In this study, a significant correlation was found between higher MHR values with the increase of values in many of the components in the blood cells, including WBC, neutrophil, lymphocyte, monocyte, basophil, hemoglobin, and platelet. We found that HDL-C and MHR were independent factors for predicting an increased HbA1c in older diabetic patients. Conspicuously lower HDL-C was independently associated with higher Hba1c values in all models. Furthermore, in Models 1 and 2, we performed the regression analysis to determine whether HDL-C or monocyte was the predictor of increased HbA1c in older diabetic patients. We showed that lower HDL-C had a more significant role in the severity of predicting increased HbA1c.

We conducted the study in a single center with a relatively small sample, which can be considered the major limitation of our study. Another limitation is the lack of adequate assessment of the effect of exercise and smoking on HDL-C value due to the study's retrospective nature. However, this study may inspire future studies in which the impact of exercise and smoking will also be evaluated. Although the cause-and-effect relationship can not be inferred from the study, it is noteworthy that we focused on the value of interesting blood cell parameters predicting increased HbA1c in older diabetic patients.

Table 3: Multivariate regression analysis for predicting an increased HbA1c in older diabetic patients

	Odds Ratio (95% CI)	p-value
Model 1		
HDL-C	**0.88 (0.82-0.94)**	**<0.001**
Neutrophil	1.37 (0.91-2.07)	0.131
Lymphocyte	1.74 (0.69-4.38)	0.237
Monocyte	143.43 (0.80-25602.11)	0.060
Mean platelet volume	0.96 (0.62-1.50)	0.871
Model 2		
HDL-C	**0.87 (0.82-0.93)**	**<0.001**
Neutrophil	1.37 (0.91-2.06)	0.133
Lymphocyte	1.75 (0.70-4.39)	0.234
Monocyte	143.43 (0.87-26014.76)	0.057
Model 3		
HDL-C	**0.84 (0.80-0.89)**	**<0.001**
Neutrophil	**1.60 (1.09-2.33)**	**0.017**
Lymphocyte	**2.47 (1.01-6.04)**	**0.047**
Model 4		
MHR	**1.45 (1.27-1.65)**	**<0.001**
Neutrophil	1.25 (0.85-1.83)	0.255
Lymphocyte	1.59 (0.69-3.68)	0.277

HDL-C: High-density lipoprotein cholesterol, MHR: Monocyt-to-HDL cholesterol ratio. Significant p values are bolded. p<0.05 was considered statistically significant.

CONCLUSION

A strong association and moderately strong correlation were detected between increased MHR values and HbA1c levels, as well as an increase in various components of blood cells, including WBC, neutrophil, lymphocyte, monocyte, basophil, hemoglobin, and platelet in older patient with poorly controlled DM. HDL-C and MHR were identified as independent factors for predicting increased HbA1c in older diabetic patients. Lower levels of HDL-C played a more significant role in predicting the severity of increased HbA1c compared to monocyte counts. In conclusion, MHR can help predict the severity of diabetes in older patients. Therefore, this parameter can serve as a clinically useful and potentially predictive inflammation-based marker for identifying patients with uncontrolled blood glucose who are at higher risk of complications related to DM.

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THE DETERMINANTS IN THE MANAGEMENT OF PREGNANCIES COMPLICATED WITH IMMUNE THROMBOCYTOPENIA*

İMMÜN TROMBOSİTOPENİYLE KOMPLİKE GEBELİKLERİN YÖNETİMİNDE BELİRLEYİCİLER

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ABSTRACT

Objective: This study aims to determine the hematologic and obstetric factors that would affect the management of immune thrombocytopenia (ITP) during pregnancy.

Material and Method: This is a retrospective review of 54 pregnancies that were complicated by ITP at a single tertiary center. All of the patients were followed-up and delivered at the same center. Subgroup analysis for obstetric outcomes was made according to the platelet counts at the time of delivery (<50x103/mm^3 or ≥50x10^3/mm^3), the time of diagnosis (before or during pregnancy) and neonatal platelet counts (≤100x10^3/mm^3 or >100x10^3/mm^3).

Result: Transfusion of blood products, steroid administration per se, or in combination with intravenous immunoglobulins (IVIG), were significantly more often administered in those with platelet counts <50x10^3/mm^3 at the time of delivery (p=0.020, p=0.020, and p=0.004, respectively). The patients who were first diagnosed with ITP during pregnancy had higher rates of transfusion of blood products (p=0.041), higher rates of vaginal deliveries (p=0.048), and lower rates of preterm delivery (p=0.044) when compared to the patients who had ITP diagnosed before the on-

ÖZET

Amaç: Bu çalışma, gebelikte immün trombositopeni (İTP) yönetimini etkileyecek hematolojik ve obstetrik faktörleri belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: İTP nedeniyle hastanemizde tedavi edilen ve doğumu hastanemizde yaptırılan İTP ile komplike olmuş 54 gebelik retrospektif olarak incelenmiştir. Obstetrik sonuçlar için alt grup analizi, doğum anındaki (<50x10^3/mm^3 veya ≥50x10^3/mm^3) ve tanı anındaki (gebelik öncesi veya gebelik sırasında) trombosit sayısı ve neonatal trombosit sayısına (≤100x10^3/mm^3 veya >100x10^3/mm^3) göre yapılmıştır.

Bulgular: Doğumda trombosit sayısı <50x10^3/mm^3 olan gebeliklerde steroid uygulaması, intravenöz immünoglobulinler (İVİG) ile birlikte steroid kullanımı ve kan ürünleri transfüzyonu anlamlı olarak daha yüksek saptanmıştır (sırasıyla, p=0,020, p=0,020, p=0,004). Gebelik öncesi İTP tanısı alan hastalara göre gebelikte İTP tanısı alan hastalarda, gebelik esnasında transfüzyon ve vajinal doğum oranının anlamlı olarak daha yüksek, erken doğum oranının anlamlı olarak daha düşük olduğu ve doğum anındaki gebelik yaşı, doğum ağırlığı ve neonatal trombosit sayısının an-

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set of pregnancy. Gestational age at birth (p=0.020), birth weight (p=0.002) and neonatal platelet count (p=0.002) were significantly higher in those who were diagnosed during the pregnancy. History of maternal splenectomy, intensive care unit admission, IVIG administration, and blood transfusion were significantly more frequent in neonates with platelet counts ≤100x10^3/mm^3 (p=0.028, p=0.001, p=0.001, and p=0.025, respectively).

Conclusion: The women diagnosed with ITP before the pregnancy and those who were diagnosed during the pregnancy had comparable rates of postpartum bleeding. However, there was a tendency towards overtreatment of the women who developed ITP during pregnancy.

Keywords: Immune thrombocytopenia, pregnancy, bleeding

lamlı olarak daha yüksek olduğu belirlenmiştir (sırasıyla, p=0,041, p=0,048, p=0,044, p=0,020, p=0,002 ve p=0,002). Trombosit sayısı ≤100x10^3/mm^3 olan yenidoğanlarda maternal splenektomi öyküsü, yoğun bakım gereksinimi, IVIG tedavisi ve kan transfüzyon gereksinimi anlamlı olarak daha yüksek bulunmuştur (sırasıyla p=0,028, p=0,001, p=0,001 ve p=0,025).

Sonuç: Gebelik öncesi İTP tanısı alan kadınlar ve gebelik sırasında İTP tanısı konulan kadınlar, postpartum kanama bakımından benzerdir. Buna karşılık, gebelik sırasında İTP gelişen kadınların gereğinden fazla tedavi edilmesine yönelik bir eğilim söz konusudur.

Anahtar Kelimeler: İmmun trombositopeni, gebelik, kanama

INTRODUCTION

Thrombocytopenia is the second most common hematological disorder in pregnancy after iron deficiency anemia (1). Thrombocytopenia refers to a platelet count less than 150x10^3/mm^3 and its prevalence ranges between 6.6% and 11.6% in pregnancy (2).

Immune thrombocytopenia (ITP) has an incidence of 1.6 to 3.9 per 100,000 patient-years. It has been reported that this incidence increases with age and has a slight female predominance (3). ITP affects 1 or 2 of every 1000 pregnancies and accounts for 5% of pregnancies with thrombocytopenia (4). This autoimmune disease can be diagnosed for the first time during pregnancy as its onset may be triggered by gestation (5). ITP during pregnancy might also present as an exacerbation of a previously diagnosed disease, particularly in the last trimester (5, 6).

The prevalence of chronic active ITP corresponds to 245 cases per million in adults and 10%-15% of this adult population comprises women of childbearing age (7). Considering that each woman at reproductive age has an average of two children in most European countries, it can be estimated that about 2 out of 10,000 women with chronic active ITP will become pregnant (6, 7). Similarly, the incidence of severe chronic ITP has been designated as 0.83 in 10,000 pregnant women by a nationwide survey conducted in the United Kingdom (8).

The most important maternal concern related to ITP is the risk of intractable bleeding especially at the time of delivery (9). Similarly, the major ITP-related fetal problem is the risk of intracranial hemorrhage due to neonatal thrombocytopenia induced by the transplacental passage of maternal antiplatelet antibodies (10). Therefore, prompt diagnosis and treatment of ITP should be made to prevent complications (11).

This study aims to determine the hematologic and obstetric factors that would affect the management of ITP during pregnancy.

MATERIAL and METHODS

The present study was approved by the Institutional Review Board and Ethical Committee of Istanbul University Istanbul Faculty of Medicine where the study was conducted (Date: 05.28.2021, No:11). This is a retrospective review of 54 pregnancies of 49 women complicated with ITP and, treated and delivered at the obstetrics department of the study center between January 2013 and May 2020. The study includes the pregnancies that were complicated with ITP and got the first diagnosis during that index pregnancy (n=17) and all pregnancies of the women who had a known diagnosis of ITP before pregnancy (n=37).

The diagnosis of ITP was made by a senior hematologist. The patients with platelet count <150x10^3/mm^3 with normal white and red blood cell counts, whose bone marrow biopsy showed a normal or increased number of megakaryocytes, and who had other obstetric and hereditary causes of thrombocytopenia were excluded. Other causes of thrombocytopenia that were excluded consisted of incidental gestational thrombocytopenia, preeclampsia, HELLP syndrome (Hemolysis, Elevated Liver enzyme levels, Low Platelets), viral infections such as hepatitis C, cytomegalovirus, human immunodeficiency virus, sepsis, disseminated intravascular coagulation, drug-induced thrombocytopenia, liver disease and autoimmune conditions such as systemic lupus erythematosus, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura and other hereditary thrombocytopenias. The pregnant women who received anticoagulant drugs and the pregnant women who were diagnosed with gestational thrombocytopenia were also excluded from the study. The diagnosis of gestational thrombocytopenia was made in patients with platelet counts >70x10^3/mm^3 and

in those with platelet counts within a normal range preceding or succeeding the pregnancy.

Data related to maternal age, time of ITP diagnosis (before or during pregnancy), minimum platelet count during pregnancy, medical treatment during pregnancy (steroids or steroids combined with IVIG), history of maternal splenectomy, transfusion of blood products during pregnancy, mode of delivery (vaginal or cesarean section), platelet counts at the time of delivery, postpartum bleeding, gestational age (GA) at delivery, preterm delivery and birth weight were acquired from medical records. Data related to the neonates including platelet counts, need for intensive care, length of stay at the intensive care unit, medical treatment (IVIG, phototherapy, or transfusion of blood products) and intracranial bleeding were also recorded.

Corticosteroid treatment was carried out by administering prednisone at a daily dose of 40 - 60 mg for a period of one week to nine months until delivery. IVIG treatment was initiated at daily doses of 400 mg/kg for five days. Preterm delivery was defined as delivery before 37 weeks of gestation. Postpartum bleeding has been identified as blood loss of more than 500 ml within 24 hours following a vaginal delivery or more than 1000 ml within 24 hours following cesarean delivery.

Subgroup analysis for perinatal outcomes was made according to the platelet counts at the time of delivery ($<50x10^3/mm^3$ or $\geq50x10^3/mm^3$), the time of ITP diagnosis (before or during pregnancy) and neonatal platelet counts ($\leq100x10^3/mm^3$ or $>100x10/mm^3$).

Statistical analysis

Collected data were analyzed using Statistical Package for Social Sciences version 17.0 (IBM Corporation, Armonk, NY, USA). The distribution of continuous variables was tested by a Shapiro-Wilk test and the assumption of homogeneity of variances was examined using a Levene test. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum) while categorical variables were denoted as numbers and percentages where appropriate. A Student's t-test and Mann-Whitney U test were used to compare the continuous variables whereas a Pearson's chi-square test, continuity-adjusted chi-square test, Fisher's exact test and, Fisher-Freeman-Halton test were used to compare the categorical variables. Two-tailed p-values less than 0.05 were statistically significant.

RESULTS

The perinatal outcomes of pregnancies with ITP based on platelet counts at the time of delivery are demonstrated in Table 1. When compared to the pregnancies with platelet counts $\geq50x10^3/mm^3$ at delivery, steroid administration, use of steroids in combination with IVIG, and transfusion of blood products were significantly more frequently observed in pregnancies with platelet counts $<50x10^3/mm^3$ at delivery (p=0.020, p=0.020 and p=0.004 respectively).

Table 1: Perinatal outcomes of pregnancies with ITP based on the platelet counts at delivery

	Platelet counts $<50x10^3/mm^3$ (n=15)	Platelet counts $\geq50x10^3/mm^3$ (n=39)	p value
Maternal age (years)	26.7±5.5	29.0±5.3	0.150
ITP diagnosed before pregnancy (n, %)	12 (80.0)	25 (64.1)	0.338
ITP diagnosed during pregnancy (n, %)	3 (20.0)	14 (35.9)	0.338
Steroid use during pregnancy (n, %)	8 (53.3)	15 (38.5)	0.020*
Steroid+IVIG use during pregnancy (n, %)	5 (33.3)	4 (10.3)	0.020*
History of splenectomy (n, %)	0 (0.0)	5 (12.8)	0.306
Transfusion during pregnancy (n, %)	14 (93.3)	18 (46.2)	0.004*
Vaginal delivery (n, %)	7 (46.7)	18 (46.2)	0.999
Cesarean delivery (n, %)	8 (53.3)	21 (53.8)	0.999
Postpartum bleeding (n, %)	2 (13.3)	1 (2.6)	0.183
Gestational age at delivery (weeks)	39 (31-40)	39 (31-41)	0.625
Preterm delivery (<37 weeks) (n, %)	3 (20.0)	6 (15.4)	0.696
Birth weight (gr)	3285.0±383.2	3195.4±621.2	0.605
Neonatal platelet count ($x10^3/mm^3$)	174.4±57.4	166.9±95.8	0.727
Neonatal platelet counts $\leq100x10^3/mm^3$ (n, %)	1 (6.7)	8 (20.5)	0.417
Need for neonatal intensive care (n, %)	3 (20.0)	9 (23.1)	0.999
Stay at neonatal intensive care unit (days)	10 (5-16)	6 (3-16)	0.482
Neonatal IVIG treatment (n, %)	1 (6.7)	7 (17.9)	0.419
Neonatal phototherapy (n, %)	1 (6.7)	2 (5.1)	0.999
Neonatal platelet transfusion (n, %)	0 (0.0)	2 (5.1)	0.999

*p<0.05 was accepted statistically significant, ITP: Immune thrombocytopenia, IVIG: Intravenous immunoglobulins.

The perinatal outcomes of pregnancies with ITP depending on the time of diagnosis are summarized in Table 2. The patients who were first diagnosed during the pregnancy had higher rates of blood transfusions, vaginal deliveries, GA at birth, birth weight, and neonatal platelet counts when compared to the patients who had the diagnosis of ITP before the pregnancy (p=0.041, p=0.048, p=0.020, p=0.002 and p=0.002 respectively). Preterm deliveries were significantly lower in those with a first diagnosis of ITP during the pregnancy (p=0.044).

The perinatal outcomes based on neonatal platelet counts are displayed in Table 3. When compared to the

Table 2: Perinatal outcomes of pregnancies with ITP based on the time of diagnosis

	ITP diagnosed before pregnancy (n=37)	ITP diagnosed during pregnancy (n=17)	p value
Maternal age (years)	28.4±5.7	28.3±5.0	0.932
History of splenectomy (n, %)	5 (13.5)	0 (0.0)	0.168
Transfusion during pregnancy (n, %)	18 (48.6)	14 (82.4)	0.041*
Platelet count at delivery (x10^3/mm^3)	65.7 (2.8-322.0)	63.0 (34.0-101.0)	0.948
Platelet count <50x10^3/mm^3 at delivery (n, %)	12 (32.4)	3 (17.6)	0.338
Vaginal delivery (n, %)	16 (43.2)	13 (76.5)	0.048*
Cesarean delivery (n, %)	21 (56.8)	4 (23.5)	0.048*
Postpartum bleeding (n, %)	3 (8.1)	0 (0.0)	0.544
Gestational age at delivery (weeks)	38 (31-41)	39 (38-41	0.020*
Preterm delivery (<37 weeks) (n, %)	9 (24.3)	0 (0.0)	0.044*
Birth weight (gr)	3066.3±568.8	3555.3±385.2	0.002*
Neonatal platelet count (x10^3/mm^3)	145.5±77.6	220.0±84.6	0.002*
Neonatal platelet count ≤100x10^3/mm^3 (n, %)	8 (21.6)	1 (5.9)	0.244
Need for neonatal intensive care (n, %)	11 (29.7)	1 (5.9)	0.078
Stay at neonatal intensive care unit (days)	7 (3-16)	5 (5-5)	0.568
Neonatal IVIG treatment (n, %)	7 (18.9)	1 (5.9)	0.411
Neonatal phototherapy (n, %)	2 (5.4)	1 (5.9)	0.999

*p<0.05 was accepted statistically significant, IVIG: Intravenous immunoglobulins.

Table 3: Perinatal outcomes of pregnancies with ITP based on neonatal platelet counts

	Neonatal platelet counts ≤100x10^3/mm^3 (n=9)	Neonatal platelet counts >100x10^3/mm^3 (n=45)	p value
Maternal age (years)	28.3±5.8	28.4±5.4	0.974
Maternal platelet nadir during pregnancy	55.0 (3.0-287.0)	56.2 (3.3-362.0)	0.972
ITP diagnosed before pregnancy (n, %)	8 (88.9)	29 (64.4)	0.244
ITP diagnosed during pregnancy (n, %)	1 (11.1)	16 (35.6)	0.244
Steroid use during pregnancy (n, %)	3 (33.3)	20 (44.4)	0.446
Steroid+IVIG use during pregnancy (n, %)	3 (33.3)	6 (13.3)	0.446
History of splenectomy (n, %)	3 (33.3)	2 (4.4)	0.028*
Transfusion during pregnancy (n, %)	5 (55.6)	27 (60.0)	0.999
Platelet count <50x10^3/mm^3 at delivery (n, %)	1 (11.1)	14 (31.1)	0.417
Vaginal delivery (n, %)	5 (55.6)	24 (53.3)	0.999
Cesarean delivery (n, %)	4 (44.4)	21 (46.7)	0.999
Gestational age at delivery	38 (31-40)	39 (31-41)	0.281
Preterm delivery (<37 weeks) (n, %)	2 (22.2)	7 (15.6)	0.635
Birth weight (grams)	2902.2±774.8	3283.9±498.0	0.063
Need for neonatal intensive care (n, %)	7 (77.8)	5 (11.1)	0.001*
Stay at neonatal intensive care unit (days)	7 (5-16)	6 (3-16)	0.530
Neonatal IVIG treatment (n, %)	8 (88.9)	0 (0.0)	0.001*
Neonatal phototherapy (n, %)	2 (22.2)	1 (2.2)	0.069
Neonatal platelet transfusion (n, %)	2 (22.2)	0 (0.0)	0.025*

*p<0.05 was accepted statistically significant, ITP: Immune thrombocytopenia, IVIG: Intravenous immunoglobulins.

neonates born with platelet counts >100x10³/mm³, rates of maternal splenectomy, need for neonatal intensive care, neonatal administration of IVIG, and blood transfusions were significantly more frequently observed in the neonates born with platelet counts ≤100x10³/mm³ (p=0.028, p=0.001, p=0.001 and p=0.025 respectively).

The clinical characteristics of nine neonates (16.7%) that were born with platelet counts ≤100x10³/mm³ are shown in Table 4. Five of these neonates were delivered vaginally while the remaining four (44.4%) were by cesarean section. Eight neonates (88.9%) received IVIG while two neonates (22.2%) underwent phototherapy in combination with IVIG therapy. Intracranial bleeding occurred in only one neonate who was born by cesarean section with a neonatal platelet count of 38,000/mm³.

with IVIG and transfusion of blood products were significantly more frequently administered to ITP patients with platelet counts <50x10³/mm³ compared to those with platelet counts ≥50x10³/mm³ at the time of delivery. This finding suggests that pregnant women with platelet counts <50x10³/mm³ are more likely to undergo medical treatment and transfusion even though the management of ITP in pregnancy should aim to reduce the risk of postpartum bleeding instead of increasing maternal platelet counts. Such a contradictory finding can be due to our retrospective study design and the relatively small cohort size. Another reason can be the fact that the study center is a tertiary university center that receives many referrals of high- risk pregnancies. The possible overtreatment of asymptomatic patients with ITP might be also considered

Table 4: Clinical characteristics of newborns with platelet count ≤100x10³/mm³

Case Number	Maternal splenectomy	Gestational age at delivery (weeks)	Delivery mode	Birth weight (grams)	Neonatal platelet count	Neonatal treatment	Neonatal intracranial bleeding
1	No	37	Cesarean	2510	38000	IVIG	Yes
2	No	39	Vaginal	3460	40900	IVIG+ phototherapy	No
3	No	36	Vaginal	2340	18800	IVIG+ phototherapy	No
4	Yes	38	Cesarean	2500	17000	IVIG	No
5	Yes	40	Cesarean	3730	93300	None	No
6	No	39	Vaginal	3920	15000	IVIG	No
7	No	31	Cesarean	1480	8400	IVIG	No
8	No	37	Vaginal	2940	16500	IVIG	No
9	No	39	Vaginal	3880	19000	IVIG	No

IVIG: Intravenous immunoglobulins.

DISCUSSION

The management of pregnancies complicated with ITP is a challenging issue (12). The American Society of Hematology recommends the treatment of pregnancies with ITP only if platelet counts are <30x10³/mm³ and/or there are symptoms of thrombocytopenia (13). Treatment is not required until 36 weeks of gestation or the expected time of delivery if platelet counts are ≥30x10³/mm³ without any symptoms of thrombocytopenia (13). A platelet count of ≥50x10³/mm³ is accepted as a safe lower limit for vaginal delivery and cesarean section (4).

In this study, rates of postpartum bleeding and neonatal complications did not differ between pregnancies associated with platelet counts <50x10³/mm³ or ≥50x10³/mm³. However, steroid therapy, steroid therapy in combination as an underlying factor, as suggested by Care et al. (8). Her nationwide survey and a Canadian study have defined the usually benign course of ITP in pregnant women (8, 14). These studies have specified that pregnancies complicated with ITP and healthy pregnancies were comparable with respect to postpartum bleeding and the risk of postpartum bleeding was unrelated to maternal platelet counts (8, 14).

Corticosteroids and IVIG have been considered as the first-line treatment for pregnancies complicated with ITP (12-14). It has been reported that about 30% to 35% of women receive medical treatment for ITP during pregnancy (15). In this study, corticosteroids were used in 42.6% of the pregnancies and IVIG in combination with steroids was administered in 16.7% of the pregnancies. The relatively high incidence of medical treatment in this study may be

interpreted as the evidence supporting the possibility of overtreatment of asymptomatic patients with ITP diagnosed during pregnancy. The findings of large-scale studies concerning the treatment with corticosteroids, IVIG, or both failed to yield any significant difference in terms of either maternal or fetal outcomes (8, 14, 16).

In this study, neonatal platelet counts were significantly higher in the patients who had ITP diagnosed during the pregnancy than in the patients who had ITP diagnosed before the pregnancy. Samuels et al. were the first to show that neonates born to mothers who had ITP diagnosed before pregnancy were more likely to have severe thrombocytopenia (17). A Japanese study also confirmed the significantly dramatic fall in platelet counts of newborns that were delivered by women with a known history of ITP (18). However, three other studies were unable to detect the relationship between the pre-pregnancy history of ITP and neonatal thrombocytopenia (19-21). Such discrepancy can be attributed to the heterogeneity in the demographic and clinical characteristics of the reviewed patients. It may be speculated that the relatively longer duration of the disease and/or the relatively higher number of exacerbations in pregnant women with a prior history of ITP enhance the production of anti-platelet auto-antibodies. This excessive load of autoantibodies may be conveyed to the fetus in utero, thus, inducing the destruction of fetal platelets and leading to the development of neonatal thrombocytopenia.

This study has indicated that vaginal delivery is significantly more frequently observed and the preterm delivery rate is significantly lower in patients who had an ITP diagnosis during the pregnancy than those diagnosed with ITP before the onset of pregnancy. In fact, the decision for the mode of delivery in pregnancies with ITP should be solely based on obstetric indications. Uncomplicated vaginal delivery appears as safe as cesarean section for the newborn and even safer for the mother (22, 23). However, cesarean section is usually preferred for the pregnancies complicated with ITP. The rationale behind this preference is the theoretically assumed decrease in the risk of intracranial bleeding for the neonates of affected mothers. Similar to our study, the rate of cesarean delivery was 51.7% in a Korean study (24). Obstetric indications might be the underlying reason for the significantly higher rate of cesarean delivery in the pregnancies of women who had a known history of ITP. The evidence favoring this suggestion is the significantly higher rates of preterm delivery in pregnant women with a known history of ITP. That is, indications for emergency preterm cesarean delivery might have been made based on the underlying etiologic factors such as fetal distress, premature rupture of membranes and malpresentation. In this study, the rate of preterm delivery has been estimated as 24.3% for the pregnant women who had ITP diagnosed before pregnancy. This number is higher than the incidence of preterm delivery which has been reported as 15.2% in previously published studies (9, 22).

In this study, the neonates with platelet counts ≤100x10^3/mm^3 or >100x10^3/mm^3 were statistically comparable with respect to minimum maternal platelet count during pregnancy and severe maternal thrombocytopenia (<50x10^3/mm^3) at the time of delivery. This finding supports the existence of a poor correlation between maternal and fetal platelet counts in pregnancies complicated with ITP (20-24). It has been declared that thrombocytopenia is relatively rare in newborns delivered by women with ITP. Previously published studies have yielded an incidence of 10% for thrombocytopenia in infants born to affected mothers (20). On the other hand, the risk of intracranial hemorrhage has been estimated as <1.5% with mortality rates of <1% in newborns with thrombocytopenia (21). In the present study, nine (17.6%) newborns had platelet counts ≤100x10^3/mm^3 and six newborns (11.1%) had platelet counts <30x10^3/mm^3 but only one newborn was diagnosed with intracranial hemorrhage and no deaths occurred. This finding can be the result of vigorous treatment received by the thrombocytopenic neonates.

It has been well established that the management of pregnancies complicated with ITP requires the collaboration of obstetricians, hematologists, and pediatricians at a tertiary center. Our findings imply that and the diagnosis of ITP before pregnancy appears as a risk factor for preterm delivery and cesarean section. Further research has been warranted to standardize the approach for the management of pregnancies complicated with ITP.

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EFFICACY AND SAFETY OF POSTOPERATIVE INTRAVESICAL ADMINISTRATION OF TRANEXAMIC ACID AFTER TRANSURETHRAL RESECTION OF THE PROSTATE*

TRANSÜRETRAL PROSTAT REZEKSİYONU SONRASI POSTOPERATİF İNTRAVEZİKAL TRANEKSAMİK ASİT UYGULAMASININ ETKİNLİĞİ VE GÜVENLİĞİ

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ABSTRACT

Objective: To evaluate the safety and efficacy of postoperative intravesical administration of tranexamic acid after transurethral resection of the prostate.

Material and Method: The data of 112 patients who underwent surgery for lower urinary tract symptoms associated with benign prostatic obstruction (BPO) were retrospectively analysed. We formed two groups: Group 1 consisted of 57 patients who received tranexamic acid by irrigation fluid after the operation; group 2 consisted of 55 patients who did not receive tranexamic acid. Demographic data of patients and prostate characters, as well as operative and postoperative data were analysed. Postoperative bleeding in all patients was evaluated using the haemoglobin levels at the preoperative, and at 0- and 24-h postoperative were evaluated and noted.

Result: The mean ages of the patients were 66.9±7.2 (55-81) years in the intervention group, and those in the control group were 68.6±7.6 (55-80) years. There were no significant differences between the groups for demographic data, prostate volume and International Prostate Symptom Score (IPSS). The reduction in Hb at 24 hours postoperatively was greater in the control group compared to the tranexamic acid (TXA) group. Statistically significant differences were found between the two groups in terms of postoperative haemoglobin decrease, bladder irrigation time and total amount of irrigation fluid. There were no statistically significant differences between each group regarding the operation, weight of resected adenoma, hospitalization time and catheter removal time.

ÖZET

Amaç: Benign prostat hiperplazili hastalarda transüretral prostat rezeksiyonu sonrası postoperatif intravezikal traneksamik asit uygulamasının güvenlik ve etkinliğini değerlendirmek.

Gereç ve Yöntem: Benign prostat hiperplazisine bağlı alt üriner sistem semptomları nedeniyle ameliyat edilen 112 hastanın verileri geriye dönük olarak incelendi. İki grup oluşturuldu: Grup 1'de operasyon sonrası irrigasyon sıvısı ile traneksamik asit uygulanan 57 hasta, grup 2'de traneksamik asit uygulanmayan 55 hasta mevcuttu. Hastaların demografik verileri, prostat özellikleri, operatif ve postoperatif verileri analiz edildi. Tüm hastalarda ameliyat sonrası takiplerindeki kanama miktarları; preoperatif ve postoperatif 0. ve 24. saatlerde hemoglobin düzeyleri kullanılarak değerlendirildi ve not edildi.

Bulgular: Traneksamik asit grubundaki hastaların yaş ortalaması 66,9±7,2 (55-81) yıl, kontrol grubundakiler ise 68,6±7,6 (55-80) yıl idi. Demografik veriler, prostat hacmi ve Uluslararası prostat semptom skoru açısından gruplar arasında anlamlı fark yoktu. Postoperatif 24 saatte hemoglobindeki azalma, traneksamik asit grubuna kıyasla kontrol grubunda daha fazlaydı. Postoperatif hemoglobin düşüşü, mesane irrigasyon süresi ve toplam irrigasyon sıvısı miktarı açısından iki grup arasında istatistiksel olarak anlamlı fark bulundu. Ameliyat süresi, rezeke edilen adenomun ağırlığı, hastanede kalış süresi ve kateter çıkarma süresi açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu.

* The study was presented as an oral presentation at the Turkish Urology Society's Symposium, 2023 / Eser Türk Üroloji Dernekleri Sempozyumu 2023'te sözlü bildiri olarak sunulmuştur.

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Conclusion: A postoperative follow-up process with less bleeding and complications is possible with tranexamic acid added to the intravesical irrigation fluid used after transurethral prostate resection (TURP) surgery.

Keywords: Tranexamic acid, transurethral resection of the prostate, irrigation fluid, postoperative bleeding

Sonuç: Transüretral prostat rezeksiyonu ameliyatı sonrası kullanılan intravezikal irrigasyon sıvısına eklenen traneksamik asit ile ameliyat sonrası daha az kanama ve komplikasyon ile takip süreci mümkündür.

Anahtar Kelimeler: Traneksamik asit, transuretral prostat rezeksiyonu, irrigasyon sıvısı, postoperatif kanama

INTRODUCTION

Lower urinary tract symptoms (LUTS) are a common complaint in aging men and occur most frequently associated with benign prostatic obstruction. Especially surgical treatment is performed in cases resistant to medical treatment (1, 2). Despite the recent development of alternative surgical techniques, transurethral prostate resection (TURP) is still accepted as the gold standard for the surgical treatment of benign prostatic obstruction (BPO). However, bleeding is a major perioperative complication, and transfusion rates after TURP have been shown to be around 0.4-7.1% in patients. The amount of bleeding varies depending on the patient's use of anticoagulant medication, comorbidity, size of the prostate, duration of the operation, and the amount of resected tissue (3, 4).

Many interventions have been recommended to reduce perioperative bleeding in prostate surgery such as intravenous oestrogen, erythropoietin, finasteride, intraprostatic vasopressin, controlled hypotension, and the use of antifibrinolytics (5).

Bleeding associated with urinary tract surgery is thought to be due to the fibrinolytic effect of high plasminogen concentration in the urine. Therefore, the use of tranexamic acid (TXA) has been investigated in previous studies to reduce intraoperative and postoperative bleeding in prostate surgeries. However, it has not been adequately accepted in urology practice (6, 7).

In this study, we aimed to investigate the effect of tranexamic acid, which was used in the irrigation fluid postoperatively, on reducing the amount of perioperative bleeding in bipolar TURP.

MATERIAL and METHODS

We included 112 patients operated on for BPO-related lower urinary tract symptoms and designed two groups with similar characteristics. The study was designed by scanning data of patients on whom bipolar TURP for benign prostatic obstruction was performed between February 2018 and July 2022 retrospectively. All operations were performed by two expert endourologists in a tertiary hospital. Group 1 consisted of 57 patients who had tranexamic acid in the irrigation fluid following the operation; group 2 consisted of 55 patients who did not have tranexamic acid in the irrigation fluid. Approved written informed consent describing the surgical procedure, benefits, and potential risks appropriately was read and completed by all study patients prior to surgery. Ethics committee approval was obtained from Istinye University Clinical Research Ethics Committee (Date: 07.12.2022, No: 3/2022.K-91). The study was conducted in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its subsequent amendments. We performed a digital rectum examination, a routine blood examination and urine test, prostate-specific antigen (PSA) levels, a transrectal ultrasound scan, and International Prostate Symptom Score (IPSS). The haemoglobin levels of the patients at the preoperative, and at 0- and 24-h postoperatively were evaluated and noted. Inclusion criteria were as follows: age ≤ 81, Qmax≤10 mL/h, IPSS≥16, and prostate volume measured by transrectal US between 40-100 mL. The exclusion criteria were suspected/confirmed bladder or prostate cancer, neurogenic bladder, previous lower urinary tract surgery (urethral and/or prostate), serious comorbidities (unstable angina, symptomatic CHF, poorly controlled COPD, recent (less than six months ago) myocardial infarction or stroke), coagulopathy.

When the operation was over, a 22F 3-way urethral catheter was inserted and bladder irrigation was continued until the postoperative flush was cleared. While 5 ampoules of tranexamic acid (5 mL 250 mg/1 ampoule) were applied to the first postoperative irrigation fluid (0.9% Sodium Chloride Irrigation, 3000 mL), 3 ampoules of tranexamic acid were added to the postoperative maintenance irrigation fluids. In total, 17-29 ampoules of tranexamic acid were added in irrigation fluids in all patients of the intervention group.

Statistical analysis

Statistical analyses were performed with SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA) and data were displayed as mean±standard deviation (SD) (range). The chi-square test, Manne-Whitney U test, and one-way analysis of variance (ANOVA) were used for statistical comparisons. A 5% level of significance was used for all statistical testing. A P-value<0.05 was considered significant.

RESULTS

Data from 57 (51%) patients treated with TXA and 55 (49%) control patients were analysed. The mean age of

the patients was 66.9±7.2 (55-81) years in the intervention group, and those in the control group was 68.6±7.6 (55-80) years. Body mass index (BMI) was calculated as 30.5±3.6 (21-36) in the intervention group and 28.8±4.1 (22-35) in the control group, respectively. While 46 (81%) patients had ASA I-II and 11 (19%) patients had ASA III-IV in the intervention group, 47 (85%) patients had ASA I-II and ASA III-IV was 8 (15%) patients in the control group. The prostate volumes of the patients were 69.6±10.9 (40-92) mL and 66±11.3 (48-91) mL, respectively. There were no statistical differences between each group in age, BMI, IPSS, prostate size and patients' comorbidity. Demographic data and preoperative results of patients are shown in Table 1. The reduction in Hb at 24 hours postoperatively was statistically significant in the control group compared to the TXA group ($p<0.001$). The mean duration of operation was 73.8±14.5 (40-110) minutes in the intervention group and 76.3±17.1 (48-125) in the control group. The weight of resected adenoma was 35.1±7.8 grams in group 1 and 34.7±6.4 grams in group 2. The mean hospitalization time of patients was 1.8±0.7 (1-3) days and 2±0.8 (1-5) days, respectively. Catheter removal times were 2.4±0.7 days and 2.8±1 days in group 1 and group 2, respectively. There were no statistical differences between each group regarding the duration of the operation, weight of resected adenoma, hospitalization time, and catheter removal time. Postoperative bladder irrigation time was 12.4±5.1 hours in the intervention group, while it was 15.5±7.3 hours in the control group. According to our analysis of patients' data, statistically significant differences were found between the two groups in postoperative bladder irrigation time and the total amount of irrigation fluid (Table 2). No patient had haematuria requiring blood transfusion in both groups.

DISCUSSION

The prostate tissue, which has a rich blood supply, contains large venous sinuses. During prostate resection, these venous sinuses are opened, fibrinolytic enzymes pass into the vascular system and fibrinolysis is activated. Bleeding becomes inevitable with fibrin degradation (7-9).

TXA is a synthetic derivative of lysine and is an antifibrinolytic. Its mechanism of action is to prevent the formation of plasmin by binding to plasminogen, to prevent the breakdown of fibrin polymers, and to stabilize blood clots, respectively. Thus, it reduces blood loss and the need for transfusion in surgeries. Thanks to this effect, TXA is used in acute trauma, cardiac surgery, orthopaedics and liver surgery operations (5, 7, 10). Although it was used in some previous studies in urological surgery, it did not gain much interest in the urology practice.

Despite the developing technology in TURP operations, blood loss continues to be a problem. Significant bleeding can increase surgical morbidity and mortality. TXA, which is used effectively in reducing blood loss in different surgical branches, has also been used in TURP operations recently, but its effectiveness has been a matter of debate (11, 12). In the studies, the route of administration of TXA was performed intravenously, as in other surgical specialties. However, in our study, TXA was added to irrigation fluids by the intravesical route, and its efficacy and safety were evaluated.

In the literature, there are studies that evaluated the decrease in haemoglobin after TURP surgery and found a significant difference in the TXA group (13), as well as studies stating that there was no difference (14). In the present study, we found that the urine colour was lighter, and the amount of bleeding decreased with TXA added to the irrigation fluid in the postoperative follow-ups. It showed that the decrease in Hb at the postoperative 24th hour was statistically less significant in the TXA group ($p<0.001$).

Some studies found a statistical decrease in the volume of irrigation fluid used intraoperatively with intravenous TXA administered perioperatively (12, 13). However, there have also been studies that applied TXA with the same method and did not detect any difference (15, 16). Unlike our study, TXA was applied only in the postoperative period and was added to the irrigation fluid. There was a statistical difference in the postoperative total amount of

Table 1: Preoperative demographic characteristics of the patients

	Tranexamic acid (n=57)	Control (n=55)	P value
Age (years)	66.9±7.2 (55-81)	68.6±7.6 (55-80)	0.67
Body mass index	30.5±3.6 (21-36)	28.8±4.1 (22-35)	0.29
ASA category I + II (n)	46	47	0.44
ASA category III + IV (n)	11	8	0.17
Preoperative haemoglobin (g/dl)	13.9±0.9	14.2±0.8	0,52
Prostate volume (ml)	69.6±10.9 (40-92)	66±11.3 (48-91)	0.15
IPSS	22.5±2.3	22.1±2.6	0.61

ASA: American Society of Anaesthesiologists, IPSS: International Prostate Symptom Score

Table 2: Comparison of postoperative parameters and complications

	Tranexamic acid (n=57)	Control (n=55)	P value
Haemoglobin (g/dl)			
preoperative	13.9±0.9	14.2±0.8	0.52
postoperative 0-h	12.1±1	12.5±1.3	0.21
postoperative 24-h	11.8±1.1	10.6±1.4	0.001
Duration of operation (min)	73.8±14.5 (40-110)	76.3±17.1 (48-125)	0.45
Postoperative bladder irrigation time (h)	12.4±5.1	15.5±7.3	0.001
Total amount of irrigation fluid (L)	18.44±2.16	24.08±3.5	0.001
Weight of resected adenoma (g)	35.1±7.8	34.7±6.4	0.62
Hospitalization time (day)	1.8±0.7 (1-3)	2±0.8 (1-5)	0.37
Catheter removal (day)	2.4±0.7 (2-5)	2.8±1 (1-6)	0.35

irrigation fluid and bladder irrigation time in the intervention group. We state that our study differs from the other studies in this aspect.

In addition, the effect of intravenous TXA, which is applied to provide better haemostasis and better imaging during surgery, was evaluated in some studies in the literature, and significantly shorter operative times were found in the intervention group (7, 11, 13). In our study, TXA was applied to the postoperative irrigation fluid and therefore its effect on the operation time could not be evaluated.

On the other hand, some studies have shown that TXA may be associated with postoperative neurological complications in a dose-dependent manner. While it has been reported that using TXA may increase the risk of epilepsy in children undergoing cardiac surgery (10), in another study it was shown that the use of TXA may cause complications such as convulsions of the central nervous system in a dose-dependent manner (17). There were no neurological complications in any of the patients after the operation in our study. We attribute this situation to the fact that the route of administration is not intravenous, but intravesical (into the bladder irrigation fluid) and its minimal passage into the vascular system. Another important complication of administering TXA to patients undergoing prostate surgery is the thromboembolic risk. It has been stated that this risk exists especially in patients with thrombophilia (18). Although studies in the literature have shown that TXA does not increase the risk of thromboembolic complications, its effect on this complication remains unclear (19). In our study, we conclude that the TXA application method is safe, considering that systemic transmission is minimal.

The main limitations of the study were the small sample size, and the inability to evaluate total and mean blood losses. Further studies are needed on the use of intravesical TXA after TURP operation.

CONCLUSION

The use of intravesical TXA offers a safe postoperative follow-up process with less bleeding and lower irrigation fluid volumes after TURP surgeries. In addition, we think that intravesical use of TXA is superior to intravenous use in terms of systemic complications. Further studies supporting the results of this study will be required.

Ethics Committee Approval: This study was approved by Istinye University Clinical Research Ethics Committee (Date: 07.12.2022, No: 3/2022.K-91)

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EVALUATION OF BILATERAL CHRONIC SUBDURAL HEMATOMAS IN PATIENTS UNDER 50 YEARS OF AGE

50 YAŞ ALTINDAKİ BİLATERAL KRONİK SUBDURAL HEMATOMU TANILI HASTALARIN İNCELENMESİ

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ABSTRACT

Objective: Chronic subdural hematoma (CSDH) is typically seen in elderly people with unilateral hemorrhages. The aim of this study was to examine the clinical outcomes of patients under the age of 50 who were treated at our clinic for bilateral CSDHs.

Material and Method: This retrospective study included 20 patients under the age of 50 who had been diagnosed with bilateral CSDHs and treated with burr-hole drainage between 2000 and 2022 at Istanbul Faculty of Medicine, Department of Neurosurgery, Istanbul University. The patients' demographic information, clinical data, and radiological images were obtained retrospectively from the hospital system. The data were subjected to descriptive statistical analysis using the IBM SPSS statistics 28.0.0 program.

Result: There were 14 (70%) males and 6 (30%) females in our study, with a mean age of 20.5 years. The most common complaints among the patients were headaches in nine patients (45%), newly developed paresis in five patients (25%), and seizures in four patients (20%). It was discovered that 17 patients (85%) had no history of head trauma. CSDH was evacuated by bilateral burr-holes in 14 patients (70%). Three (21.4%) of 14 patients with bilateral burr-holes, and 3 (50%) of the remaining six patients were reoperated due to recurrent bleeding in the follow-up period.

Conclusion: In our study, trauma history and use of antiaggregants and anticoagulants were low. More comprehensive studies on the etiology of bilateral CSDH in patients under 50 years of age are required.

Keywords: Burr-hole, chronic subdural hematomas, intracranial hematoma

ÖZET

Amaç: Kronik subdural hematom (KSDH) genelde yaşlı popülasyonda ve unilateral olarak izlenir. Bu çalışmada 50 yaşın altında tanı almış bilateral KSDH hastalarının klinik özelliklerinin incelenmesi planlandı.

Gereç ve Yöntem: Bu çalışmaya İstanbul Üniversitesi, İstanbul Tıp Fakültesi, Beyin ve Sinir Cerrahisi anabilim dalında 50 yaşın altında bilateral KSDH tanısı almış ve "burr-hole" drenajı ile tedavi edilmiş olan 20 hasta dahil edildi. Hastaların demografik, klinik, radyolojik bilgilerine hastane sisteminden retrospektif olarak ulaşıldı. Tüm veriler IBM SPPS 28.0.0 programı kullanılarak istatiksel olarak değerlendirildi.

Bulgular: Çalışmaya, 14 (%70) erkek ve altı (%30) kadın hasta dahil edildi. Ortalama yaşın 20,5 olduğu görüldü. En sık hastaneye başvurma semptomları incelendiğinde dokuz (%45) hastada baş ağrısı, beş (%25) hastada yeni gelişen parezi ve dört (%20) hastada nöbet geçirme olduğu görüldü. On yedi (%85) hastada kafa travması öyküsünün olmadığı saptandı. KSDH 14 hastada bilateral *"burr-hole"* ile boşaltıldı. Bu 14 hastanın takiplerinde üçünün (%21,4) ve geri kalan altı hastanın üçünün (%50) rekürren kanama nedeniyle tekrar opere edildiği saptandı.

Sonuç: Çalışmamızda, genç bilateral KSDH tanılı hastalarda travma öyküsünün, antiagregan ve antikoagülan kullanımının az olduğu görüldü. Elli yaş altında karşılaşılan bilateral KSDH etiyolojisini aydınlatmak için daha geniş çaplı çalışmalara ihtiyaç bulunmaktadır.

Anahtar Kelimeler: Burr-hole, kronik subdural hematom, intrakranyal hematom

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INTRODUCTION

One of the most common types of intracranial hemorrhage is chronic subdural hematoma (CSDH) with an incidence of approximately 5.3–13.5/100,000/yr (1). The incidence rate of CSDH increases with age (2). Bilateral CSDH has a high recurrence rate and variable clinical features. The most frequent factor in the etiology of CSDH is head trauma. Other etiological factors are alcoholism, liver cirrhosis, chronic renal failure, history of anti-aggregant or anticoagulant drug use, and hematological diseases (1). However, recent studies show that the etiological factors are not limited to these. Many factors contribute to the development of CSDH, including age-related changes in patients' physiological immune responses and angiogenic pathways, genomic instability, epigenetic defects, dysregulation of metabolic pathways, increased cell aging, impaired cell regeneration, increased reactive oxygen species in mitochondria, and loss of proteostasis (3). Young-onset CSDHs are often associated with predisposing factors, such as arachnoid cysts (AC), coagulation disorders, and ventriculoperitoneal (V/P) shunts (4). CSDH can occur in young people without any underlying predisposing factor (5). Bilateral subdural hematomas are characterized by severe symptoms, rapid progression, and clinical deterioration, and they should be treated as soon as possible. Various surgical techniques, such as burr-hole drainage, craniotomy, twist–drill craniostomy drainage, and subdural–peritoneal shunt, are used in the surgical treatment (1,6). Middle meningeal artery embolization is an alternative treatment for CSDH (7). Our study aims to present a cohort of young patients diagnosed with CSDH, focusing on presentation, surgical treatment, and outcome, and emphasizing the differences between them and the elderly group.

MATERIAL and METHODS

Patients with bilateral CSDHs were reviewed retrospectively between January 2000 and June 2022 at Istanbul Faculty of Medicine, Department of Neurosurgery, Istanbul University. This study was approved by the institutional ethics review committee at the Istanbul Faculty of Medicine (Date: 11.11.2022, No: 20). Patients over the age of 50, patients with subdural hematomas with acute or subacute components, patients with CSDHs who had been followed up with a conservative approach, and patients who had had craniotomy or twist–drill craniotomy as surgical treatment were excluded from the study. The radiological images of the patients were accessed from the hospital ventriculoperitoneal (V/P). The study included 20 patients whose diagnosis of bilateral CSDHs was confirmed by preoperative radiological imaging and who underwent burr-hole drainage. Age, gender, admission complaint, use of anticoagulant or antiaggregant drugs, comorbid disease, admission Glasgow Coma Scale (GCS), preferred surgical method, and reoperation needs were evaluated retrospectively. The outpatient clinic application notes were used to evaluate follow-up times. The results were subjected to descriptive statistical analysis using the SPSS ver.28.0 (IBM Corporation, Armonk, NY, USA). Univariate analyses were performed using the Mann–Whitney U test for non-normally distributed scale parameters. Median and range calculations were used for the description of scale parameters. All analyses were performed with a 95% confidence interval and a significance level of 0.05.

RESULTS

The study included fourteen (70%) males and 6 (30%) females. The mean age was 20.5 years. At the same time, the mean age for men was 22.9 and 14.8 for women. The most common complaint seen in nine patients (45%) was a headache, followed by newly developed paresis in five patients (25%) and seizures in four patients (20%) (Table 1). In 17 patients (85%), no previous head trauma was discovered. While no patients were found to be using anticoagulant or antiaggregant drugs, eight patients (40%) had at least one disease that could cause comorbidity. Three patients (15%) had V/P shunts. While the GCS at admission was 15 in 18 patients (90%), one patient (5%) presented with a GCS of 14 (E4M6V4), and one patient (5%) presented with a GCS of 10 (E4M3V3). An examination of the preoperative cranial imaging of the patients included in the study revealed no midline shift. Drainage was provided with a total of four burr-holes, two on the right side and two on the left, in 14 patients (70%). A unilateral subduraperitoneal shunt was inserted after drainage in one patient with one burr-hole, and a bilateral subduraperitoneal shunt was inserted after drainage in one patient with two biparietal burr-holes. In the first operation, 18 patients (90%) had bilateral burr-hole drainage (Table 2). No postoperative complications were observed in the patients, except for rebleeding. Six patients (30%) were reoperated due to rebleeding within the first three months after the first operation. Due to rebleeding, 3 (21.4%) of 14 patients with bilateral four burr-holes and 3 (50%) of six patients with less than four burr-holes were reoperated.

DISCUSSION

Chronic subdural hematomas are hemorrhages caused by the rupture of the parasagittal bridging veins which become stretched due to cerebral atrophy. CSDH is typically characterized by unilateral bleeding in the elderly. Although the pathophysiology of bilateral CSDH is unknown, traumatic injury to the bridging veins is believed to be the cause (8).

In a meta-analysis comparing young and old patients with CSDH, Bartek et al. stated that they considered 50

Table 1: Clinical features of chronic subdural hematomas

Results	Male	Female
Number of patients	14 (70%)	6 (30%)
Average age (years)	22.9	14.8
Complaints		
Headache	3 (15%)	6 (30%)
Newly developing paresis	5 (25%)	0 (0%)
Seizure	2 (10%)	2 (10%)
Trauma	2 (10%)	1 (5%)
Co-morbid diseases		
V/P shunt	2 (10%)	1 (5%)
Arachnoid cyst	2 (10%)	0 (0%)
Hypertension	1 (5%)	0 (0%)
Thrombotic thrombocytopenic purpura	0 (0%)	1 (5%)
Urinary system pathology	1 (5%)	2 (10%)
Surgical treatment/recurrent bleeding		
One-sided burr-hole	2/1	1/1
1 burr-hole in total on one side	1/0	0/0
2 burr-hole in total on one side	1/1	1/1
Bilateral burr-hole	12/3	5/1
Bilateral total 2 burr-holes	2/0	0/0
Bilateral total 3 burr-holes	1/1	0/0
Bilateral total 4 burr-holes	9/2	5/1

Table 2: Recurrent bleeding in young patients with bilateral chronic subdural hematoma

Variable	Recurrent bleeding (n=6)	No recurrent bleeding (n=14)	P value (p<0.05)
Gender			0.904
Male	4 (67.6%)	10 (71.4%)	
Female	2 (33.3%)	4 (28.5%)	
V/P shunt			0.019*
Patient with V/P shunt	3 (50%)	0 (0%)	
Patient without V/P shunt	3 (50%)	14 (100%)	
Arachnoid cyst			0.516
Patient with arachnoid cyst	0 (0%)	2 (14.3%)	
Patient without arachnoid cyst	6 (100%)	12 (85.7%)	
Bilateral/unilateral dranaige			0.258
One-sided burr-hole	2 (33.3%)	1 (0.07%)	
Bilateral burr-hole	4 (66.7%)	13 (92.8%)	

* Statistically significant, V/P: Ventriculoperitoneal

years of age to be the limit because, in their study, brain atrophy began to increase after the age of 50 (4). In our study, we selected a younger age group and investigated the clinical outcomes of patients with bilateral CSDHs who were all under the age of 50.

Previous studies demonstrated that CSDH manifests with symptoms of increased intracranial pressure more frequently in younger patients under the age of 50, while it manifests with neurological deficits more frequently in elderly patients. This is because there is no significant age-related atrophy in the human brain until the age of 50. Bleeding in the subdural space causes an increase in intracranial pressure and has a mass effect. Therefore, symptoms appear earlier and, in most cases, before the onset of neurological deficits (4). This information is supported by our study, which found that headache, nausea, and vomiting were the presenting complaints of 18 patients (90%). In comparison, only five patients (20%) experienced new weakness in any extremity.

Various risk factors for bilateral CSDH were identified in a previous study, including age (>75 years), coagulopathy, use of antiaggregant or anticoagulant medication, and hemodialysis (9). However, no patients in our study received antiaggregant or anticoagulant therapy, and only one patient received peritoneal dialysis due to chronic renal failure caused by thrombotic thrombocytopenic purpura. Most of the risk factors for bilateral CSDH were absent in the young patients with bilateral CSDH included in our study. Bilateral CSDH seen at a young age is caused by other risk factors. To determine these, more research on young-age bilateral CSDH is required.

CSHD is one of the complications of arachnoid cysts, and CSDHs associated with arachnoid cysts are more common in the elderly and infants (10). Approximately 2%-4% of patients with arachnoid cysts are found to have CSDH. Men are three times more likely than women to suffer CSDH caused by arachnoid cysts (11). ACs were discovered in preoperative cranial computed tomography (CT) images of two male patients aged 3 and 30. According to Benek et al., the presence of arachnoid cysts in young adults is a predisposing factor for developing CSDH (12). In a study on young patients with CSDHs conducted by Ou et al., it was discovered that when patients with arachnoid cyst (AC) or V/P were compared with patients without AC or V/P shunt, the history of head trauma was statistically significantly higher in the group with AC or V/P shunt (5). There were five patients in our study who had AC or V/P shunts, three who had V/P shunts, and two who had arachnoid cysts. There was no history of head trauma in any of these patients. In our study, head trauma history was not significant in the group with AC and V/P (p=0.553). In the same study, no significant difference in recurrence rates was found between the two groups.

Six patients were reoperated for rebleeding in our study, and three of the reoperated patients had V/P shunts. Our results showed that rebleeding was significantly higher in patients with a history of V/P shunts (p=0.019) (Figure 1).

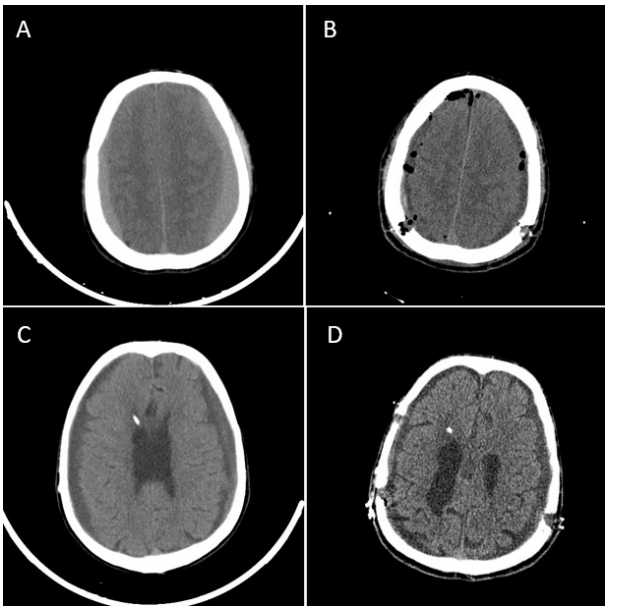

Figure 1: Pre-operative axial CT scan of bilateral chronic subdural hematoma is seen (A). CT scan after bilateral burr-hole drainage (B). Another patient with VP shunt and bilateral chronic subdural hematoma is shown (C). Post-operative image after burr-hole drainage is appreciated (D). (CT. Computed tomography, VP. Ventriculoperitoneal)

Compression of the bilateral cerebral hemispheres provides a relatively buffering effect in bilateral CSDH, and hematoma leading to midline shift is less common in these patients (13). This was confirmed in our study where there was no midline shift in the preoperative CT images of the patients.

Andersen-Ranberg et al. discovered that evacuation of unilateral hematoma in treating bilateral CSDHs increased the rate of ipsilateral or contralateral reoperation (13). In our study, 18 patients had bilateral burr-hole drainage, and two had unilateral burr-hole drainage. One of the two patients who had unilateral burr-hole drainage had to be reoperated due to an increase in the size of the hematoma on the opposite side. Only five of 18 patients who had bilateral burr-hole drainage had to be reoperated. In terms of rebleeding, our results showed that there was no significant difference between unilateral and bilateral drainages (p=0.258).

The limitations of our study include retrospective data collection, the small number of patients diagnosed with bilateral CSDHs under the age of 50, and the exclusion of surgical treatments other than burr-hole drainage.

CONCLUSIONS

In our study, patients under the age of 50 with CSDHs had a low trauma and antiaggregants and anticoagulants usage history. The factors involved in the etiology of young patients with bilateral CSDHs differ from those seen in the elderly. A conclusion of our study is that more comprehensive studies on the etiology of bilateral CSDH in patients under 50 years of age are required.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 11.11.2022, No: 20).

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CALCULATION OF LENS POWER WITH NEW BIOMETRIC FORMULAS

LENS GÜCÜNÜN YENİ BİOMETRİ FORMÜLLERİ İLE HESAPLANMASI

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ABSTRACT

Objective: Comparison of the accuracy of six biometric formulas based on refractive findings using patients' biometric and refractive data before phacoemulsification surgery.

Material and Method: A retrospective analysis was conducted of the data of 65 eyes of 43 patients who underwent phacoemulsification at the Ophthalmology Department of Istanbul University Istanbul Faculty of Medicine between January 2016 and July 2019. The intraocular lens (IOL) power corresponding to the target refraction value in patients was calculated using the SRK/T formula. The patients' final refraction values were obtained by examinations conducted after the third postoperative month. After implanting IOLs with the same refractive power, target refraction values were calculated using the optical biometry measurements of the patients and the Hoffer Q, T2, Ladas Super Formula (Ladas), Barrett Universal II (BU II), and Hill-RBF formulas. The refractive refraction deviation values between the formulas were compared, as well as the difference between the target refraction values determined by the formulas and the spherical equivalents of the patients' result refractions.

Result: The normal age of the 43 patients in the study was 64.65±8.23 (47-86) years. The mean axial length was 23.5±0.7mm (22.01-24.5). The refractive deviation was 0.29±0.29 D with SRK/T, 0.27±0.27 D with T2, 0.3±0.24 D with Hoffer Q, 0.3±0.26 D with Ladas, and 0.33±0.28 D with BU II, and 0.27±0.29 D with Hill-RBF. The refractive deviation percentages of the formulas in the range of -1.00 D to +1.00 D were as follows: 98.5% Hoffer Q and Hill-RBF; 96.9% T2, Ladas, BU II, and SRK/T. In terms of refractive deviation values, there was no statistically significant difference between the formulas (p>0.05).

ÖZET

Amaç: Hastaların fakoemülsifikasyon cerrahisi öncesindeki biometrik ve refraktif verileri kullanılarak, altı biometrik formülün refraktif sonuçlara göre doğruluklarının karşılaştırılması.

Gereç ve Yöntem: Retrospektif olarak 2016 Ocak ve 2019 Temmuz tarihleri arasında İstanbul Üniversitesi İstanbul Tıp Fakültesi Göz Hastalıkları kliniğinde fakoemülsifikasyon uygulanan 43 hastanın 65 gözünün verileri retrospektif olarak incelendi. Hastalarda hedeflediğimiz refraksiyon değerine karşılık gelen göz içi lens (GİL) gücü SRK/T formülüne göre hesaplandı. Postoperatif 3. aydan sonra yapılan muayenelerde hastaların sonuç refraksiyon değerleri saptandı. Hastaların optik biometri ölçümleri kullanılarak, aynı kırma gücüne sahip GİL implante edildiğinde, Hoffer Q, T2, Ladas Süper Formülü (Ladas), Barrett Universal II (BU II) ve Hill-RBF formüllerine göre hedef refraksiyon değerleri hesaplandı. Formüllerin saptadığı hedef refraksiyon değerleriyle, hastaların sonuç refraksiyonlarının sferik eşdeğerleri arasındaki fark alındı ve formüller arasındaki refraktif sapma değerleri karşılaştırıldı.

Bulgular: Çalışmaya alınan 43 hastanın yaş ortalaması 64,65±8,23 (47-86) yıl idi. Ortalama aksiyel uzunluk 23,5±0,7mm (22,01-24,5) olarak saptandı. SRK/T ile refraktif sapma 0,29±0,29 D, T2 ile 0,27±0,27 D, Hoffer Q ile 0,3±0,24 D, Ladas ile 0,3±0,26 D, BU II ile 0,33±0,28 D, Hill-RBF ile 0,27±0,29 D idi. Formüllerin -1,00 D ile +1,00 D aralığında bulunan refraktif sapma yüzdeleri şu şekildeydi: %98,5 Hoffer Q ve Hill-RBF; %96,9 T2, Ladas, BU II ve SRK/T. Refraktif sapma değerleri açısından formüller arasında istatistiksel olarak anlamlı bir farklılık izlenmedi (p>0,05).

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Conclusion: The probability of obtaining the target refractive value with a refractive deviation within ±1 D of the six biometry formulas included in the study is 96.9% and higher. Any of these formulas can be employed safely to compute preoperative IOL power in the eyes of normal length.

Keywords: Cataract surgery, biometrics, new generation formulas

Sonuç: Çalışmada yer alan altı biometri formülünün ±1 D içinde refraktif sapma ile hedef refraktif değere ulaşma şansı %96,9 ve üzerindedir. Bu formüllerin her biri normal uzunluktaki gözlerde preoperatif GİL gücünü hesaplamak için güvenli bir şekilde kullanılabilir.

Anahtar Kelimeler: Katarakt cerrahisi, biometri, yeni jenerasyon formüller

INTRODUCTION

Intraocular lens (IOL) implantation, performed for almost 60 years, is modern medicine's most prevalent and successful surgical procedure. This procedure's success and safety result from ongoing advancements in surgical and measuring techniques (1). Today, cataract surgery is becoming a refractive surgery method (2). Patients with cataract surgery expect to gain visual ability independently of glasses after cataract surgery (3, 4).

Obtaining the target refractive outcome has become a fundamental component of cataract procedures. Thankfully, the advent of optical biometrics and the development of new-generation IOL calculation formulas have enhanced our ability to anticipate refractive outcomes following cataract surgery correctly (5). Accurate estimation of refractive results is important as it will also eliminate patient dissatisfaction (6).

The SRK/T formula, which is a third-generation formula we used in our study, is a more customized form of the SRK formula developed by Sanders, Retzlaff, and Kraff (7). It represents a combination of a theoretical eye model and a linear regression method. SRK/T also includes empirical regression methodology for optimization, providing greater precision. It can be calculated using the same constants A used with the SRK formula, or with anterior chamber depth (ACD) estimates.

Sheard et al. observed a non-physiological behavior while calculating the corrected axial length and corneal height in the SRK/T formula. Therefore, they developed the T2 formula using a regression formula for corneal height obtained from the growth subset. They concluded that the accuracy of refractive results can be increased by 10% with the T2 formula (8).

In 2015, Ladas et al. introduced the concept of an IOL 'super formula' and developed a solution to address the need for a single formula that can be adapted to any eye (9). They introduced a new methodology for displaying previous-generation IOL formulas in three dimensions. Based on peer-reviewed literature, they developed an IOL 'super surface' by selecting the best parts of each of the modern IOL formulas. The 'super formula' is derived from this super surface.

In 1993 and 2000, Hoffer tried to analyze the most accurate formula using AU measurements taken by immersion ultrasound in long and short eyes and showed that the Hoffer Q formula gave the most reliable results in short eyes (AU<22.0 mm) (10). Hoffer Q; personalized ACD is a formula based on AU and corneal curvature.

The Barrett formula was developed based on a theoretical model eye in which anterior chamber depth is related to axial length and keratometry (11). In this formula, the user does not need to know the material and constant of the lens. The principle of refraction of the intraocular lens and the position of its planes is preserved as a relevant variable in the formula.

Unlike other formulas, the Hill-RBF formula is a pattern recognition algorithm that uses some kind of data interpolation. This formula provides potential independence by eliminating computational errors from biometrics and the need to customize constants (12).

This study compares the success of these six biometry formulas in reaching the target refractive value in normal-length eyes.

MATERIAL and METHODS

The data from 196 eyes of 118 patients diagnosed with cataracts and who underwent phacoemulsification surgery at the Ophthalmology clinic of the Istanbul University Istanbul School of Medicine between January 2016 and July 2019 were retrospectively evaluated. Amblyopic eyes, eyes with any pathology affecting refraction in the optic axis, retina, or optic disc, and eyes that had undergone eye surgery (keratoplasty, refractive surgery, vitrectomy, etc.) were excluded from the study. Also, eyes in which sutures were placed at the incision site during surgery, with surgery-related astigmatism (SRA) above 0.5 D, and with postoperative tilt and decentralization in the IOL were excluded from the study. Eyes with an axial length of 22-25 mm were included in the study. All study patients had surgery scheduled using the SRK/T calculation. Ethics committee approval was obtained from Istanbul Medical Faculty's Ethics Committee (Date: 28.05.2021, No: 11).

The gender of the patients who underwent surgery, age at the time of surgery, the side of the eye undergoing

surgery, preoperative uncorrected visual acuity (UVA) and best corrected visual acuity (BCVA), biomicroscopic examination and the degree of existing cataract according to LOCS III were recorded (13). UVA and BCVA levels of the patients at the earliest three months after surgery were determined according to the logMAR chart. Targeted refractive values were recorded according to the biometry results obtained through measurements made using the IOL Master 500 (Carl Zeiss AG, Germany). IOL power calculation with a biometric formula was performed for AcrySof SN60WF in 31 eyes and for AcrySof SA60AT IOL in 34 eyes.

The power of the IOL planned to be implanted was calculated preoperatively with the help of the SRK/T formula. Axial length (AU), anterior chamber depth (ACD), K1 (flat keratometry value), K2 (vertical keratometry value), corneal astigmatism, white-to-white (WTW) included in the biometric measurements were recorded. In the postoperative examinations of the patients, the new K1, K2, and corneal astigmatism values obtained with the Topcon TRK-1P auto-refractometer device were recorded. Spherical equivalents of UVA, BCVA, and subjective refractions were taken. The difference between the targeted refraction's spherical equivalent (TRSE) and the postoperative refraction's spherical equivalent (PRSE) and the absolute value of this difference (AVD) was recorded. The size and axis of astigmatism developed due to surgery were calculated. HRSE, the difference between PRSE and HRSE, and AVD were recorded individually with Hoffer Q, T2, Ladas Super Formula, Barrett Universal II, and Hill-RBF formulas according to the power of the IOL implanted during surgery. The website of the User Group for Laser Interference Biometry (ULIB) was used to obtain the A constant and pACD constant values of the implanted IOLs (14).

The surgeries were performed through a 2.4 mm transparent corneal incision in the temporal quadrant with the Infiniti Vision system (Alcon Laboratories, Inc., Fort Worth, TX, USA) using a 30º Kelman 0.9 mm TurboSonics Mini-Flared ABS phaco handpiece tip and Alcon MicroSmooth Ultra Infusion Sleeve. An Alcon Monarch III injector and D cartridge were utilized for IOL insertion.

Anterior segment examination was performed in all postoperative controls, dilated fundus examinations were performed at the first and third postoperative follow-ups, other pathologies that may impact vision were assessed, and eyes with pathology in the optic axis were eliminated from the study. At the postoperative third-month examination, the PRSE of the patients was calculated.

While calculating the SRA, the vectorial analysis program was used (15).

IBM® SPSS (Statistical Package for Social Sciences) version 23.0 was used for the statistical analysis of the data. Pearson chi-square test was used when comparing nominal data, the Shapiro-Wilk test to determine whether the data were normally distributed, the ANOVA test was used when comparing continuous variables with normal distribution, the Mann-Whitney U test was used for correlation analysis, and the Spearman test was used for correlation analysis. Continuously variable data with normal distribution were expressed as mean ± standard deviation, and non-normally distributed data were expressed as median, mode, or range. In categorical measurements, numbers and percentages were given. Statistical significance was accepted as $p<0.05$.

RESULTS

Sixty five eyes of 43 patients met all the criteria and were included in the study. The mean age of the patients included in the study was 64.6±8.3 years. Of these patients, 24 (55.8%) were male, and 19 (44.2%) were female. Of the 65 eyes that underwent surgery, 29 (44.6%) were right, and 36 (55.4%) were left eyes.

The refraction data (Table 1) and biometric data (Table 2) obtained in the preoperative period and the patients' third postoperative month control exams were recorded - the calculated mean values of the obtained data.

To compare the target refraction with the final refraction, the spherical equivalent values of the final refraction obtained at the last examination of the patients were utilized. The mean spherical equivalent value of the resulting refraction was calculated as -0.04±0.44 D.

Table 1: Mean refraction data of patients before and after phacoemulsification surgery

Mean Values	UVA (logMAR)	Spherical value (D)	Astigmatism value (D)	Astigmatism Axis (degrees)	BCVA (logMAR)	LOCS-NO
Pre-op	0.9±0.45	-1.17±2.6	-0.9±0.6	87.9±40.43	0.44±0.4	3.97±0.97
Post-op	0.05±0.14	0.27±0.4	-0.62±0.4	73.45±29.9	0.08±0.04	-
P value	P<0.001	P<0.001	P=0.098		P<0.001	-

D: Diopter, UVA: Uncorrected visual acuity, logMAR: logarithm of the Minimum Angle of Resolution, BCVA: Best corrected visual acuity, LOCS-NO: Lens Opacities Classification System III - Grade of nuclear opacification

After surgery, there was a significant increase in the UVA values of the patients (p<0.001), but there was also a significant decrease in the spherical values (p<0.001). The difference between the astigmatism values before and after surgery was insignificant (p=0.098). BCVAs were significantly higher after surgery (p<0.001) (Table 1).

Figure 1. When the results of the formulas were compared within the range of ±0.50 D, no statistically significant difference was found between each other (p>0.05 for all, Table 4).

When the results of the formulas in the range of ±1 D are compared, there was no statistically significant difference

Table 2: Normal biometric data of patients before and after phacoemulsification surgery

Mean Values	Pre-operative	Post-operative
AL (mm)	23.44±0.64	-
SNR	21.71±57.48	-
K1 (D)	43.18±1.42	43.44±1.56
K1 axis (degree)	90.83±57.26	127.02±64.06
K2 (D)	43.91±1.51	43.62±1.55
K2 axis (degree)	90.83±50.78	82.02±20.44
Astigmatism (D)	-0.74±0.37	-0.58±0.37
Astigmatism axis (degree)	90.83±57.26	97.98±62.64
WTW (mm)	11.93±0.29	-
ACD (mm)	3.19±0.4	-

AL: Axial Length, SNR: Signal to Noise Ratio, K1: Mean flat keratometry, K2: Mean steep keratometry, WTW: white-to-white distance, ACD: Anterior Chamber Depth

Table 3: Target and result refractive measurements measured with the biometry device

Formula	Normal target refractive value	Mean refractive deviation	Standard deviation	Maximum refractive deviation
Hoffer Q	-0.07 D	0.302 D	0.237	1.43 D
T2	-0.10 D	0.269 D	0.259	1.52 D
LADAS	-0.04 D	0.296 D	0.255	1.36 D
Barrett	-0.14 D	0.316 D	0.267	1.47 D
Hill-RBF	-0.06 D	0.271 D	0.278	1.38 D
SRK/T	-0.13 D	0.286 D	0.283	1.52 D

D: Diopter

The mean SRA value was 0.43±0.35 D, and the mean axis of astigmatism due to SRA was 84.5±45.17 degrees. Mean refractive deviation Hoffer Q formula 0.3 D±0.24, T2 formula 0.27 D±0.26, Ladas Super Formula 0.3 D±0.26, Barret Universal II 0.32 D±0.27 D±0.28 in Hill-RBF, 0.29 D±0.28 in SRK/T formula. The formulas had no statistically significant difference regarding mean refractive deviation values (p>0.05) (Table 3).

The lowest refractive deviation was obtained in Ladas Super Formula with 1.36 D. Hill-RBF followed this with 1.38 D, Hoffer Q with 1.43 D, Barrett Universal II with 1.47 D, T2 and SRK/T formula with 1.52 D (Table 3).

The percentages of the refractive deviations of the formulas in the range of ±0.50 and ±1.00 Diopters are shown in

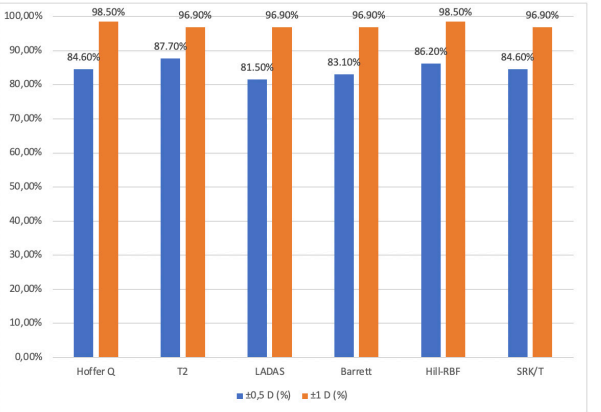

Figure 1: The percentages of the resultant refractive values of the formulas in the range of ±0.50 D and ±1 D

between the Hoffer Q and Hill-RBF formulas and the T2, Ladas Super Formula, Barrett Universal II, and SRK/T formulas (p=0.708).

Table 4: Comparison of the results of the formulas in the range of ±0.50 D

T2	Hill-RBF	P=0.875
T2	Hoffer Q	P=0.649
T2	SRK/T	P=0.649
T2	Barrett U. II	P=0.284
T2	Ladas S. F.	P=0.059
Hill-RBF	Hoffer Q	P=0.719
Hill-RBF	SRK/T	P=0.719
Hill-RBF	Barrett U. II	P=0.627
Hill-RBF	Ladas S. F.	P=0.198
Hoffer Q	Barrett U. II	P=0.819
SRK/T	Barrett U. II	P=0.819
Hoffer Q	Ladas S. F.	P=0.204
SRK/T	Ladas S. F.	P=0.204
SRK/T	Barrett U. II	P=0.819
Hoffer Q	Ladas S. F.	P=0.204
SRK/T	Ladas S. F.	P=0.204
Barrett U. II	Ladas S. F.	P=0.586

Barrett U. II: Barrett Universal II, Ladas S. F.: Ladas Super Formula

DISCUSSION

Today, achieving the optimal refraction and the maximum uncorrected visual acuity after cataract surgery is just as crucial as removing a condenser lens. The precise estimation of preoperative IOL power is one of the most critical elements impacting the success of cataract surgery, which has reached a level that may be deemed refractive surgery due to technological breakthroughs in biometry devices and the improvement of IOL quality (16).

This study compared the success of new-generation formulas in eyes with normal axial length. According to the results of our study, the T2 formula has the lowest normal refractive deviation with the IOL Master 500 device, followed by Hill-RBF, SRK/T, Ladas Super Formula, Hoffer Q, and Barrett Universal II. However, when the mean refractive deviation values of these formulas were compared, no statistically significant difference was discovered (p>0.05).

In their study, Sánchez-Liñan et al. showed that Kane, SRK/T, Hoffer Q, Haigis, Holladay I, and Barrett formulas were not statistically superior to each other in eyes with an axial length of 22-25 mm (17). Our findings are consistent with this study. They suggested that in this axial length range, ±0.50 diopters postoperative refractive error range was the highest in the eyes with biometry calculated according to Holladay I (88.9%). After Holladay I, the highest rate was obtained from Hoffer Q and SRK/T formulas (87.1%). The percentage of biometrics performed with Barrett in the range of ±0.50 diopters (82.5%) was similar to our study (83.1%).

The refractive formulas of Olsen, Haigis, Holladay 1, Hoffer Q, SRK/T, and SRK II formulas were compared in a study by Cooke et al. utilizing optical low coherence reflectometry (OLCR) and partial coherence interferometry (PCI) methodologies (18). The study utilized the Olsen formula, showing that the OLCR method outperformed the PCI method. Compared to other formulas, the Olsen method with the OLCR formula produced more accurate results for both short and long eyes. Some formulas performed similarly with either method.

Barrett Universal II, Olsen, Holladay 2, Haigis, Ladas Super Formula, Holladay 1, and SRK/T were compared in a different study by Cooke et al. (19). When measured with PCI, including all axial-length formulas, the refractive deviation percentage of the Barrett Universal II formula within the eyes' range of 1 D was found to be 99.3%. Haigis and T2 were followed by Holladay 1 (98.4%), Ladas Super Formula (98.3%), Holladay 2 and SRK/T (98.1%), and Hoffer Q (97.4%), respectively. The Olsen formula produced the most accurate results with the OLCR, significantly superior to the formula that performed best with PCI. It was determined that Barrett Universal II provided the best results with the PCI method.

Unlike the Cooke et al. study, in our study, only eyes with normal axial length were included, and only the PCI method was used. The formulas compared in our study are Hoffer Q, T2, Ladas Super Formula, SRK/T, Hill-RBF, and Barrett Universal II formulas. Percentages of the refractive values of these formulas in the range of 1 D were as follows: 98.5% for Hoffer Q and Hill-RBF and 96.9% for T2, Ladas, Barrett, and SRK/T.

In their study, Kane et al. compared the measurements made using the PCI method with the formulas of Barrett Universal II, Haigis, Hoffer Q, Holladay 1, Holladay 2, SRK/T, and T2 (20). A study involving 3241 patients found that Barrett Universal II produced results with less refractive deviation than other formulas in eyes with regular, medium-long, and long axial lengths (p<0.001).

In their study, Nemeth G. et al. compared the refractive results of the SRK/T, Hill-RBF, and Barrett Universal II formulas after cataract surgery with the biometric data obtained by the Optical Low Coherence Interferometry (ODCI) method (21). The study included 186 eyes with axial lengths between 20.72 and 28.78 mm. When all eyes of these axial lengths were evaluated, the percentage of eyes within an

estimation error of ±0.5 D was 74.01% using the SRK/T formula, 79.66% using the Barrett Universal II formula, and 83.62% using the Hill-RBF method. Statistically, the mean and median absolute refractive errors were not different.

In our study, the percentage of eyes with an estimation error of 0.5 D was found to be 86.2% using the Hill-RBF method, 84.6% using the SRK/T formula, and 83.3% using the Barrett Universal II formula.

In their study utilizing the PCI method, Aristodemou et al. compared the refractive results of the Hoffer Q formula with the SRK/T formula in normal-length eyes; however, they did not find a statistically significant difference in mean absolute error, as we found (22).

Sheard et al. established the T2 formula with their study to understand the causes of non-physiological behaviors of the SRK/T formula and to propose solutions for it (23). They compared the performance of the T2 and SRK/T formulas with their study and found that the estimation error in the T2 formula was 9.7% less than in the SRK/T formula. Moreover, they found that significantly higher eye rates were achieved within the ±0.50 D range ($p<0.0001$). They concluded that significantly improved prediction accuracy was achieved with the T2 formula, which is a modification of the SRK/T formula algorithm.

In our study, the mean refractive deviation value of the T2 formula was found to be 0.269 D, whereas that of the SRK/T formula was found to be 0.286 D. Nonetheless, it was concluded that this difference was not statistically significant ($p>0.05$).

The cases in our study underwent micro coaxial phacoemulsification surgery, and the mean postoperative SRA value was 0.43±0.35 D. Similar results had been observed in the literature after micro coaxial phacoemulsification surgery (24).

This study shows that the Hoffer Q, T2, Ladas Super Formula, Barrett Universal II, Hill-RBF, and SRK/T formulas can be safely favored by the surgeon before phacoemulsification surgery in eyes with normal axial length (22-25 mm), as measured by the PCI method. Using these formulas, the chance of reaching the target refractive value with a refractive deviation within ±1 D is 96.9% and above. A refractive deviation rate remaining within the range of ±0.50 D will be at the lowest level of 81.5%.

One of the areas for improvement in our study is the limited number of cases covered. Another drawback of our study is the inclusion of both eyes of some patients.

CONCLUSION

In conclusion, our study group had a limited sample size, with six biometer formulas, in more than 95% of the eyes' final refractive outcome was within the ±1 diopter. Targeting fewer standard deviations and results in different patient populations can help us to compare biometry formulas more accurately.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 28.05.2021, No: 11).

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CELIAC DISEASE SCREENING IN A LARGE DOWN SYNDROME COHORT: COMPARISON OF DIAGNOSTIC YIELD OF DIFFERENT SEROLOGICAL SCREENING TESTS

GENİŞ BİR DOWN SENDROMU KOHORTUNDA ÇÖLYAK HASTALIĞI TARAMASI: FARKLI SEROLOJİK TARAMA TESTLERİNİN TANISAL VERİMLERİNİN KARŞILAŞTIRILMASI

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ABSTRACT

Objective: Down syndrome (DS) patients have a higher risk of developing Celiac disease (CD) than the general population. This study aimed to estimate the prevalence of CD in DS patients and compare the diagnostic performance of the screening algorithms.

Material and Method: A cohort of 1117 DS patients were included. Patients were grouped according to the initial screening method. Anti-gliadin antibody (AGA)-IgA/IgG were measured in the first, endomysial antibody-IgA (EMA) in the second, and tissue transglutaminase (tTG)-IgA/IgG in the third group. Additionally, EMA was also measured in patients with elevated tTG-IgA or tTG-IgG levels. In the follow-up, 225 patients were re-screened. Intestinal biopsy was planned in patients with positive AGA-IgA/IgG, positive EMA, or more than threefold elevated tTG-IgA levels.

Result: Based on the initial screening, 34.5% of the patients in the first group underwent a biopsy, and 2.3% were diagnosed with CD. In the second and third groups, 1.8% and 1.6% of patients underwent biopsy, and CD was diagnosed in 0.5% and 1.3%, respectively. Among all patients, 1.3% were diagnosed

ÖZET

Amaç: Down sendromlu (DS) hastalarda, Çölyak hastalığı (ÇH) riski yüksektir. Bu çalışmada DS tanılı hastalarda ÇH sıklığının araştırılması ve tarama algoritmalarının tanısal veriminin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya 1117 DS tanılı hasta dahil edildi. Hastalar ilk uygulanan tarama yöntemine göre üç gruba ayrıldı. Birinci grup anti-gliadin antikor (AGA)-IgA/IgG, ikinci grup anti-endomisyum IgA antikoru (anti-EMA) ve üçüncü grup doku transglutaminaz (tTG)-IgA/IgG ile tarandı. Üçüncü grupta tTG-IgA veya tTG-IgG düzeyi yüksek saptanan hastalarda ikinci basamak test olarak anti-EMA düzeyi de ölçüldü. Olguların takibinde 225 hastada tarama tekrarlandı. AGA-IgA/IgG yüksekliği, anti-EMA pozitifliği veya 3 kattan fazla tTG-IgA yüksekliği olan hastalarda ince bağırsak biyopsisi planlandı.

Bulgular: İlk taramada birinci gruptaki hastaların %34,5'ine ince bağırsak biyopsisi yapıldı, %2,3'ü ÇH tanısı aldı. İkinci ve üçüncü gruplarda hastaların %1,8'ine ve %1,6'sına ince bağırsak biyopsisi yapıldı ve sırasıyla %0,5 ve %1,3'üne ÇH tanısı konuldu. İlk taramada, tüm hastaların %1,3'ü ÇH tanısı aldı. İzlemde çölyak antikor testi veya bağırsak biyopsisi negatif çıkan 225 hastada ta-

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with CD at initial screening. Two hundred twenty-five patients with negative initial screening tests or intestinal biopsy were re-screened; 8% underwent biopsy and CD was confirmed in 4.9%. Overall, 2.3% of patients were diagnosed with CD. The positive predictive value of AGA-IgA and AGA-IgG was low (13.6% and 7.2%, respectively) compared to EMA (69.6%) and tTG-IgA (66.7%). Gastrointestinal or extraintestinal symptoms were present in 42.3% of CD patients, and none of them had short stature.

Conclusion: Celiac disease was detected in 2.3% of DS patients. The CD detection rate was 1.3% at initial screening but increased to 4.9% at rescreening. Our results strongly suggest that CD screening should be performed regularly in all DS patients, whether they are symptomatic or not.

Keywords: Celiac disease, Down syndrome, screening

rama tekrarlandı, bu hastaların %8'ine ince bağırsak biyopsisi yapıldı ve %4,9'u ÇH tanısı aldı. Toplamda tüm hastaların %2.3'üne ÇH tanısı konuldu. AGA-IgA ve AGA-IgG'nin pozitif prediktif değeri (sırasıyla %13,6 ve %7,2), anti-EMA (%69,6) ve tTG-IgA'ya (%66,7) göre düşük bulundu. ÇH olanların %42,3'ünde gastrointestinal veya ekstraintestinal semptomlarmevcuttu.

Sonuç: Bu çalışmada DS'lu hastalarda ÇH sıklığı %2,3 saptandı. İlk taramada ÇH saptanma oranı %1,3 iken, tarama tekrarlandığında bu oran %4.,9'a yükseldi. Sonuçlarımız, semptomatik olsun ya da olmasın, tüm DS hastalarında ÇH taramasının düzenli olarak yapılması gerektiğini desteklemektedir.

Anahtar Kelimeler: Çölyak hastalığı, Down sendromu, tarama

INTRODUCTION

Down Syndrome (DS) is the most common chromosomal disorder characterized by facial dysmorphism, intellectual disability, and congenital malformations. Patients with DS are at increased risk of developing autoimmune diseases, including Celiac disease (CD), compared to the general population (1). Celiac disease is an autoimmune disorder of the small intestine triggered by gluten consumption. Classical symptoms include diarrhea, steatorrhea, abdominal distention, weight loss, or failure to thrive (2). In a large meta-analysis, the global prevalence of biopsy-proven CD in a normal population is documented to be 0.7% (3).

The American Academy of Pediatrics (AAP) reported that 1-5% of DS children have CD (4). In different studies, the prevalence varies between 0-19% (5-9). In a recent meta-analysis of 31 studies considering 4383 DS patients, CD was diagnosed in 5.8% of patients (10).

Celiac disease screening in DS patients is important because of the increased risk, the asymptomatic nature of the disease, and the intellectual disability-associated limitations of DS patients in communicating gastrointestinal symptoms. However, there is no consensus on guidelines for CD screening in DS patients (11). The AAP guideline recommends reviewing CD symptoms at each visit and performing serological testing only in symptomatic DS patients (4). In contrast, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guideline recommends CD screening in all DS patients (12).

This study aims to determine the frequency of CD in DS patients, describe clinical and serological findings of the CD, and compare different serologic testing methods in a large cohort of DS patients from a single tertiary center with records collected over 30 years.

MATERIAL and METHODS

Down syndrome patients who were screened for CD between January 1992 and March 2023 were investigated. A total of 1117 patients who had been on a gluten-containing diet for at least one year before screening were included. The male-to-female ratio was 1.12, and the median follow-up duration was 62 months (range:1-281 months). Trisomy 21 was confirmed in all patients by karyotype analysis.

Clinical data was obtained from patient records. Growth patterns were evaluated according to the National Down Syndrome-specific growth charts (13). Celiac disease patients with gastrointestinal (abdominal pain/distension, diarrhea, constipation) and/or extraintestinal symptoms were defined as symptomatic CD, and patients without symptoms were defined as asymptomatic CD. Patients with positive serologic tests but a normal intestinal biopsy were defined as latent CD.

Anti-gliadin antibodies (AGAs) and tissue transglutaminase (tTG) antibodies were investigated by the enzyme-linked immunosorbent assay (ELISA) method. The manufacturer-recommended values were used as cutoff values. Values above 50 AU/ml for AGA-IgA and AGA-IgG and above 18U/ml for tTG-IgA and tTG-IgG were accepted as positive. Endomysial antibody-IgA (EMA) was determined by the indirect immunofluorescent method, and the results were reported as positive or negative. Serum IgA levels were measured in 856 patients, and levels below 0.05 g/L were accepted as selective IgA deficiency.

The CD screening algorithm has been modified over the years with advances in serologic testing. Before the 2000s, AGA-IgA and AGA-IgG were used for screening. Since the 2000s, EMA and tTG antibodies have also been included in CD screening. To compare the diagnostic potency of these screening tests, we divided the DS patient cohort into three groups according to the initial serologic test used for CD screening:

In group 1, AGA-IgA and AGA-IgG were measured in 344 patients. Patients with at least one positive test result were scheduled for intestinal biopsy.

In group 2, EMA was measured in 392 patients. In patients with a positive EMA test, an intestinal biopsy was planned.

In group 3, tTG-IgA and tTG-IgG were measured in 381 patients. If serum tTG-IgA or tTG-IgG levels were elevated, an EMA test was performed. If the EMA test was negative and the tTG-IgA level was elevated less than threefold, the patient was observed without undergoing an intestinal biopsy. If the EMA test was positive or the tTG-IgA level was elevated more than threefold, an intestinal biopsy was planned.

Among patients who underwent intestinal biopsy, patients with increased intraepithelial lymphocytes and crypt hyperplasia (Marsh II), and villous atrophy (Marsh IIIa: partial villous atrophy, Marsh IIIb: subtotal villous atrophy, Marsh IIIc: total villous atrophy) were diagnosed as CD (14).

Rescreening of patients: In 225 of the patients whose initial screening tests or intestinal biopsy were negative, tTG-IgA and tTG-IgG, and/or EMA were measured during follow-up. If tTG-IgA or tTG-IgG levels were elevated, EMA was performed. If EMA was positive or tTG-IgA was elevated more than threefold, an intestinal biopsy was planned.

Written informed consent was obtained from all patients. The study was approved by the local ethics committee (Date:21.02.2023, No: 626135).

RESULTS

Initial screening for CD

Patients were divided into three groups according to the initial screening algorithm, which changed over time according to recommendations and advancements in screening tests. The initial screening results in the different test groups are shown in Table 1 and Figure 1.

In the first group, 344 patients were screened with AGA-IgA and AGA-IgG. Of these patients, 174 (50.6%) had at least one positive serological test result. AGA-IgA was positive in nine patients, AGA-IgG was positive in 114 patients and both tests were positive in 51 patients. Intestinal biopsy was performed in 119 (34.5%) patients. Fifty-five patients either refused to permit biopsy or were lost to follow-up. Celiac disease was diagnosed in eight patients (Table 1, Figure 1).

In the second group, 392 patients were screened with an EMA test, which was positive in 13 patients. An intestinal biopsy was performed on seven patients, and two were diagnosed with CD. Six patients either refused to permit a biopsy or were lost to follow-up (Table 1, Figure 1).

In the third group, 381 patients were screened by tTG-IgA and tTG-IgG. Eighty-three patients had a positive result in at least one test. tTG-IgA was positive in two patients (tTG-IgA <3X in both), tTG-IgG in 65 patients, and both tTG-IgA and tTG-IgG were positive in 16 patients (tTG-IgA <3X in nine, tTG-IgA ≥ 3X and <10X in four, and tTG-IgA ≥10X in three patients). Endomysial antibody was performed on 76 patients and found positive in six patients. Endomysial antibodies could not be performed in seven patients because they were lost to follow-up. Biopsy was not allowed in three patients; two patients refused intestinal biopsy (one had elevated tTG-IgA <3X, positive tTG-IgG and EMA, second had elevated tTG-IgA ≥10X, positive tTG-IgG and negative EMA) and the third patient who had positive tTG-IgG, positive EMA and negative tTG-IgA was diagnosed with acute leukemia concomitantly. Intestinal biopsy was performed in six patients and CD was diagnosed in five (Table 1, Figure 1).

As a result, 270 (24.2%) patients had at least one positive test result at the initial screening. Among them, 132 (11.8%) patients underwent intestinal biopsy, and 15 were diagnosed with CD. In the entire group, the CD detection rate at initial screening was 1.3%. Selective IgA deficiency was detected in four patients, all with normal tTG-IgG or AGA-IgG levels. Seventy-one patients who had at least one positive serological test either refused to permit further testing or were lost to follow-up.

Rescreening for CD

A total of 225 patients were rescreened for CD by tTG-IgA and tTG-IgG and/or EMA during the follow-up. Thirty-six (16%) patients had at least one positive result (Table 1, Figure 2).

Four patients had elevated tTG-IgA less than threefold and negative EMA levels; they were followed up without intestinal biopsy. Fourteen patients had negative tTG-IgA but positive tTG-IgG levels. EMA was positive in one of them who had a normal intestinal biopsy (Figure 2).

tTG-IgA was elevated ≥3X and <10X in six and ≥10X in 11 patients. Endomysial antibody was measured, and an intestinal biopsy was performed in 16 of them. One patient with elevated tTG-IgA≥10X refused further EMA testing and intestinal biopsy. EMA was negative in six patients, and one was diagnosed with CD by intestinal biopsy. Endomysial antibody was positive in ten, and CD was confirmed by intestinal biopsy in nine of them. Normal histopathology was observed in one patient who had elevated tTG-IgA≥ 10X and positive EMA tests. By rescreening, 18 patients underwent intestinal biopsy, and CD was confirmed in 11 patients. The CD detection rate was 4.9% at rescreening (Table 1, Figure 2). While the mean age of these patients

Table 1: Celiac disease screening results of patients

	At least one positive test result n (%)	Biopsy n (%)	CD diagnosis n	CD diagnosis rate of the biopsy (%)	CD diagnosis rate within the group (%)
Initial CD screening (n=1117)	**270 (24.2)**	**132 (11.8)**	**15**	**11.4**	**1.3**
Group 1 (n=344)	174 (50.6)	119 (34.5)	8	6.7	2.3
Group 2 (n=392)	13 (3.3)	7 (1.8)	2	28.6	0.5
Group 3 (n=381)	83 (21.7)	6 (1.6)	5	83.3	1.3
Rescreening (n=225)	**36 (16)**	**18 (8)**	**11**	**61.1**	**4.9**
Total (n=1117)	**304* (27.2)**	**148* (13.3)**	**26**	**17.3**	**2.3**

*Two patients had positive serologic test in the initial screening and rescreening, they were biopsied twice. CD: Celiac disease

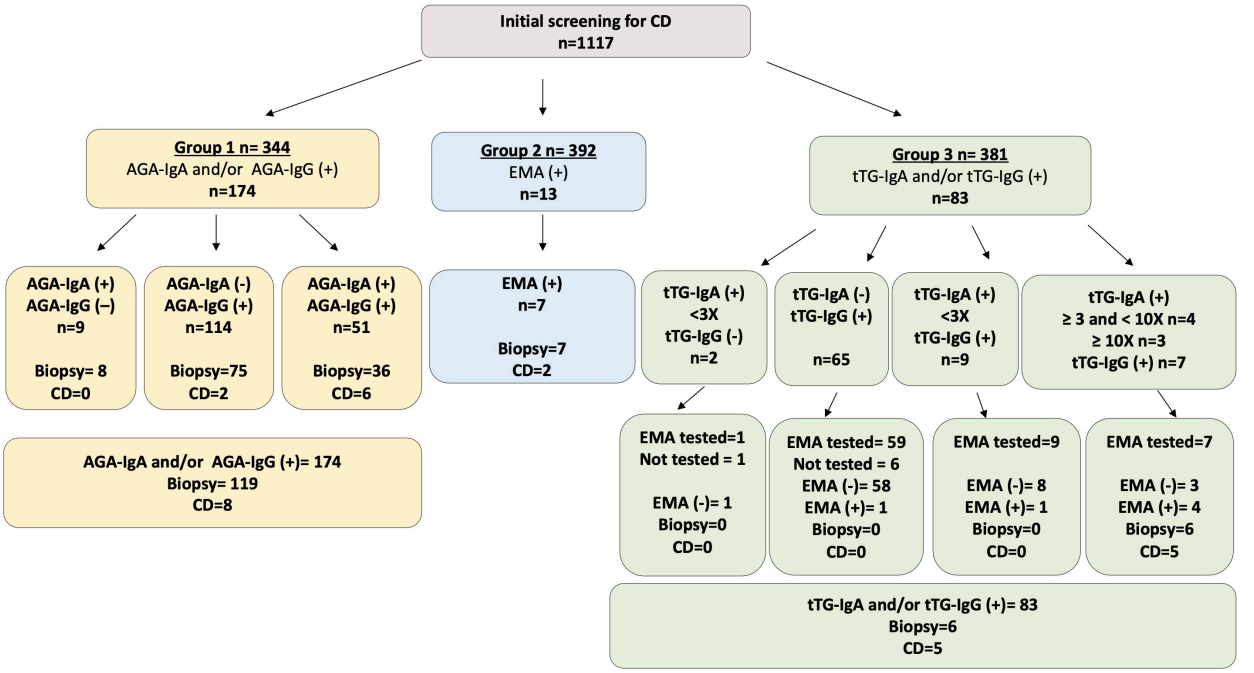

Figure 1: Initial Celiac disease screening in the whole cohort
AGA: Anti gliadin antibody, CD: Celiac disease, EMA: Endomysial antibody, tTG: Tissue transglutaminase antibody

was 3.2 years at initial screening, the mean age at which they were diagnosed with CD was 8.1 years.

As a result, a total of 26 patients were diagnosed with CD (2.3%). Of the patients with CD, 15 were diagnosed at the initial screening. Rescreening for CD was performed in 225 patients, and 11 patients who had normal at initial screening were diagnosed with CD during the follow-up. Biopsy could not be performed in 72 patients who refused further testing or lost to follow-up.

Clinical and laboratory features of patients with CD

The diagnosis of CD was confirmed by intestinal biopsy in 26 patients. Gastrointestinal or extraintestinal symptoms were only present in 42.3% of patients with CD. Gastrointestinal symptoms were present in three and extraintestinal symptoms were present in seven patients. One patient had both gastrointestinal and extraintestinal symptoms (Table 2). None of the patients had short stature. Fifteen patients who had no gastrointestinal or extraintestinal symptoms were classified as asymptomatic patients. Intestinal biopsy revealed Marsh IIIa and Marsh IIIc lesions in 11 and 15 patients, respectively (Table 2).

Diagnostic accuracy of serological tests

Intestinal biopsy was performed in 148 patients due to positive screening tests in our cohort. Among the patients who underwent biopsy, 119 of them had elevated

Table 2: The serological tests, clinical and pathological findings of patients with Celiac disease

No	AGA-IgA (AU/ml)	AGA-IgG (AU ml)	tTG-IgA (U/ml)	tTG-IgG (U/ml)	EMA	Clinical findings	Pathology (Marsh modified)	Initial screening test
1	16	74				Diarrhea	Type 3c	
2	184	420				Asymptomatic	Type 3a	
3	Positive	Positive				Autoimmune thyroiditis	Type 3c	
4	Negative	Positive				Diarrhea	Type 3c	
5	Positive	Positive				Asymptomatic	Type 3a	
6	131	144				Asymptomatic	Type 3a	
7	82	51				Asymptomatic	Type 3a	
8	11.3	142				Asymptomatic	Type 3a	
9					Positive	Asymptomatic	Type 3c	
10					Positive	Autoimmune thyroiditis	Type 3c	tTG-IgA (-), tTG-IgG (-)
11					Positive	Asymptomatic	Type 3a	
12			300	82	Positive	Iron deficiency anemia	Type 3c	EMA (-)
13			300	193	Positive	Iron deficiency anemia	Type 3a	tTG-IgA (-), tTG-IgG (-)
14			170	29.3	Positive	Diarrhea,iron deficiency anemia	Type 3c	tTG-IgA (-), tTG-IgG (-)
15			300	41	Positive	Asymptomatic	Type 3a	
16			57.7	19	Positive	Autoimmune thyroiditis	Type 3a	AGA-IgA (-),AGA-IgG (-)
17			192	6.2	Positive	Diarrhea	Type 3c	EMA (-)
18			300	59	Positive	Asymptomatic	Type 3c	
19			300	187	Positive	Asymptomatic	Type 3c	tTG-IgA (-), tTG-IgG (-)
20			277	300	Positive	Asymptomatic	Type 3a	AGA-IgA(-), AGA-IgG (-)
21			91	14.6	Positive	Asymptomatic	Type 3a	tTG-IgA (-), tTG-IgG (-)
22			166	187	Negative	Asymptomatic	Type 3a	
23			158	12.5	Positive	Autoimmune thyroiditis	Type 3a	AGA-IgA (-),AGA-IgG (-)
24			300	123	Positive	Asymptomatic	Type 3c	
25			300	12	Negative	Autoimmune thyroiditis	Type 3a	tTG-IgA (-), tTG-IgG (-)
26			300	98	Positive	Asymptomatic	Type 3a	

AGA: Anti gliadin antibody, CD: Celiac disease, EMA: Endomysial antibody, tTG: Tissue transglutaminase antibody

AGA-IgA and/or, AGA-IgG levels. Celiac disease was confirmed in six of 44 patients with elevated AGA-IgA and eight out of 111 patients with elevated AGA-IgG levels. The positive predictive value (PPV) of AGA-IgA and AGA-IgG were 13.6% and 7.2%, respectively.

Thirty-one patients with EMA testing underwent intestinal biopsy. Of these patients, EMA was negative in eight patients (tTG-IgA≥3X in all these patients) and positive in 23 patients. Two of eight EMA-negative patients and 16 of 23 EMA-positive patients were diagnosed with CD.

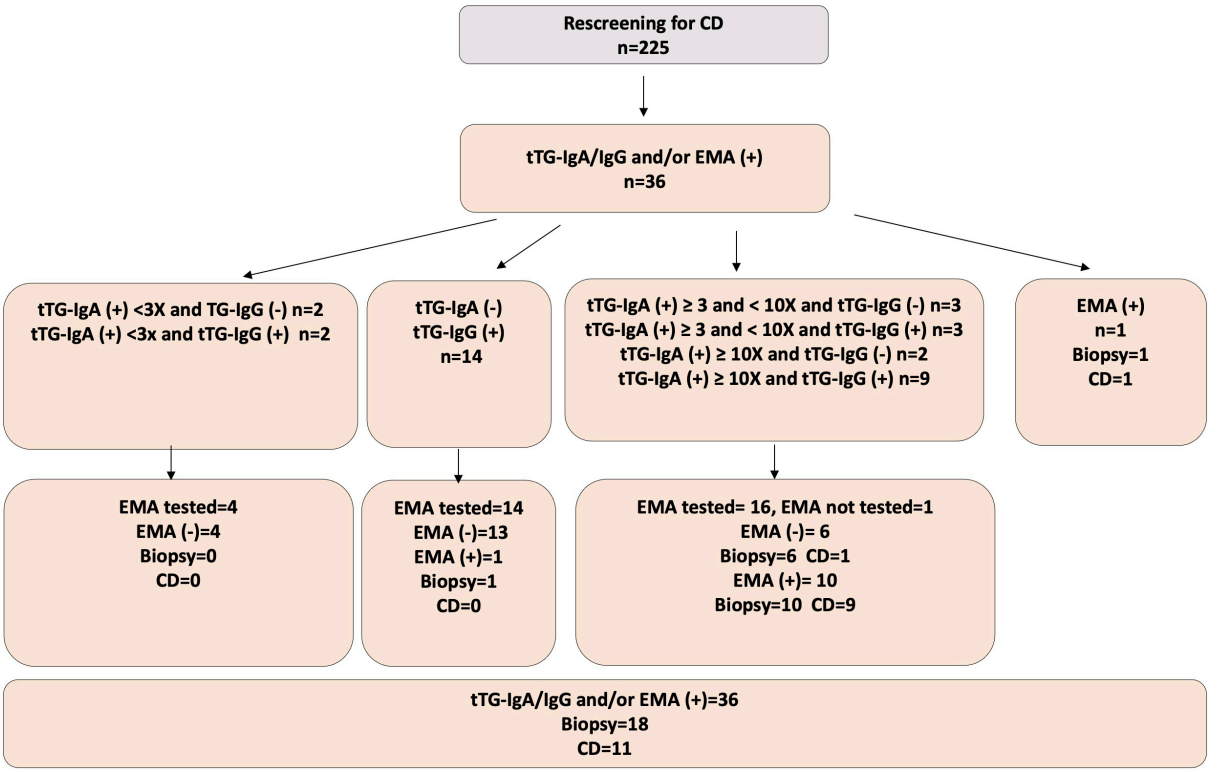

Figure 2: Celiac disease rescreening in patients who had normal serology or biopsy at initial screening
AGA: Anti gliadin antibody, CD: Celiac disease, EMA: Endomysial antibody, tTG: Tissue transglutaminase antibody

The PPV of EMA was 69.6%. A total of 21 patients with elevated tTG-IgA underwent intestinal biopsy and CD was confirmed in 14 of them. The PPV of tTG-IgA was 66.7%.

DISCUSSION

Overall, among the 1117 DS patients considered in this study, 26 patients were diagnosed with CD. The prevalence of CD in our DS patients was 2.3%, lower than previous large-cohort studies; one of which included 1317 patients and reported CD in 9.8%, and the second included 1202 patients and reported CD in 4.6% (6,15). A recent meta-analysis that included studies from European countries and the United States reported that the prevalence of CD was 6% and 5.7%, respectively, in DS patients (10). Studies on the prevalence of CD in DS patients from Turkiye were limited. In one study, CD screening was performed based on EMA in 100 DS patients. One patient was found to be EMA positive, but an intestinal biopsy could not be performed because the patient refused the biopsy (16). The prevalence of CD in DS was reported to be 6.4% and 3.1% in two studies from Turkiye, including 47 and 98 patients, respectively (17,18). In a previous study of our center which included 164 patients, CD was reported in 3% of DS patients (19). In this study, we performed an intestinal biopsy on 148 DS patients; however, 72 patients with positive serologic tests refused further testing or were lost to follow-up. If we could also perform a biopsy on these patients, the prevalence of CD in our cohort would increase even more.

Celiac disease can develop at any age, from infancy to adulthood. Therefore, it is crucial to repeat CD screening regularly in high-risk patients whose serologic tests or biopsies are initially negative. In our cohort, 225 patients were rescreened, and CD was diagnosed in 11 of them. The CD detection rate was 1.3% at initial screening and increased to 4.9% at rescreening. Similarly, Ostermaier et al. emphasized that CD screening in DS should not be limited to one time as the frequency of CD increases with age (7).

The classical gastrointestinal presentation of CD has been observed less frequently in recent years, and many CD patients are diagnosed with mild gastrointestinal or extraintestinal findings or are asymptomatic (20). In our cohort, 57.7% of CD patients were asymptomatic, and only 15.4% had gastrointestinal symptoms.

According to the AAP, CD testing was recommended for symptomatic DS patients (2). However, if only symptomatic patients were tested, and a significant number of CD patients would be missed. Liu et al. reported that almost half of CD patients detected by routine screening had no symptoms, and if routine screening had not

been performed, 82% of CD patients would have been undiagnosed (15). In addition, the complaints of symptomatic patients overlap with the symptoms commonly seen in DS patients. Sharr et al. reported that gastrointestinal problems were present in 30.7% of patients, whereas the new CD was diagnosed in <1% (21). In our cohort, more than half of CD patients were asymptomatic, and 42.3% of CD patients had normal initial screening. While the mean age of these patients was 3.2 years at initial screening, the mean age at which they were diagnosed with CD was 8.1 years. Therefore, we recommend regular screening for CD in the management of DS patients.

Serologic tests offered in the screening have changed over the years due to advances in technology. In the early 1980s, AGA was the only serologic test available. It was widely used until the discovery of EMA and tTG antibodies. Both tTG antibodies and EMA have high sensitivity and specificity. The endomysial antibody is more expensive and labor-intensive than tTG antibodies. Therefore, tTG-IgA, along with serum IgA, has been a first-line test in the screening of CD worldwide (22). Toftedal et al. investigated the PPV of CD screening methods in a large cohort of patients (23). They reported the PPV of AGA-IgA, AGA-IgG, EMA, and tTG-IgA was 79.6%, 39.5%, 80.7%, and 60.2%, respectively. In our study, the PPV of AGA-IgA and AGA-IgG were relatively low (13.6% and 7.2%, respectively). We found PPV of EMA was 69.6%, and tTG-IgA was 66.7%. Only one patient with normal tTG-IgA underwent intestinal biopsy, and it was found normal. Celiac disease diagnosis without biopsy is possible in patients with elevated tTG-IgA ≥10X and positive EMA (10). In our cohort, CD could not be confirmed with biopsy in one patient that had elevated tTG-IgA ≥10X and positive EMA. Therefore, in patients diagnosed without biopsy, the risk of a false-positive diagnosis should be considered, and if possible, the CD diagnosis should be confirmed by intestinal biopsy.

CONCLUSION

In conclusion, we demonstrated the prevalence of CD in a large cohort of DS patients from a single tertiary center as 2.3%. The CD detection rate was 1.3% at initial screening, whereas it increased to 4.9% at rescreening. More than half of the patients were asymptomatic, and only 15.4% of them had gastrointestinal symptoms. Due to the increased risk of CD and the presence of asymptomatic patients, we strongly recommend CD screening in DS. In our cohort, 42.3% of CD patients were diagnosed at rescreening, which supports that rescreening should also be performed regularly.

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JAG1 MUTATION SPECTRUM IN CASES WITH ALAGILLE SYNDROME FROM TURKIYE

TÜRKİYE'DE ALAGILLE SENDROMLU OLGULARDA *JAG1* MUTASYON SPREKTRUMU

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ABSTRACT

Objective: Alagille syndrome (ALGS), known as arteriohepatic dysplasia, is an autosomal dominant multisystem disorder primarily linked to *JAG1* gene variants. It features distinctive anomalies in the liver, heart, eyes, spine, and facial morphology.

Material and Method: Patients diagnosed with ALGS and referred to Istanbul Faculty of Medicine, Department of Medical Genetics between January 2016 and December 2022 were included in the study. The clinical, radiological, cytogenetic, and molecular findings of the patients as well as their families were re-assessed retrospectively. Karyotype, fluorescence in situ hybridization (FISH), array comparative genomic hybridization (aCGH), and *JAG1* gene sequencing utilizing next-generation and Sanger sequencing methodologies were conducted.

Result: The presence of both large deletion and small variants associated with Alagille syndrome was detected in all cases. In karyotype and aCGH analysis of a single case, a 20p deletion was identified. Subsequent next-generation sequencing (NGS) of the *JAG1* gene revealed the following findings: a heterozygous pathogenic variant c.2122_2125del/p.(Gln708Valfs*34), a heterozygous likely

ÖZET

Amaç: Arteriyohepatik displazi olarak da bilinen Alagille sendromu (ALGS), çoğunlukla *JAG1* genindeki mutasyonların neden olduğu otozomal dominant kalıtılan bir multisistem hastalığıdır. Karaciğer, kalp, göz, vertebra ve yüz morfolojisinde belirgin anomaliler içerir.

Gereç ve Yöntem: Çalışmamıza Ocak 2016-Aralık 2022 tarihleri arasında ALGS tanısı alan ve İstanbul Tıp Fakültesi Tıbbi Genetik Anabilim Dalı'na sevk edilen hastalar dahil edildi. Hastalar ve ailelerinin klinik, radyolojik, sitogenetik ve moleküler bulguları retrospektif olarak yeniden değerlendirildi. Karyotip, floresan in situ hibridizasyon (FISH), karşılaştırmalı genomik hibridizasyon (aCGH) yöntemi ile yeni nesil ve Sanger dizileme teknolojisi kullanılarak yapılan *JAG1* geni moleküler ve moleküler sitogenetik sonuçları incelendi.

Bulgular: Tüm vakalarda Alagille sendromuyla ilişkili büyük delesyon veya nokta mutasyonlarının varlığı tespit edildi. Karyotip ve aCGH analizi ile tek bir vakada *de novo* 20p delesyonu saptadı. *JAG1* geninin yeni nesil dizileme analizi aşağıdaki bulguları ortaya çıkardı; heterozigot patojenik c.2122_2125del/p.

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pathogenic variant c.1754_1755del/p.(Asn585Argfs*4), a heterozygous pathogenic variant c.2026del/p.(Cys676Alafs*67), a heterozygous pathogenic variant c.753C>A/p.(Cys251*), and a heterozygous likely pathogenic variant c.2458+2_2458+4delTAAinsGAC/p.(?). In one case, FISH analysis revealed a 20p deletion inherited from the mother. Analysis of available family members further indicated that three variants were inherited within the family. One of the two novel truncating variants, the c.1754_1755del variant was identified as *de novo*, while the other c.2458+2_2458+4delTAAinsGAC variant was determined to be familial.

Conclusion: In summary, the research effectively identified various *JAG1* gene alterations and underlined the significance of incorporating molecular cytogenetic analysis in conjunction with sequence analysis of the *JAG1* gene for accurate genetic diagnosis and counseling. Furthermore, study highlights the valuable outcome of screening parents, siblings, and children to clarify the genetic etiopathogenesis, as there is a remarkable intra- and inter-familial phenotypic variability in patients with ALGS.

Keywords: Alagille syndrome, *JAG1*, arteriohepatic dysplasia

(Gln708Valfs*34), heterozigot olası patojenik c.1754_1755del/p.(Asn585Argfs*4), heterozigot patojenik c.2026del/p.(Cys676Alafs*67), heterozigot patojenik c.753C>A/p.(Cys251*), heterozigot olası patojenik c.2458+2_2458+4delTAAinsGAC/p.(?) varyantları olduğu anlaşıldı. Bir vakada ise FISH analizi ile anneden kalıtılan 20p delesyonu saptandı. Mevcut aile üyelerinin analizi sonrasında üç varyantın ailesel olduğunu anlaşıldı. İki novel varyanttan biri olan c.1754_1755del varyantı *de novo* olarak tanımlanırken, diğer c.2458+2_2458+4delTAAinsGAC novel varyantının ailesel olduğu belirlendi.

Sonuç: Özetle, araştırmamız farklı *JAG1* geni varyantlarını tanımlamakla birlikte ve doğru genetik tanı ve genetik danışmanlık için *JAG1* geninin dizi analizi ile birlikte moleküler sitogenetik analizi birleştirmenin önemli olduğunun altını çizdi. Ayrıca çalışmamız, ALGS'li hastalarda dikkate değer aileler arasında ve aile içi fenotipik değişkenlik olduğundan, genetik etiyopatogenezi netleştirmek için ebeveynleri, kardeşleri ve çocukları taramanın katkısını vurgulamaktadır.

Anahtar Kelimeler: Alagille sendromu, *JAG1*, arteriyohepatik displazi

INTRODUCTION

Alagille syndrome (ALGS), is an autosomal-dominant, multisystem disorder caused by a defective NOTCH signaling pathway with a broad spectrum of clinical variability, spanning from severe life-threatening cardiac or liver complications to mild clinical manifestations. Its prevalence is estimated at 1:30,000 to 1:50,000 live births (1). ALGS is defined by the presence of three of the following five major clinical features along with hepatic bile duct paucity; cholestasis presented with cholestatic liver disease, congenital heart disease (CHD) (commonly pulmonic stenosis), skeletal abnormalities (typically butterfly vertebrae), ocular findings (especially posterior embryotoxon), and recognizable facial features (2). Typical facial features include a prominent broad forehead, deeply set eyes, long nose with a bulbous tip and a pointed chin, giving the appearance of a triangular face. Less frequently, clinical involvement of renal and vascular abnormalities, growth failure, developmental delay and delayed puberty can also occur (3, 4). The clinical phenotype associated with Alagille syndrome manifests considerable interfamilial and intrafamilial variation (5). Clinical findings in heterozygous individuals are unpredictable and can vary from subclinical manifestation to severe liver disease. Early diagnosis and treatment are important for mortality and morbidity in ALGS. The prognosis is related to the severity of bile flow obstruction and scarring of the liver and cardiovascular involvement (3,6). Ninety-four percent of patients exhibit monoallelic pathogenic alterations in the Notch signaling ligand, JAGGED1 (*JAG1*), while 2.5% of patients carry monoallelic pathogenic variants in the Notch signaling receptor NOTCH2 (7, 8). Small sequence variants within the *JAG1* gene account for roughly 85% of the identified pathogenic alterations in ALGS. Further molecular diagnoses, amounting to approximately 9%, are facilitated by employing techniques such as fluorescence in situ hybridization (FISH), array comparative genomic hybridization (aCGH), or multiplex ligation-dependent probe amplification (MLPA) to detect deletions or duplications (8). No genotype-phenotype correlations for *JAG1* and *NOTCH2* pathogenic variants causing ALGS were noted. Only a very small number (3.2%) of individuals clinically diagnosed with ALGS exhibit an identified disease-causing mutation in either of the two genes (8). The *JAG1* gene encodes a transmembrane protein that is a ligand of Notch receptors involved in cell differentiation. So far, 766 variations in the *JAG1* gene have been reported in the Human Gene Mutation Database (HGMD) Professional subscription (November 2022). The pathogenic variants protein truncation which include frameshift, nonsense, exon level deletions and splice site are frequently found in patients with ALGS, although missense variants and whole gene deletions were also demonstrated in the cases. In this study, we conducted a comprehensive analysis of the molecular and clinical characteristics of seven ALGS cases from Turkiye. Notably, one of these cases was diagnosed with ALGS prenatally. We further compared the genetic profiles of these cases with those documented in existing literature.

MATERIAL and METHODS

Patients

The study encompassed cases that had received a confirmed diagnosis of ALGS and had been referred to the clinic of the Department of Medical Genetics at Istanbul Faculty of Medicine, Istanbul University between the years

2016 and 2022. The clinical, biochemical, cytogenetic and molecular findings of the patients were retrospectively reviewed. The study includes probands and their affected family members with ALGS. The study underwent an extensive review process and received approval from the institutional review board at Istanbul University (Date: 07.10.2022, No: 18). Additionally, prior to conducting genetic testing, written informed consent was appropriately obtained from all parents or legal guardians of the participating patients. The research involved reviewing the family history, clinical details, biochemical analyses, pathological assessments, and radiological examinations of the individuals.

Genetic tests

DNA extractions were performed using a kit (MagNaPure, Roche). Genetic testing was carried out using a sequential methodology. Initially, cytogenetic and molecular cytogenetic tests were conducted, and individuals with normal results proceeded to undergo molecular genetic investigation. All encoded exons and exon-intron regions of the *JAG1* gene (NM_000214.3) were sequenced using next generation sequencing (NGS) technology (Miseq, Illumina Inc., San Diego, CA, USA) and confirmed by Sanger sequencing as well as segregated in available parents, except for Case 3 whose parents were also sequenced with *JAG1* by NGS. The variants were checked with the ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and HGMD (http://www.hgmd.cf.ac.uk/ac/) databases. Single nucleotide polymorphism (SNP) and novel variants were assessed by using dbSNP, gnomAD (https://gnomad.broadinstitute.org/). In silico prediction software, Mutation Taster (https://www.mutationtaster.org/), Sorting Intolerant from Tolerant (SIFT, https://sift.bii.a-star.edu.sg), and PolyPhen-2 HumVar, (http://genetics.bwh.harvard.edu/pph2/) were used to predict the pathogenicity. The splice site affect was searched from Splice AI (9). The classification of the variants according to The American College of Medical Genetics and Genomics was based on the Varsome (10) and Franklin databases (https://franklin.genoox.com/). The Karyotype and aCGH analysis were performed in Case 1 due to the diagnosis of multiple congenital anomalies (MCA). A Karyotype analysis was performed using G-banded chromosomes at 500-550 band levels. The aCGH was performed using the Agilent SurePrintG3 CGH+SNP Microarray Kit 4x180K (Agilent Technologies Inc, Santa Clara, CA, USA) according to the manufacturer protocol. The 20p12 band was investigated with FISH using a *JAG1* specific probe (Diagen, Ankara, Turkiye) and was performed in Case 7 with a clinical diagnosis of ALGS whose *JAG1* gene sequence analysis was normal.

RESULTS

Patient characteristics

Seven of the index patients were from distinct families. Among them, two were males and five were females. The clinical, radiological, and molecular findings are summarized in Table 1. In three families, there was a history of individuals similarly affected by the condition (Case 4, Case 6, and Case 7). All cases exhibited facial dysmorphism consistent with ALGS, along with the cardiovascular complications and skeletal abnormalities (as shown in Figure 1). Furthermore, posterior embryotoxon was observed in each postnatal case that underwent eye examination.

Clinical findings

Case 1; a female fetus was the first child of a non-consanguineous couple. A Gestation (G)1 Medical Abortion (MA)1, was terminated at the 20th Gestation Week (GW) due to MCA. The first trimester ultrasound revealed cystic hygroma. Polyhydramnios, a single umbilical artery, hypoplastic left heart syndrome (HLHS), scoliosis, suspicion of hemivertebrae, bilateral pes equinovarus, and shortness of all tubular bones in the ultrasound performed at the 20thGW. The postmortem evaluation revealed characteristic facial findings (hypertelorism, depressed nasal root, bulbous nasal tip, wide columella, thin lips) associated with ALGS and X-ray findings (rib fusion, hemivertebra, vertebral cleft, butterfly vertebra).

Case 2; a 9-year-old male patient, the third child born to non-consanguineous parents (G3P3), was delivered at the 38thGW by cesarean section (C/S) but due to prolonged labor the birth weight was 2550 g (-1.41 SD). His birth length measured 48 cm (-0.05 SD) and his head circumference (HC) was 33 cm (-0.91 SD). The family history did not reveal any notable conditions. His parents and siblings were in good health. He presented dysmorphic facies (sparse hair, broad forehead, triangular face, deep-set eyes, hypertelorism, long nose with a bulbous tip, pointed chin). He was evaluated for jaundice at two months

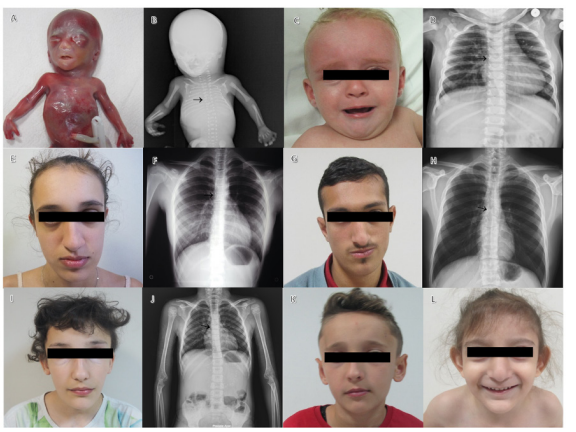

Figure 1: Characteristic facial dysmorphism and skeletal anomalies of ALGS cases
Case 1 (A and B), Case 3 (C and D), Case 4 (E and F), Case 5 (G and H), Case 6 (I and J), Case 2 (K), Case 7 (L). Arrows indicate butterfly vertebrae.

Table 1: Summary of clinical and molecular findings of *JAG1* gene related ALGS

Case	Affecting family members	Liver (biopsy)	Eye	Cardiac	Skeletal	Variant type • dbSNP • Clinvar	Genetic results • nucleotide • peptide
Case I [♀]	none *de novo*	unknown	unknown	hypoplastic left heart	scoliosis, hemivertebrae	gross deletion NA NA	20p13p12 deletion NA NA
Case II [♂]	none *de novo*	cholestasis, bile duct paucity	posterior embryotoxon	PPS	butterfly vertebrae	small deletion rs727504412 VCV000177941.29 **SCV004023385**	c.2122_2125del p.(Gln708Valfs*34)[23]
Case III [♀]	none *de novo*	cholestasis, mild bile duct proliferation	posterior embryotoxon, peripapillary atrophy	BAV, aortic stenosis, mild AR, PDA	butterfly vertebrae	small deletion NA **SCV004023386**	c.1754_1755 del p.(Asn585Argfs*4)
Case IV [♀]	paternal	unknown	posterior embryotoxon	PPS, peripheral pulmonary vascularization	scoliosis, butterfly vertebrae	small deletion NA **SCV004023387**	c.2026 del p.(Cys676Alafs*67)[22]
Case V [♂]	none unknown	bile duct paucity	posterior embryotoxon	PPS	butterfly vertebrae, scoliosis	Nonsense NA **SCV004023388**	c.753C>A p.(Cys251*)[21]
Case VI [♀]	maternal	unknown	posterior embryotoxon	PPS	butterfly vertebrae, scoliosis	splicing small deletion NA **SCV004023389**	c.2458+2_2458+4delTAAinsGAC p. (?)
Case VII [♀]	maternal	bile duct paucity	posterior embryotoxon	PPS	butterfly vertebrae	gross deletion	20p12.2 deletion

PPS: Peripheral pulmonary stenosis, BAV: Bicuspid aortic valve, PDA: Patent ductus arterious, AR: Aortic regurgitation, NA: Not available, VCV: (Variation ClinVar record), SVC: Submitted record in ClinVar

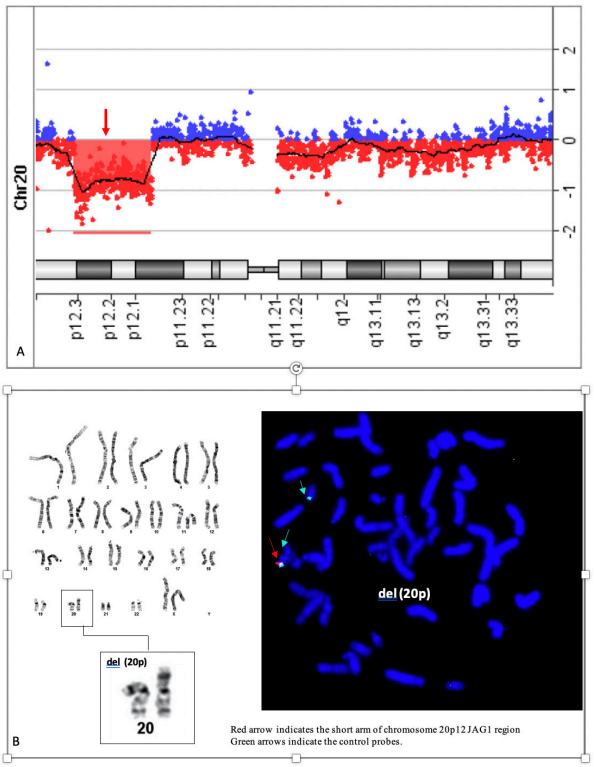

Figure 2: Cytogenetic and molecular cytogenetic results of Case 1 and Case 7

A aCGH showed a 9.5 Megabase (Mb) deletion in the 20p13p12.1 region, including the *JAG1* gene [arr[GRCh37] 20p13p12.1(4709272_14175391)x1] in Case 1.

B Full and partial karyotype and FISH study using JAG1 specific probe showed a deletion on 20p12.2. Red signal is absent on one chromosome 20 in case 7.

of age. The echocardiography revealed peripheral pulmonary stenosis (PPS). He was found to have butterfly vertebrae. A Histopathological examination of the liver at five months of age revealed cholestasis which is associated with the loss of the intrahepatic bile ducts (paucity of interlobular bile ducts). His eye examination showed bilateral posterior embryotoxon, and he underwent a hepaticojejunostomy at the age of two. His growth parameters and motor developmental milestones were normal.

Case 3; a 7-year-old female, the first child born to non-consanguineous parents from the same village (G1P1). The family history was unremarkable. Prenatal ultrasound at the first trimester showed nasal bone hypoplasia and nuchal translucency (NT). Cytogenetic analysis of amniotic fluid cells performed for pathologic ultrasound revealed a normal karyotype. The NT was normal in further scans. She was delivered at term via C/S due to oligohydramnios with a birth weight of 2760 g (-0.84 SD) and a birth length of 47 cm (-1.03 SD). Postnatally, she showed cholestasis (conjugated hyperbilirubinemia with

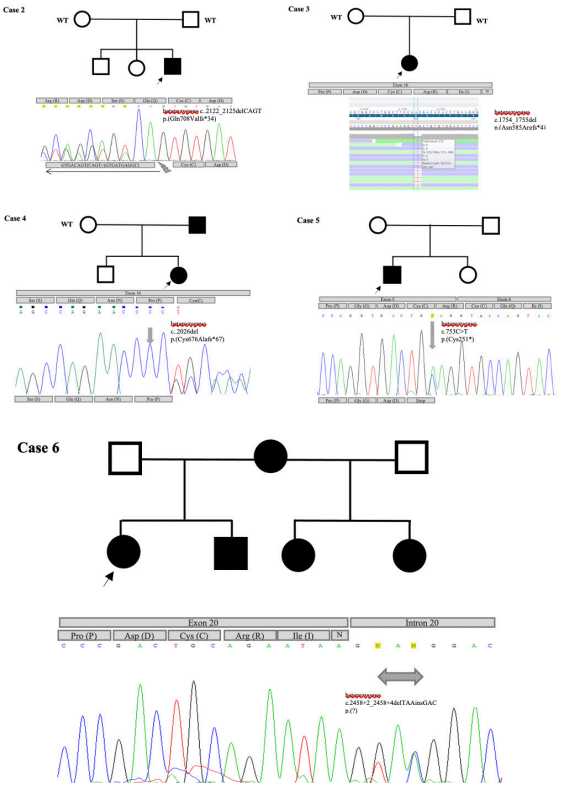

Figure 3: Pedigree analysis and molecular results of Case 2-6. Sanger sequencing of Case 2, 4, 5, 6 and next generation sequencing of Case 3 and her parents revealed *de novo/novel* heterozygous c.1754_1755 del p.(Asn585Argfs*4) variant. WT: Wild Type

high hepatic enzymes) which manifested as jaundice. The echocardiography revealed a mild aortic regurgitation (AR) with aortic stenosis, bicuspid aortic valve, and patent ductus arteriosus. A histopathological examination done at 3.5 months old, revealed cholestasis and mild ductal proliferation. At nine months of age, an eye examination identified posterior embryotoxon and the presence of peripapillary atrophy. Butterfly vertebra in the thoracolumbar region was detected. A physical examination at 10 months of age revealed failure to thrive with a weight 6600 g (-2.53 SD), the length 66 cm (-2.36 SD), and OFC: 44 cm (-0.76 SD). Her physical examination was remarkable for mild jaundice and dysmorphic facial dysmorphic features (pronounced forehead, deeply located eyes, slightly narrow palpebral fissures, flattened nasal root, thin lips, fish mouth, high palate). Her motor developmental milestones were normal.

Case 4; an 18-year-old female patient was the second child born to non-consanguineous parents (G2P2). She was born via C/S (due to history of previous C/S) at the 38th GW with a weight of 3130 g (0.12 SD), a height of 49 cm (-0.05 SD) and a head circumference of 33 cm (-0.91 SD). Her father had unilateral renal hypoplasia. There was

a history of jaundice that did not require postnatal phototherapy. At the age of eight, an increased level of liver enzymes was detected during a routine screening. The echocardiography revealed PPS. Thoracal kyphoscoliosis secondary to butterfly vertebra was detected in a vertebral X-ray. On a thorax MR angiography, bilateral peripheral pulmonary vascularization was slightly decreased. Posterior embryotoxon was detected in an eye examination. Facial dysmorphic findings (broad forehead, deeply located eyes, prominent nasal root, malar/midfacial hypoplasia, short philtrum, wide columella) were observed in the physical examination. Her growth parameters and motor developmental milestones were normal.

Case 5; a 19-year-old male patient was the second child born to non-consanguineous parents (G2P2). His parents and his older brother were healthy. He was delivered via normal vaginal delivery (NVD) at the 34th GW with a weight of 2870 g (2.22 SD). Direct hyperbilirubinemia was found at the postnatal on the third day. An Echocardiography revealed pulmonary stenosis, a doppler ultrasound revealed the absence of bile ducts, and an ophthalmic examination revealed posterior embryotoxon. A liver biopsy revealed an absence of bile ducts in the portal area. At 3.5-years-old the patient presented with complaints of severe itching, jaundice, and swelling in the abdomen. A liver transplant was performed at the age of eleven because of persistent itching. The patient was found to have hyperglycemia on the fourth day after the transplant, and was diagnosed with Type 1 DM in the follow-ups and insulin therapy was started. Butterfly vertebrae and mild thoracolumbar scoliosis were found on vertebral radiographs at nine years of age. He had an operation for urinary incontinence at the age of 11. He was diagnosed with a hepatitis B virus (HBV) infection at the age of 15, received interferon treatment for a duration of one year and subsequently underwent lamivudine treatment. Aseptic necrosis was detected in the femoral head at the age of 15. A physical examination at almost 19 years of age showed growth retardation [Weight: 50 kg (-2.7 SD), Height: 159.5 cm (-2.63 SD)] was present. Facial dysmorphic findings (bitemporal flattening, prominent glabella, synophyria, upward slanted palpebral fissures, malar hypoplasia, prominent nasal arch, inferior columella, short philtrum, prognathia, simple/slightly posteriorly located ears, high palate, posteriorly located upper lateral incisors) were present. His motor developmental milestones and mental development were normal.

Case 6; a 17 year old female patient was the first child of non-consanguineous parents. She was born via NVD at term with a weight of 2950 g (-1.01 SD). There was a family history of the mother affected with posterior embryotoxon and BAV and sisters and a brother affected with vertebral anomalies and hyperbilirubinemia. She was evaluated for direct hyperbilirubinemia at the postnatal on the fourth day of life. A liver biopsy revealed the absence of bile ducts. An abdominal ultrasound performed at the age of seven found a left renal cortical cyst. An eye examination revealed posterior embryotoxon. Pulmonary stenosis was detected on an echocardiography. Butterfly vertebra and thoracolumbar scoliosis were found on an X-Ray. A prominent broad forehead, up upslanting palpebral fissures, hypertelorism, deep set eyes, malar hypoplasia were noted as dysmorphic facial features.

Case7; A 2-year-old female patient was the third child of non-consanguineous parents. Her twin sister and brother were diagnosed with ALGS and her brother died at the age of 2.5 years after a liver transplant. Her mother had facial dysmorphism compatible with ALGS, including renal anomaly (focal ectasia), cardiac anomalies (mild mitral insufficiency, and patent foramen ovale). She was born via C/S (due to history of previous C/S) at the 37th GW with a weight of 2500 g (-0.93 SD). She was admitted at 15 months because of the family history. Facial dysmorphic findings (prominent forehead, upslanting palpebral fissures, malar hypoplasia, hemangioma on the left side of the nose, bulbous nasal tip, antevert ears) were present. Her growth parameters were all normal. Butterfly vertebra was detected in the vertebral X-ray. An Echocardiography revealed pulmonary stenosis. An increased level of liver enzymes was detected. Her growth parameters and motor developmental milestones were normal.

Genetic results

An examination of the available parents' genetic profiles showed that three of the pathological variants were inherited (Case 4-paternal, Case 6-maternal, Case 7-maternal), while the remaining three were *de novo* (Case 1, Case 2, and Case 3) occurrences. Segregation analysis was not feasible for Case 5 because the parents would not consent to undergo testing themselves.

Case 1 had a heterozygous gross deletion on chromosome 20p, which was detected on fetal karyotype analysis. aCGH showed a 9.5 megabase (Mb) deletion in the 20p13p12.1 region, including the *JAG1* gene (Figure 2A). Karyotype analysis of the parents was normal. It was determined that the case was a *de novo* novel gross deletion. Next generation sequencing of the *JAG1* gene revealed a heterozygous c.2122_2125del/p.(Gln708Valfs*34) in Case 2, a heterozygous *novel* c.1754_1755del/p.(Asn585Argfs*4) in Case 3, a heterozygous c.2026del /p.(Cys676Alafs*67) in Case 4, a heterozygous c.753C>A/p.(Cys251*) in Case 5, and a heterozygous novel c.2458+2_2458+4delTAAinsGAC/p.(?) in Case 6, in *JAG1* (Figure 3). In Case 7, *JAG1* gene sequencing yielded normal results. However, upon conducting a FISH examination, a 20p12 deletion was detected. The karyotype and FISH analysis was interpreted as follows: 46,X,del(20)(p12.2).ish del(20)(p12.2)(JAG1-) (Figure 2B). This deletion was also observed in

the affected mother and affected sister, indicating that the variant was inherited within the familial.

All variants were truncating types of mutations including three small deletions and one small deletion insertion resulting in frameshift mutation, and one nonsense mutation (Figure 3). The previously reported pathogenic variants were identified in a total of three individuals (c. c.2122_2125del, c.753C>A, c.2026del). The two variants (c.1754_1755del and c.2458+2_2458+4delTAAinsGAC) were novel truncating and predicted as likely pathogenic [PVS1 (pathogenic very strong), PM2 (pathogenic moderate)] according to ACMG criteria. The deep learning splicing prediction analysis (SpliceAI) of c.2458+2_2458+4delTAAinsGAC was predicted to abolish the Splice Donor site of the pre-mRNA of the *JAG1* showing a maximum pathogenicity score of 1.0.

DISCUSSION

In this study, our objective was to elucidate the clinical, radiological, cytogenetic, and molecular attributes of seven index cases with Alagille syndrome, which also goes by the name arteriohepatic dysplasia. This autosomal dominant multisystem disorder arises from pathogenic variants occurring in the *JAG1* gene. The diagnosis of ALGS in infants and children primarily hinges on their clinical manifestations. Chronic cholestasis stands out as the most common initial symptom, while distinctive facial features play a pivotal role as reliable indicators for ALGS diagnosis.

All six individuals diagnosed postnatally exhibited all five major clinical features. Since it is difficult to detect liver findings, facial dysmorphism and ocular findings in the prenatal period, ALGS must be considered in fetal cases with multiple anomalies including the heart and vertebra. Especially, fetal hemivertebrae detected by detailed ultrasound scan may be a clue for ALGS (11). In Case 1, which had a gross heterozygous deletion of 9.5 Mb, including the *JAG1* gene region, the vertebral anomalies accompanying the hypoplastic left heart syndrome were noted in the prenatal period. In the literature, the diagnosis of ALGS in the prenatal period is rare and is often found with a history of affected parents (12-15). However, a case of HLHS with a de novo gross 20p deletion has been reported, as in our case (16). HLHS is a rare severe CHD characterized by underdevelopment of left heart components and dysfunction of the left ventricle. Our case is a second fetal ALGS case with HLHS in the prenatal period, which was found to have a deletion of the 20p and contributed to the literature in this respect.

Liver disease including biliary tract failure and cholestasis, one of the five main clinical findings of ALGS, is an important suggestive finding for ALGS documented by liver biopsy. The characteristic hepatic pathology in ALGS is defined by a paucity of interlobular bile ducts, accompanied by an absence of significant bile ductular reaction. Currently, a liver biopsy may not be mandatory if there are other characteristic major findings of ALGS syndrome, including cholestasis (17). In our case series, a liver biopsy was done in four of the six postnatal diagnosed cases (Case 2, 3, 5 and 6). The histopathological findings of all cases were consistent with ALGS, except in Case 3, who underwent liver biopsy in the neonatal period.

Case 3, who presented with cholestasis, posterior embryotoxon and bicuspid aortic findings, ductal proliferation, received a liver biopsy in the neonatal period. Although progressive insufficiency of the intrahepatic bile ducts are considered to be the most important and constant feature of ALGS, paucity of the intrahepatic bile ducts may not always be seen in infants younger than six months of age, and a normal ratio of portal tracts to bile ducts, bile duct proliferation, or neonatal giant cell hepatitis may be observed (18). Since ductal proliferation is also seen in a liver biopsy in biliary atresia, it is important to evaluate the liver biopsy results of patients with ALGS in the neonatal period with clinical findings.

About 20% to 70% of ALGS cases may require a liver transplant by age 18 due to liver failure or intense itching. A liver transplant (LT) is advised for pediatric ALGS patients. Selecting appropriate donors for the living donor LT (LDLT) is crucial due to ALGS's autosomal dominant nature. Although genotype-phenotype correlation is unclear, potential asymptomatic donors are often overlooked. Donors can be screened using liver function tests and imaging; if normal, first-degree relatives may serve as LDLT donors. Genetic studies' role in ALGS-related organ donation remains undefined (19). ALGS, a genetic disorder, can lead to early childhood liver transplants with high morbidity and mortality. In Case 7, a sibling history exists: a liver transplant at 2.5 years resulted in fatality. The prognosis is worse for neonatal cholestatic jaundice cases.

The clinical history and findings in ALGS patients underscore notable inter- and intra-familial phenotypic variability, including liver severity and manifestations in other organs. While affected cases often display three or more main features, our case series, excluding prenatal cases, commonly meets all criteria. Affected relatives typically present a single additional criterion besides shared facial appearance. Case 4, Case 6, and Case 7 are familial: one paternal and two maternal inheritance patterns. Case 4 exemplifies intra-familial variation, with an affected father displaying renal hypoplasia and mild facial dysmorphism. Similarly, Case 6 and Caser 7 feature mildly affected siblings and mothers.

In our series of cases, even in the absence of established genotype-phenotype correlations for *JAG1*, we have

observed instances of ALGS patients exhibiting supplementary anomalies such as developmental delay, hearing loss, and autism. Remarkably, these individuals were identified to possess a larger deletion encompassing *JAG1* on chromosome 20p12 (20). Similarly, the presence of HLHS in the fetal case (Case 1) with a 9,5 Mb deletion supports the prediction that large deletions may be associated with additional anomalies in ALGS. In accordance with the literature, it is suggested that microscopic and submicroscopic chromosomal deletions should be excluded before *JAG1* gene sequence analysis, since developmental delay and/or the presence of additional anomalies in addition to the common features in ALGS in our case series may increase the suspicion of chromosomal deletion.

Analysis of available family members revealed that three variants were familial inherited, and two were *novel* single nucleotide variation. The variants (c.753C>A, c.2026del, c.2122_2125del) are rare variants previously reported as a single case report in the literature (21-23). Case 3 and Case 6 had *novel* variants, whereas Case 4, Case 6, and Case 7 were familial.

In this study, a noteworthy fraction of familial cases was noted, with three out of seven patients originating from familial clusters. In ALGS, roughly 30%-50% of cases inherit the pathogenic variant from an affected family member, while the remaining 50%-70% exhibit a *de novo* pathogenic variant.

The presence of multiple affected individuals within Case 6 and Case 7 accentuates the critical role of genetic counseling. In these instances, the diagnosis of ALGS was established in more than one child of a mildly affected mother, leading to significant implications for the family, given the pronounced morbidity and mortality associated with this disorder. Deciphering the underlying molecular etiopathogenesis of the condition in its early stages, combined with well-directed genetic counseling, is poised to enhance the management of familial cases of this nature.

CONCLUSION

Our study highlights the significance of comprehensive assessment of parents, siblings, and children of affected cases, particularly after elucidating the genetic etiopathogenesis. This methodology is crucial due to the notable intra- and inter-familial phenotypic variability observed in patients with ALGS. Such an approach not only deepens the comprehension of the disorder but also holds substantial implications for clinical management strategies and genetic counseling.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 07.10.2022, No: 18).

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STRUCTURAL ABERRATIONS OF 1p36 IN HEMATOLOGIC MALIGNANCIES*

HEMATOLOJİK KANSERLERDE 1p36'NIN YAPISAL ANOMALİLERİ

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ABSTRACT

Objective: Structural aberrations of 1p36 are very common in most hematologic malignancies. 1p36 consists of genes that are important in oncogenesis. The aim of this study was to define 1p36 abnormalities and their distributions within different hematologic malignancies.

Materials and Methods: To achieve this goal, we retrospectively evaluated the cytogenetic results of our hematological cancer cases.

Result: We found deletions or rearrangements of breakpoint 1p36 in 18 patients with various hematologic malignancies, including myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), multiple myeloma (MM), chronic myeloid leukemia (CML), lymphoma, B cell acute lymphoblastic leukemia (B-ALL), idiopathic thrombocytopenic purpura (ITP) and aplastic anemia (AA). We observed t(1;3)(p36;p21) in one AML-M2 patient and t(1;3)(p36;q21) in two CML patients. Eight patients (1 MDS, 2 MM, 3 CML, 1 AML, and 1 AA) had translocations and rearrangements. One ITP patient had der(1)t(1;1)(p36;q21) and another CML patient had der(1)t(1;1)(p36;q12). We demonstrated several terminal deletions with different breakpoints between 1p11 and 1p36 in five patients, (2 MDS, 2 lymphomas, and 1 B cell acute lymphocytic leukemia).

Conclusion: The 1p36 breakpoint is a hot spot for cancer-related chromosome rearrangements and is associated with poor prognosis. In order to emphasize the importance of 1p36 in hematologic malignancies it essential to build a large data pool on the

ÖZET

Amaç: 1p36 bölgesinin yapı anomalileri bir çok hematolojik kanserde oldukça yaygındır. 1p36 bölgesi, kanser gelişiminde etkili olan önemli genlere sahiptir. Bu çalışmanın amacı, olgularımıza ait 1p36 anomalilerini ve farklı hematolojik kanserlerdeki dağılımlarını belirtmektir.

Gereç ve Yöntem: Bu çalışma için hematolojik kanser olgularımızın sitogenetik sonuçları retrospektif olarak değerlendirilmiştir.

Bulgular: Myelodisplastik sendrom (MDS), akut myeloid lösemi (AML), multipl myelom (MM), kronik myeloid lösemi (KML), lenfoma, B hücreli akut lenfoblastik lösemi (B-ALL), idyopatik trombositopenik purpura (ITP) ve aplastik anemi (AA) hastası olmak üzere 18 farklı hematolojik kanser olgusunda 1p36 kırık noktasına ait delesyon ya da yeniden düzenlenmeler saptanmıştır. Bir AML-M2 hastasında t(1;3)(p36;p21) ve iki KML hastasında t(1;3)(p36;q21) gözlemlenirken, sekiz hastada (1 MDS, 2 MM, 3 KML, 1 AML and 1 AA) translokasyon ve yeniden düzenlenmeler tespit edilmiştir. Bir ITP hastası der(1)t(1;1)(p36;q21) ve bir KML hastasında ise der(1)t(1;1)(p36;q12) kromozom yapısı saptanmıştır. Beş hastada (2 MDS, 2 lenfoma, ve 1 B hücreli akut lenfositik lösemi)1p11 ve 1p36 arasındaki farklı kırık noktalarında çeşitli terminal delesyonlar gözlenmiştir.

Sonuç: 1p36 kanserle ilişkili kromozom yeniden düzenlemeler için sıcak noktadır ve kötü prognozla ilişkilendirilmektedir. 1p36 bölgesinin hematolojik kanserlerdeki önemini vurgulamak için, konuyla ilgili geniş bir veri havuzu oluşturmak önemlidir. Serimiz-

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subject. The distribution of breakpoints in 1p abnormalities in our series was remarkable, as 12 out of 18 1p breakpoints were 1p36. However, while 1p breakpoints aggregated on 1p36 in all translocations, there was only one 1p36 breakpoint in five deletions. With this paper, we contribute to the relevant literature by reporting our results.

Keywords: 1p36, leukemia, lymphoid malignancies, myeloid malignancies, cytogenetics, bone marrow

deki 1p36 anomalilerinin dağılımı, 18 hastanın 12'sinde 1p kırık noktasının 1p36 olması nedeniyle dikkat çekicidir. Ancak, bütün translokasyonların kırık noktaları 1p36'da yoğunlaşırken, beş delesyonun sadece birinde kırık noktası 1p36 idi. Bu çalışma ile sonuçlarımızı sunarak bu alandaki literatüre katkı sağlayacağımızı düşünmekteyiz.

Anahtar Kelimeler: 1p36, lösemi, lenfoid kanserler, myeloid kanserler, sitogenetik, kemik iliği

INTRODUCTION

Conventional cytogenetic testing is a major tool in the diagnosis, classification, and follow-up of hematologic malignancies. Structural aberrations of chromosome 1p36, including translocations, inversions, deletions, and duplications are common in several hematologic malignancies. These aberrations are mostly observed in myeloproliferative disorders (MPD), myelodysplastic syndrome (MDS), and multiple myeloma (MM) (1). Although rarely, 1p36 abnormalities may also be observed in acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), and non-Hodgkin's lymphoma (NHL) (1-3). Furthermore, a shorter overall survival has been correlated with breaks in the 1p32–p36 region in malignancies (4-8). There are various reports on relevant genes such as *CDC2L1* and *CDC2L2* (cell division control 1 and 2), *PRDM16* (PR/SET domain 16), *TNFRSF14* (a member of the tumor necrosis factor receptor family), *DFFB* (DNA fragmentation factor subunit beta), *PRKCZ* (protein kinase C zeta), *MMP23* (metalloproteinase), SKI (sarcoma virus homolog), *ERRFI1* (a cell growth regulator) that are located on 1p (4,7,9-16). According to the literature, molecular mechanisms of these genes are involved in several different malignancies.

This study aims to determine the 1p36 abnormalities and their distribution across different hematologic malignancies. For this purpose, we retrospectively evaluated the cytogenetic results of our hematological cancer cases. We intend to contribute to the relevant literature by presenting the cytogenetic findings of 18 cases with various hematologic malignancies and different 1p abnormalities.

MATERIAL and METHODS

In this study, cytogenetic results of 5,098 hematologic cancer cases referred from IU-C, Cerrahpasa Faculty of Medicine, Department of Internal Medicine, Division of Hematology, to the Cytogenetics Laboratory of the Medical Biology Department of Cerrahpasa Faculty of Medicine, IU-C, between 1994 and 2017 were evaluated retrospectively in terms of chromosome 1p abnormalities. Eighteen cases (12 males, six females) with a median age of 62.5 (range 31-86) constituted the study group. Distribution of the patients was as follows: chronic myeloid leukemia (CML, 6 cases), MDS (3 cases), acute myeloid leukemia (AML, 2 cases), MM (2 cases), lymphoma (2 cases; one with diffuse large B-cell lymphoma (DLBCL) and one with follicular non-Hodgkin's lymphoma, B-ALL (1 case), idiopathic thrombocytopenic purpura (ITP, 1 case) and aplastic anemia (AA, 1 case). Fifteen of these patients were newly diagnosed, and 3 (1 CML, 1AML, and 1AA) were follow-up patients. The study was approved by the institutional Medical Ethics Committee (Date: 03.07.2018, No: A-38).

Bone marrow (BM) and/or peripheral blood samples were used for conventional cytogenetic analyses. Cytogenetic analyses were performed with 24-h or 48-h unstimulated BM cultures, and 72-h peripheral blood cultures using standard procedures (17). Two cultures were set up for each patient by adding 0.1 ml of heparinized bone marrow aspiration material to 5 ml of medium for BM cultures. Similarly, two cultures were set up for each patient by adding 0.2 ml of heparinized peripheral blood to 5 ml of medium in a 72-hour culture.

After harvesting, the GTL (G-bands using trypsin and staining with Leishman) banding technique was applied to the slides, and karyotypes were described according to the An International System for Human Cytogenomic Nomenclature (ISCN), 2016 (18).

RESULTS

This study presents deletions and rearrangements of 1p in 18 patients with hematologic malignancies. The aberrations we observed include six additions (33%), five deletions (28%), four translocations (22%), two derivative chromosomes (11%), and one inversion (6%).

Additions were the most observed abnormalities with the accumulation of breakpoints at 1p36 in five cases. One AML, two CML, and two MM cases had add(1)(p36). The other chromosomal addition seen in our study was add(1)(p34) in a patient with AML.

Five patients had deletions with different breakpoints from 1p11 to 1p36. These deletions were del(1)(p35), and

del(1)(p11) in two MDS cases, del(1)(p32p36) in DLBCL, del(1)(p22) in ALL, and del(1)(p21) in follicular non-Hodgkin lymphoma.

We observed reciprocal translocations of 1p36 with other chromosomes in five patients. These translocations were: t(1;3)(p36;q21) in two patients with CML, t(1;3)(p36;p21) (previously reported (19)), in one patient with AML M2, t(1;2)(p36;q11) in one patient with MDS and, t(1;10)(p36;q21) in one patient with CML.

We identified derivative chromosomes 1 in two cases. One of them was der(1)t(1;1)(p36;q21) in an ITP case, and the other was der(1)(1qter→1q12::1p36→1qter) in a CML case.

Apart from these, we observed inv(1)(p36q41) in one patient with AA.

Finally, t(1;2)(p36;q11), t(1;10)(p36;q21), inv(1)(p36q41) and der(1)t(1;1)(p36;q21) were observed as sole abnormalities.

Characteristics, diagnoses, and karyotype formulas of our patients are shown in Table 1. The distribution of structural aberrations of chromosome 1p in our cases is presented in Table 2. The distribution of hematologic malignancies by breakpoints in chromosome 1 ideogram is demonstrated in Figure 1. The most commonly observed breakpoint was 1p36 in our study. It was detected in 12 cases, 6 of whom had CML while 2 had AML, 2 had MM, 1 had AA, and 1 had ITP. Examples of deletion and rearrangements at 1p36 are shown in Figure 2.

Table 1: Patient characteristics and karyotype formulas

Case	Age, years	Gender	Clinical diagnosis	Karyotype
1	35	F	AML M2	44~46,XX,t(1;3)(p36;p21)[21],-21[3],+mar1[3],+mar2[2][cp21]
2	57	F	MM	38~46,X,-X[6],add(1)(p16)[6],inv(11)(p15;q11)[3], add(19)(p or q13)[2],+mar1[6],+mar2[3][cp6]/46,XX[10]
3	70	M	MDS	46,XY,t(1;2)(p36;q11)[2]/46,XY[4]
4	55	F	CML	45~46,XX,der(1)(1qter→1q12::1p36→1qter),t(9;22)(q34;q11)[36] [cp36]/46~48,XX,t(9;22)(q34;q11)[4],+der(22)t(9;22)(q34;q11)[3], +mar[4][cp4]/46,XX,t(9;22)(q34;q11)[10]
5	51	M	CML	44~46,XY,t(1;10)(p36;q21)[cp4]/46,XY[10]
6	86	M	ITP	40~46,XYder(1)t(1;1)(p36;q21)[cp10]/46,XY[7]
7	80	M	CML	36~50,X,-Y[20],add(1)(p36)[17],del(2)(q21q23)[17], add(3)(p21)[17],-4[3],-5[3],add(5)(q22?)[5],del(6)(q13)[17],-7[3], add(8)(q23)[16],-10[6],del(11)(q23)[16],-13[16],add(15)(q25)[10], -18[5],-19[3],-20[3],-22[3],+r[3],+r[1],+mar1[17], +mar1[8],+mar1[1],+mar2[11],+mar2[3],+mar3[7], +mar4[4],+mar5[9],+mar6[3],+mar7[3],+mar8[2], +mar9[3],+mar10[5],+mar10[2],1~2dmins[3][cp26]/46,XY[10]
8	31	M	AA	46,XY,inv(1)(p36q41)[3]/46,XY[12]
9	55	F	AML recurrence	36~46,XX,add(1)(p34)[13],add(1)(p36)[11],-9 [3],der(9)t(9;?)(q?;?) [14],del(11)(q13)[24][cp24]/46,XX[2]
10	69	M	MM	49~51,Y,del(X)(q25)[4],add(1)(p36)[4],del(4)(q32)[4],+5[2], add(5)(p13)[2],+6[2],add(6)(q12)[4],add(7)(p22)[4], add(9)(q34)[4],add(10)(q25)[3],-13[4],i(15)(q10)[4],+mar1[4], +mar2[4],+mar3[4],+mar4[3][cp4]/46,XY[9]
11	76	F	CML	42~44,XX,t(1;3)(p36;q21)[17],-15[3][cp17]
12	66	M	CML	39~47,XY,add(1)(p36)[4],t(3;22)(q28;q11)[12], +der(22)t(3;22)[3][cp12]/46,XY[3]
13	61	M	CML	45~46,XY,t(1;3)(p36;q21)[cp7],del(2)(p12)[3],-7[6], i(15)(q10)[2] [cp7]
14	64	M	MDS	45~47,XY,del(1)(p35)[cp9]/45,X,-Y[4]/46,XY[7]

Table 1: Continue

Case	Age, years	Gender	Clinical diagnosis	Karyotype
15	70	M	DLBCL	39~44,XY,+1[2],del(1)(p32p36.1)[9],del(1)(p31)[3], t(1;9)(p31;p22)[2],-6[15],add(6)(p25)[15],add(7)(p22)[15], del(8)(q24.1)[15],del(9)(q22)[13], add(9)(p24)[11], add(10) (q26)[15],+11[15],-13[3],add(14)(q32)[15] -15[11],-16[6],add(16)(p13.3)[15],-17[15],-18[5], add(18)(p11.3)[10],-19[7], add(19)(p11)[6],-20[3], add(22)(p11.2)[cp15]
16	75	M	B-ALL	45~50,XY,+1[12],del(1)(p22)[12],t(5;8)(p13?;q13?)[12],+7[8], t(7;8)(q11?;q11?)[10],-8[12],-9[10],add(9)(p23?)[11],+12[11], t(12;13)(q12;q12)[12],-13[12],add(14)(q32)[12],add(18)(q21?)[8], +19[10],der(19)t(19;?)(p13?;?)[12],+mar1[11],+mar2[5][cp12] / 46,XY[24]
17	39	F	Follicular NHL	46~50,XX,+X[4],+1[3],del(1)(p21)[4],+3[3],+7[6],add(8)(q23)[3], -9[6],add(14)(q32)[4],+mar1[4],+mar2[3][cp6]
18	56	M	MDS	39~44,(XY),+1[15],del(1)(p11)[16],-5[17],-7[17],-12[17],-14[4], -15[9],-16[17],-17[3],-19[17],-20[6],-22[17],+mar1[17],+mar3[17], +mar4[5],+mar5[2],+mar6[14],+mar7[2],+mar8[3][cp17]

MDS: Myelodysplastic syndrome, AML: Acute myeloid leukemia, AML M2: acute myeloblastic leukemia with maturation, ALL: acute lymphocytic leukemia, B-ALL: B cell acute lymphocytic leukemia, CML: Chronic myeloid leukemia, MM; Multiple myeloma, ITP: Idiopathic thrombocytopenic purpura, DLBCL: Diffuse large B-cell lymphoma, NHL: Non-Hodgkin's lymphoma, AA: Aplastic anemia

Table 2: Distribution of chromosome 1p aberrations in our cases

1p abnormalities	MDS	AML	ALL	CML	MM	ITP	DLBCL	Follicular NHL	AA
del(1)(p32p36)							1		
del(1)(p35)	1								
del(1)(p22)			1						
del(1)(p21)								1	
del(1)(p11)	1								
add(1)(p36)		1		2	2				
add(1)(p34)		1							
t(1;3)(p36;p21)		1							
t(1;3)(p36;q21)				2					
t(1;10)(p36;q21)				1					
t(1;2)(p36;q11)	1								
inv(1)(p36q41)									1
der(1)t(1;1)(p36;q21)						1			
der(1) (1qter→1q12::1p36→1qter)				1					

MDS: myelodysplastic syndrome, AML: acute myeloid leukemia, ALL: acute lymphocytic leukemia, CML: chronic myeloid leukemia, MM: multiple myeloma, ITP: idiopathic thrombocytopenic purpura, DLBCL: diffuse large B-cell lymphoma, NHL: Non-Hodgkin's lymphoma, AA: aplastic anemia

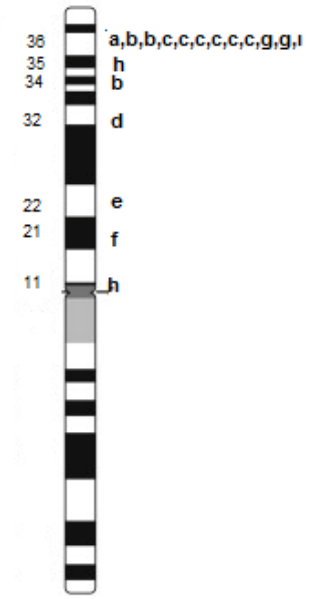

Figure 1: Distribution of hematologic malignancies by breakpoints in chromosome 1 ideogram
a: AA; b: AML, c: CML, d: DLBCL, e: ALL, f: Folicular NHL, g: MM, h: MDS, ı:ITP

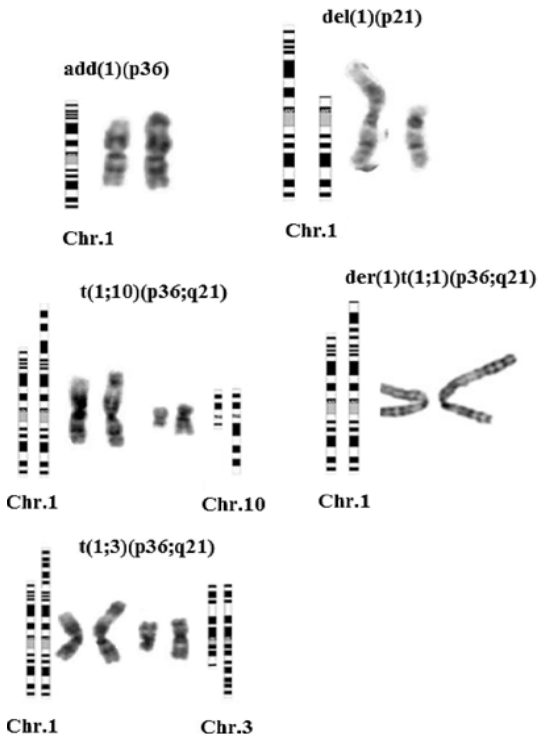

Figure 2: Examples of deletion and rearrangements at 1p36 with ideograms
Chr: Chromosome, add: Addition, del: Deletion, t: Translocation, der: Derivative

DISCUSSION

Structural aberrations of the short arm of chromosome 1 (from 1p11 to 1p36) involving balanced and unbalanced translocations, inversions, deletions, and duplications are very common in most hematologic malignancies. 1p contains numerous genes that are important in oncogenesis (4, 5, 9, 20, 21). *PRDM16* encodes a zinc-finger transcription factor, and this protein is known to induce the development of myeloid leukemia. It is an important predictive marker for poor prognosis in adult AML patients (6, 10, 20, 21). Deletion of the *CDC2L1* gene locus, which codes a protein kinase implicated in apoptotic signaling, has been observed in 88.5% of NHL cases containing 1p36 abnormalities (4). TNFRSF14 is a tumor necrosis factor receptor family member and a tumor suppressor whose loss promotes germinal center lymphomagenesis. *TNFRSF14* mutations tend to occur later in the pathogenesis of FL (7). Additionally, tumor suppressor genes such as DFFB, PRKCZ, MMP23B, ERRF11, and the SK1 proto-oncogene have been reported to be associated with different solid tumors localized to 1p36 (12-16).

The most commonly observed abnormality was add(1)(p36) in our series. We detected this addition in five patients (one AML, two CML, and two MM cases). The add(1)(p36) finding was also reported by Duhoux et al. as the most frequent abnormality in their hematologic malignancy series with 1p36 aberrations (22). Yoshida et al. also reported a case with add(1)(p36) in a complex karyotype of an AML case (2).

The other chromosomal addition in our study was add(1)(p34) in an AML patient. We could not find another case with this abnormality in our literature and database research (23).

Deletions that involve the 1p36 region are frequently seen in both myeloid and lymphoid neoplasms. We detected five patients with deletions at different breakpoints from 1p11 to 1p36, which were: del(1)(p11) and del(1)(p35) in MDS, del(1)(p21) in follicular non-Hodgkin's lymphoma, del(1)(p22) in ALL, and del(1)(p32p36) in DLBCL. Although there was no report for del(1)(p11) in our search of the literature, we found two reports of MDS cases with the 1p11 breakpoint in translocations with different chromosomes, namely der(1)t(1;16)(p11;p11.1) (24), and t(1;7)(p11;p11) (25). While not reported in the literature/database as del(1)(p35), we found a deletion of the region within an interstitial deletion as del(1)(p34p36) in an MDS case in our database research (23). We detected deletion of 1p21 in one patient with follicular non-Hodgkin's lymphoma. There are reports of the same deletion in follicular lymphoma patients (26, 27). We observed a del(1)(p22) in ALL, and Carbone et al. reported a FAB-L1 ALL case with del(1)(p22), too (28). We had a DLBCL case with an interstitial deletion of del(1)(p32p36). Belaud-Ro-

tureau et al. showed a terminal deletion at 1p36 in four of their large B cell lymphoma patients (29).

Patients with loss of heterozygosity (LOH) of 1p in MDS, AML, and MM are reported to have poor survival (4, 6, 30-32). Several researchers working on MDS reported that chromosome 1 abnormalities are often involved in the cytogenetic evolution of disease (33, 34). Frequent observations of 1p deletions in both hematologic malignancies and solid tumors suggest the presence of tumor suppressor genes encoded in this region. Most 1p deletions involve large regions; therefore, multiple tumor-suppressive genes might be lost in this setting (34-36). Various research groups have reported that deletion 1p correlates with tumor histopathology, tumor evolution, and disease progression (3, 37, 38). Because numerous genes with a potential role in malignant transformation are located at 1p22~1p36, detection of these deletions in chromosome analyses may indicate progression of the malignancy (30, 39-41). Süreyya et al. also reported in their case series that MM cases in which they detected deletions between the p21-p36 regions had short survival times (42).

We observed reciprocal translocation of 1p with other chromosomes in five patients as follows: t(1;3)(p36;q21) in 2 patients with CML, t(1;3)(p36;p21) in one patient with AML M2, t(1;2)(p36;q11) in one patient with MDS and, t(1;10)(p36;q21) in one patient with CML.

The t(1;3)(p36;q21) finding, which we observed in two CML patients, one of whom also had metastatic lung cancer, is a prominent finding in hematologic malignancies (9, 15, 43).

We detected t(1;3)(p36;p21) in one patient with AML M2. Sato et al. reported the finding of t(1;3)(p36;p21) in various hematologic malignancies such as MDS, AML, and CML. In the same way, we found t(1;3)(p36;p21) together with structural and numerical abnormalities of other chromosomes in our case. This patient was in the high-risk group based on the International Prognostic Scoring System (IPSS) and had a poor prognosis. Bai et al. also reported that they had AML patients with the same finding and poor prognosis (44).

We also observed t(1;2)(p36;q11) in one patient with MDS and t(1;10)(p36;q21) in one patient with CML. We could not find the exact match of these abnormalities in our literature search.

We identified derivative chromosomes in two cases. One of them was der(1)t(1;1)(p36;q21) in an ITP case and the other was der(1)(1qter→1q12::1p36→1qter) in a CML case, Duhoux et al. reported t(1;1)(p36;q12) as the most common anomaly in hematologic cancers (9). The inv(1)(p36q41) we detected in an AA case was the only inversion in our series, and we could not find the same inversion in the literature.

The distribution of breakpoints in different 1p abnormalities was remarkable in our study. In total, 12 out of 18 1p breakpoints were 1p36. However, while 1p breakpoints aggregated on 1p36 in all translocations, there was only one 1p36 breakpoint in five deletions, and it was one of the two breakpoints of the interstitial deletion.

It is also noteworthy that rearrangements involving 1p36 were observed mostly in CML cases in our series. Six out of 12 patients with 1p36 anomalies were CML, while others had different diagnoses.

The 1p36 breakpoint is well known as a hot spot for cancer-related chromosome rearrangements. There are different reports in the literature with rearrangements of 1p36 in different malignancies, and multiple genes in 1p36 are reported to have prognostic effects in various neoplasms. These genes are significantly associated with worse treatment response to targeted therapies and poor prognosis (4, 45-49). The PR/SET domain containing 16 (PRDM16), one of the genes that reside on 1p36, is fused with AF3p21 at 3p21 in t(1;3)(p36;p21), while with RPN1 (Ribophorin 1) at 3q21 in t(1;3)(p36;q21) in AML and MDS (43,50). It is reported that translocations of PRDM16 with RPN1 at 3q21 lead to its overexpression of PRDM16, and affected patients (AML, MDS, and CML) have a poor response to chemotherapy as well as poor prognosis (9). Sato Y et al. reported the finding of t(1;3)(p36;p21) in various hematologic malignancies such as MDS, AML, and CML. Also, they declared that the karyotypes in all cases were complex, and the t(1;3)(p36;p21) had been found together with structural and numerical abnormalities of other chromosomes. It has been observed that the prognosis of the patients varies from case to case (1).

Even in the new era of Next Generation Sequencing (NGS), cytogenetics, which is the only technique capable of detecting balanced chromosome abnormalities while observing the genome as a whole, remains the gold standard for the evaluation of hematologic malignancies. However, due to the technical difficulties of cancer cytogenetic studies and new developments in molecular techniques, the addition of new karyotype findings to the literature has been decreasing in recent years. Therefore, it is crucial to add cytogenetic results to the literature whenever possible, especially with complete karyotype formulas, which is the only way to access rare and previously unmentioned abnormalities (38).

CONCLUSION

In conclusion, we demonstrated rearrangements of 1p in 18 cases with hematologic malignancies by conventional cytogenetic methods and compared our results with

the literature. 1p rearrangements are seen as one of the main irregularities in myeloid and lymphoid hematologic malignancies. The frequency of these abnormalities in hematologic cancers implies the importance of this genomic region in carcinogenesis and disease progression. Survival data suggest that patients with myeloid malignancy and 1p rearrangements have a poor prognosis (9). Finally, these abnormalities can serve as biomarkers for prognosis when detected during routine cytogenetic follow-up of the patients. Therefore, the application of conventional cytogenetics during follow-up as well as at the time of diagnosis continues to be important in predicting the prognosis.

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INVESTIGATION OF COPING STRATEGIES AND SOCIAL SUPPORT OF CANCER PATIENTS IN TIMES OF GLOBAL CRISIS

KANSER HASTALARINDA KÜRESEL KRİZ DÖNEMLERİNDE SOSYAL DESTEK VE BAŞA ÇIKMA STRATEJİLERİNİN RUH SAĞLIKLARI ÜZERİNDEKİ KORUYUCU ETKİSİNİN ARAŞTIRILMASI

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ABSTRACT

Objective: This study aimed to investigate the role of social support and coping strategies in moderating the psychological distress of cancer patients during high-stress health crises.

Material and Method: From June 2022 to January 2023, we collected data from 206 cancer patients and 202 healthy controls at Florence Nightingale Hospital. Minimizing the immediate psychosocial impacts and aiming to investigate more chronic, longer-term psychological responses, during a 'return to normalcy' participants completed the Beck Anxiety and Depression Inventories, Fear of COVID-19 Scale, Brief Coping Orientation to Problems Experienced Questionnaire, and Multidimensional Scale of Perceived Social Support.

Result: Cancer patients reported higher levels of anxiety and depression than healthy controls (13.73±7.18 vs. 11.15±7.70, 12.94±5.39 vs. 9.98±6.93, p<0.001). Higher perceived social support, especially from family (b=-0.043; p=0.024 for anxiety, b=-0.028; p=0.044 for depression) and significant others (romantic or life partners) (b=-0.021; p=0.028 for anxiety), moderated the relationship between fear and mental health outcomes, reducing the severity of anxiety and depression symptoms. In contrast, the use of maladaptive coping strategies was found to amplify these outcomes (b=0.162; p<0.001 for anxiety, b=0.1307; p<0.001 for depression).

Conclusion: Being the first study in the literature to investigate the buffering role of social support and coping mechanisms on fear, depression, and anxiety within a cancer patient cohort, it

ÖZET

Amaç: Bu çalışmada, küresel sağlık krizleri sırasında kanser hastalarının karşılaştıkları psikolojik problemleri hafifletmede sosyal destek ve başa çıkma stratejilerinin rolünün araştırılması amaçlanmıştır.

Gereç ve Yöntem: Haziran 2022 - Ocak 2023 tarihleri arasında Florence Nightingale Hastanesi'nde 206 kanser hastası ve 202 sağlıklı kontrol çalışmaya dahil edilmiştir. Ani psikososyal etkileri en aza indirgemeyi ve daha kronik, uzun vadeli psikolojik tepkileri araştırmayı amaçlayarak 'normale dönüş' döneminde katılımcılara Beck Anksiyete ve Depresyon Envanterleri, COVID-19 Korkusu Ölçeği, Çok Boyutlu Algılanan Sosyal Destek Ölçeği ve Başa Çıkma Stratejileri Anketi-Kısa Formu uygulandı.

Bulgular: Kanser hastalarının anksiyete ve depresyon düzeyleri sağlıklı kontrollere göre daha yüksek saptanmıştır (13,73±7,18 vs. 11,15±7,70; 12,94±5,39 vs. 9,98±6,93, p<0,001). Özellikle aile (anksiyete için b=-0,043; p=0,024, depresyon için b=-0,028; p=0,044) ve özel insan (eş, romantik partner) (anksiyete için b=-0,021; p=0,028) tarafından görülen sosyal desteğin, korkunun yol açtığı anksiyete ve depresyon semptomlarının şiddetini hafiflettiği tespit edilmiştir. Buna karşılık, uyumsuz başa çıkma stratejilerinin kullanımının bu düzeyleri daha da kötüleştirdiği saptanmıştır (anksiyete için b=0,162; p<0,001; depresyon için b=0,1307; p<0,001).

Sonuç: Bu çalışma literatürde bir ilk olarak kanser hastalarında, global kriz sonrasında korku, depresyon ve anksiyete üzerinde sosyal desteğin ve başa çıkma mekanizmalarının tamponlayıcı rolünü araştıran bir çalışma olması sebebiyle klinisyenler için

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provides valuable insights for practitioners. These findings are of practical relevance to clinicians aiming to improve mental health among cancer patients in times of global crises, emphasizing the importance of fostering social support and promoting adaptive coping strategies.

Keywords: Anxiety, coping strategies, depression, psycho-oncology, social support

değerli bilgiler sunmaktadır. Kanser hastalarınca algılanan sosyal desteğin güçlendirilmesi ve uyumlu başa çıkma stratejilerini geliştirmesinin, kriz dönemlerinde hastaların biyopsikososyal yönetimi açısından terapötik odak noktası olarak değerlendirilmesi önem arz etmektedir.

Anahtar Kelimeler: Anksiyete, baş etme stratejileri, depresyon, psiko-onkoloji, sosyal destek

INTRODUCTION

As our world becomes increasingly interconnected, we are confronted with global health crises that have the potential to dramatically influence societies and healthcare systems, as evidenced by the recent COVID-19 pandemic that originated in Wuhan, China, in December 2019 (1-3). The overwhelming nature, along with the uncertainty regarding the pandemic's long-term impacts, amplify the fear and anxiety associated with such widespread health crises (4). Certain populations, such as cancer patients, face heightened risks during pandemics due to compromised immunity from disease progression, treatment side effects, and malnutrition. Existing evidence indicates a worse prognosis for COVID-19 infection among these individuals (4-8).

A pressing concern arising from this is the emotional well-being of cancer patients during such health crises. Events like pandemics can magnify feelings of uncertainty, helplessness, and fear of illness or death in these patients, exacerbating the emotional distress experienced by the general population. Moreover, necessary medical visits for diagnosis, treatment planning, and follow-ups can further heighten anxiety (9-11).

Prior research emphasizes the role of social support and positive coping mechanisms in reducing anxiety and depression during health crises, as well as in enhancing overall psychosocial well-being (12). Perceived social support can mitigate the impact of stressful life events, including the emotional distress experienced by cancer patients and individuals with other health conditions (13). However, social isolation, which is often necessitated by a pandemic, can exacerbate emotional distress in cancer patients, potentially affecting treatment adherence and overall quality of life (14).

In light of this, our study aimed to assess levels of depression and anxiety in cancer patients during a significant health crisis. Specifically, we explored the potential mediating roles of coping strategies and perceived social support in the relationship between health crisis-related fear and symptoms of depression and anxiety. We hypothesized that perceived social support and effective coping strategies could buffer the adverse psychological effects of fear associated with significant health crises among this vulnerable population. While our study focused on the most recent global health crisis, we aimed to shed light on potential psychological responses to other similar health crises in the future. This underscores the vital role of social support and adaptive coping strategies in managing fear and uncertainty during such crises.

MATERIAL and METHODS

This research, sanctioned by the Ethics Committee of Istanbul Bilgi University (Date: 26.05.2022 Project no: 2022-40034-70), conformed to the principles of the Declaration of Helsinki. All involved parties provided their consent in writing.

Design, patients, and recruitment

The study included 206 cancer patients and 202 healthy controls, matched for age, gender, education level, and employment status. Controls, relatives, or friends of healthcare workers at Florence Nightingale Hospital, were not caregivers, had no chronic diseases, or family members diagnosed with cancer. Cancer patients were recruited from the Chemotherapy Unit of Florence Nightingale Hospital between June 2022 and January 2023. To minimize the immediate psychosocial impacts of the pandemic and to study more chronic, longer-term psychological responses, patients were recruited approximately two years after the pandemic's peak, during a period often described as a 'return to normality'. Eligible cancer patients had either been living with their diagnosis for at least two years or had undergone chemotherapy during the pandemic period, and ensured that their psychological responses were not immediate reactions to the acute crisis of diagnosis or initial treatment but rather represented their adaptive processes and coping mechanisms.

To be included in the study, participants had to be at least 18 years old and capable of providing written informed consent. Those with dementia or any other organic neurological conditions that might interfere with their ability to provide informed consent or to complete the study measures were excluded from participation.

Measurements

Participants completed a Sociodemographic Data Form, Fear of COVID-19 Scale, the Brief Coping Orientation

to Problems Experienced (Brief-COPE) Questionnaire, the Multidimensional Perceived Social Support Scale (MPSSS), the Beck Depression Inventory (BDI), and the Beck Anxiety Inventory (BAI).

The Fear of COVID-19 Scale, developed by Ahorsu et al., was used to assess the fear levels and the associated psychological stress caused by COVID-19, serving as a representation of fear induced by a recent global health crisis. Higher scores indicate a higher fear level. In this study, the internal consistency of the scale was found to be 0.82 (15). A higher score on the scale indicates a higher level of fear. Based on certain research protocols and following a cut-off point of 3 for each question, a total score of 21 was used as a threshold in our study to distinguish between individuals with low and high fear of COVID-19 (16). This served as a specific measure of stress and fear levels associated with the most recent global health crisis, providing a real-world context for our exploration of potential responses to future, similarly stressful situations.

The Beck Depression Inventory (BDI), a 21-item self-report questionnaire, assesses the severity of depression symptoms. Higher scores indicate more severe symptoms. It has been validated and adapted to Turkish (17). In our study, we found a high Cronbach's alpha of 0.877, indicating strong internal consistency of the BDI items in our sample.

The Beck Anxiety Inventory (BAI) measures the severity of anxiety symptoms in adults. Higher scores indicate greater symptom severity. The BAI has been validated and adapted to Turkish (18). In this study, we found a Cronbach's alpha of 0.893 indicating high internal consistency of the BAI items in our sample.

The Turkish variant of the Brief Coping Orientation to Problems Experienced (Brief COPE) was used to evaluate coping strategies. This is a more succinct version of the COPE inventory Higher scores denote a higher inclination towards using a given strategy. These strategies fall into two categories: adaptive coping strategies (acceptance, planning, active coping, use of instrumental support, positive reframing, use of emotional support, humor, and religious coping) and maladaptive coping strategies (self-blame, denial, self-distraction, venting, disengagement, and substance use). The Turkish validity and reliability study of the scale was conducted by Bacanlı et al., indicating good psychometric properties (19). In our study, we found that the Cronbach's alpha values for the sub-scales were higher than 0.60, indicating acceptable to good internal consistency.

The Multidimensional Perceived Social Support Scale (MPSSS) evaluated social support across three dimensions: family, friends, and significant others. Higher scores mean higher perceived support. It has been validated and adapted to Turkish (20). High internal consistency was found in our study for all three dimensions with Cronbach's alpha values above 0.88.

Statistical analysis

Statistical analysis was carried out using SPSS 22. Normality checks were conducted with the Kolmogorov-Smirnov test and kurtosis skewness values. Depending on data distribution, correlations between variables were assessed with Pearson's or Spearman's tests. Group comparisons were made with independent samples t-test or Mann-Whitney U-test. To identify independent predictors of anxiety or depression in cancer patients, regression analyses were performed. The moderating effects of social support and coping styles on the relationship between fear and anxiety/depression symptoms were evaluated using the PROCESS for SPSS Macro(Model 1). The direct and mediated effects of fear on depression and anxiety were examined using process modeling, with bootstrapping used for non-normal distributions. The significance level was set at $p < 0.05$. The analysis included only complete questionnaires, ensuring no missing data.

RESULTS

The study comprised 206 cancer patients (average age: 60.45±12.40 years, male/female ratio: 86/120) and 202 healthy controls (average age: 57.34±13.23 years, male/female ratio: 87/115). No significant differences were observed between the cancer patient and healthy control groups in terms of sex (p=0.78), marital status (p=0.21), and education levels (p=0.89).

Among the cancer patient group, female patients had significantly higher BDI scores than male patients (13.73±5.16 vs 11.83±5.53, p=0.01). No significant differences were observed in BDI and BAI scores for cancer stage, recurrence, therapy, history of operation, or marital status.

Cancer patients generally showed significantly higher scores than healthy controls in the Fear of COVID-19 Scale, BAI, BDI, and MPSSS (Table 2).

For individuals with a Fear Scale score below 21, cancer patients displayed significantly higher mean BAI and BDI scores than healthy controls (BAI=13.21 vs. 10.33, p=0.003; BDI=12.66 vs. 8.96, p<0.001). However, for those with a Fear Scale score of 21 or above, no notable differences in BAI or BDI scores were observed between cancer patients and the healthy control group (Table 3).

In the cancer cohort, negative correlations were found between BAI and BDI scores and MPSSS subscores, as well as certain Brief-COPE subscores. However, BAI and

Table 1: Sociodemographic and Clinical Features

Age mean±SD		**Cancer patients (n=206) n (%)**	**Healthy controls (n=202) n (%)**	**p-value**
		60.45±12.40	**57.34 ± 13.23**	**0.01**
Gender	Female	120 (58.3)	115 (56.9)	0.78
	Male	86 (41.7)	87 (43.1)	
Marital status	Single	8 (3.9)	18 (8.9)	
	Married	170 (82.5)	160 (79.2)	0.21
	Divorced	11 (5.3)	10 (5.0)	
	Widow	17 (8.3)	14 (6.9)	
Education	Primary school	44 (21.4)	48 (23.8)	0.89
	Secondary school	24 (11.7)	22 (10.9)	
	High school	61 (29.6)	64 (31.7)	
	College	67 (32.5)	61 (30.2)	
	PhD	10 (4.9)	7 (3.5)	
Stage of the disease	2	22 (10.7)		
	3	44 (21.4)		
	4	140 (68.0)		
Recurrence	Yes	62 (30.1)		
	No	144 (69.9)		
Treatment history	Chemotherapy	206 (100)		
	Hormonotherapy	28 (13.6)		
	Radiation therapy	81 (39.3)		
	Surgery	124 (60.2)		
Diagnosis of cancer type	Breast	54 (26.2)		
	Lung	38 (18.4)		
	Colorectal	33 (16.0)		
	Gastric	18 (8.7)		
	Pancreatic	11 (5.3)		
	Head and neck	10 (4.9)		
	Other*	42 (20.4)		

*Ovarian, testicular, bladder cancer; cholangiocarcinoma, mesothelioma; Numbers indicate mean ± Standard Deviation or n (%) and p value denotes Student's t test or chi square test where appropriate.

BDI scores were positively correlated with the Self Blame subscores (Table 4).

Univariate regression analysis identified fear, MPSSS subscores, and certain coping strategies as significant predictors of anxiety and depression levels. Following multivariate analysis, these predictors were narrowed down to fear, MPSSS significant others, and select coping strategies for BAI, and fear, MPSSS friends, significant others, and specific coping strategies for BDI (Supplementary Table 1).

Model 1, including fear, MPSSS family, significant other, active coping, acceptance, and religious coping as independent variables, accounted for 65% of the variance in BAI scores ($F(4,201)= 27582$, $p<0.001$). Model 2, comprising fear, MPSSS significant other, active coping, acceptance, positive reframing, use of instrumental support, and acceptance as independent variables, explained 56% of the variance in BDI scores ($F(4,201)= 22696$, $p<0.001$).

Mediator analyses were conducted to investigate the indirect effects of fear on depression and anxiety symptoms through perceived social support and coping styles. MPSSS family showed a significant and negative moderating effect on the relationship between fear and depression and anxiety symptoms severity ($b=-0.028$, $t=-2.020$, $p=0.044$, $R2=0.08$, $\Delta R2=0.02$ for depression; $b=-0.043$, $t=-2.020$, $p=0.024$, $R2=0.08$, $\Delta R2=0.02$ for anxiety) (Figure 1,2).

Maladaptive coping styles demonstrated a significant and positive moderating effect on the relationship between fear and severity of depression and anxiety symptoms ($b=0.1307$, $t=6.581$, $p<0.001$, $R2=0.22$, $\Delta R2=0.16$ for depression; $b=0.1620$, $t=6.036$, $p<0.001$, $R2=0.20$, $\Delta R2=0.14$ for anxiety) (Figure 1,2).

MPSSS significant other also showed a significant and negative moderating effect on the relationship between fear and severity of anxiety symptoms ($b=-0.021$, $t=2.222$, $p=0.028$, $R2=0.61$, $\Delta R2=0.09$) (Figure 2).

Table 2: Comparison of Scale Scores between cancer patients and healthy controls

	Cancer patients (n=206)	Healthy controls (n=202)	p-value
Beck anxiety inventory	13.73±7.18	11.15±7.70	<0.001
Beck depression inventory	12.94±5.39	9.98±6.93	<0.001
Fear of COVID-19 Scale	21.71±6.34	16.25±4.27	<0.001
MPSSS	61.85±8.69	48.89±7.33	<0.001
MPSSS family	22.34±3.71	17.62±3.89	<0.001
MPSSS friends	20.08±4.13	18.34±3.98	<0.001
MPSSS significant other	19.43±5.50	12.93±4.50	<0.001
Adaptive COPE			
Active coping	4.34±1.73	4.92±1.76	0.001
Planning	2.53±0.75	5.93±1.18	<0.001
Positive reframing	2.63±0.94	4.54±1.10	<0.001
Use of instrumental support	5.72±1.48	3.56±1.25	<0.001
Use of emotional support	6.19±1.18	5.85±1.08	0.003
Acceptance	6.82±1.69	5.26±1.55	<0.001
Religious Coping	6.20±1.36	6.31±1.44	0.45
Maladaptive COPE			
Humor	2.93±0.98	5.47±1.50	<0.001
Denial	2.47±0.73	4.38±1.45	<0.001
Disengagement	2.83±0.92	6.18±1.54	<0.001
Self–distraction	4.21±1.65	4.35±1.21	0.33
Venting	3.26±1.15	5.33±1.57	<0.001
Substance use	2.29±0.58	4.63±1.66	<0.001
Selfblame	4.12±1.09	4.04±1.67	0.58

Brief-COPE: Brief coping orientation to problems experienced questionnaire, MPSSS: Multidimensional Perceived Social Support Scale

Table 3: Comparison of Anxiety (BAI) and Depression (BDI) Levels in Cancer Patients and Healthy Controls Based on Fear of COVID-19 Scale Score Threshold

		Fear of COVID-19 Scale Score	Number of patients	Mean	Standard deviation	p-value
BAI	Cancer patients	<21	86	13.21	7.28	0.003
	Healthy controls		165	10.33	7.04	
BDI	Cancer patients	<21	86	12.66	5.73	<0.001
	Healthy controls		165	8.96	6.04	
BAI	Cancer patients	≥21	120	14.11	7.10	0.68
	Healthy controls		37	14.78	9.39	
BDI	Cancer patients	≥21	120	13.13	7.10	0.35
	Healthy controls		37	14.54	8.69	

BAI: Beck Anxiety inventory, BDI: Beck depression inventory

Table 4: Correlation Analysis of Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Multidimensional Perceived Social Support Scale (MPSSS), Brief Coping Orientation to Problems Experienced (Brief-COPE) Questionnaire Scores and Subscores

	BDI	BAI
BDI	1	0.173*
BAI	0.173*	1
MPSSS	-0.584**	-0.514**
MPSSS family	-0.176*	-0.146
MPSSS friends	-0.374**	-0.309**
MPSSS significant other	-0.525**	-0.618**
Adaptive coping orientation to problems experienced subscores		
Active Coping	-0.320**	-0.208**
Planning	-0.108	-0.152*
Positive Reframing	-0.275**	-0.227**
Use of Instrumental Support	-0.244**	-0.202**
Use of Emotional Support	-0.055	-0.130
Acceptance	-0.341**	-0.139*
Religious Coping	-0.219**	-0.246**
Humor	-0.005	-0.037
Maladaptive coping orientation to problems experienced subscores		
Denial	0.027	0.001
Disengagement	-0.146*	-0.177*
Self–distraction	0.088	0.043
Venting	-0.099	-0.142*
Substance Use	-0.037	-0.004
Selfblame	0.263**	0.182**

*p<0.05, **p<0.01, MPSSS: The Multidimensional Perceived Social Support Scale, BDI: The beck depression inventory, BAI: The beck anxiety inventory

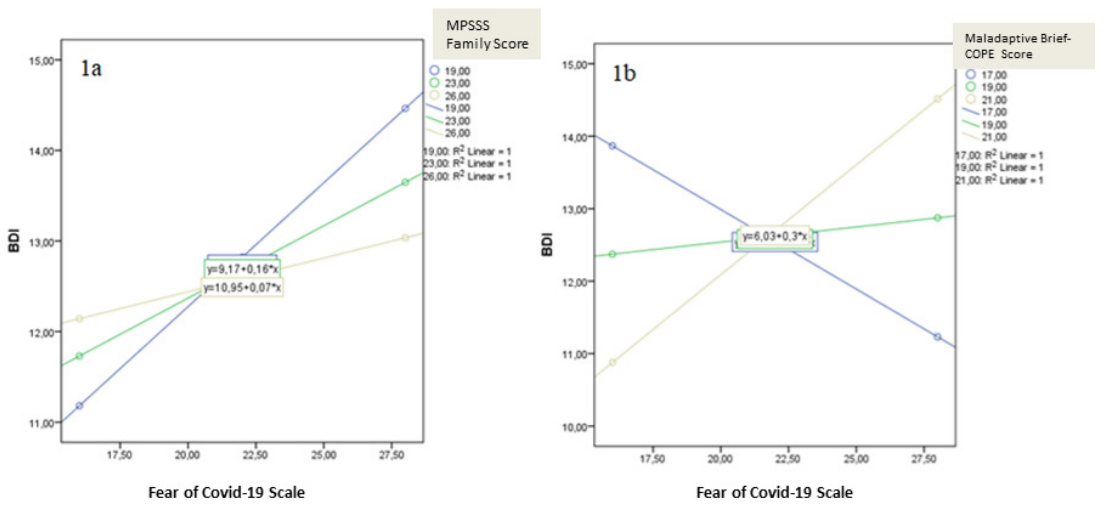

Figure 1: Interaction Effects of Perceived Social Support from Family (1a) and Maladaptive Coping Styles (1b) on the Relationship between Fear of COVID-19 and Depression Symptom Severity
Brief-COPE: The Brief Coping Orientation to Problems Experienced, MPSSS: The Multidimensional Perceived Social Support Scale, BDI: The beck depression inventory, BAI: The beck anxiety inventory

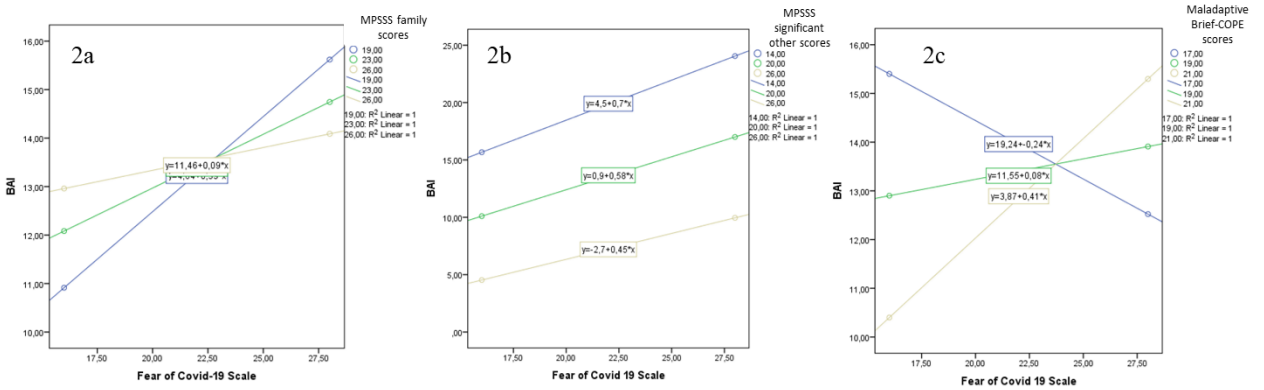

Figure 2: Interaction Effects of Perceived Social Support from Family (2a), from Significant Others (2b), and Maladaptive Coping Styles (2c) on the Relationship between Fear of COVID-19 and Anxiety Symptom Severity
Brief-COPE: The Brief Coping Orientation to Problems Experienced, MPSSS: The Multidimensional Perceived Social Support Scale, BDI: the beck depression inventory, BAI: The beck anxiety inventory

DISCUSSION

This research explores the psychological repercussions of global crises on cancer patients as a vulnerable group, using the pandemic as the current context. Our key findings underline the need for targeted interventions to support their mental health, revealing that cancer patients exhibited higher levels of fear, anxiety, and depression related to health crises compared to healthy controls. We also found that adaptive coping and strong social support were associated with reduced anxiety and depression among cancer patients, thus playing a protective role. Importantly, these factors, along with fear, accounted for a significant portion of the variance in anxiety and depression scores. Additionally, our mediation analyses revealed that social support and maladaptive coping styles moderated the relationship between fear and the severity of anxiety and depression symptoms.

Cancer patients reported higher levels of fear, anxiety, and depression due to the crisis compared to healthy controls. However, a stronger social support network and adaptive coping strategies reduced the levels of anxiety and depression, indicating their protective role during crises. These factors accounted for a significant portion of the variance in anxiety and depression scores. The association between high perceived social support and lower depression and anxiety levels aligns with previous studies (21-23).

Importantly, patients with a lower fear of the global crisis (as measured by fear scores less than 21) still experienced higher levels of anxiety and depression, suggesting the stress of cancer diagnosis amplifies the psychological effects of the crisis. This underscores the need for robust mental health support for cancer patients, particularly during times of global uncertainty (24).

Interestingly, the differences in anxiety and depression levels between cancer patients and healthy controls diminished among those with higher fear scores, suggesting that extreme fear might act as a dominant stressor that blurs the distinction between these two groups. This reveals the necessity to provide comprehensive support for both vulnerable groups and the general population during crisis times.

The study also found that low levels of perceived social support correlated with higher levels of depression among cancer patients, emphasizing the importance of social support networks during times of health crises, aligning with previous studies that highlight social support as a crucial factor in adjustment to illness (25-27). Identifying patients struggling to receive social support can enable referrals to appropriate support networks and programs, thereby improving their quality of life. Furthermore, maladaptive coping styles like "Self Blame" were positively correlated with anxiety and depression in line with the literature (28), highlighting the need to promote adaptive coping methods in vulnerable populations.

Our study affirms social support and coping strategies buffer pandemic-induced anxiety and depression. Research indicates that social support can serve as a shield, mitigating psychological strain in periods of crisis. The buffering hypothesis posits that social support can moderate, or "buffer," the impact of stressful events on an individual's well-being (29).

Our research indicates that the level of perceived social support, particularly from family and significant others, has a substantial moderating effect on the intensity of anxiety and depression symptoms related to fear during a crisis. Specifically, higher levels of perceived social support were linked to a decrease in the severity of these symptoms, explaining a significant portion of their vari-

ance. Conversely, the use of maladaptive coping strategies intensified anxiety and depression symptoms in relation to crisis-related fear. This underscores the pivotal role of adaptive coping strategies in managing mental health symptoms during global crises.

The results from this study are not only applicable to the COVID-19 pandemic but also point towards potential impacts of future global crises. These elements may not be unique to this pandemic but pertinent in any context involving widespread fear and uncertainty, like future pandemics, epidemics, or large-scale natural disasters. The findings emphasize the pivotal role of social support and adaptive coping strategies in mitigating fear-induced mental health impacts in cancer patients, during any health crisis. Our findings provide evidence-based insights for crafting interventions for future crises. They underline the importance of ongoing research into the psychological impacts of global crises, especially on vulnerable groups, to bolster societal resilience. Notably, fostering social support networks and promoting adaptive coping strategies could help mitigate the psychological impact of health crises on cancer patients.

Limitations

The cross-sectional design limits our ability to definitively establish the causality or directionality of the observed relationships. Our reliance on self-reported measures raises potential issues such as response biases. Furthermore, the study did not control for pre-existing mental health conditions, which can significantly influence the severity of anxiety and depression symptoms.

Clinical implications

The findings underscore the need for robust mental health support during global crises. Understanding that individuals differ in their sources of support and coping strategies can inform the development of customized intervention approaches. Such strategies can enhance mental health responses during crises, aiding in better management of anxiety and depression symptoms among vulnerable groups like cancer patients.

CONCLUSION

The study illuminates the psychological challenges faced by cancer patients during global health crises. These individuals experience significantly elevated levels of anxiety and depression, pointing towards the necessity of comprehensive mental health support for these patients. Fostering social support and promoting adaptive coping strategies can help to mitigate the psychological impact of crises.

Future research should further investigate these factors in the post-crisis recovery phase, further elucidating their role in shaping mental health outcomes in vulnerable groups. Ultimately, the study emphasizes the importance of comprehensive, tailored mental health interventions that account for individual fears, social support systems, and coping mechanisms during global crises.

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IMPACT OF POSTOPERATIVE COMPLICATIONS ON PORTAL THROMBOSIS IN SPLENECTOMY PATIENTS

SPLENEKTOMİ YAPILAN HASTALARDA POSTOPERATİF KOMPLİKASYON GELİŞİMİNİN PORTAL VEN TROMBOZUNA ETKİSİ

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ABSTRACT

Objective: Venous thromboembolism is one of the significant complications after elective and emergency splenectomy. Up to 35% of portal and splenic venous thromboembolism has been reported in the first two months after splenectomy for hematologic malignancy. Our objectives were to compare emergency and elective splenectomy and their complications, and to analyze the risks on the development of portal vein thrombosis (PVT).

Material and Method: A total of 78 splenectomy cases performed between 2017-2023 and that had complete medical records were included in this study. Of these cases, 39 were emergency and 39 were elective procedures. The two groups were compared retrospectively for risks of PVT.

Result: We found a significant relationship between the development of postoperative complications and the risk of PVT (p=0.004). The risk of developing PVT in emergency cases in the post-operative 2 weeks was significantly higher than elective cases (p=0.048). Shorter operation times, larger spleen sizes, lower platelet counts and malignancy in pathology results were found to be significantly in favor of elective cases (p=0.007, p=0.004, p<0.001, p=0.001, respectively). In emergency cases, the need for RBC transfusion and complications were more frequent (p<0.001, p=0.021).

Conclusion: High-risk patients should be evaluated for prophylactic anticoagulation with low-molecular-weight heparin in the postoperative period and after discharge. Anticoagulation should be considered for emergency splenectomy, factoring in cost-benefit, and a low suspicion for venous thromboembolism

ÖZET

Amaç: Terapötik ve acil splenektomi sonrası gelişen önemli komplikasyonlardan biri venöz tromboembolidir. Hematolojik malignite nedeniyle splenektomi sonrası ilk iki ay içerisinde %35'e varan portal ve splenik venöz tromboembolizm bildirilmiştir. Bu çalışmada, acil ve elektif splenektomi operasyonlarını ve komplikasyonlarını karşılaştırarak portal ven trombozu (PVT) gelişimi üzerindeki risklerin incelenmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya 2017-2023 yılları arasında gerçekleştirilen ve kayıtları eksiksiz olan 78 splenektomi vakası dahil edildi. Bu vakalardan 39'u acil, 39'u ise elektif prosedürlerdi. İki grup portal tromboembolizm ve riskleri açısından retrospektif olarak karşılaştırıldı.

Bulgular: Ameliyat sonrası komplikasyon görülmesi ile PVT gelişimi riski arasında anlamlı bir ilişki saptanmıştır (p=0,004). Operasyon tipi olarak incelediğimizdeyse ameliyat sonrası ilk iki haftalık süreçteki acil vakalarda PVT gelişimi riski, elektif vakalara göre anlamlı ölçüde yüksek bulunmuştur (p=0,048). Ayrıca, kısa ameliyat süresi, büyük dalak boyutu, düşük trombosit sayısı ve patoloji sonuçlarında malignite olması elektif vakalar lehine anlamlı bulunmuştur (sırasıyla p=0,007, p=0,004, p<0,001, p=0,001, p=0,001). Acil vakalardaysa kan replasmanı ihtiyacı ve komplikasyonlar daha sık görülmüştür (sırasıyla p<0,001, p=0,021).

Sonuç: Yüksek riskli hastalar ameliyat sonrasındaki dönemde ve taburculuk sonrasında düşük molekül ağırlıklı heparin ile profilaktik antikoagülasyon açısından değerlendirilmelidir. Acil splenektomi vakalarında kar/zarar oranı göz önünde bulundurularak antikoagülasyon düşünülmeli ve olası venöz tromboemboli için

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should be maintained with timely investigation. In this sense, our study supports the existing data with its current results.

Keywords: Splenectomy, portal thrombosis, emergency surgery, splenomegaly

şüphe eşiği düşük tutulup erken tetkik edilmelidir. Bu anlamda çalışmamız güncel sonuçları ile mevcut verileri desteklemektedir.

Anahtar Kelimeler: Splenektomi, portal tromboz, acil cerrahi, splenomegali

INTRODUCTION

Splenectomy is performed both for diagnosis and treatment of hereditary, hematologic, and oncologic diseases, as well as in cases of unexplained splenomegaly or traumatic splenic injury. Splenectomy is the complete removal of the spleen after ligation of all the arteries and veins of the spleen, including the accessory tissues of the spleen. In addition to laparoscopic and open procedures in adult patients, partial splenectomy may be performed in children to preserve immune function, and cholecystectomy may be performed in some patient groups due to the risk of pigment stone formation (1,2).

Possible complications after splenectomy include thrombosis, thromboembolism, disruption of vascular smooth muscle structure, arterial or venous stenosis or occlusion due to vasospasm or atherosclerosis, bleeding, infection, cardiovascular events, pulmonary hypertension, and splenosis (3). In a retrospective study by van`t Riet et al, venous thromboembolism was found in 6-7% of patients after elective splenectomy (4). Venous thromboembolism includes deep vein thrombosis (DVT), portal vein thrombosis, splenic vein thrombosis, and pulmonary thromboembolism. Portal vein thrombosis is an increasingly recognized and reported complication after splenectomy (4).

The purpose of this study was to evaluate the effect of elective and emergency splenectomy and the effect of patient demographic and clinical parameters on the development of portal vein thrombosis. In addition, clinical and surgical characteristics of patients with and without postoperative complications were analyzed and compared. The risk factors for venous thromboembolism in the patient group were evaluated, and the mortality and bleeding rates of the patients were analyzed.

MATERIAL and METHODS

In our study, patients who underwent splenectomy at our university hospital, in the Department of General Surgery between 2017 and 2023, were retrospectively reviewed through electronic medical records. Patients with complete records of demographic data, pathologic data, operative notes, preoperative clinical notes, preoperative imaging, preoperative and postoperative laboratory values, treatment and follow-up data, and whose necessary permissions were obtained were included in the study. Specimen weight was evaluated by comparison with pathology reports and preoperative imaging or clinical notes.

After all the data were collected and grouped, statistical analyses were performed using SPSS ver.26.0 (IBM Corporation, Armonk, NY, USA). For continuous data, normality was assessed by Kolmogrov-Smirnov test; data with normal distribution were assessed by Student's t-test, and data with non-normal distribution were assessed by Mann-Whitney U test. Chi-square test was used to compare categorical data. The confidence interval in our study was set at 95%, and $p<0.05$ was considered statistically significant. Survival analysis was performed by the Kaplan-Meier method, and risk factors for venous thromboembolism were evaluated by regression analysis.

The collected data were divided into two groups as elective and emergency surgery patients. Age, sex, comorbidities, mean operative time, mean need for blood product replacement, platelet and INR levels, preoperative appearance, venous thromboembolism during follow-up, complications, and survival were compared between these two groups. Risk factors for venous thromboembolism were evaluated between groups and the effect of risk factors on survival was analyzed.

This study was approved by Ege University Clinical Research Ethics Committee (Date: 21.09.2023, No: 23-9.1T/39).

RESULTS

A total of 78 patients were enrolled in the study who were within the inclusion criteria. Of these patients, 39 underwent emergency surgery and 39 underwent elective surgery. Demographic data, need for a blood product replacement, preoperative hemogram parameters, the length of hospital stay, development of complications, and pathology results are summarized in Table 1.

Fifty-one patients (65.4%) had no comorbidities as shown in Figure 1. Fifteen patients (19.2%) had previous abdominal surgery. The mean platelet count was 261,628 (5,000-1,401,000). The mean International Normalized Ratio (INR) was 1.06 (0.8-2.8) and the mean hematocrit was 33.99 (17.30-46.80). The preoperative imaging included ultrasound (USG) in two patients (2.6%) and computed tomography (CT) in the remaining patients.

Table 1: Comparison between two groups

		Elective n, [CI], (%)	Emergency n, [CI], (%)	p value
Age	Year	47.6 [42.4-52.8]	42.04 [33.7-50.3]	p=0.184
Operation time	Min	97.4 [93.7-101.3]	107.9 [102.3-113.6]	**p=0.007**
Erythrocyte	Units	0.21 [0.11-0.52]	0.96 [0.47-1.46]	**p<0.001**
Spleen size	cm	16.2 [13.5-18.8]	8.3 [5.6-11.1]	**p=0.004**
PLT number		145.1 [109.3-180.8]	337.5 [222.3-452.7]	**p<0.001**
INR		1.04 [0.99-1.08]	1.08 [1.01-1.15]	p=0.522
Hematocrit		32.5 [30.3-34.8]	35.4 [33.3-37.5]	p=0.150
Length of stay	Day	9.4 [7.8-11.1]	11.3 [7.9-14.5]	p=0.362
Previous operation	No	27 (74.4%)	34 (87.2%)	p=0.151
	Yes	10 (25.6%)	5 (12.8%)	
Gender	Female	21 (53.8%)	10 (25.6%)	**p=0.018**
	Male	17 (43.6%)	29 (74.4%)	
Complication	No	39 (100%)	34 (87.2%)	**p=0.021**
	Yes	0 (0%)	5 (12.8%)	
Portal vein Thrombosis	No	39 (100%)	35 (89.7%)	**p=0.040**
	Yes	0	4 (10.3%)	
Pathology result	Benign	27 (69.2%)	38 (97.4%)	**p=0.001**
	Malign	12 (30.8%)	1 (2.6%)	

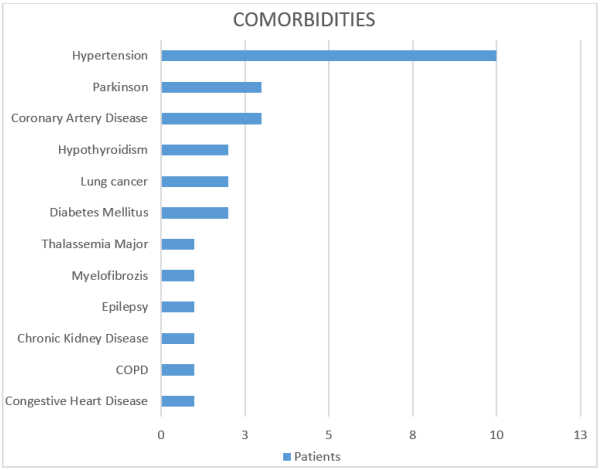

Figure 1: Comorbidities

Thirty-nine patients underwent emergency surgery and their indications are summarized in Table 2. Among the 15 patients with preoperative diagnoses, 12 patients (15.4%) had idiopathic thrombocytic purpura (ITP) and three patients (3.8%) had hereditary spherocytosis. No patient was diagnosed with splenic hemangioma and autoimmune hemolytic anemia. Twenty-four patients received a diagnosis after pathological examination and simple cysts were reported in two patients (2.6%), lipoma in one patient (1.28%), hemosiderosis in one patient (1.28%), and nonspecific hemorrhagic foci in dense congested tissue in the remaining 20 patients (25.6%).

Table 2: Indications for emergency surgery

Indication		Patient number	Percentage
Trauma	Grade 3	10	12.8%
	Grade 4	18	23.1%
	Grade 5	8	10.3%
Splenic abscess		3	3.8%

Comparing elective and emergency patients in terms of age, INR, hematocrit, hospital stay and previous surgery, no statistically significant difference was found (p=0.184, p=0.522, p=0.150, p=0.362, p=0.151). In addition, a shorter operation time, larger spleen sizes, a lower platelet count and more malignancy in pathology results were found to be significantly in favor of elective cases (p=0.007, p=0.004, p<0.001, p=0.001, p=0.001 respectively). In emergency cases, the need for RBC exchange was more frequent and complications and portal vein thrombosis were more frequent (p<0.001, p=0.021, p=0.040, respectively). Gender was not equally distributed between the two groups (p=0.018). The mean follow-up of the patients was 35.73 months (2-64). The associated parameters are summarized in Table 3.

Table 3: Assessments for patients with portal vein thrombosis

		Portal vein	Thrombosis	p value
		Absent n, [CI], (%)	Present n, [CI], (%)	
Operation type	**Elective**	39 (100%)	0	**p=0.040**
	Emergency	35 (89.7%)	4 (10.3%)	
Gender	**Female**	30 (93.8%)	2 (6.3%)	p=0.708
	Male	44 (95.7%)	2 (4.3%)	
Pathology report	**Benign**	61 (93.8%)	4 (6.2%)	p=0.358
	Malign	13 (100%)	0	
Age	**Year**	45.6 [40.9-50.2]	39.3 [36.13-78.79]	p=0.654
Operation time	**Min**	100.87 [97.65-104.09]	120 [70.32-169.68]	p=0.170
Erythrocyte	**Units**	0.54 [0.24-0.84]	0 [0-0]	p=0.218
Spleen size	**cm**	13.33 [11.23-15.44]	5.67 [4.3-11.3]	p=0.398
PLT number		204.4 [160.9-247.8]	631.0 [102.5-228.7]	p=0.060
INR		1.06 [1.01-1.10]	0.97 [0.89-1.05]	p=0.341
Hematocrit		34.03 [32.2-35.8]	35.5 [25.9-45.1]	p=0.904
Hospitalization	**Days**	10.1 [8.4-11.8]	11.3 [7.6-16.8]	p=0.607

The relationship between the type of surgery and the development of DVT during follow-up is shown in Figure 2. The development of portal vein thrombosis during follow-up was significantly different between the two groups in favor of emergency cases (p=0.045).

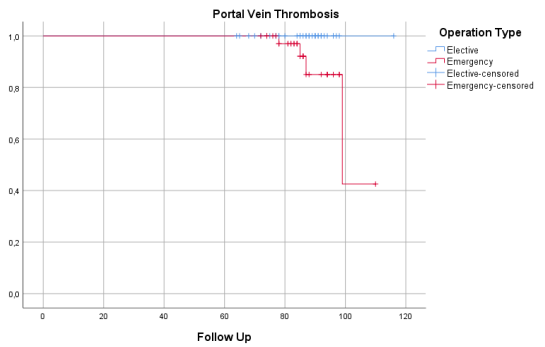

Figure 2: Development of portal vein thrombosis by type of surgery

DISCUSSION

Although the spleen is an important organ for the immune system and coagulation mechanisms, it can be compensated by other organs and tissues. Splenectomy may be performed as part of treatment or diagnosis in emergency or elective conditions, depending on the risk/benefit ratio. The indications for splenectomy in the patients included in our study were mostly splenic injuries and hematologic diseases.

The indication for splenectomy is made with a multidisciplinary approach by evaluating clinical, laboratory, and radiologic imaging studies. Szasz et al. also reported that the importance of complete blood count and computed tomography in the indication for splenectomy was higher than other tests (5). In our clinical practice, blood tests and radiological imaging are performed in all patients diagnosed by the hematology department and referred to us, and blood tests and all radiological imaging are performed in all patients admitted from the emergency department, unless there is hemodynamic instability.

Although the majority of patients (93.59%) had an uneventful postoperative follow-up, the most common complications were portal vein thrombosis (5.06%), bleeding (2.53%), and infection (1.26%). There was a difference in venous thrombosis between the two groups, with a statistically higher incidence of venous thrombosis in the group that underwent emergency splenectomy. A study by Dendle et al. found that venous thrombosis increased after splenectomy in both elective and emergency cases, regardless of the indication for surgery (6).

Apart from venous thromboembolism, the most common complications in our study group were infection and bleeding. Venous thromboembolism and other complications were evaluated on a patient-by-patient basis, and it was found that venous thromboembolism did not correlate with other complications in our study. In this context, the possibility of venous thromboembolism in the subgroup without postoperative complications, which was the majority of our patients, was also evaluated. Since

no additional imaging and testing was performed in this uncomplicated group, the relationship between venous thromboembolism, which may occur in the follow-up of patients, and the surgical procedure and technique used was evaluated. Crary et al. showed in a study that the risk of postoperative venous thromboembolism peaks in the first three weeks postoperatively and then the possibility of development decreases (3). Given the average length of hospital stay in our study, it is concluded that the number of patients missed, not imaged because of lack of suspicion, but who developed venous thromboembolism would not significantly change the data.

Fujita et al. reported a thrombosis frequency of 1.5% in splenectomies of hematologic origin (7). In a prospective analysis, Chaffanjon et al. reported thrombosis rate of 6.7% in sixty cases of open splenectomy. In another prospective analysis, Hassn et al. reported an incidence of venous thromboembolism of 10% in 50 cases of open splenectomy (8,9). Harris et al. examined laparoscopic techniques and found a 14% PVT rate in 17 individuals having elective splenectomy over a year (10). In 64 open, and 37 laparoscopic cases it was found that the incidence of portal vein thrombosis was 8%, with no discernible difference between the open and laparoscopic procedures (11). The findings of Tsamalaidze and colleagues, who reported a postoperative thrombosis rate of 6.6% in 229 splenectomized patients over 21 years, are consistent with this (12). Ikeda et al. showed that the incidence of portal vein thrombosis was statistically significantly higher in the CT images of patients who had undergone splenectomy (13). In our study, portal vein thrombosis was detected in 5 patients (5.06%) on control CT imaging, and the detection rate of this thrombosis was found to be higher in the first two months. Our study has a similar incidence of venous thromboembolism compared to case reports in the literature. Due to possible additional comorbidities, it has been observed that the risk of thrombosis is higher in emergent cases than in elective cases.

In our study, splenectomy was performed in all patients, including elective cases diagnosed by the hematology department. Laparoscopic surgery was not performed in any patient. However, in the literature, Segalini et al. performed laparoscopic surgery in 21 patients in a series of 202 patients with splenic trauma and reported a mortality rate of 2.5% and a morbidity rate of 7.7%. These rates are encouraging for laparoscopic surgery even in emergency situations (14). Di Buono et al. showed that laparoscopy was associated with a lower rate of reoperation and postoperative recurrence of anemia in a comparison of all surgical splenectomy techniques (15).

From a thrombosis standpoint, laparoscopic surgery is beneficial because it is associated with less trauma and quicker postoperative recovery than open surgery, but the incidence of venous stasis and thrombosis is significantly increased because the pneumoperitoneum created during laparoscopy changes the hemodynamics of the splenic portal venous system. Another study included 149 normal and cirrhotic patients undergoing laparoscopy and found that the risk of postoperative thrombosis was 32% in cirrhotic patients and 9.5% in patients without cirrhosis (16).

A systematic review was performed to investigate the effect of laparoscopy, especially non-splenectomy laparoscopic surgery with only intra-abdominal insufflation and pneumoperitoneum, on portal vein thrombosis. It has also been found in non-splenectomy surgical cases where laparoscopy was performed such as cholecystectomy, fundoplication, gastric bypass, appendectomy. In this review, James et al. found a dose-dependent relationship between insufflation pressures and venous stasis in laparoscopic cases (17).

CONCLUSION

In high-risk patients, venous thromboembolism is a rather frequent consequence following splenectomy. Although it may be fatal, anticoagulation is a viable treatment option. The presence of pain or fever after splenectomy is suggestive of venous thromboembolism. Due to the high risk of thromboembolism in the first two months, low-molecular-weight heparin should be considered for prophylactic anticoagulation in high-risk patients, and anticoagulation should be continued after the patient is sent home. Therefore, anticoagulation should be considered in emergency cases and especially in multiple trauma cases with difficult-to-control bleeding foci, taking into account the risk/benefit ratio, attention should be paid to possible venous thromboembolism. In this sense, our study supports the current data with its current results.

The single center and small number of patients are the limitations of our study. To evaluate the development of venous thromboembolism in patients undergoing splenectomy, to determine the risk factors, and to take appropriate preoperative or postoperative precautions, multicenter studies with larger groups of patients are needed.

Ethics Committee Approval: This study was approved by Ege University Clinical Research Ethics Committee, (Date: 21.09.2023, No: 23-9.1T/39).

Peer Review: Externally peer-reviewed.

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

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MORPHOMETRIC AND MORPHOLOGIC EVALUATION OF ANTERIOR TIBIAL ARTERY*

ARTERIA TIBIALIS ANTERIOR'UN MORFOMETRİK VE MORFOLOJİK DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: Previous studies related to the anatomy of the anterior tibial artery have focused mainly on morphology. The number of studies examining arterial morphometry is limited. Consequently, we aimed to examine the morphology and morphometry of this artery in detail.

Material and Method: The study was performed on 30 lower extremities injected with colored silicone. Morphological features of anterior tibial and popliteal arteries were assessed. The morphometrical evaluation included the tibiofibular trunk length, diameters of popliteal, anterior tibial, posterior tibial, fibular, dorsalis pedis arteries, and the vertical distances between the origin of the anterior tibial artery and the head of the fibula and tibial tuberosity.

Result: Five types of the anterior tibial artery were determined according to branching morphology, location, and course. The mean length of the tibiofibular trunk was 32.0±9.9 mm. Mean diameters of popliteal, anterior tibial, posterior tibial, fibular, and dorsalis pedis arteries were 5.8±1 mm, 4.1±0.6 mm, 3.5±0.6 mm, 3.7±0.7 mm and 2.8±0.4 mm, respectively. The mean vertical distance of the origin of the tibialis anterior artery to the head of the fibula and tibial tuberosity was 38±10.2 mm and 23.6±8.0 mm, respectively.

ÖZET

Amaç: Arteria (a.) tibialis anterior anatomisi ile ilgili yapılmış çalışmalar ağırlıklı olarak arter morfolojisine odaklanmıştır. Arterin morfometrisini inceleyen sınırlı sayıda çalışma bulunmaktadır. Bu doğrultuda, arter morfolojisi ve morfometrisini ayrıntılı olarak incelemeyi amaçladık.

Gereç ve Yöntem: Çalışma renkli silikon enjekte edilen 30 alt ekstremite üzerinde gerçekleştirildi. *A. tibialis* anterior'un ve a. poplitea'nın morfolojik özellikleri değerlendirildi. Truncus tibiofibularis'in uzunluğu, a. poplitea, a. tibialis anterior, a. tibialis posterior, a. fibularis ve a. dorsalis pedis'in çapları ile a. tibialis anterior'un orijin yerinin caput fibulae'ya ve tuberositas tibiae'ye vertikal uzaklığı morfometrik olarak incelendi.

Bulgular: *A. tibialis* anterior'un dallanma morfolojisi, yeri ve seyrine göre beş tipi belirlendi. Truncus tibiofibularis'in ortalama uzunluğu 32,0±9,9 mm idi. A. poplitea, a. tibialis anterior, a. tibialis posterior, a. fibularis ve a. dorsalis pedis'in ortalama çapları sırasıyla 5,8±1,0 mm, 4,1±0,6 mm, 3,5±0,6 mm, 3,7±0,7 mm ve 2,8±0,4 mm olarak bulundu. A. tibialis anterior'un orijin yerinin caput fibulae'ye vertikal uzaklığı ortalama 38±10,2 mm; tuberositas tibiae'ye mesafesi ise ortalama 23,6±8,0 mm olarak ölçüldü.

*This study is derived from the thesis entitled "Morphometric evaluation of anterior tibial artery" (Yök Thesis No: 541254). In addition, the Turkish and English abstracts of this study with less than 300 words were presented as a poster presentation at the 20th National Anatomy Congress on 27-31 August 2019 and received the "Best Cadaver-Based Clinical Anatomical Study" award.

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Conclusion: Knowledge regarding anterior tibial artery anatomy and popliteal artery branching variations are essential for endovascular interventions around the knee, infrapopliteal bypass procedures planned for peripheral arterial disease, and orthopedic operations involving the tibial plateau. We believe that our results will help orthopedic and vascular surgeons.

Keywords: Popliteal artery, anterior tibial artery, tibiofibular trunk, posterior tibial artery, fibular artery

Sonuç: A. tibialis anterior'un anatomisini ve a. poplitea'dan dallanma varyasyonlarını bilmek; diz çevresindeki endovasküler girişimler, periferik arter hastalığı için planlanan infrapopliteal bypass, ve tibial platoyu ilgilendiren ortopedik operasyonlar açısından oldukça önemlidir. Elde ettiğimiz sonuçların ortopedik ve vasküler cerrahlara yardımcı olacağı düşüncesindeyiz.

Anahtar Kelimeler: Arteria poplitea, arteria tibialis anterior, truncus tibiofibularis, arteria tibialis posterior, arteria fibularis

INTRODUCTION

The femoral artery passes through the adductor canal and reaches the popliteal fossa on the posterior aspect of the leg, and it is called the popliteal artery (PA). When the PA comes in line with the distal edge of the popliteus muscle, it branches into the anterior tibial artery (ATA) and the posterior tibial artery (PTA). PTA then gives off the fibular artery (FA) branch. ATA is initially located in the posterior (flexor) compartment of the leg. Passing between the two heads of the posterior tibial muscle, it reaches the oval opening in the upper part of the interosseous membrane of the leg, where it passes into the anterior (extensor) compartment of the leg. In the anterior compartment of the leg, the ATA passes just medial to the head of the fibula. Here it runs over the interosseous membrane and between the extensor muscles of the leg towards the ankle. It then passes under the inferior extensor retinaculum and becomes the dorsalis pedis artery (DPA). Some authors use the "tibiofibular trunk" (TFT) definition for the portion of the popliteal artery after giving the ATA and subsequently dividing into PTA and FA (1,2). There is no consensus on the use of this definition and it is not included in Terminologia Anatomica (3). However, in this study, the definition of TFT was used to be compatible with the current literature.

Although the PTA and FA injury rates are low, ATA accounts for one-third of vascular injuries (4). Injuries of ATA due to high-energy trauma, tibia fractures, and blunt traumas have been reported (4). In addition, it has been reported in the literature that ATA has iatrogenic injuries during procedures such as intramedullary nailing, tibial osteotomy, external fixation, and arthroscopic reduction.

There are various studies on the clinical significance and anatomy of the ATA, but these studies examined branching variations of ATA from the PA. In our study, we aimed to examine the course, morphometry, and morphology of ATA in detail.

MATERIAL and METHODS

The study was carried out between November 2017 and July 2018 at the Department of Anatomy of the Istanbul Faculty of Medicine. The cadavers with no signs of size difference, shape abnormality, trauma, burns, or surgical scars in the lower extremities were included in the study. Thus, the bilateral lower limbs of 15 cadavers were dissected for examination of the ATA. The cadavers were embalmed with a mixture of formaldehyde-phenol-glycerin-ethanol. The study was approved by the Ethics Committee of the Istanbul Faculty of Medicine (Date:13.10.2017, No: 16). Written consent was obtained from the donor-cadaver before death.

Colored silicone injection

To better follow the ATA and its branches during the dissection, the colored silicone injection method developed by Sanan et al. was modified and used (5). Pebeo brand 514/5 numbered red acrylic paint, Polisan brand synthetic thinner as diluent, Ottosil BS 15 mold silicone, and Ottosil BS Cat as catalyst were used in this mixture. Firstly, 50 ml of silicone and 4 ml of red acrylic paint were mixed with a wooden tongue depressor until the mixture was homogeneous in plastic containers of appropriate size. The silicone was diluted 1:1 with a synthetic thinner to increase its flowability. Next, the popliteal fossa was dissected, the PA was found, and a window was opened in its wall. Plastic cannulas were inserted into the opened window. The vessel was ligated to prevent the reflux of dye. A 3% catalyst was added to the prepared silicone-paint mixture and mixed homogeneously. The mixture was injected into the PA with a 100 cc syringe. The mixture was allowed to cure for at least 48 hours.

Dissection protocol

A vertical incision was made into the popliteal fossa. After the popliteal adipose tissue was removed, the common fibular nerve, tibial nerve, popliteal vein, and artery were identified. After the PA was separated from the adjacent anatomical structures by fine dissection, it was cannulated, and a colored silicone mixture was injected. After the mixture was cured, the PA was dissected distally. TFT, ATA, PTA, and FA were defined. In addition, a vertical skin incision was made in the anterior leg region from the tibial tuberosity to the inferior extensor retinaculum on the dorsum of the foot. The skin and crural fascia were released laterally and the anterior compartment muscles of the leg were defined. ATA was dissected from the interosseous membrane of the leg to the inferior extensor retinaculum level. And finally, DPA was identified distal to the retinaculum.

Morphometric evaluation

1. Leg length regarding the most protruding points of the head of the fibula and lateral malleolus,

2. Vertical distance from the origin of the ATA to the head of the fibula,

3. Diameter of PA before and after giving ATA,

4. Diameter of ATA, PTA, FA, and DPA at their origin point

5. TFT length,

6. The vertical distance between the tibial tuberosity and the point the ATA reaches the anterior leg compartment from the interosseous membrane of the leg was measured.

All measurements were made with a digital caliper (Mitutoyo Corporation, Kawasaki-shi, Kanagawa, Japan) with a measurement accuracy of 0.01 mm. The measurements were repeated twice by an experienced investigator and the mean values were used. If the difference between the two measurements was more than 10% the measurement was repeated.

Morphological evaluation

1. Branching morphologies of ATA, PTA, and FA from PA were recorded.

2. The leg region was divided into three parts, proximal, middle, and distal. The number of muscular branches in each part of ATA was recorded.

Statistical analysis

A priori power analysis was performed based on the findings of the study by Heidari et al. (6). Taking the study of 40 unilateral extremities as a reference, the minimum required sample size was estimated as n=26 unilateral extremities with a power of 0.80 and an alpha value of 0.05. Power analysis was performed under G*Power 3.1.9.4 (http://www.gpower.hhu.de/). Whether the obtained parametric values showed normal distribution or not was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics were made for the values showing normal distribution. The comparison of the number of branches according to the side and leg length was evaluated with the Kruskal Wallis test. PTA and AF diameters, as well as differences between both sex were compared with the ANOVA test. SPSS ver.21.0 (IBM Corp., Armonk, NY) software was used for the analysis, and $p<0.05$ was considered significant.

RESULTS

Eight cases were female, and seven were male, aged 52 to 79 years (mean 68.8±6.78). Morphometric values were found to have a normal distribution for the right and left sides. The mean values of the morphometric measurements are shown in Table 1.

When morphometric parameters were compared according to gender, only leg length was found to be statistically significantly longer in males ($p<0.001$). No significant difference was observed when the parameters were compared according to body sides. The comparison of morphometric measurement values according to gender and body sides and their statistical significance are shown in Table 2.

The mean number of muscular branches of ATA in the proximal, middle, and distal sections were found as 6, 5, and 5, respectively. There was no statistically significant difference between these values ($p=0.67$).

ATA was divided into five types according to branching morphology from PA, place of origin, and course.

Table 1: Measurement values of morphometric parameters

	Sample (n)	Mean±SD (mm)
Leg length	30	356.6±24.8
The vertical distance between the origin of ATA and the head of fibula	30	38.0±10.2
Diameter of the PA before giving ATA	30	5.8±1.0
Diameter of the PA after giving ATA	26*	4.8±0.8
Diameter of the ATA	30	4.1±0.6
Diameter of the PTA	30	3.5±0.6
Diameter of the FA	30	3.7±0.7
Diameter of the DPA	30	2.8±0.4
Length of the TFT	26*	32.0±9.9
The vertical distance between tibial tuberosity and ATA	30	23.6±8.0

* Since the TFT was not observed in cases with trifurcation, these parameters could not be measured
ATA: Anterior Tibial Artery, PA: Popliteal Artery, PTA: Posterior Tibial Artery, FA: Fibular Artery, DPA: Dorsalis Pedis Artery, TFT: Tibiofibular Trunk, n: Number, SD: Standard Deviation

Table 2: Comparison of morphometric parameters by sex and body sides

	Gender			Body sides		
	Male (mm)	Female (mm)	p value	Right (mm)	Left (mm)	p value
Leg length	378.6	337.3	**<0.01**	355.3	357.8	0.724
The vertical distance between the origin of ATA and head of the fibula	40.0	36.3	0.337	39.2	36.8	0.468
Diameter of the PA before giving ATA	6.1	5.5	0.100	5.7	5.8	0.468
Diameter of the PA after giving ATA	5.0	4.74	0.417	4.9	4.7	0.740
Diameter of the ATA	4.1	4.08	0.662	4.1	4.1	0.846
Diameter of the PTA	3.7	3.41	0.119	3.6	3.4	0.361
Diameter of the FA	3.84	3.60	0.428	3.7	3.6	0.468
Diameter of the DPA	3.0	2.71	0.073	2.9	2.7	0.225
Length of the TFT	31.2	32.6	0.269	34.5	29.6	0.901
The vertical distance between tibial tuberosity and ATA	27.3	20.9	0.053	21.5	25.6	0.950

ATA: Anterior Tibial Artery, PA: Popliteal Artery, PTA: Posterior Tibial Artery, FA: Fibular Artery, DPA: Dorsalis Pedis Artery, TFT: Tibiofibular Trunk

- **Type-1 (Classical pattern):** After the PA passes the lower edge or more distal of the popliteus muscle, it divides into ATA and TFT. TFT is divided into PTA and FA. This was the most common type and was found in 24 (80%) cases (Figure 1).
- **Type-2 (Anterior TFT):** PA is divided into PTA and TFT. TFT is then split into ATA and FA. This finding was found in 1 (3.3%) case (Figure 2).
- **Type-3 (Trifurcation):** It is the separation of ATA, FA, and PTA less than 5 millimeters apart. This pattern was found in 3 (10%) cases (Figure 3).
- **Type-4 (High division):** PA gives ATA proximal to the lower edge of the popliteus muscle. This type was observed in 1 (3.3%) case. And in this case, it was seen that ATA originated from the medial aspect of the PA (Figure 4).

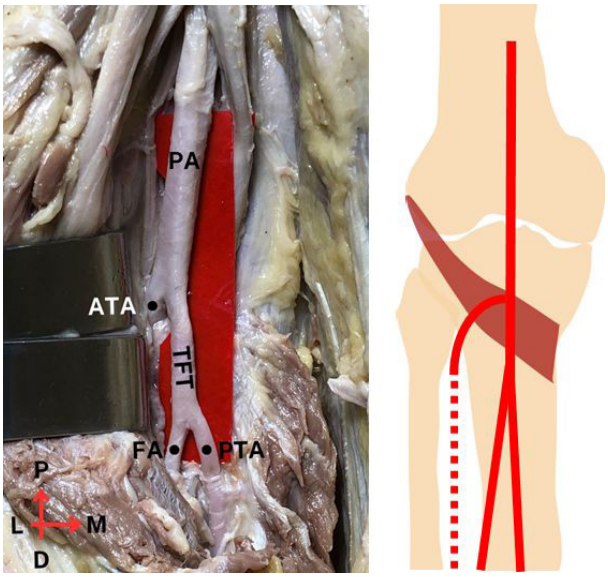

Figure 1: Type-1 (Classical pattern)
Posterior view of left leg
PA: Popliteal Artery, ATA: Anterior Tibial Artery, TFT: Tibiofibular Trunk, FA: Fibular artery, PTA: Posterior Tibial Artery, P: Proximal, D: Distal, L: Lateral, M: Medial

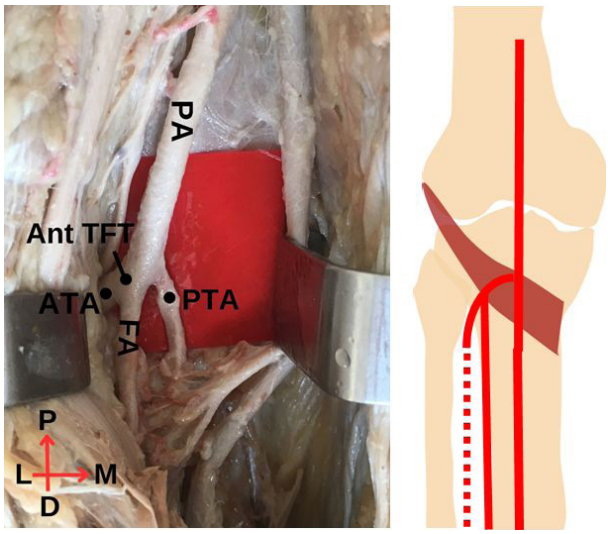

Figure 2: Type-2 (Anterior TFT)
Posterior view of left leg
PA: Popliteal Artery, PV: Popliteal Vein, ATA: Anterior Tibial Artery, FA: Fibular artery, PTA: Posterior Tibial Artery, P: Proximal, D: Distal, L: Lateral, M: Medial

- **Type-5 (Hypoplasia/Aplasia):** ATA is hypoplasic/aplasic. Hypoplasic ATA was found in one case (3.3%). In this case, it was observed that DPA originated from FA (Figure 5).

Accordingly, 24 (80%) of the 30 lower extremities showed branching in the general pattern, and 6 (20%) showed branching in other patterns. Of these six extremities, four were unilateral and one was bilateral. If ATA showed branching according to the classical pattern in one half of the body, the probability of anatomical variability on the other side was found to be 28.5%. And if there was anatomical variability in ATA branching morphology on one side of the body, the probability of variability on the other side was found to be 20%.

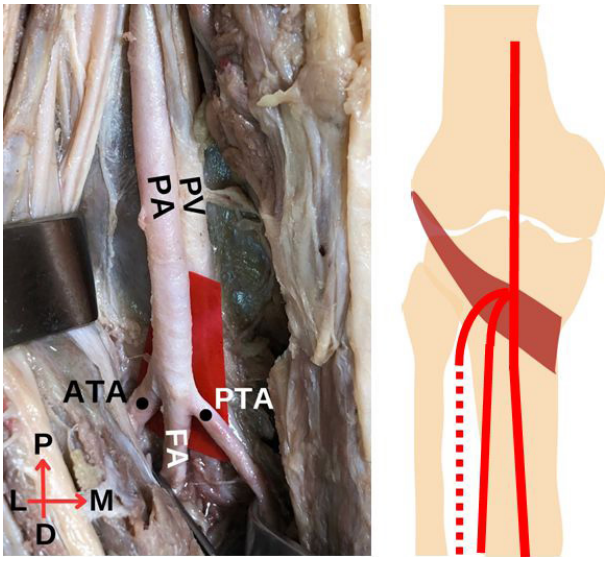

Figure 3: Type-3 (Trifurcation)
Posterior view of left leg
PA: Popliteal Artery, ATA: Anterior Tibial Artery, Ant TFT: Anterior Tibiofibular Trunk, FA: Fibular artery, PTA: Posterior Tibial Artery, P: Proximal, D: Distal, L: Lateral, M: Medial

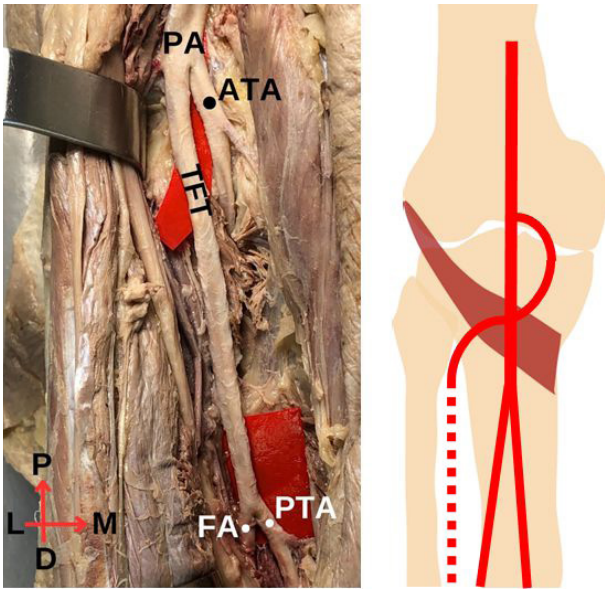

Figure 4: Type-4 (High division)
Posterior view of left leg
PA: Popliteal Artery, ATA: Anterior Tibial Artery, TFT: Tibiofibular Trunk, FA: Fibular artery, PTA: Posterior Tibial Artery, P: Proximal, D: Distal, L: Lateral, M: Medial

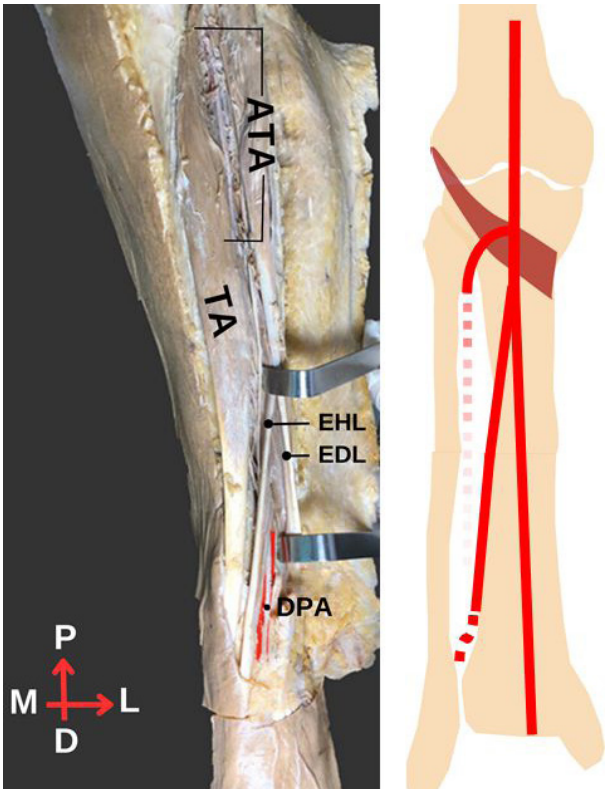

Figure 5: Type-5 (Hypoplasia/Aplasia)
Anterior (in cadaver image) and posterior (in schematic diagram) views of left leg
ATA: Anterior Tibial Artery, TA: Tibialis Anterior Muscle, EHL: Extensor Hallucis Longus Muscle, EDL: Extensor Digitorum Longus Muscle, DPA: Dorsalis Pedis Artery, P: Proximal, D: Distal, L: Lateral, M: Medial

DISCUSSION

To explain the branching variations of ATA, it is necessary to know the embryological development of the lower extremity arteries. The axial artery, which provides the arterial supply of the lower extremity, develops from the umbilical artery originating from the dorsal aorta. In the 11-12th stages of embryological development, the lower extremity bud is observed for the first time. At stages 13-16, the axial artery runs along the lower extremity bud. The axial artery develops in stages 16-17 and is called the ischiadic artery in the thigh, the poplitea profunda artery in the knee region, and the interosseous artery in the leg. The external iliac artery originates from the umbilical artery, runs distally, and extends towards the knee as the

femoral artery. A branch of the femoral artery, called ramus communicans superior, passes posteriorly and joins the ischiadic artery. In stage 18, a branch called poplitea superficialis emerges between the poplitea profunda and the interosseous arteries. Two new arteries arise from the poplitea superficialis, the tibialis posterior superficialis and the peroneal posterior superficialis. At this stage, an artery named ramus perforans cruris emerges from the interosseous artery, passes through the tibiofibular interspace, and forms the primitive ATA. At this time, there are three arteries in the leg. Also, the proximal portion of the ischiadic artery begins to regress at this stage and remains the inferior gluteal artery in adults. In stage 19, ATA develops as the distal part of the ramus perforans cruris. An artery called ramus communicans inferius arises from the peronea posterior superficialis artery. At this stage, there are five arteries in the leg (tibialis posterior superficialis, peronea posterior superficialis, ramus communicans inferior, interosseous, and anterior tibial arteries). In stage 20, the ramus communicans inferius fuses with the interosseous artery to form the adult peroneal (fibular) artery. At this stage, a connection called ramus communicans medius is formed between the peroneal artery and the deep popliteal. This branch eventually becomes the proximal part of ATA. With the regression of the popliteal profunda, interosseous, and peronea posterior superficialis arteries, the leg arteries take their adult form (7,8).

Variations of ATA can be explained by the deviation of these developmental steps. As a result of the lack of regression of the anterior part of the ischiadic artery, anterior TFT, which is the common root containing ATA and FA, occurs (9). The permanence of the distal portion of the ischiadic artery enables anastomosis with the popliteal artery, thus forming a trifurcation (1). Failure in the formation of the ramus communicans medius causes the anterior tibial artery to be of high origin (10).

Morphometry

In intramedullary nailing for tibial fractures requiring anatomical reduction and fixation, the locking holes are located close to the ATA and are therefore at risk of iatrogenic injury (6). For this reason, it is important to know the distances of ATA to adjacent bone structures in determining the position of the nailing holes in new surgical techniques. Heidari et al. found the mean distance between the ATA and the head of the fibula as 35.7±9.0 mm, and May et al. found this distance as 36.5±6.0 mm (6,11). In this study, this distance was 38±10.2 mm.

The most common peripheral artery aneurysm is seen in the PA (12). The diameter of the vessels should be determined in the diagnosis of the aneurysm and the selection of the treatment method (12). While the diameter of the PA in the study by Hölzle et al. was 5.5 mm on the right and 5.4 mm on the left, it was found as 5.8±1.0 mm in the current study (13). While Ozgur et al. found the diameters of ATA, PTA, and FA to be 6.1±1.1 mm, 4.5±0.9 mm, and 4.4±0.9 mm, respectively, in this study, these values were 4.1±0.6 mm, 3.5±0.6 mm, and 3.7±0.7 mm (14). In the literature, the diameter of the DPA ranges from 1.5 mm to 5.0 mm, and in this study, it was 2.8±0.4 mm (15).

Current anatomy sources state that ATA and PTA are the two terminal branches of AP, and AF is a sub-branch of PTA (7,16). However, Adachi expressed his thoughts on these branches as follows: "Although I use the term truncus peronaeo-tibialis posterior, my view is that the peronaeal artery, the continuation of the popliteal artery, is very variable and the tibialis posterior artery is considered as a lateral branch of the peroneal artery." (17). Therefore, this study compared FA and PTA diameters and found no statistically significant difference (p=0.452). In line with this information, the authors' knowledge that FA is a branch of PTA should be re-examined.

The importance of TTF length in the planning of the endovascular treatment of peripheral arterial diseases and the selection of appropriate equipment and the planning of infrapopliteal bypass operations was emphasized (18,19). The length of the TFT was determined by Ozgur et al. as 30.3±16.2 mm, Celtikci et al. as 30.5 mm, and Kim et al. as 39 mm (14,18,19). In the present study, this was found to be 32.0±9.9 mm. In addition, Celtikci et al. created two subclasses because there was a statistically significant difference between the right and left sides in cases with a general pattern (Type 1A) (18). They classified the cases with TTF longer than 3 cm as Type 1-A-L (Long) and those below as Type 1-A-S (Short). According to this classification, they found 363 (51.7%) cases as 1-A-L and 339 (48.3%) cases as 1-A-S. In the present study, 16 (66.6%) 1-A-L and 8 (33.3%) 1-A-S cases were found according to this subclassification. Similarly, the 1-A-L subtype was more common in both studies.

Morphology

Many classifications have been proposed for the branching morphology of the PA (17,19,20). The classification of Kim et al. is the most widely used today (19). In this study, three main categories and three subcategories for each of these were defined for the PA branching pattern. In this classification, In this classification, Category-1 is normal branching of PA, Category-2 is high-origin branching, and Category-3 is explains hypoplastic/aplastic arteries. Kim et al. reported that 92.2% of PA showed normal branching (19). This prevalence ranges from 72% to 96% (1,17). Similarly, it was found that 80% of the lower extremities examined in our study showed normal branching patterns.

The cases in which the first branch originating from the PA was PTA and then the common roots of ATA and FA were defined as anterior TFT. The incidence of this type varies

between 0.1% and 5%, and anterior TFT was found in one case (3.3%) in our study (21,22). Kim et al. defined the branching of ATA, PTA, and FA within 0.5 cm as trifurcation, and they found this type of branching in 12 cases (2%) (19). In this study, trifurcation was found in 3 cases (10%). The reason why this rate was higher in this study compared to other studies may be the number of samples.

The definition of high origin was used for the branches originating from the PA in the proximal of the lower end of the popliteus muscle in cadaver studies and in the proximal of the tibial plateau in angiographic studies (2,10,17,18,20,21). In this study, ATA separated from the PA proximal to the lower end of the popliteus muscle was found in one case (3.3%). In addition, in this case, it was observed that ATA emerged from the medial side of the PA, not from the lateral side as it should normally be. Kim et al. divided high-origin ATA into two subclasses, with the normal course and medial origin at the beginning, and this type was found in 4 cases (0.7%), and Celtikci et al. in 5 cases (0.6%) (18,19). In cases where the PA branches are hypoplastic/aplastic, the nutrition of the distal leg changes. In the case of hypoplastic/aplastic ATA, DPA originates from FA or PTA (13,19,23). In the present study, hypoplastic ATA was found in one case and it was observed that FA gave DPA.

Limitations

This study was designed as a preliminary study. It is planned to extend the study as a multi-center study to increase the sample size and add radiological data.

CONCLUSION

This study highlights ATA morphometry and variations in the hope that this information will be incorporated into future procedures and reduce avoidable complications. It was concluded that the branching pattern of the ATA differed from the classical pattern in 20% of the cases included in the study, with trifurcation being more common. In addition, no significant difference was found between the diameters of the FA and PTA. Therefore, we believe that the information that the FA is a branch of the PTA should be reconsidered and that it would be more appropriate to use the nomenclature "tibiofibular trunk" instead.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 13.10.2017, No: 16).

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A COMPARISON OF THE EFFECTS OF BALANCE–PROPRIOCEPTION AND AEROBIC EXERCISES ON FUNCTIONAL STATUS, PAIN, AND BALANCE IN PATIENTS WITH FIBROMYALGIA SYNDROME - A RANDOMIZED CONTROLLED STUDY

FİBROMİYALJİ HASTALARINDA DENGE-PROPRİOSEPSİYON VE AEROBİK EGZERSİZ UYGULAMALARININ FONKSİYONEL DURUM, AĞRI VE DENGE ÜZERİNE ETKİSİ-RANDOMİZE KONTROLLÜ ÇALIŞMA

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ABSTRACT

Objective: Difficulty in performing daily activities and loss of balance are common complaints in addition to generalized pain in fibromyalgia syndrome (FMS) patients. Exercise is an effective treatment for fibromyalgia. There are a variety of forms of exercise used to treat fibromyalgia. This study aimed to compare the effects of aerobic and balance-proprioception exercises on pain, functional status, and balance in female patients with fibromyalgia.

Material and Method: Female patients with fibromyalgia syndrome who applied to the university physical medicine and rehabilitation department clinic were evaluated for eligibility. Patients were allocated into two groups: the aerobic exercise group and balance-proprioception group. These two groups exercised under the supervision of a physiotherapist three days a week for a total of 6 weeks. Visual Analogue Scale (VAS) was used for pain severity, Fibromyalgia Impact Questionnaire (FIQ) was used for functional status assessment, and balance-stabili-

ÖZET

Amaç: Fibromiyalji sendromunda yaygın ağrıya ek olarak günlük aktiviteleri gerçekleştirmede güçlük ve denge kaybı sık görülen şikayetlerdir. Çalışmamızda fibromiyaljideki bu şikayetler üzerine etkili olabileceğini düşündüğümüz farklı tip egzersiz programlarının (aerobik ve denge-propriyosepsiyon) ağrı, fonksiyonel durum ve denge parametreleri üzerine etkilerini karşılaştırmayı amaçladık. Bu nedenle randomize kontrollü, paralel gruplar içeren, tek merkezli ve tek kör bir çalışma tasarladık.

Gereç ve Yöntem: Üniversitenin fizik tedavi ve rehabilitasyon bölümü kliniğine başvuran fibromiyalji sendromlu kadın hastalar uygunluk açısından değerlendirildi. Hastalar aerobik egzersiz grubu ve denge-propriyosepsiyon grubu olarak iki gruba ayrıldı. Bu iki grup haftada 3 gün fizyoterapist gözetiminde toplam 6 hafta egzersiz yaptı. Ağrı şiddeti için Visual Analog Scale (VAS), fonksiyonel durum değerlendirmesi için Fibromiyalji Etki Anketi (FEA), denge durumu değerlendirmesi için denge-stabilite sistemi (Biodex Balance System) kullanıldı. Her ölçüm teda-

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ty system (Biodex Balance System) was used for balance status assessment. Each measurement was repeated twice, before and after the treatment, and the results were compared.

Result: Fifty-one patients were enrolled including 26 patients in the aerobic exercise group and 25 patients in the balance-proprioception group. Both aerobic exercise and balance proprioception exercise groups showed significant improvement following the treatment in FIQ (34.63±11.85, 29.60±12.77, respectively, p<0.001) and VAS (4.54±1.83; 4.28±1.92, respectively, p<0.001), all Eyes-Closed Mediolateral Stability Index (EC-MLSI) (0.41±0.43, 0.35±0.19, respectively, p=0.39), Eyes Closed Overall Stability Index (EC-OSI) (0.85±0.53; 0.80±0.33, respectively, p<0,001), Eyes Closed Anteroposterior (EC-APSI) Stability Index (0.65±0.32, 0.62±0.29, respectively, p<0.001) and Eyes-Opened Mediolateral Stability (EO-MLSI) (0.15±0.07, 0.14±0.05, respectively, p=0.019). Similar to before-treatment findings, there was no statistically significant difference between groups in the FIQ, VAS, and balance scores after treatment (p>0.05).

Conclusion: Both aerobic exercise and balance-proprioception exercises are effective methods in improving pain, functional status, and balance abilities of patients with FMS. In addition to aerobic exercise programs that are often prescribed nowadays, programs consisting of balance–proprioception exercises can also be a preferable option in FMS treatment.

Keywords: Fibromyalgia, aerobic exercise, balance-proprioception exercise, pain, functional status

vi öncesi ve sonrası olmak üzere iki kez tekrarlandı ve sonuçlar karşılaştırıldı.

Bulgular: Aerobik egzersiz grubunda 26 ve denge-propriyosepsiyon grubunda 25 hasta çalışmayı tamamladı. Hem aerobik egzersiz hem de denge propriyosepsiyon egzersiz gruplarında, FIQ'da (sırasıyla 34,63±11,85; 29,60±12,77, p<0,001) VAS'ta (sırasıyla 4,54±1,83; 4,28±1,92, p<0,001), gözler kapalı OSI (sırasıyla 0,85±0,53; 0,80±0,33, p<0,001), gözler kapalı MLSI (sırasıyla 0,41±043; 035,±0,19, p=0,39), gözler kapalı APSI (sırasıyla 0,65±0,32; 0,62±0,29, p<0,001), gözler açık MLSI (sırasıyla 0,15±0,07; 0,14±0,05, p=0.019) parametrelerinde iyileşme saptandı. Tedavi öncesi bulgulara benzer şekilde tedavi sonrasında da FIQ, VAS ve denge skorlarında gruplar arasında istatistiksel olarak anlamlı fark yoktu (p>0,05).

Sonuç: Hem aerobik egzersiz hem de denge-propriyosepsiyon egzersizleri, FMS'li hastaların ağrı, fonksiyonel durum ve denge yeteneklerini iyileştirmede etkili yöntemlerdir. FMS tedavisinde günümüzde sıklıkla reçete edilen aerobik egzersiz programlarının yanı sıra denge-propriyosepsiyon egzersizlerinden oluşan programlar da tercih edilebilir.

Anahtar Kelimeler: Fibromiyalji, aerobik egzersiz, denge-propriyosepsiyon egzersizi, ağrı, fonksiyonel durum

INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic disease characterized by generalized pain, fatigue, sleep disorder, cognitive impairment, and other physical symptoms that negatively affect physical and sensory functions while lowering quality of life (1). The prevalence of FMS is 2%-4% in the population, with a female/male ratio of 9:1. People between the ages of 45 and 60 are most commonly affected (2). It is believed that numerous mechanisms contribute to the development of FMS. There is evidence of biochemical, neurohormonal, central nervous system, immunological, psychological, and environmental factors (3).

Fibromyalgia significantly affects the health-related quality of life of patients by restricting their ability to perform daily activities including walking, lifting, and carrying objects (4,5,6). Patients with FMS have reduced functional abilities, poor health status, and lower quality of life in comparison to both healthy individuals or those with other chronic conditions (7,8). These patients tend to maintain a sedentary lifestyle due to their impaired physical fitness, which exacerbates symptoms and increases the risk of other morbidities (9-11).

There are two options for the treatment of FMS: pharmacological and non-pharmacological. Education, cognitive behavior therapy, exercise, and complementary and alternative medicine are the four most effective non-pharmacological treatment approaches commonly used and have a 1A level of evidence (12). Exercise training is a non-pharmacological management strategy for FMS that is effective and affordable. Exercise improves the quality of life, cognitive function, anxiety, depression, pain, sleep quality, and stress responses by increasing the "status of energy" (13). Despite these effects, studies demonstrate that women with FMS spend 48%-71% of their time in sedentary behaviors and engage in activities that do not require elevated energy expenditure (14-16).

The literature indicates that various exercise programs have positively impacted pain and functionality, with no significant adverse effects reported in individuals with FMS (17). Research on the type, intensity, and frequency of exercise has increased significantly in recent times. Aerobic exercise (AE) is frequently suggested as the predominant modality of exercise for the management of FMS. Many exercise programs involve both strengthening and flexibility types of exercise. Approximately 80% of the studies investigated the effects of AE or a combination of exercises including aerobic, flexibility, and strength (13).

Balance problems are another prominent functional symptom of FMS, in addition to pain and chronic fatigue. It is reported that 45%-68% of the FMS cases have balance problems. Jones et al. reported that individuals diagnosed with FMS exhibit balance problems and are susceptible to falls. The authors emphasize the importance of developing protective measures for postural stability, given that the dis-

ease affects the mechanisms that regulate postural control (18). It is shown that exercise programs improving balance increase postural stability and decrease the fall risk in patients with FMS (19). In the literature, the number of studies testing the efficacy of different exercise programs on balance disorders is limited. Furthermore, there is not much data on the influence of various exercise types on balance and the possible pain-balance relationship. Therefore, the goal of our study was to evaluate and compare the effects of aerobic and balance-proprioception exercises on pain, functionality, and balance parameters in patients with FMS.

MATERIAL AND METHODS

This randomized controlled, double-center, single-blinded, parallel-group study was approved by the local research ethics committee (Clinical Research Ethics Committee of Istanbul University Faculty of Medicine (Date: 22.09.2017, No: 15)) and registered on the ClinicalTrial.gov website (registration number NCT04437524). The study has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Patients included in the study were verbally informed regarding the study's objective, the process, the methods to be used, and any potential side effects. Their written consent was obtained by having them sign the "Informed Consent Form."

Eligibility criteria

The study comprised 62 female FMS patients admitted to our physical medicine and rehabilitation department outpatient clinic and met the study requirements. The test and rehabilitation programs of the patients were completed in the exercise test laboratories of the Istanbul Faculty of Medicine, Department of Sports Medicine. The following were the inclusion criteria: patients aged between 18 and 60 years old, patients whose symptoms lasted more than three months, and patients who agreed to undergo treatment for six weeks, three days per week. Additionally, there was no anticipated possibility of any changes in the medical treatment they received for FMS during the study process. Another criterion for inclusion was that the patient had a Pain Location Inventory (PLI) score of 17 or higher and a Symptom Impact Questionnaire (SIQR) score of 21 or higher, as defined by the 2011 American College of Rheumatology (ACR) criteria (20). The exclusion criteria were: the presence of a central or peripheral nervous system disease, progressive neurological damage, severe cardiovascular pathology, loss of sensation or position sense, unhealed fractures or surgical wounds, uncontrolled hypertension, and the inability to understand or follow simple commands.

Randomization

The cases were randomized using a simple random-number drawing procedure. Those who picked odd numbers from the bag of odd and even numbers were assigned to the aerobic exercise group (AEG), whereas those who picked even numbers were assigned to the balance-proprioception exercise group (BPEG).

Group assignment

Exercise therapy programs were designed independently for each group and were performed three days a week under the supervision of a physiotherapist for six weeks in the study. Exercise programs were conducted in the Department of Sports Medicine's exercise laboratory.

The AEG's exercise program was thoroughly explained to the patient, and documentation was provided in both written and graphic form. Each exercise session was carried out under the supervision of a physiotherapist in a clinical environment. Total exercise time ranged from a minimum of 30 minutes to a maximum of 60 minutes, including warm-up (low-intensity foot ergometer followed by short-duration stretching of major muscle groups) and cool-down (heart rate was gradually decreased following treadmill use, followed by stretching and abdominal breathing exercises). The patients began with a low-intensity walk on a treadmill at 55%-60% of maximal heart rate (calculated using the formula 220−age in years). The intensity and duration of walking on the treadmill were gradually increased to a moderate level. Subjective exertion was assessed using the Borg Scale of perceived exertion. The intensity level was kept at a moderate level for each individual once they had reached moderate intensity during the exercise program (21). The duration was increased by 5 minutes in each exercise session of the first two weeks to reach 60 minutes of exercise duration (22).

The BPEG's exercise program was thoroughly explained to the patient, and documentation was provided in both written and graphic form. Each exercise session was carried out under the supervision of a physiotherapist in a clinical environment. Total exercise time ranged from 30 minutes to a maximum of 60 minutes, including warm-up (low-intensity foot ergometer followed by short-term stretching of large muscle groups) and cool-down (short-term stretching exercises followed by abdominal breathing exercises). Balance exercises included exercises on fixed surfaces and progressed to those on mobile surfaces (balance board, Pilates ball). Furthermore, if the patients successfully completed the exercises, they were asked to perform the exercises with their eyes closed to make the exercises more challenging. The proprioception exercise program included: standing on one leg, bending forward-backward-two sides with eyes open, bending forward-backward-two sides with eyes closed, and sitting on the Pilates ball with arms open and one leg extended. As the patients progressed, they were asked to do the same exercises on balance pads while holding a small exercise ball.

Outcome measures

First, demographic data on the study's participants were obtained. The patients' pain intensity was assessed using the Visual Analogue Scale (VAS), their functional status

was assessed using the Fibromyalgia Impact Questionnaire (FIQ), and their balance was assessed using the "Biodex Balance System" (Biodex, Inc., Shirley, New York) device, which was found to be valid and reliable (23,24).

The balance test was applied on the platform of the device in a standing position with both feet for 20 seconds, in triplicate. The mean score of these three times was calculated and recorded as the result. The rest period between repetitions was 60 seconds (25). Overall Stability Index (OSI), Anterior/Posterior Stability Index (APSI), and Medial/Lateral Stability Index (MLSI) data were obtained as test parameters (26).

A blinded physiotherapist who aggregated the outcome data into a specialized database evaluated all the aforementioned scales on the first and last days of the six-week exercise program.

Statistical analysis

G*Power (v3.1.9) software was used to do a power analysis to calculate the number of samples. Repeated measures analysis of variance was used to determine the minimal clinically significant difference (MCID=14%) in the FIQ, the study's main outcome measure based on values acquired from the literature (27,28). The probability of Type 1 error (significance level) was 0.05, and the power of the test was 80% (Type 2 error: 20%). The total number of cases for each group was calculated as 26 and was determined by assessing the likelihood of participants dropping out of the study. A total of 72 patients were evaluated, with 10 of them being excluded because they did not meet the inclusion criteria. As a result, 62 patients participated in the study. The CONSORT flowchart is shown in Figure 1. SPSS ver. 21.0 (IBM Corp., Armonk, NY) was used to analyze the data in the study. Shapiro-Wilk test was used to assess the data's conformity to the normal distribution. The Chi-square test was used to analyze independent qualitative data, whereas the Pearson Chi-Square likelihood ratio was used to evaluate the predicted values of the data in the cross tables. Independent samples t-test was used to examine independent (between-group) two-group normally distributed quantitative data, whereas the paired samples t-test was used to compare two dependent (within-group) quantitative variables. A value of $p<0.05$ was accepted as the statistical significance threshold.

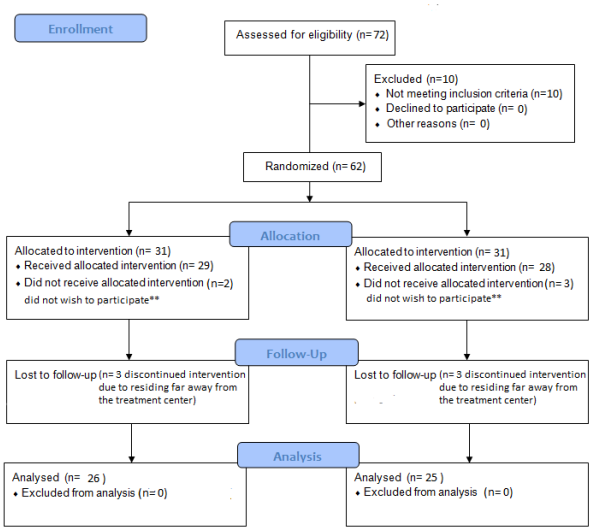

Figure 1: The CONSORT flowchart

RESULTS

A total of 11 of the 62 patients dropped out of the study during the treatment due to the fact that five patients refused to continue treatment, and six of them resided far away from the treatment center and were unable to continue treatment. Twenty-six out of 31 patients in the AEG, and 25 out of 31 patients in the BPEG completed their exercise programs successfully in the study, and the data of 51 patients were analyzed. Table 1 shows the baseline demographic (age, weight, body mass index, etc.) characteristics of the groups. In our study, all the participants were female. There was no statistically significant difference between the demographic characteristics of the groups ($p>0.05$).

At the beginning of the study, there was no statistically significant difference between the FIQ, VAS, and balance assessment values of the groups ($p>0.05$) (Table 2).

Similar to before-treatment findings, there was no statistically significant difference between groups in the evaluation of the FIQ, VAS, and balance scores after treatment ($p>0.05$) (Table 3).

The difference between the before-treatment and after-treatment FIQ and VAS scores was statistically significant in both the groups ($p<0.001$ each) on within-group comparison. After treatment, the FIQ and VAS scores of the groups decreased (Table 4). The results of the within-group comparison showed that values of the Eyes Open Overall Stability Index (EO-OSI) and Eyes Open Anteroposterior Stability Index (EO-APSI) parameters in the BPEG after treatment were decreased and statistically significant ($p=0.008$ and $p=0.043$, respectively), whereas there was no significant difference in the same parameters in the AEG compared with the before-treatment values ($p>0.05$). The changes in Eyes Open Mediolateral Stability Index (EO-MLSI), Eyes Closed Overall Stability Index (EC-OSI), Eyes Closed Anteroposterior Stability Index, and Eyes Closed Mediolateral Stability Index parameters were statistically significant in both the AEG (respectively; $p=0.019$, $p=0.001$, $p<0.001$, $p=0.039$) and BPEG (respectively; $p=0.002$, $p<0.001$, $p=0.002$, $p<0.001$). The results of balance parameters improved following treatment in both the groups (Table 4).

Table 1: Demographic characteristics of the patients

	AEG (n=26) (mean±SD)	BPEG (n=25) (mean±SD)	P value
Age (years)	38.12±9.02	41±5.81	0.180
Body weight (kg)	70.77±14.16	66.36±11.29	0.226
Body mass index (kg/m²)	27.40±5.64	26.43±3.77	0.469
Occupation status	**n (%)**	**n (%)**	
Employed	10 (38.5)	12 (48.0%)	0.206
Unemployed	13 (50.0%)	13 (52.0%)	
Student	3 (11.5%)	0 (0%)	

AEG: Aerobic Exercise Group, BPEG: Balance-proprioception Exercise Group, SD: Standard deviation, n: Number of samples, %: percentage

Table 2: Comparison of the FIQ, VAS, and balance parameters of the groups before treatment

	AEG (n=26) mean±SD	BPEG (n=25) mean±SD	P value
FIQ	72.01±9.31	67.46±13.00	0.156
VAS	8.03±1.37	8.06±1.32	0.955
EO-OSI	0.43±0.14	0.44±0.14	0.817
EO-APSI	0.32±0.14	0.32±0.12	0.912
EO-MLSI	0.21±0.10	0.23±0.12	0.582
EC-OSI	1.29±0.58	1.36±0.49	0.671
EC-APSI	0.97±0.51	0.95±0.49	0.911
EC-MLSI	0.63±0.34	0.71±0.38	0.432

AEG: Aerobic Exercise Group, BPEG: Balance-proprioception Exercise Group, FIQ: Fibromyalgia Impact Questionnaire, VAS: Visual Analogue Scale, EO-OSI: Eyes Open Overall Stability Index, EO-APSI: Eyes Open Anteroposterior Stability Index, EO-MLSI: Eyes Open Mediolateral Stability Index, EC-OSI: Eyes Closed Overall Stability Index, EC-APSI: Eyes Closed Anteroposterior Stability Index, EC-MLSI: Eyes Closed Mediolateral Stability Index, SD: Standard deviation

Table 3: Comparison of the FIQ, VAS, and balance parameters of the groups after treatment

	AEG (n=26) mean±SD	BPEG (n=25) mean±SD	P value
FIQ	34.63±11.85	29.60±12.77	0.152
VAS	4.54±1.83	4.28±1.92	0.626
EO-OSI	0.39±0.17	0.34±0.13	0.208
EO-APSI	0.31±0.16	0.25±0.12	0.177
EO-MLSI	0.15±0.07	0.14±0.05	0.823
EC-OSI	0.85±0.53	0.80±0.33	0.692
EC-APSI	0.65±0.32	0.62±0.29	0.701
EC-MLSI	0.41±0.43	0.35±0.19	0.537

AEG: Aerobic Exercise Group, BPEG: Balance-proprioception Exercise Group, FIQ: The Fibromyalgia Impact Questionnaire, VAS: Visual Analogue Scale, EO-OSI: Eyes Open Overall Stability Index, EO-APSI: Eyes Open Anteroposterior Stability Index, EO-MLSI: Eyes Open Mediolateral Stability Index, EC-OSI: Eyes Closed Overall Stability Index, EC-AP: Eyes Closed Anteroposterior Stability Index, EC-MLSI: Eyes Closed Mediolateral Stability Index, SD: Standard deviation

Table 4: Within-group comparison of changes in the FIQ, VAS, and balance scores

	AEG (n=26)			BPEG (n=25)		
	B.T.	A.T. mean±SD	P value	B.T. mean±SD	A.T. mean±SD	P value
FIQ	72.01±9.31	34.63±11.85	**0.001**	67.46±13.00	29.60±12.77	**0.001**
VAS	8.03±1.37	4.54±1.83	**0.001**	8.06±1.32	4.28±1.92	**0.001**
EO-OSI	0.43±0.14	0.39±0.17	0.350	0.44±0.14	0.34±0.13	**0.008**
EO-APSI	0.32±0.14	0.31±0.16	0.711	0.32±0.12	0.25±0.12	**0.043**
EO-MLSI	0.21±0.10	0.15±0.07	**0.019**	0.23±0.12	0.14±0.05	**0.002**
EC-OSI	1.29±0.58	0.85±0.53	**0.001**	1.36±0.49	0.80±0.33	**0.001**
EC-APSI	0.97±0.51	0.65±0.32	**0.001**	0.95±0.49	0.62±0.29	**0.002**
EC-MLSI	0.63±0.34	0.41±0.43	**0.039**	0.71±0.38	0.35±0.19	**0.001**

AEG: Aerobic Exercise Group, BPEG: Balance-Proprioception Exercise Group, B.T.: Before Treatment, A.T.: After Treatment, FIQ: The Fibromyalgia Impact Questionnaire, VAS: Visual Analogue Scale, EO-OSI: Eyes Open Overall Stability Index, EO-APSI: Eyes Open Anteroposterior Stability Index, EO-MLSI: Eyes Open Mediolateral Stability Index, EC-OSI: Eyes Closed Overall Stability Index, EC-APSI: Eyes Closed Anteroposterior Stability Index, EC-MLSI: Eyes Closed Mediolateral Stability Index, SD: standard deviation

DISCUSSION

AE and BPE programs were found to be effective in improving the functional status, pain, and balance of patients with FMS in our study. However, it was shown that there was no difference between the exercise programs in terms of reducing pain and improving functionality. Whilst the EO-OSI and EO-APSI balance parameters improved in both groups, the improvement in the AEG was not statistically significant. On the other hand, the improvement was statistically significant in the BPEG.

The implementation of diverse exercise modalities, encompassing aerobics, stretching, strengthening, balance, and flexibility has been observed to yield superior outcomes in pain reduction, quality of life enhancement, and functional status improvement among FMS patients, as compared to exercise programs that do not incorporate therapeutic exercises (29-34). This study indicated that both AE and BPE statistically significantly improved the pain and functional status of female patients with FMS. However, we could not find any statistically significant difference between two exercise programs, consistent with the findings of Demir-Göçmen et al. (35). In this context, our findings emphasize the need for individuals with FMS to participate in an exercise program that is appropriate for them to live a pain-free life with high levels of function.

In a study conducted by Duruturk et al., it was shown that the aerobic exercise program had no significant effect on balance parameters, whilst the balance exercise program showed considerable improvements in two of the eight parameters tested (balance on a pad with eyes open and balance in head-up position with eyes closed) (1). In this study, four balance parameters improved in the AEG, whereas all the balance parameters improved in the BPEG. This difference could be attributed to the use of a different balance exercise program in this study compared to Duruturk et al (1). An exercise program that comprised both static and dynamic balance and proprioceptive exercises was used in this study. Moreover, the level of difficulty of the exercises was gradually increased based on the performance of the individual. On the other hand, Colledge et al. examined the relative contributions of proprioceptive, visual, and vestibular components of balance ability in different age groups. The authors argued that the maintenance of balance across all age groups is more dependent on proprioception than vision (36). In this context, we believe that the proprioception exercises performed in this study may have additional contribution balance results. In addition, the younger mean age of the patients in the groups could play a role in the different balance outcomes achieved as young people, by definition, have better physical performance than the elderly in terms of muscle strength, endurance, and reaction time (37). These factors may also have a favorable impact on exercise program compliance and gains, explaining why patients in our study showed significant improvements in numerous parameters.

Eleven of the 62 patients dropped out of the study during the treatment; 6 of them stated residing far away from the treatment center as the reason. A recent study investigating the effects of a Telerehabilitation-based aerobic exercise program on pain intensity, mechanical pain sensitivity, and psychological stress in patients with FMS noted significant improvements, similar to previous face-to-face studies (38). This method could be an appropriate solution for patients with FMS to continue their exercise programs from home, also considering the COVID-19 pandemic conditions, to prevent loss of motivation and interruption of treatment.

The strength of this study arises from the evaluation techniques and equipment utilized for evaluation which were regularly calibrated and had a high level of sensitivity and reliability. Thus, we can confidently state that our study findings are objective and valuable. Furthermore, regular patient follow-up and the supervised implementation of exercise programs in clinical settings provided appropriate exercise performance and safety in terms of any adverse effects.

The limitations of this study include the small number of participants, the lack of a non-exercising control group, and the inability to investigate the long-term effects of exercise.

CONCLUSION

As the outcomes of the two exercise programs assessed for their efficacy on FMS were similar, we believe both exercise regimens can be recommended. Furthermore, we assume that an exercise model tailored to an individual's preferences will be more practical and will help in exercise program adherence over a long-term period. In this context, we suggest that exercises should be incorporated into the treatment of FMS. As a matter of fact, the balance proprioception exercises, apart from the AE models that are often prescribed today, can also be a preferable option.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 22.09.2017, No: 15).

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EVALUATION OF PHYSICAL FITNESS AND ISOKINETIC TEST PARAMETERS OF AMPUTEE FOOTBALL PLAYERS

AMPÜTE FUTBOLCULARIN FİZİKSEL UYGUNLUK VE İZOKİNETİK TEST PARAMETRELERİNİN DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: This study was designed to investigate the effect of participation in sports on the functional capacity of a person with an amputation.

Material and Method: The study included a sports group of 29 male football players with unilateral lower limb loss aged between 18-45 years and a control group of 11 sedentary persons with an amputation. Body composition, postural stability, and trunk muscle strength were measured with a skinfold, Biodex Stability System, and dynamometer. A pulmonary function test and cardiopulmonary exercise test were performed. Aerobic capacity was evaluated by cardiopulmonary exercise test using the breath-by-breath method.

Result: Skinfold thickness measurements performed at the triceps, thigh, and calf regions were higher in the sports group ($p<0.05$), whereas body fat percentage indicated no significant difference among both groups ($p>0.05$). The sports group had higher postural stability, trunk muscle strength, and endurance ($p<0.05$). Predicted maximum voluntary ventilation (MVV%) and peak expiratory flow (PEF%) values were significantly higher in the sports group ($p<0.05$). The sports group had higher heart rates corresponding to the anaerobic threshold ($p<0.05$). At the same time, no significant difference was observed between the two groups concerning resting and maximum heart rate ($p>0.05$). The sports group had longer exercise times and higher gas exchange values ($p<0.05$).

ÖZET

Amaç: Bu çalışma, ampütasyonu olan kişilerin spora katılımının fonksiyonel kapasiteleri üzerindeki etkisini araştırmak için yapılmıştır.

Gereç ve Yöntem: Çalışmaya 18-45 yaş arası tek taraflı alt ekstremite kaybı olan 29 erkek futbolcudan oluşan spor grubu ve ampütasyonu olan sedanter 11 kişiden oluşan kontrol grubu dahil edildi. Vücut kompozisyonu, postural stabilite ve gövde kas kuvveti sırasıyla skinfold, Biodex Stabilite Sistemi ve izokinetik dinamometre ile ölçüldü. Solunum fonksiyon testi ve kardiyopulmoner egzersiz testi yapıldı. Aerobik kapasite, breath-by-breath (her nefeste) yöntemi kullanılarak kardiyopulmoner egzersiz testi ile değerlendirildi.

Bulgular: Triseps, uyluk ve baldır bölgelerinden yapılan deri kıvrım kalınlığı ölçümleri spor yapan grupta daha yüksek bulundu ($p<0,05$), vücut yağ yüzdesi ise her iki grup arasında anlamlı bir fark göstermedi ($p>0,05$). Postural stabilite, gövde kas kuvveti ve dayanıklılığı spor yapan grupta anlamlı olarak yüksekti ($p<0,05$). Tahmin edilen maksimum istemli ventilasyon (%MVV) ve tepe ekspiratuar akış (%PEF) değerleri spor yapan grupta anlamlı olarak yüksekti ($p<0,05$). Anaerobik eşiğe karşılık gelen kalp hızları spor grubunda daha yüksek bulunurken ($p<0,05$), istirahat ve maksimum kalp hızı açısından iki grup arasında anlamlı bir fark gözlemlenmedi ($p>0,05$). Spor yapan grubun egzersiz süreleri ve gaz değişim değerleri daha yüksekti ($p<0,05$).

*This study is based on the master thesis of the first author.
**The study was presented as an oral presentation at the 44th National Congress of Physiology in Turkey, held on November 1st-4th, 2018.
***In this study, 6 participants with upper extremity amputations included in the sports group were excluded to ensure homogeneity, and the results were re-evaluated.

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Conclusion: Postural stability, trunk muscle strength, and physical condition were better in football players. These findings suggest that performing regular physical activities positively affects the development of physical performance in a person with an amputation.

Keywords: Football, cardiopulmonary exercise test, muscle strength, amputation

Sonuç: Postural stabilite, gövde kas kuvveti ve fiziksel kondisyon futbolcularda daha iyi seviyedeydi. Bu bulgular, ampütasyonu olan kişilerde düzenli fiziksel aktivite yapmanın fiziksel performans gelişimi üzerine olumlu etkileri olduğunu düşündürmektedir.

Anahtar Kelimeler: Futbol, kardiyopulmoner egzersiz testi, kas gücü, ampütasyon

INTRODUCTION

Amputation that disrupts the biomechanics of the musculoskeletal system is a significant trauma leading to physical, psychological, and occupational losses. It also leads to decreased walking and running activities and increased energy needs, difficulty in adapting to a prosthesis, fatigue, atrophy in the stump, joint limitation, and loss of physical ability, thereby leading to immobilization and, as a result of complications, worsened general health condition (1-4). In disabled individuals, physical and sports activities improve public health, reduce the risk of chronic diseases, prevent complications, and decrease anxiety and depression (2, 5, 6). In addition, encouraging disabled individuals to participate in such sports activities may also lead to reduced health expenditures (7).

Studies evaluating body composition, respiratory capacity, and physical fitness level in healthy professional athletes are frequently encountered in the literature (8, 9). However, studies examining the effect of sports activities on amputees' lifestyles are limited. In most studies, indirect measurement-field tests determine aerobic capacity and physical condition (10-12). Although field tests provide information on individuals' aerobic capacity, there is a need for evaluation with laboratory test methods, which can provide more reliable results. In addition, although many studies investigate the physical ability of healthy sedentary individuals, there are only a limited number of studies investigating the sedentary lifestyle caused by amputation (2, 13).

Amputee football is becoming a growingly popular sport in Turkiye and the world. Moreover, amputee football has recently emerged as an exciting subject among sports scientists. However, since there are a limited number of studies on this subject, it is not easy to standardize the data obtained due to the wide variation in the evaluation methods used by these studies. A recent systematic review showed that studies investigating amputee football are scarce (14). Thus, there is a need for more research on the characteristics of this sport, particularly in terms of the physiological and anthropometric parameters of the athletes (14). In this cross-sectional controlled study, we aimed to investigate the effect of playing football on body composition, postural stability, trunk muscle strength, pulmonary functions, and aerobic capabilities in individuals with unilateral lower limb loss.

MATERIAL and METHODS

Design and participants

This study included a sports group of 29 male football players with unilateral lower limb loss aged between years (recruited at Pendikspor Amputee Football Team) and a control group of 11 sedentary peer individuals who applied to a prosthetics unit at Istanbul. All the participants had unilateral lower limb loss and had adequate cognitive and physical abilities to complete the tests in the study. The inclusion criteria were playing football actively for at least one year for the sports group and not regularly participating in any sport for at least six months before the study for the control group. We excluded a person with amputation with visual and cognitive defects and chronic systemic diseases from the survey.

Procedures

We performed all the tests in two days between 09.00 and 11.00 AM. On the first day, we recorded the descriptive and clinical characteristics of the participants and measured body composition, postural stability, trunk strength, and endurance. On the second day, we performed pulmonary function tests (PFTs) and cardiopulmonary exercise tests (CPET). Following data analysis, the participants were informed about the results obtained in the study.

Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Holtain skinfold caliper (Cambridge Scientific Industries, Cambridge, MD, USA) was used to determine body fat percentage. Skinfold measurements were performed on the right side in a standing position. In the participants with right limb loss, measurements were obtained on the left side, and eight values obtained from different regions were recorded. Body fat percentage was measured using the Jackson Pollock (J-P) method (15).

Biodex Balance System (Biodex, Inc, Shirley, New York) platform was used to evaluate single-leg stance postural stability. During the test, all the participants were barefoot and remained on one foot, with hands parallel to the body and eyes open and fixed on the horizon. At the

beginning of the trial, the participants were instructed to maintain balance throughout the procedure. The same procedure was repeated three times for the non-amputated limb, and each repetition lasted twenty seconds, with a 10-second rest interval. Overall Stability Index (OSI), Anterior-Posterior Stability Index (APSI), and Medial-Lateral Stability Index (MLSI) were assessed for each participant.

Isokinetic trunk flexion and extension strength were evaluated using a computerized isokinetic dynamometer (Cybex Humac Norm 2, USA). Pads stabilize the lower limb or limbs. A belt was used to secure the pelvis and limit hip flexor muscles' use. A shoulder harness and backrest provided anchorage to the moving upper section of the apparatus. Strength was measured with a trunk flexion-extension movement consisting of 5 repetitions at 60°/sec, and the endurance test was performed with 15 repetitions at 90°/sec. The interval (rest time) was 20 sec. Peak torque for flexor and extensor muscles was measured under isokinetic conditions, and the muscle torque was adjusted to body weight (BW).

The lung volumes, capacities, and flow velocities were measured by spirometry (Spirobank). The slow vital capacity maneuver, forced vital capacity, and maximal voluntary ventilation were performed three times, and the highest value was calculated for each. The highest values of forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), forced expiratory ratio ([FEV1/FVC] x100), predicted peak expiratory flow (%PEF), vital capacity (VC), and predicted maximum voluntary ventilation (%MVV) were recorded. These maneuvers were performed in the sitting position with the nasal clip attached.

After obtaining resting electrocardiograms (ECG), cardiopulmonary exercise tests were performed on a Quinton 65 double-arm ergometry bicycle with a Q 5000 stress test system (Quinton 5000, USA) using an Ergospirometry system (Metalyzer 3B system, Metasoft 2.7 software, Cortex, Germany) to measure cardiopulmonary parameters including oxygen uptake and carbon dioxide output, using the breath-by-breath method with a two-way non-rebreathing facemask (Series 7910-Hans Rudolph Inc, Kansas City, Missouri, USA). After a 3-minute steady-state workload at 25 watts, the workload was increased continuously by 15 watts every 3 min. After reaching maximal volitional fatigue, participants cycled for recovery every 3 minutes at 0 watts. Twelve-lead ECG and gas exchange measurements were recorded continuously (Mason-Likar type). The breath-by-breath gas exchange method measured ventilation, oxygen consumption, and carbon dioxide production, and data were averaged in 10 seconds periods. A Peak Oxygen Consumption (VO_2 peak) was calculated as the mean value of three measures of VO_2 during the final 10 seconds of the exercise. Exercise duration (min), peak, and resting heart rate were measured. The anaerobic threshold value was calculated using the V-Slope method.

G*Power Analysis program (http://www.gpower.hhu.de/) was used to determine the sample size. According to the data from the studies, the size of effect size was evaluated at 0.97. We concluded that we could obtain meaningful data when we included a minimum of 24 participants in the evaluations, where we received a Type 1 error amount (α value) of 0.05 and a Type II error amount (β value) of 0.5 (12).

The protocol for this study was approved by the Ethics Committee of Istanbul University (Date: 27.10.2017, No: 17) and performed following the principles of Declarations of Helsinki. A written declaration of informed consent was obtained from each participant.

Statistical analysis

Data were analyzed using SPSS ver.21.0 (IBM Corp. Armonk, NY). Descriptive statistics were expressed as frequencies (n) and percentages (%) for categorical variables and as mean, standard deviation (SD), and median for continuous variables. Anthropometric parameters, including postural stability, muscle strength, and aerobic capacity, were compared between the two groups using the Student's t-test. A p-value of <0.05 was considered significant.

RESULTS

The two groups had similar demographic characteristics ($p>0.05$) (Table 1). The amputation features of the participants in both groups are presented in Table 2. Table

Table 1: Demographic characteristics of the participants

Parameters	Control group (n=11)	Sports group (n=29)	p
Age (years)	30.4±8.57	30.3±6.07	0.97
Height (cm)	175±3.7	174±6.39	0.63
Weight (kg)	75±16	67.9±10.3	0.11
BMI (kg/m^2)	24.36±5.1	22.38±3	0.81
Age at amputation (years)	12±11.7	15.8±7.76	0.24

BMI: Body mass index

3 shows the body composition of the participants. The measurements performed at the triceps, femur, and calf regions were significantly lower in the sports group compared to the control group (p<0.05). No significant difference was found between the two groups concerning body fat percentage (p>0.05) (Table 3). The OSI – APSI values were lower in the sports group (p<0.05). The MLSI value was significantly lower in the sports group compared to the control group (p=0.01) (Table 3). It means the sports group had better postural stability than the control group. According to trunk muscle strength assessment, the flexor and extensor muscle strength at 60⁰/sec angular velocity values were significantly higher in the sports group compared to the control group (p<0.05) (Table 3). In addition, 60°/sec flexor and extensor peak torque/%body weight values were significantly higher in the sports group (p=0.01) (Table 3). The flexor and extensor muscle endurance at 90°/sec angular velocity values were significantly higher in the sports group (p<0.05), and at 90°/sec, flexor and extensor peak torque/%body weight values were higher in the sports group than the control group (p=0.01) (Table 3).

In the respiratory capacity assessment, the %PEF and %MVV values were significantly higher in the sports group compared to the control group (p<0.05) (Table 4). CPET results showed that the sports group had higher heart rates corresponding to the anaerobic threshold,

Table 2: Amputation features of the participants

Parameters		Control group (n=11)	Sports group (n=29)
Amputation level (n, %)	Above knee	7 (63.6)	19 (65.5)
	Below knee	4 (36.4)	10 (34.5)
Amputation Side (n, %)	Right	5 (45.5)	13 (44.8)
	Left	6 (54.5)	16 (55.2)
Cause of amputation (n, %)	Congenital	1 (9.09)	3 (10.35)
	Traumatic	10 (90.9)	23 (79.31)
	Neoplasm	0	3 (10.35)

Table 3: Comparison of body composition, balance, and trunk muscle strength parameter values between two groups

Parameters	Control group (n=11)	Sports group (n=29)	p
Abdominal (mm)	23.57±12.05	18.98±10.03	0.28
Pectoral (mm)	11.15±6.66	8.05±4.66	0.18
Suprailiac (mm)	23.35±12.43	15.38±8.34	0.07
Biceps (mm)	7.71±5.26	4.59±1.38	0.08
Triceps (mm)	12.85±4.52	8.02±3.21	0.006*
Subscapular (mm)	21.16±11.14	14.97±7.47	0.11
Femur (mm)	15.93±8.52	8.4±4.05	0.016*
Calf (mm)	8.78±3.24	4.59±2.44	0.001*
Body fat percentage (%)	15.16±7.82	10.47±5.25	0.09
OSI (°)	1.44±0.71	0.92±0.29	0.04*
APSI (°)	1.02±0.58	0.61±0.26	0.04*
MLSI (°)	0.95±0.45	0.55±0.22	0.01*
60°/sec FPT	224.55±62.85	276.45±56.74	0.02*
60°/sec FPT %BW	302.45±70.93	408.41±72.95	0.001*
60°/sec EPT	184.27±53.73	228.35±49.97	0.035*
60°/sec EPT %BW	246.36±54.88	339.79±80.62	0.001*
90°/sec FPT	220.45±54.79	271.07±53.27	0.02*
90°/sec FPT %BW	295.82±59.35	401.41±71.34	0.001*
90°/sec EPT	163±51.26	204±55.2	0.046*
90°/sec EPT %BW	217.18±55.21	304.28±87.56	0.001*

Values are mean±SD, APSI: Anterior-Posterior Stability Index, MLSI: Medial-Lateral Stability Index, OSI: Overall Stability Index, FPT: Flexor peak torque, EPT: Extensor peak torque, %BW: % Body weight, *Statistical significance (p<0.05)

and this group exercised longer than the control group ($p<0.05$). However, no significant difference was found between the groups regarding resting and maximum heart rate ($p>0.05$) was found. The mean ventilation (anVE, VE peak), oxygen consumption ($anVO_2$, VO_2 peak), and carbon dioxide production ($anCO_2$, CO_2 peak) values were significantly higher in the sports group compared to the control group ($p=0.01$) (Table 4).

DISCUSSION

In this study, the effect of football on amputees was measured with different physical fitness tests (body composition, postural stability, strength, pulmonary functions, aerobic and anaerobic capacity), and the results were compared with the values of sedentary amputees and evaluated statistically. In the skinfold fat measurement used to determine the body composition, the fat ratio of the triceps region of the amputee football players was lower. This may be due to the use of crutches during training and matches. In addition, the fat ratios of the thigh and calf regions were also found to be lower than sedentary amputees. These regions show the positive effect of football-specified activities on the body composition of amputee football players. When the body fat percentage obtained by J-P method was compared, no difference was found between the groups. The fact that the fat ratios in the chest and abdomen regions were similar in both groups may have caused this result. The J-P method may not be a specific measurement method for this amputee football players. However, when the literature is examined, the body fat ratio of amputee players is similar to the results in our study (10, 12, 16).

Football-specific movements such as defending, running, attacking, throwing, and dribbling are performed by providing postural stabilization. The ability to kick the ball and perform different technical movements in football requires a standing posture on one leg. In amputee football, while the football players fix their bodies with forearm crutches,

Table 4: Comparison of respiratory function and cardiopulmonary exercise test parameters values between two groups

Parameters	Control group (n=11)	Sports group (n=29)	p
%FVC	89.64±16.08	91.26±12.28	0.77
$\%FEV_1$	95.18±13.33	97.47±12.32	0.64
$\%FEV_1/FVC$	110.55±11.47	109.43±7.14	0.77
FEV %25-75	99.09±16.97	101.57±24.16	0.73
FEV %50	93.63±16.65	97.57±24.53	0.59
%PEF	76.55±11.04	88±15.82	0.021*
%MVV	88.64±13.70	107.00±15.88	0.002*
%IC	89.18±22.26	85.08±13.56	0.58
HR-rest (bpm)	78.27±8.91	80.22±14.85	0.64
HR-peak (bpm)	150.73±19.39	164.26±25.75	0.10
HR-AT (bpm)	108.27±12.7	133.52±19.22	0.001*
Exercise duration (sec)	273.09±136.76	483.86±180.79	0.001*
$anVO_2$ (L/min)	0.95±0.26	1.44±0.38	0.001*
$anVO_2$ (ml/kg/min)	14±3.66	21±6.33	0.001*
$anVCO_2$ (L/min)	0.92±0.24	1.41±0.41	0.001*
anVE	28.23±7.8	40.57±11.86	0.001*
VO_2peak (L/min)	1.15±0.33	2.00±0.65	0.001*
VO_2peak (ml/kg/dk)	17.36±3.88	29.65±9.49	0.001*
VCO_2peak (L/min)	1.29±0.44	2.23±0.78	0.001*
VEpeak	41.38±15.3	66.34±21.46	0.001*

Values are presented as mean±SD, FVC: Forced vital capacity, FEV_1:Forced expiratory volume in the first second, FEV: Forced expiratory ratio, %PEF: Predicted peak expiratory flow, %MVV: Predicted maximum voluntary ventilation, IC: Inspiratory capacity, HR: Heart rate, AT: Anaerobic threshold, $anVO_2$: Oxygen consumption at anaerobic threshold, $anVCO_2$: Production of carbon dioxide at anaerobic threshold, anVE: Ventilation amount at anaerobic threshold, VO_2peak: Peak oxygen consumption, VCO_2peak: Peak carbon dioxide production, VE-peak: Peak ventilation amount, *Statistical significance ($p<0.05$)

they interfere with the ball with their intact limbs. When we examined the postural stability on one leg in our study, it was observed that amputee football players' general, anterior-posterior, and medial-lateral stability index values were lower than sedentary amputees.

Due to the displacement of the center of gravity in amputees, the balance is disturbed, and more energy is needed to control the balance (2). It is known that amputees need more power in daily life activities and depend on using assistive devices (2, 4). This can result in amputees getting tired more quickly, a lack of motivation during mobility, and increased energy costs (2, 4, 5). However, this study also shows that amputee football players' physical condition values were higher than the control group, indicating that participation in sports reduces the disadvantages of amputation.

Buckley et al. compared static and dynamic balance values of six healthy and six amputee individuals and reported that the balance values were worse in a person with an amputation (17). The authors also noted that the anterior-posterior balance control was worse than the medial-lateral direction balance control in dynamic balance testing. In our study, amputated individuals could not be compared with healthy individuals since there was no healthy control group. However, in our study, amputee football players showed better postural stability than sedentary amputees. Therefore, we can say that football positively affects postural stability.

Trunk stabilization is explained according to the principle of proximal stability for distal mobility (18). Good trunk stabilization is required for football-specific technical skills such as dribbling, passing, shooting, tackling, and defending. Guchan et al. evaluated the strength and endurance of back extensor and abdominal muscles in amputated football players and sedentary amputee individuals (12). They reported that football players' trunk muscle strength (flexion, extension) and endurance improved (12). In our study, the strength and endurance of the trunk flexor and extensor muscles were evaluated at 60°/sec and 90°/sec angular velocities. Moreover, we found that amputee football players had higher trunk muscle strength and endurance. According to these data, we can say that football positively affects strength, which is one of the physical fitness parameters.

The central nervous system, musculoskeletal system, and cardiopulmonary system should coordinate to perform different movements in a 50-minute football match. Low and high levels of effort can be completed by inhaling oxygen, ensuring the passage of inhaled oxygen from the lungs to the blood, transmitting oxygen through the blood, and ultimately generating energy. Therefore, a pulmonary function test is essential in determining physical fitness. In this study, %FEV1, %FVC, %FEV1/FVC values were similar. These results depend on many factors, such as respiratory muscle strength, lung capacity, and airway resistance. The fact that there was no significant difference in respiratory muscle test results between amputee football players and sedentary amputees suggests that respiratory functions may be similar. However, further research may be needed to determine the exact reasons for these results.

Vital capacitiy is another parameter that is evaluated in football players. However, maximum voluntary ventilation is the value to be considered (%MVV) (19). Vital capacity can give misleading results because it is affected by factors such as body structure, body condition during measurement, the strength of respiratory muscles, and lung and chest wall ability to expand. Therefore, the %MVV value should be examined. %MVV, 110-120 lt/min in normal individuals, increases to 170-180 lt/min in football players (19). In our study, the %MVV value of the amputee football players was 107 lt/min. The shorter duration of the match and the differences in the game characteristics of amputee football may have caused the %MVV value to be lower. However, in this study, amputee football players' %MVV value was significantly higher than sedentary amputees. Considering this result, we can say that football positively affects respiratory functions, one of the physical fitness parameters. In addition, the present study is the first to evaluate the respiratory functions of amputee football players.

As stated in the study, the average resting and maximum heart rate values were similar between amputee football players and sedentary amputees. This is because resting and maximum heart rates are typically determined by genetic factors, training level, overall health, and related exercise capacity (21). Therefore, even high-level athletes like amputee football players may have similar maximum heart rate values as sedentary amputees. However, more research is needed to understand this relationship fully. Anaerobic capacity is a metabolic pathway the body uses to produce energy without oxygen. The pathway is used during high-intensity exercise and is essential for short, intense activities. High-performance athletes like amputee football players can increase their anaerobic capacity by working out according to their training programs. This can result in high anaerobic heart rate values than sedentary amputees. Our results support this pathway's effects. The mean maximum heart rate run by the football players corresponded to 85.69% of the targeted heart rate value. A previous study that involved eight amputee players and 20 healthy individuals reported that the mean heart rate of amputee players was 161 bpm in the cardiopulmonary exercise test (double-arm ergometer bicycle test), which corresponded to 86% of the targeted heart rate value (20). These results are consistent with those of our study.

In our study, the peak oxygen value used by the mus-

cles during the double-arm ergometer bicycle test was determined by the Breath-by-Breath method. The mean VO_2 peak value reached 29.65 ml/kg/min in the amputee football players. Mikami et al. evaluated eight amputee players using the Arm Ergometer Bicycle Test and Breath-by-Breath method and reported a mean VO_2 peak value of 30.3 ml/kg/min (20). This finding is similar to our study. However, the VO_2 peak value during the double-arm ergometer bicycle test is approximately 70% of that in bicycle ergometer exercise due to the smaller muscle mass and the maximum achievable workload. Many studies have shown that the cycling ergometer VO_2 peak value is approximately 89–95% of the value obtained with treadmill exercise (21, 22). Therefore, measurement with a double-arm ergometer bicycle may have resulted in a lower VO_2 peak value.

The VO_2 level is an indicator of the use of oxygen by the muscles during exercise. Considering that one of the extremities of the athletes included in our study is amputated, it is seen that a large muscle group that will carry the most oxygen is removed from the body during exercise. In addition, the VO_2 values found in these athletes are inevitably below the expected values since the blood circulation in the entire lower extremity does not increase as much as in a test performed with treadmill since the test in this study was performed with the arm ergometer.

The high heart rate at the anaerobic threshold (HR-AT) and oxygen consumption capacity (anVO_2) of amputee football players are indicators of improvement in aerobic capacity. The high amount of oxygen used by the muscles in amputee football players during the cardiopulmonary exercise test is an essential indicator of the development of aerobic capacity (26). Likewise, the significant increase in the VO_2 peak values of football players supports this finding. Moreover, our metabolic evaluation findings indicated that the mean anVO_2 (L/min), anVO_2 (ml/kg/min), anVCO_2 (L/min), anVCO_2 (ml/kg/min), VO_2 peak (L/min), VO_2 peak (ml/kg/min), VCO_2 peak (L/min), and VCO_2 peak (ml/kg/min) were also significantly higher in the amputee football players. This notion supports the hypothesis that performing sports activities positively affects the aerobic conditions of amputated individuals.

In conclusion, the results indicated that playing football positively affects body composition, postural stability, muscle strength, pulmonary functions, and aerobic and anaerobic capacity in amputee players. This is the first study to compare sedentary amputees and amputee football players in a laboratory environment. Our findings indicated that physiological parameter variability would guide health scientists studying this field. Further studies are needed to substantiate our findings.

The limitation of this study is the small number of amputee athletes included since amputee football is a disabled sport played with seven players in each team (six outfield players and one goalkeeper). Outfield players have lower-extremity amputations, and goalkeepers have upper-extremity amputations. We could not include and evaluate goalkeepers in this study, as we could not get sedentary amputees with upper extremity amputation to participate. Also, laboratory test that measure aerobic and unaerobic capacity in goalkeepers are different from outfield players (treadmill vs arm ergometer). For this reason, the values obtained may be lower than expected. We propose developing a cardiopulmonary exercise test specifically for amputee football players.

CONCLUSION

This study proves that amputee football players have significantly better physical conditions than sedentary amputees. The findings suggest that participation in amputee football can positively impact the physical condition of amputees. Further research is needed to identify strategies to encourage more amputees to participate in football-specified activities. The study highlights the importance of promoting football activities and training programs for amputees to improve their health.

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NEEDLE PENETRATION DEPTH ACCORDING TO GENDER AND BODY MASS INDEX IN VENTROGLUTEAL INTRAMUSCULAR INJECTIONS IN ADULTS

YETİŞKİNLERDE VENTROGLUTEAL İNTRAMUSKÜLER ENJEKSİYONLARDA CİNSİYET VE BEDEN KİTLE İNDEKSİNE GÖRE İĞNE PENETRASYON DERİNLİĞİ

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ABSTRACT

Objective: This study aimed to investigate the needle penetration depth in ventrogluteal intramuscular injections in adults, taking into account gender and body mass index (BMI).

Material and Method: This study was designed as correlational research with a sample of 232 patients. The ventrogluteal intramuscular injection area was identified using V and G methods and these points were examined under ultrasonography; the subcutaneous tissue, M. gluteus medius, and M. gluteus minimus thicknesses were defined by considering the gender and BMI. Data analysis was performed using arithmetic mean, standard deviation, frequency, percentage, Independent Samples t Test, and ANOVA.

Result: Needle penetration depth is between 20-48 mm in thin women, 18-53 mm in normal weight women, 29-62 mm in overweight women, and 26-88 mm in obese women; 23-37 mm in thin men, 18-41 mm in normal weight men, 25-50 mm in overweight men, and 17-82 mm in obese men. In addition, it was determined that needle penetration depth was statistically different according to the BMI category for both women and men ($p<0.001$) and also statistically different according to gender ($p<0.001$).

Conclusion: Particularly in overweight and obese women, longer needles should be used. In addition, considering BMI, the needle penetration depth in women should be greater than in men. It was found that the range of needle penetration depths

ÖZET

Amaç: Bu çalışma, yetişkinlerde ventrogluteal bölgeye intramüsküler enjeksiyon sırasında cinsiyete ve beden kitle indeksi (BKİ) dikkate alınarak iğne penetrasyon derinliğini belirlemek amacıyla yapıldı.

Gereç ve Yöntem: İlişki arayıcı türde yapılan araştırmanın örneklemi 232 hastadan oluştu. V ve G yöntemleri ile ventrogluteal intramusküler enjeksiyon alanı belirlendi ve bu noktalar ultrasonografi altında incelendi. Cinsiyet ve BKİ dikkate alınarak deri altı doku, M. gluteus medius ve M. gluteus minimus kalınlıkları saptandı. Veri analizi, aritmetik ortalama, standart sapma, frekans, yüzde, bağımsız örneklem t testi ve ANOVA kullanılarak yapıldı.

Bulgular: İğne penetrasyon derinliği zayıf kadınlarda 20-48 mm, normal kilolularda 18-53, kilolularda 29-62 mm, obezlerde 26-88 mm arasında; zayıf erkeklerde 23-37 mm, normal kilolularda 18-41 mm, fazla kilolularda 25-50 mm, obezlerde 17-82 mm arası uzunlukta bulundu. Ayrıca iğne penetrasyon derinliğinin BKİ sınıflamasına göre kadın ve erkeklerde istatistiksel olarak farklı olduğu belirlendi ($p<0,001$) ve cinsiyete göre de istatistiksel olarak farklıydı ($p<0,001$)

Sonuç: Özellikle kilolu ve obez kadınlarda daha uzun iğneler tercih edilmelidir ve BKI dikkate alınarak kadınlardaki iğne penetrasyon derinliği erkeklerden fazla olmalıdır. Ayrıca iğne penetrasyon derinliği aralığının geniş olduğu görülmektedir ve bu nedenle IM enjeksiyon uygulamasında, bireye özgü değerlendir-

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is wide and should therefore be assessed individually during IM injection; adipose tissue thickness and muscle condition should be assessed by palpating the area.

Keywords: Body mass index, gender, intramuscular injection, ventrogluteal area, needle penetration depth

me yapılmalı, yağ dokusunun kalınlığı ve kasların durumu bölge palpe edilerek tanılanmalıdır

Anahtar Kelimeler: Beden kitle indeksi, cinsiyet, kas içi enjeksiyon, ventrogluteal bölge, iğne penetrasyonu

INTRODUCTION

Intramuscular (IM) injections involve many risks. Potential complications include abscesses, necrosis, tissue irritation, muscle tissue fibrosis, bone injury, and sciatic nerve damage. Of these, especially bone injury and injection of the medication into the subcutaneous tissue can be prevented by applying the needle to the correct location during injection, and specifically, by penetration into muscle (1-4).

For the drug to reach the gluteus medius muscle, all of the injector needles must reach the fascia part of the muscle. The interval to the gluteus medius muscle is defined by two elements: the thickness of subcutaneous adipose directly beneath the injection area, and the availability or tonus of the gluteus medius muscle (5-8). The needle length for IM injection is selected based on the patient's muscle development, body weight, and injection type (2).

Many needles that are available in healthcare environments are not long enough to reach muscle tissue, especially in women and obese individuals. Since most institutions only have needles ranging from 3/8 to 1.5 inches in length, nurses must seek alternate routes for medication, especially when IM injections are ordered for obese and women patients (9, 10).

The standard IM injection needle used in clinical practice (1.25 inches, 32 mm) reaches a penetration depth of about 30 mm (6-7). Subcutaneous adipose tissue thicker than 25 mm causes undesired drug accumulation, slower drug absorption, reduced drug efficacy, and local tissue damage (11). In IM injection, to effectively inject into the muscle tissue without damaging the bone by passing the subcutaneous tissue, the needle must have a sufficient length and an internal diameter that can vary depending on the type of drug. However, standard needles are sometimes unsuitable for injection into the gluteal muscle. Therefore, problems related to the issues of needle length and the type and amount of fluid to be injected IM should be adequately examined with evidence-based studies (7–9). Kaya et al.'s study provided a significant response to the questions regarding determining the area (3).

A needle of appropriate length should be chosen to allow the needle to penetrate the muscle during IM injection (1,3). The appropriate length can be determined according to the gender and BMI of the individual (12-14). Gender, body weight, and height affect muscle and subcutaneous adipose distribution in the gluteal area (7,12). This study was conducted to define needle penetration depth (NPD) according to gender and body mass index for IM injections in the ventrogluteal area of adults. The research questions are as follows:

Does BMI affect NPD when IM injection is applied to the ventrogluteal area?

Does gender affect NPD when applying IM injection to the ventrogluteal area?

MATERIAL and METHODS

Study design

The study was conducted with a correlational design to define the NPD according to gender and BMI during IM injection in the ventrogluteal area in adults.

Study population

The population of the study consisted of patients hospitalized in a university hospital between September 2017 and June 2018. The sample consisted of 232 randomly selected individuals.

Data collection tools and procedures

Patient information form: Data were collected by a patient information form consisting of 14 questions created by reviewing the literature (1,3,6,12,13,15,16). This form, developed by the researchers, consists of two parts. In the first part, age, gender, height, weight, and BMI data were questioned. In the second part, ventrogluteal area data were examined under ultrasonography (presence and location of M. gluteus medius and M. gluteus minimus in the area defined by the G and V methods, the thickness of subcutaneous tissue in the designated area, M. gluteus medius and M. gluteus minimus thickness, etc.) were noted.

The individual who decided to be included in the study was informed in written and verbal ways, their volunteering was confirmed, height-weight was measured, and gender was recorded. The researcher determined the ventrogluteal area by the V method described in textbooks of nursing principles and marked the puncture area with a dermograph as "V" (9,13). At the same time, the ventrogluteal area was determined again by the method specified in the literature and named the

geometric method and this puncture area was marked with a dermograph as "G"(3,17). Another researcher authorized to perform ultrasonography determined the presence of M. gluteus medius and M. gluteus minimus, subcutaneous (SC) tissue, M. gluteus medius, and M. gluteus minimus thickness in the marked areas using ultrasonography. The distance between the skin and the bone was determined by collecting SC tissue, M. gluteus medius, and M. gluteus minimus thickness in the areas determined by the G and V methods. In IM injection, the needle tip is desired to come to the middle of the muscle layer. Therefore, to determine the NPD, M. gluteus medius and M. gluteus minimus thickness were summed and divided into two, and SC tissue thickness was added to this result.

It was carried out in incompliance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 22.04.2015, No: 870). Participants were aware of the aim and advantages of the survey and their roles in the study. The written and verbal permit was obtained from the participants, denoting that they were aware of the pertinent aspects of the study.

Data analysis

Data were analyzed in the Statistical Package for Social Sciences Windows 22.0 program. Minimum, maximum values, arithmetic mean, and standard deviation were used for the evaluation of ordinal (continuous) data; frequency and percentage calculations were used to evaluate nominal (discontinuous) data. A Group Kolmogorov-Smirnov Goodness of Fit Test was applied to analyze the obtained data's normality. It was determined that the distributions were normal, and a t-test was used to determine the difference between the mean of two groups in independent groups, and one-way ANOVA methods were used to determine the difference between the means of more than two groups. Bonferroni method was applied for the Multiple Comparisons in cases where there was a significant difference. The level of significance for all analyses was set at $p \leq 0.05$.

RESULTS

The average age of the patients included in the study was 35.02±10.62 years (minimum=18, maximum=70), 58.2% were women and 41.8% were men. Among all cases, it was determined that 23.3% were underweight, 31.9% were normal weight, 25.4% were overweight, 19.4% were obese, and the average BMI was 24.31±5.61 (minimum=15, maximum=41). BMI classes according to gender are shown in Figure 1. Accordingly, 26.7% of women were underweight, 31.9% were normal weight according to height, 20.7% were overweight, and 20.7% were obese, and the average BMI was 24.11 (SD=6.08, minimum=15, maximum=41). Also, the situation for men was 18.6% underweight, 32% normal weight, 32% (n=31) overweight, and 17% obese, and the mean BMI was 24.58 (SD=4.91, minimum=17.90, maximum = 40).

Needle penetration depth, SC tissue, M. Gluteus medius, M. Gluteus minimus, and total thickness values below the injection puncture point determined according to the G and V methods in women and men were examined according to BMI (Tables 1,2,3 and 4).

In the G method, needle penetration depth was found to be between 20.4-48.3 mm for under-weight women, 18.6-53.8 mm for normal-weight women, 29.7-62.5 mm for overweight women, and 26.7-88.0 mm for obese women. In addition, it was determined that NPD was statistically different according to BMI classes ($p<0.001$) and this difference was because the mean value of depth of the needle in under-weight and normal-weight women was statistically significantly lower than in overweight and obese women (Table 1). Similar results were obtained in the V method (Table 2).

When the area was determined according to the G method, needle penetration depth was found to be between 23.0-37.5 mm for under-weight men, 18.9-41.5 mm for normal-weight, 25.7-50.4 mm for overweight, and 17.5-82.3 mm for obese. In addition, it was determined that the needle length was statistically different according to BMI classes ($p<0.001$). Multiple comparisons showed that the mean depth of needle value was statistically lower in under-weight men than obese, and in normal-weight men than in overweight and obese men (Table 3). Similar results were obtained in the measurements obtained by determining the area with the V method (Table 4).

Table 5: Shows that the NPD was statistically different according to gender in both methods ($p<0.001$.

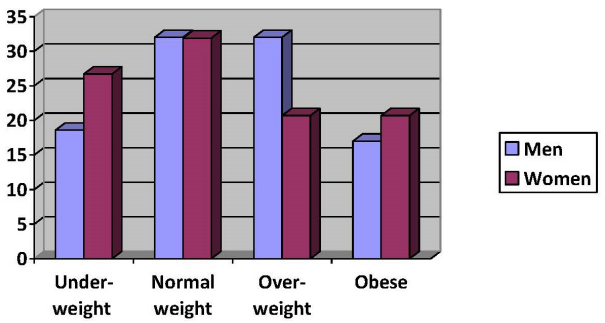

Figure 1: Distribution of body mass index categories by gender

Table 1: Distribution of thickness values for SC tissue. *M. gluteus* medius. and *M. gluteus* minimus, and needle penetration depth according to BMI categories of women in areas determined by G methods (n=135)

Body mass index categories	n (%)	SC tissue thickness	MG medius thickness	MG minimus thickness	Total thickness
		Mean±SD (Min.-Max.)	Mean±SD (Min.-Max.)	Mean±SD (Min.-Max.)	Mean±SD (Min.-Max.)
			MG medius+MG minimus thickness/2		
			Mean±SD (Min.-Max.)		
Under-weight (a)	36 (26.7)	12.8±3.9 4.5-17.5	17.9±5.6 8.1-28.1	20.2±7.2 9.2-33.5	50.8±11.8 32.1-79.1
Needle penetration depth* (w)			19.0±4.7 11.8-30.8		31.8±7.4 20.4-48.3
Normal weight (b)	43 (31.9)	16.2±5.6 6.1-26.5	22.0±5.1 10.0-30.0	16.7±5.5 7.3-30.6	54.8±11.6 31.1-83.6
Needle penetration depth* (x)			19.3±4.2 11.0-29.8		35.5±8.1 18.6-53.8
Overweight (c)	28 (20.7)	23.6±8.0 10.5-47.0	24.4±5.8 9.5-34.0	18.0±7.0 6.5-35.0	66.0±11.1 46.7-86.8
Needle penetration depth* (y)			21.2±5.3 10.8-31.5		44.8±8.1 29.7-62.5
Obese (d)	28 (20.7)	26.0±12.5 10.2-59.0	23.4±8.4 9.0-39.9	19.9±6.1 9.4-32.0	69.3±16.7 41.2-117.0
Needle penetration depth* (z)			21.6±5.7 14.5-33.6		47.6±13.6 26.7-88.0
ANOVA for tissue thicknesses		F=20.897 p=0.000 a<c,d; b<c,d	F=7.002 p=0.000 a<b,c,d	**F=2.451 p=0.066**	F=15.228 p=0.000 a<c,d; b<c,d
ANOVA for needle penetration depth			**F=2.239 p=0.087**		F=20.794 p=0.000 w<y,z; x<y,z

BMI: Body Mass Index, SD: Standard deviation, Min: Minimum, Max: Maximum, a: Under-weight, w: Needle penetration depth for under-weight, b: Normal weight, x: Needle penetration depth for normal weight, c: Overweight, y: Needle penetration depth for overweight, d: Obese, z: Needle penetration depth for obese, *: Needle penetration depth is half of the total thickness of m.gluteus medius and m.gluteus minimus plus the sum of SC tissue thickness,**: Half the total thickness of m.gluteus medius and m.gluteus minimus

DISCUSSION

In the study, the IM injection puncture point in the ventrogluteal area was determined using the V and G methods, and the thickness of the SC tissue, gluteus medius, and gluteus minimus muscles in these areas were measured using ultrasound. Furthermore, the distance from skin to bone was calculated as part of the investigation. Understanding these distances is crucial, particularly to avoid needle retention in the SC tissue and to prevent bone injuries during IM injections (8).

In the literature, it is stated that the ventrogluteal area is an area that can be used safely in place of the dorsogluteal area (13). The muscle tissue in the ventrogluteal area is thicker than the dorsogluteal area, the subcutaneous adipose tissue is thinner. The thinner subcutaneous adipose tissue in this area reduces the possibility of the injection being made into the SC tissue by mistake. On the other hand, there are no large nerves and blood vessels in this area, but it is innervated with small nerves and blood builds up through the arms of the blood vessels, which prevents the occurrence of more serious injuries (16). In addition, the ventrogluteal area is preferred because of the easy position to be given to the patient, and it is easy to determine the ventrogluteal area since bone protrusions can be easily felt by hand (2, 9, 13). Consequently, the ventrogluteal area should be used instead of the commonly-used dorsogluteal area. However, nurs-

Table 2: Distribution of thickness values for SC tissue. *M. gluteus* medius. and *M. gluteus* minimus. and needle penetration depth according to BMI categories of women in areas determined by V methods (n=135)

Body mass index categories	n (%)	SC tissue thickness	MG medius thickness	MG minimus thickness	Total thickness
		Mean±SD (Min.-Max.)	Mean±SD (Min.-Max.)	Mean±SD (Min.-Max.)	Mean±SD (Min.-Max.)
			MG medius+MG minimus thickness/2		
			Mean±SD (Min.-Max.)		
Under-weight (a)	36 (26.7)	11.9±5.8 4.9-24.0	17.2±7.3 1.7-29.4	20.0±7.4 7.1-32.7	49.1±15.6 18.0-80.9
Needle penetration depth* (w)			18.6±6.5** 4.4-30.2		30.5±9.9 13.6-50.7
Normal weight (b)	43 (31.9)	21.5±7.2 6.9-40.5	23.7±4.9 10.2-31.0	14.8±6.1 4.5-35.0	59.9±9.8 32.1-85.9
Needle penetration depth* (x)			19.2±3.8** 11.2-30.1		40.7±7.7 20.9-58.3
Overweight (c)	28 (20.7)	23.7±9.8 10.5-51.0	26.2±6.9 9.5-47.6	18.5±6.9 1.7-32.0	68.4±12.0 41.7-99.1
Needle penetration depth* (y)			22.4±5.2** 14.1-33.8		46.1±9.7 27.6-75.1
Obese (d)	28 (20.7)	29.8±13.4 10.5-58.5	25.4±10.1 10.2-48.1	19.9±7.9 7.8-38.6	75.1±13.4 41.4-96.1
Needle penetration depth* (z)			22.7±7.9** 10.4-40.8		52.4±10.8 31.0-77.3
ANOVA for tissue thicknesses		F=21.557 p=0.000 a<b,c,d; b<d	F=10.779 p=0.000 a<b,c,d	F=4.712 p=0.004 b<a,d	F=24.905 p=0.000 a<b,c,d; b<c,d
ANOVA for needle penetration depth			F=4.214 p=0.007 w<z		F=31.335 p=0.000 w<x,y,z; x<z

BMI: Body Mass Index, SD: Standard deviation, Min: Minimum, Max: Maximum, a: Under-weight, w: Needle penetration depth for under-weight, b: Normal weight, x: Needle penetration depth for normal weight, c: Overweight, y: Needle penetration depth for overweight, d: Obese, z: Needle penetration depth for obese, *: Needle penetration depth is half of the total thickness of m.gluteus medius and m.gluteus minimus plus the sum of SC tissue thickness,**: Half the total thickness of m.gluteus medius and m.gluteus minimus

es prefer the dorsogluteal area more in clinical practice. One of the reasons for this is that nurses have doubts about whether there is muscle tissue in the ventrogluteal area (12, 16).

Various tools and equipment are used in drug administration by IM injection. There are different injectors and needles. Each of these is designed to deliver a certain volume of drugs to tissues with certain properties. Nurses must decide on the tools and equipment to use considering the IM injection application area, the drug to be given, etc. Standard injectors have a capacity of 2,5,10 ml. Standard injectors are available without needles or with needles with a diameter of 18,21,22,23,25 numbers, and 10.16-76.2 mm in length. Injector needles are individually packaged and available in various sizes and diameters (2,6,7,9). In Turkiye, the inner diameter numbers of the needles are 20,21,22,23,26, and needle lengths are ½ inch (12.5 mm), 1 inch corresponds to 25 mm, 1 ¼ inch to 31.25 mm, and 1 ½ inch to 37.5 mm in length.

IM injection is usually applied to adults using 2 ml or 5 ml syringes with a 25.4-50.8 mm length and medium width (21-22 or 23 numbers in diameter) needle (9). Several research groups studied the risk of short needles inadvertently interpenetrating the intramuscular level and delivering the drug in the subcutaneous adipose tissue. Overpenetration can cause pain and/or damage to the bone or periosteum in the patient. It can also cause the needle to detach from the syringe (8,9,19). This study

Table 3: Distribution of thickness values for SC tissue. *M. gluteus* medius. and *M. gluteus* minimus. and needle penetration depth according to BMI categories of men in areas determined by G methods (n=97)

Body mass index categories	n (%)	SC tissue thickness	MG medius thickness	MG minimus thickness	Total thickness
		Mean±SD (Min.-Max.)	Mean±SD (Min.-Max.)	Mean±SD (Min.-Max.)	Mean±SD (Min.-Max.)
		MG medius+MG minimus thickness/2			
		Mean±SD (Min.-Max.)			
Under-weight (a)	18 (18.6)	8.2±4.0 4.5-16.5	22.8±8.1 10.0-34.0	24.3±4.4 16.0-29.0	55.3±9.9 41.5-69.0
Needle penetration depth* (w)			23.6±4.9** 18.5-31.5		31.8±5.8 23.0-37.5
Normal weight (b)	31 (32.0)	9.7±4.5 3.3-20.5	20.6±7.2 7.0-36.7	18.3±6.9 9.0-40.0	48.6±9.1 33.0-74.0
Needle penetration depth* (x)			19.4±4.6** 9.3-32.5		29.1±5.5 18.9-41.5
Overweight (c)	31 (32.0)	13.8±4.9 7.5-29.8	22.8±5.8 9.0-33.1	21.2±6.7 9.4-40.0	57.8±10.1 37.5-83.7
Needle penetration depth* (y)			22.0±5.0** 10.8-33.4		35.8±6.2 25.7-50.4
Obese (d)	17 (17.5)	19.5±12.5 10.0-62.2	21.3±7.5 2.9-30.9	21.1±7.6 2.0-32.0	61.8±17.4 25.0-102.3
Needle penetration depth* (z)			21.2±6.5** 7.5-29.3		40.6±13.7 17.5-82.3
ANOVA for tissue thicknesses		F=11.026 p=0.000 a<c,d; b,c<d;	**F=0.668 p=0.574**	F=3.276 p=0.025 a>b	F=5.962 p=0.001 b<c,d
ANOVA for needle penetration depth			F=2.700 p=0.05 w>x		F=9.256 p=0.000 w<z; x<y.z

BMI: Body Mass Index, SD: Standard deviation, Min.: Minimum, Max.: Maximum, a: Under-weight, w: Needle penetration depth for under-weight, b: Normal weight, x: Needle penetration depth for normal weight, c: Overweight, y: Needle penetration depth for overweight, d: Obese, z: Needle penetration depth for obese, *: Needle penetration depth is half of the total thickness of m.gluteus medius and m.gluteus minimus plus the sum of SC tissue thickness. **: Half the total thickness of m.gluteus medius and m.gluteus minimus

showed that while administering the IM injection to the ventrogluteal area, standard needles could not even pass SC tissue in overweight, obese women and men when the area was determined according to the G and V methods. Consequently, long needles should be used for IM injection, so the needle passes through the subcutaneous tissue, and reaches deep muscle tissue.

Body mass index and the amount of adipose tissue affect the choice of needle size. For instance, a 76 mm long needle is often required for an obese individual, whereas a 13 mm-25 mm long needle is sufficient for an underweight individual (3,9,13). Both BMI and gender were found to be factors affecting SC tissue thickness in this study. Ozen et al. in their study determined that subcutaneous adipose tissue (SAT) thickness values are important if IM drug injection is to be administered correctly. Unsuccessful IM injections may be seen even in patients with appropriate SAT thicknesses (18). In addition, in the study by Nisbet, 12 out of 100 individuals included in the study were found to have SC tissue thickness of more than 35 mm in the ventrogluteal area, and it was determined that muscle tissue could not be reached in these individuals when standard needles were used (20). As a result, when IM injection is applied to the ventrogluteal area, there is a risk that the needle cannot reach the target muscle mass, and the most important factor causing this risk is BMI. Thus, when intramuscular injections are to be administered to M. gluteus

Table 4: Distribution of thickness values for SC tissue. *M. gluteus* medius. and *M. gluteus* minimus. and needle penetration depth according to BMI categories of men in areas determined by V methods (n=97)

Body mass index categories	n (%)	SC Tissue Thickness	MG Medius Thickness	MG Minimus Thickness	Total Thickness
		Mean±SD (Min.-Max.)	Mean±SD (Min.-Max.)	Mean±SD (Min.-Max.)	Mean±SD (Min.-Max.)
			MG medius+MG minimus thickness/2		
			Mean±SD (Min.-Max.)		
Under-weight (a)	18 (18.6)	9.6±3.7 7.0-17.0	26.3±5.2 18.0-32.5	22.3±3.3 17.5-27.5	58.3±8.6 47.5-68.0
Needle penetration depth* (w)			24.3±3.7** 20.3-29.8		33.9±5.5 27.3-40.8
Normal weight (b)	31 (32.0)	10.7±4.9 4.4-26.3	20.9±7.5 5.0-32.9	16.8±8.6 1.1-37.5	48.5±10.1 24.0-70.5
Needle penetration depth* (x)			18.9±5.0** 7.0-32.3		29.6±6.2 16.0-45.3
Overweight (c)	31 (32.0)	16.8±4.7 10.0-30.0	24.0±8.5 7.0-38.8	19.1±7.5 6.7-36.3	59.9±12.3 32.0-87.9
Needle penetration depth* (y)			21.6±6.0** 9.8-33.6		38.4±7.1 22.0-54.4
Obese (d)	17 (17.5)	20.7±11.1 10.0-48.0	21.8±6.7 9.5-32.7	20.4±7.4 11.0-34.7	62.9±11.6 40.0-80.7
Needle penetration depth* (z)			21.1±5.7** 11.0-30.4		41.8±9.8 28.5-63.0
ANOVA for tissue thicknesses		F=14.574 p=0.000 a<c,d; b<c,d;	**F=2.393 p=0.073**	**F=2.358 p=0.077**	F=8.735 p=0.000 b<a,c,d
ANOVA for needle penetration depth			F=4.172 p=0.008 w>x		F=13.448 p=0.000 w<z; x<y,z

BMI: Body Mass Index, SD: Standard deviation, Min.: Minimum, Max.: Maximum, a: Under-weight, w: Needle penetration depth for under-weight, b: Normal weight, x: Needle penetration depth for normal weight, c: Overweight, y: Needle penetration depth for overweight, d: Obese, z: Needle penetration depth for obese*: Needle penetration depth is half of the total thickness of m.gluteus medius and m.gluteus minimus plus the sum of SC tissue thickness. **: Half the total thickness of m.gluteus medius and m.gluteus minimus

Table 5: Distribution of thickness values for SC tissue. *M. gluteus* medius. and *M. gluteus* minimus. and needle penetration depth according to gender in areas determined by G and V methods

	METHOD G			METHOD V		
	Women (n=135)	Men (n=97)	t*; p	Women (n=135)	Men (n=97)	t*; p
	Mean±SD	Mean±SD		Mean±SD	Mean±SD	
SC tissue thickness	18.8±9.3	12.4±7.6	5.598; 0.000	21.1±11.0	14.2±7.4	5.722; 0.000
MG medius thickness	21.7±6.6	21.8±7.0	**-0.159; 0.874**	22.8±8.0	23.1±7.5	**-0.251; 0.802**
MG minimus thickness	18.5±6.5	20.8±6.8	-2.586; 0.01	18.0±7.3	19.2±7.5	**-1.227; 0.221**
Total thickness	59.1±14.7	55.1±12.2	2.183; 0.030	61.9±15.8	56.5±12.1	2.841; 0.005
Needle penetration depth	39.0±11.2	33.8±8.7	3.975; 0.000	41.5±12.2	35.3±8.4	4.568; 0.000

BMI: Body Mass Index, SD: Standard deviation, Min.: Minimum, Max.: Maximum, *: Independent Samples t Test

medius and minimus, the length of the needle should be chosen according to the patient's BMI (2,7,9).

In this study, while administering the IM injection to the ventrogluteal area, when the area was determined according to the G, V methods, the SC tissue thickness of the woman was higher than man. Subcutaneous tissue is found below the layer of the dermis. Dermis and SC tissue thickness can be estimated by BMI. The subcutaneous tissue thickness of women is more than that of men across all BMI ranges (21). This finding was found to be like other studies conducted (3,21). Finally, the sample size is limited to this hospital; therefore, the generalizability of study findings to other settings may be limited.

This study showed that when administering IM injection to the ventrogluteal area, standard needles should not be used, and needle length should be decided according to gender and BMI. But the longest of the needles used for this purpose on the market is 2.5-3.75 cm. In addition, clear guidelines should be prepared about the gold standard technique for nurses (22). There are no prescribed guidelines for choosing the correct needle length based on an individual's BMI and gender. Without updated guidelines, IM injections will continue to be administered inappropriately into muscles (23).

Limitations of the study

In the IM injection, the age and level of exercise of the individual affect the depth of needle penetration. In this study, NPD could not be analyzed according to age classes (the number of individuals over 65 is insufficient and the maximum age is 70), since the individuals within the scope of the study were generally adults (35.02±10.62 years, minimum=18, maximum=70). The effect of exercise status on NPD could not be analyzed since measurement tools were not applied to determine the exercise status of the individuals within the scope of the study and the general condition of the muscles.

CONCLUSION

This study showed that NPD should be different according to BMI and gender. A needle length of 20-48 mm should be used in thin women, 18-53 mm in normal weights, 29-62 mm in overweight, and 26-88 mm in obese women. A needle length of 23-37 mm should be used in thin men, 18-41 mm in normal weights, 25-50 mm in overweight, and 17-82 mm in obese men.

Longer needles should be preferred especially in overweight and obese women, and NPD in women should be greater than in men, taking into account BMI. In addition, it is seen that the range of NPD is wide and therefore, individual evaluation should be made while injecting IM, the thickness of the adipose tissue and the condition of the muscles should be diagnosed by palpating the area.

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Ethics Committee Approval: This study was approved by Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 22.04.2015, No: 870).

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REVIEW / DERLEME
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MENTAL HEALTH IN THE AFTERMATH OF DISASTERS; PSYCHOLOGICAL EFFECTS, TREATMENT APPROACHES AND COPING

AFETLER SONRASINDA RUH SAĞLIĞI; PSİKOLOJİK ETKİLER, TEDAVİ YAKLAŞIMLARI VE BAŞ ETME

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ABSTRACT

The February 6, 2023, Kahramanmaraş earthquakes were reported as one of the biggest disasters in our country. The magnitude of the natural events, the large-scale impact, and its man-made aspect made this disaster a mass trauma that affected almost the entire country. Survivors can experience many different psychological symptoms after disasters, and although Post-Traumatic Stress Disorder (PTSD) is the most frequently reported one, all psychiatric disorders, such as depression and anxiety, can be seen. In addition to the individuals who experienced the earthquake, mental problems can be observed in rescue and health workers who go to the region to help. Different methods such as psychological first aid (PFA), psychotherapies, and drugs can be applied from very early to the following months after the disaster. Post-traumatic growth (PTG) can also develop as one of the mechanisms for coping with great suffering in individuals and communities after major traumas. This article will present the psychological effects that develop after major disasters, especially earthquakes, the treatment approaches, and discuss PTG.

Keywords: Disaster, earthquake, mental health, post traumatic stress disorder, psychological first aid

ÖZET

Altı Şubat Kahramanmaraş depremleri ülkemizdeki en büyük afetlerden biri olmuştur. Depremlerin şiddeti, geniş alana yayılması ve insan kaynaklı boyutunun da olması bu afeti neredeyse tüm ülkeyi etkisi altına alan kitlesel bir travma haline getirmiştir. Afetlerden etkilenen bireyler olaydan sonra birçok farklı psikolojik belirti yaşayabilmekte ve en sık bildirilen tanı Travma Sonrası Stres Bozukluğu (TSSB) olmasına rağmen, depresyon ve anksiyete gibi birçok psikiyatrik bozukluk görülebilmektedir. Afeti yaşayan bireylerin yanı sıra bölgeye yardım için giden kurtarma ve sağlık çalışanlarında da ruhsal sorunlar gözlemlenebilir. Psikolojik ilk yardım (PİY), psikoterapiler, ilaçlar gibi farklı yöntemler afetin çok erken döneminden itibaren sonraki aylara kadar uygulanabilir. Travma sonrası büyüme (TSB), büyük travmalardan sonra bireylerde ve topluluklarda büyük acılarla başa çıkma mekanizmalarından biri olarak gelişebilir. Bu makalede, başta deprem olmak üzere büyük afetler sonrasında gelişen psikolojik etkiler ile tedavi yaklaşımları sunulacak ve TSB anlatılacaktır.

Anahtar Kelimeler: Afet, deprem, ruh sağlığı, travma sonrası stres bozukluğu, psikolojik ilk yardım

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GENİŞ ÖZET

Altı Şubat 2023 tarihinde birkaç saat arayla meydana gelen 7.7 ve 7.6 şiddetinde merkezi Kahramanmaraş olan depremler, 11 şehri doğrudan etkileyerek ve en son açıklanan resmi sayıya göre 50 binden fazla insanın ölümü nedeniyle ülkemiz tarihinin en büyük afetlerden biri olmuştur. Depremlerin şiddeti, geniş alana yayılması, büyük sayıdaki ölüm ve yaralanmalar, ortaya çıkan güvenlik sorunları, insanların başta evlerini ve işlerini olmak üzere sahip oldukları çoğu şeyi kaybetmeleri nedeniyle zorunlu göçe yol açması ve insan kaynaklı boyutunun da olması bu afeti neredeyse tüm ülkeyi etkisi altına alan kitlesel bir travma haline getirmiştir.

Afetlerden etkilenen bireylerde birçok farklı psikolojik belirti gelişebilir. Olaydan sonraki erken dönemde görülebilen birçok belirti anormal bir olaya verilen normal tepkiler kapsamında değerlendirilir ve ilk zamanlarda birçok belirti yoğun düzeyde yaşanabilirken süreç içerisinde bunların çoğunun azalarak sonlandığı görülür. Ancak araştırmalar, afetler sonrası toplumda %10-30 arasında tanı konulacak düzeyde psikiyatrik bozukluğun geliştiğini bildirmektedir. En sık bildirilen ve üzerinde en çok çalışmanın yapıldığı bozukluk Travma Sonrası Stres Bozukluğu (TSSB) olmasına rağmen, depresyon ve anksiyete gibi birçok psikiyatrik bozukluk görülebileceği de unutulmamalıdır. TSSB'nin dört belirti kümesi vardır; yeniden yaşantılama, uyarılmışlık hali, kaçınma ve bilişsel- duygusal sorunlar. TSSB olaydan haftalar ya da aylar sonra da gelişebilir.

Afeti yaşayan bireylerin yanı sıra bölgeye yardım için giden arama- kurtarma ekipleri, sağlık çalışanları, sosyal hizmet uzmanları ve gönüllülerde de ruhsal sorunlar gözlemlenebilir. Bunlardan ilki travmatik yaşantıları deneyimleyen kişilerden ya da çeşitli kaynaklardan duyma ve öğrenme gibi dolaylı yoldan etkilenme olarak tanımlan ve belirtileri TSSB ile örtüşen ikincil travmatik strestir. İkincil travmatik stresin beklenen bir sonucu olan, yoğun ruhsal ve fiziksel yorgunluğun giderek yol açtığı empati kurma becerisinde bozulma, merhamet yorgunluğu olarak tanımlanır. Merhamet yorgunuğu yaşayanlarda birçok bedensel, zihinsel, duygusal ve davranışsal sorun görülebilir ancak en önemli özelliklerinden biri, tükenmişlik hissidir. Maslach, duygusal tükenmişlik hissi, ilgilendiği işe ve bireylere yönelik duyarsızlaşma ve kişisel başarı duygusunun azalması ile ortaya çıkan psikolojik tabloyu tükenmişlik sendromu olarak tanımlamıştır. Belirtiler, başlangıçta algılanamayabilir ancak zaman içinde giderek şiddetlenir.

Afetlerden sonra bireylerin ruhsal gereksinimlerine yönelik hem erken dönemde hem de ilerleyen zamanlarda uygulanabilecek çeşitli girişimler vardır. Bunlardan ilki, olaydan dakikalar sonrasında dahi başlanabilecek ve ruh sağlığı alanında uzmanlık eğitimi gerektirmeden de uygulanabilecek bazı basit prensipler üzerine kurulu olan Psikolojik İlk Yardımdır (PİY). PİY prensiplerine makalenin içinde geniş kapsamda değinilmiştir. Erken dönem sonrası, ruhsal belirtilerin devam ettiği ya da şiddetlendiği olgularda Travmaya Duyarlı Farkındalık, Göz Hareketleri ile Duyarsızlaştırma ve Yeniden işleme, Bilişsel Davranışçı Terapi gibi psikoterapi yöntemleri uygulanabilir. Makalede TSSB başta olmak üzere afetle ilişkili ruhsal sorunlarda başvurulabilecek psikoterapötik uygulamalara detaylı yer verilmiştir. Her ne kadar ilk tedavi yaklaşımı olmasa da, belirtilerin ilk bir aydan sonra da bireyin yaşamının birçok alanındaki işlevselliğini bozacak düzeyde sürdüğü, major depresif bozukluk ya da alkol- madde kullanım bozukluğu gibi komorbiditelerin geliştiği bireylerde psikofarmakolojik tedavilerin de başlanması gerekebilir. TSSB tedavisinde etkinliği büyük oranda kabul edilen ajanlar Sertralin, Paroksetin, Fluoksetin ve Venlafaksindir. Ek olarak farklı nörotransmisyon mekanizmaları üzerinden etkinliği gösterilen ancak halen yüksek kanıt düzeyine ulaşmayan çeşitli ajanlar da olgu bazında değerlendirme yapılarak kullanılmaktadır. Makalede çeşitli psikofarmakolojik ajanların kullanım ilkelerine değinilmiştir.

Son 25 yılda yapılan araştırmalar, afetlerden ve travmatik olaylardan kurtulan bireylerin çoğunun bu zor deneyimlerden olumlu değişikliklerle çıktığını belirten travma sonrası büyüme (TSB) kavramını ortaya çıkarmıştır. Olumlu değişimler arasında sosyal ilişkilerin olumlu yönde gelişmesi, yaşamı daha fazla takdir etme, yaşam için şükran duyma ve daha derin manevi anlamadan söz edilebilir. Afetler, bireylerin dünyanın iyi bir yer olduğu ve iyi insanların başına iyi şeylerin geleceğine dair inançlarını sorgulamasına neden olan olaylardır. Aniden gelerek büyük bir yıkıma yol açan olaylar, hayatın kontrol edilebilirliği, öngörülebilirliği ve dünyanın güvenirliğini sarsarak bireylerin kendilerini savunmasız hissetmelerine yol açar. Ancak hayatta kalan kişiler için, hiç beklemedikleri bu felaket sonrasında, önceden alışık oldukları yaşam koşulları olmadan da hayata devam ettiklerinin farkına varmak öz yeterliklerini ve kişisel güçlerini arttırabilir. Manevi bağlarının güçlenmesi, yeni yaşam amaçlarının yaratılması, ailelerin ve toplulukların bir araya gelmesi, sosyal değerlerin gelişmesi, başkalarıyla bağlantı kurma gibi yeni kazanımlar elde edebilirler. Umut her zaman vardır...

INTRODUCTION

The earthquakes with a magnitude of 7.7 and 7.6 Richter in Kahramanmaraş, dated February 6, 2023, directly affected 11 cities and was recorded as one of the most significant traumatic events in the history of our country. The number of people who lost their lives was announced as 50,096 and the number of injured people as 107,204 (1). Natural disasters are events that occur suddenly and have large-scale effects resulting from the earth's natural geological or climatic processes. In addition to experiencing the moment of disaster, being in the wreckage, experiences during the rescue, death, injuries, disabilities, witnessed destruction, delay or inadequacy of assistance, security weakness, interruption or complete disappearance of social networks, especially regarding basic needs and health needs. Natural disasters due to resource depletion, loss of housing, and workplace traumatize individuals and groups (2).

Among natural disasters, earthquakes are described as the disasters that threaten life the most and cause the most forced migration due to their uncontrollability, destructiveness, the uncertainty of the future, and the feeling of insecurity (3). In addition to the "natural" nature of disasters, there is also a "man-made" dimension. Among the reasons are the facts that the houses were built unstably against the scientifically expected earthquakes, unpreparedness, organizational problems experienced during the response and aid process, the negative attitudes of the administrators in the process following the disaster, the number of experts working on disasters and their inadequate knowledge and skills. It is known that human-made traumas cause various psychological reactions that deeply shake the individual's sense of trust and justice (4). Due to their terrifying and devastating dimensions, the February 6 Kahramanmaraş earthquakes constitute a massive trauma with a huge psychological impact (4).

In this article, although the recent earthquake disaster that our country has experienced is at the focus, the mental problems that individuals may experience after natural disasters and the solution approaches in terms of psychological-psychiatric aspects will be discussed. We expect our article to guide readers to understand the mental states that can be observed after disasters and take appropriate approaches.

Psychological reactions to trauma

Trauma is defined as an event that involves "actual or threatened death, serious injury or an equivalent threat, or extreme helplessness, fear, and terror." It includes vicarious experiences in the definition of traumatic events. Not only the person who directly experienced the event but also the people who witnessed the event, loved ones who experienced the disaster, and those who were in the environment immediately after the event due to their duties are affected by the events (5).

The February 6, 2023, Kahramanmaraş earthquakes are a trauma that affects almost the whole country, considering those who lived through the disaster at that time, had a relative in the region, went to the area to help, and witnessed all these events (4). Natural disasters may threaten individuals' and communities' psychosocial well-being in many ways and result in many short and long term consequences (2). In the early post-disaster period, psychological symptoms should often be considered a normal reaction to an abnormal event (6). Individuals may feel very intense negative emotions such as depression and anxiety, may experience physical symptoms such as palpitations, breathing difficulties, sleep disturbances, may experience as if they are reliving the event, startling easily, alertness, dullness, and an inability to focus. Although these psychological symptoms are common at first, they are expected to decrease spontaneously in most people over time (4).

Psychiatric symptoms and diseases that occur after disasters vary according to age, gender, marital status, loss of life and property after the disaster, old health problems, and the economic conditions of the country (7,8). In population-based studies, the rate of those developing any psychiatric disorder in disasters is between 10-30%. Post-Traumatic Stress Disorder (PTSD), on the other hand, is the most frequently observed mental disorder, together with natural disasters (9,10). In a study conducted 4-12 months after the 1999 Marmara Earthquake, the incidence of PTSD was found to be 25% (11).

According to The Diagnostic and Statistical Manual of Mental Disorders-5, PTSD includes four clusters of symptoms: re-experiencing, i.e., recurrent memories, nightmares, dissociative reactions; alterations in arousal such as aggressive, reckless or self-destructive behavior, sleep problems, hypervigilance; avoidance from distressing memories, thoughts, or reminders of the event; cognitive and mood alternations, i.e., persistent negative beliefs, distorted blame, or trauma-related emotions; feelings of alienation and diminished interest in life (1). PTSD can occur weeks or months after the traumatic event and last for years. Studies show that high education level, loss or serious injury of a close person in the event, forced displacement, a history of trauma experience before the traumatic event, and mental disorders are factors that increase the risk of PTSD (12). In addition, the extent of the person's perception of control over the onset, duration, and end of the traumatic event has an important place in the emergence of PTSD symptoms. Foa et al. reported higher PTSD symptoms in the earthquake experience with less sense of control (13).

Although most studies focused on PTSD, it should be kept in mind that the rates of other psychiatric diseas-

es, such as generalized anxiety disorder (GAD) and major depressive disorder (MDD), increase in individuals after disasters. It should be kept in mind that almost all diseases and symptoms known in psychiatry can be encountered (8,14). When a mental disorder develops after traumatic events, it is expected that the symptoms tend to decrease over time. If, after a few months, there are still symptoms that meet the criteria for the diagnosis of a mental disorder, it is unlikely that the symptoms will lessen spontaneously, and treatment should be started (4). Early diagnosis and intervention in psychiatric diseases will also change the course of the disease (7).

What helpers may experience

Many occupational groups as healthcare professionals, social workers, disaster relief and recovery workers, etc., are at increased risk of exposure to traumatic events in the areas of disasters. After the earthquakes, the treatment of the injured started primarily in the health institutions in the affected regions, and most of the cases were transferred to the surrounding provinces to ensure continuity of treatment. Many physicians from our country applied to participate in working activities voluntarily, and they were assigned to the necessary health institutions in the earthquake region. The management of our institution, the Istanbul University Istanbul Faculty of Medicine, created a coordination network shortly after the earthquake and sent its employees, who had received UMKE (National Medical Rescue Team) training, and then volunteers to various cities in the region at regular intervals.

In times of major disasters, the healthcare workload increases while the number of operational healthcare personnel decreases. Beyond the physical fatigue of rescue and health workers, the compelling conditions of the patients and their relatives can also affect them within the scope of secondary traumatization. When someone is indirectly exposed to a traumatic event by getting informed or hearing about it, secondary traumatic stress (STS) develops (15,16). In other words, secondary trauma occurs when an individual is indirectly exposed to trauma. Since healthcare professionals frequently contact traumatized people, STS is ubiquitous among them. STS symptoms can include reliving the trauma, avoiding reminders of the experience, and having higher arousal (17). These symptoms are similar to those of PTSD.

Understanding other people's suffering and being willing to work with them to find a solution are two characteristics of compassion (18). As a consequence of STS, psychological and physical exhaustion may decrease one's capacity for empathy, which is called compassion fatigue (CF). Signs and symptoms of CF are grouped into emotional, psychological, and physical aspects such as detachment, despair, or apathy; excessive consideration and worrying about other people's suffering; blaming oneself or others for not doing enough to help or prevent the trauma; irritability or anger; problems falling asleep, changes in appetite, stomach ache, nausea, and dizziness (19).

Burnout is a psychological syndrome emerging as a prolonged response to chronic interpersonal stressors on the job. Maslach describes burnout as a psychological syndrome of emotional exhaustion, depersonalization, and reduced personal accomplishment, which can occur among individuals who work with others in some capacity (20). Emotional exhaustion refers to feeling emotionally overextended and depleted of one's emotional resources. Depersonalization refers to a negative, callous, or excessively detached response to other people who usually receive one's service or care. Reduced personal accomplishment refers to a decline in one's feelings of competence and achievement in one's work (20). Burnout happens in employees who experience significant levels of occupational frustration, and it is more common in occupations requiring long working hours and frequent human interactions (21).

Burnout and compassion fatigue have certain similarities, but they also differ significantly. Burnout is a term used to describe a condition of exhaustion that results in low motivation and little enthusiasm for one's job. Contrarily, compassion fatigue is a specific kind of burnout that describes the unfavorable feelings and loss of empathy people experience after being exposed to the trauma, pain, and suffering of others. Compassion fatigue is most common in professionals who deal with people daily, such as physicians, nurses, psychotherapists, social workers, and teachers. Although the symptoms of burnout and compassion fatigue are similar, their underlying causes differ. In contrast to burnout, which is brought on by the workplace and is more closely related to the institutions than the patients, compassion fatigue develops due to the caring nature of helping professionals (22).

Psychological interventions in disasters

In the first moments of disasters, individuals mainly focus on sheltering, nutrition, and the basic medical care needs of people who are affected. Situations that may pose a risk in terms of mental health, such as losses, adaptation to the new environment, and stress, usually remain in second place (23). The psychological needs of people affected by disasters may become more evident over time, so psychosocial intervention methods are used to protect individuals' mental health and prevent the emergence of psychopathological conditions (23). The main goals of psychosocial interventions are to instill a sense of security, calm, reinforce the sense of self-efficacy and social competence, nurture the sense of connectedness, and increase hope (24).

Studies emphasize that structured psychotherapies are not suitable immediately after disasters and suggest im-

plementing particular psychosocial interventions in the first week, the first month, 1-3 months, and three months after the disaster (25).

Commonly used post-disaster interventions are:

- Psychological first aid (PFA)
- Trauma-sensitive mindfulness
- Eye movement desensitization and reprocessing (EMDR)
- Trauma-focused cognitive behavioral therapy (CBT)

In the first week after the disaster, interventions for PFA, psychoeducation for coping with the effects of disasters, and social support are preferred. It may be more appropriate to perform EMDR in the first month and after the disaster and structured psychotherapies such as CBT within the first three months after the disaster for people with PTSD (26).

Psychological first aid

Psychological first aid, the basic approach recommended recently after disasters, effectively prevents long-term problems at the center of the event (23). As an evidence-based approach, PFA is a supportive, practical, and humane intervention offered to individuals suffering, experiencing intense stress, and needing support (27). PFA aims to establish a non-coercive relationship with individuals affected by disasters, to reduce the stress caused by disasters with a compassionate approach, and to improve individuals' coping and adaptation skills in the short and long term (27). PFA is not a psychiatric treatment method, and it can be applied not only in the clinical setting but also in settings such as the epicenter, camps, homes, schools, and workplaces by people who have PFA training (23, 28). There is no strict time limit for PFA intervention since the effects of the disaster may last for days, weeks, or months, depending on the duration, type, and meeting the needs of individuals (28). Brymer et al. grouped PFA in eight steps and these are presented in detail in Table.1 (27).

In addition to its positive effects on disaster-affected individuals, PFA positively impacts the rescue team, healthcare staff, and volunteers working in the epicenter (29). PFA training of emergency response teams and volunteers facilitates their ability to address their needs in the post-disaster period (30). For these reasons, PFA, which can be learned and applied quickly, should be given to all health workers.

Trauma-Sensitive mindfulness

Mindfulness can be a protective factor that can reduce the combined effects of traumatic or challenging experiences and stress. The first goal of mindfulness programs is to develop the ability to recognize and express emotions, especially through the body. Another aim is to create the ability of people to recognize the threat and impulse system in terms of stress and to switch to the soothing system when they realize these. Some approaches have integrated mindfulness into the basic steps of PFA, as well as psychoeducation and relaxation exercises (31). Hechanova et al. practiced mindfulness-based PFA and reported that mindfulness is beneficial both as a calming activity at the first moment and as a tool to help them manage their stress reactions in the future (32).

In mindfulness practices, it is also important for individuals to display a non-judgmental, compassionate approach to themselves. In recent years, the "Trauma-Sensitive Mindfulness" program has been developed by Treleaven, noting that forcing oneself to focus carefully on a particular stimulus may not always help people who have experienced trauma (33). The importance of staying in the "Tolerance Range" is emphasized in the trauma-sensitive mindfulness approach. The tolerance range is an internal support area and a starting point for all trauma-sensitive interventions. Individuals in the tolerance range are more likely to feel balanced, in the present time, and regulated. The way to support an individual to stay within the tolerance range is to refocus attention (33). For example, if focusing on the breath bothers the person, she/he can be directed to focus on a neutral object.

Eye movement desensitization and reprocessing

Developed by Francine Shapiro, EMDR is a therapy technique that combines various aspects of many therapy approaches, such as psychodynamic, cognitive-behavioral, and existential (34, 35). The main purpose of EMDR is to desensitize the participant regarding the negative event by using eye movements, to process the memories normally and to eliminate the pathology in this way (35). In EMDR, the focus is on gestures or tapping when talking about the traumatic event. Focusing on hand movements or sounds when discussing the traumatic event can help change the response to trauma memories over time. In addition, the patient is instructed with skills to help relax and cope with emotional distress (35). Many studies support using EMDR for trauma treatment after natural disasters. For example, after a single session of EMDR applied to the victims of Hurricane Andrews, a 60% recovery was reported (36). EMDR was used on 18 participants with PTSD who survived the Hanshin-Awaji earthquake, and it was reported that PTSD symptoms decreased and that recovery was maintained at a rate of 80% during the follow-up period despite "aftershocks" (37). While working with participants diagnosed with PTSD after the 1999 Marmara earthquake, Konuk et al. reported that after two sessions of EMDR, trauma symptoms decreased, and individuals preserved recovery for six months (38). Mukba,

Table 1: Eight steps of psychological first aid (27)

1. Commitment and contact:	At this stage, the aim is to initiate communication with people who have experienced a traumatic event in non-intrusive, compassionate, and helpful ways. To establish a relationship based on trust and respect, the first step for the PFA practitioner is to introduce himself by saying her/his name, state via which institution she/ he is there, and for what purpose she/ he is conducting the interview. In the first interaction occurring in the acute period, it is essential at this stage to identify and meet basic needs, such as asking about the health status of the individuals, water, blankets, etc.
2. Safety and comfort:	At this stage, the PFA practitioner takes measures related to life safety, such as taking the affected people to a safe place, removing them from hazards and risky areas at the disaster/incident site, and gathering them in secure locations. In addition, interventions to meet the security needs of the affected people and provide relief by eliminating their concerns should also be evaluated.
3. Stabilization:	Symptoms such as shock, extreme fear, panic or freezing reactions, forgetfulness, distraction, startle and alertness, etc., which can be seen especially in the first 24 hours after the disaster, may require intervention. For this reason, stabilization techniques are used to return individuals to a psychologically stable state and to help them achieve emotional calm and balance. One of the important applications used for stabilization is the grounding technique. As an example of grounding, first, the individual takes a few breaths, then says the names of the five non-irritating/neutral objects around, then breathes again, then tells the five sounds that are heard and are not disturbing to the person, then breathes again. She/ he is asked to notice five bodily sensations that do not cause discomfort.
4. Information gathering:	It is necessary to understand people's physical or psychological needs after the event and to plan the most appropriate support for them. For this purpose, observation, interviews with individuals, and/or using needs analysis forms may be helpful.
5. Practical help:	In light of what is determined during the information acquisition phase, an attempt is made to meet the needs of individuals. It is a more appropriate approach to take action regarding the basic and urgent needs first and to make a plan for meeting the needs that are less urgent and important.
6. Connecting with social support:	Promoting social connections as soon as possible and helping individuals develop and maintain them is especially important in disaster situations. Being associated with others increases the likelihood of giving and receiving support. For this reason, PFA practitioners can take a series of actions to identify the existing social support mechanisms of the individuals affected by the event and activate them.
7. Giving information about coping skills:	The most important aspect of this stage is to give individuals information about post-traumatic stress reactions. This information includes the physical, mental, behavioral, and emotional changes that may occur after the event and the methods to help them cope. In addition, psychoeducation on sleep hygiene can be provided to cope with sleep disturbances seen in a large number of the affected individuals, as well as psychoeducation on breathing and relaxation exercises to cope with anxiety and encourage relaxation. Activity planning practices can be used to help them return to their previous habits.
8. Linking with other services:	The PFA practitioner supports the establishment of relations between the affected individuals and the person, team, and institutions in charge, as well as completing the mandate, etc. In case of team changes due to other reasons, he informs his teammates about the process of the victims in their follow-up and transfers them.

Tanrıverdi, and Tanhan observed that the symptoms of individuals who showed long-term PTSD symptoms after the Van earthquake improved quickly after EMDR (39).

Trauma-focused cognitive behavioral therapy

Cognitive behavioral therapy is a recommended treatment in the mid-and long-term for PTSD (40). According to the emotion processing model, PTSD becomes permanent when individuals process trauma in a way that causes an existing sense of threat (6). This permanency is thought to be due to an excessive negative evaluation of trauma, strong sensory memories, and weak autobiographical memory. Components of CBT typically include practices related to psychoeducation, relaxation training, imagery and in-vivo exposure, cognitive restructuring,

homework, and social support (41). Trauma-focused CBT has protocols that can be used for children, adolescents, and adults. In this treatment model developed by Cohen et al., introductory sessions are conducted separately with the child and family, and then the interviews are brought together (42).

Psychopharmacological treatments in the treatment of PTSD

After disasters, individuals may experience various psychological disturbances within limits, and PFA and psychotherapeutic interventions can start, as mentioned before. It should be kept in mind that trauma-focused psychotherapy methods are recommended as the first choice in treatment guidelines (43). However, in the continuation of the first month after the trauma, the fact that the individual still shows symptoms of PTSD at a level that will impair the functionality of many areas of his busy and daily life, or the development of comorbidities such as major depressive disorder and substance use disorders may lead to the necessity of starting pharmacological treatments. During treatment, all options should be discussed in detail with the patient, and joint decisions and participation should be ensured after informing.

Drug treatment targets in PTSD can be listed as follows (44):

• Reducing the severity and frequency of intrusive symptoms,

• Reducing the tendency to interpret incoming stimuli as a repetition of trauma,

• Reducing the conditioned hyperarousal response to stimuli reminding the trauma,

• Reducing avoidance,

• Correction of depressive mood and blunting,

• Reducing psychotic and dissociative symptoms,

• Reducing impulsive aggression towards self and others

According to the PTSD guideline published by the International Association for the Study of Traumatic Stress (ISTSS) in 2018, the recommended treatments are fluoxetine, sertraline, and paroxetine, which are selective serotonin reuptake blockers; and venlafaxine, which is a serotonin noradrenaline reuptake blocker (45). Sertraline and Paroxetine are approved by the Food and Drug Administration for the treatment of PTSD. The guideline states that the evidence for quetiapine's effectiveness has increased. It has also been noted that amitriptyline, imipramine, mirtazapine, olanzapine, divalproex, topiramate, lamotrigine, tiagabine, and ketamine can be used in the treatment of PTSD, but still, the level of evidence is not sufficient to recommend them (45). Second-generation antipsychotics, especially quetiapine and olanzapine, as augmenting agents in PTSD and major depressive disorder, can reduce impulsivity or the presence of psychotic symptoms. Mood stabilizers such as lamotrigine, topiramate, and divalproate can be used in the treatment of PTSD by playing a role in balancing the levels of the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter gamma amino butyric acid (GABA). Buspirone and beta-blockers can be used for hyperarousal symptoms, while Prazosin is particularly effective in preventing nightmares. The use of benzodiazepines in the treatment of PTSD is not primarily recommended due to potential disinhibition, difficulty integrating the traumatic experience, adversely affecting the psychotherapy process, and risks of abuse/dependence. However, they can be used for a short time in acute agitation.

Drug treatments effectively improve PTSD symptoms through serotonin, norepinephrine, and GABA, by stimulating amino acid glutamate and dopamine, which are effective in the fear and anxiety pathways of the brain. NMDA (n-methyl-d-aspartate) and AMPA (amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) are target receptors with many potential values. There is a need for effective drugs in the treatment of PTSD through new and more specific mechanisms (46).

Hopes for the future

Based on the research in the last 25 years, the concept of post-traumatic growth (PTG) has been defined, which states that most individuals who survive disasters and traumatic events emerge from these difficult experiences with positive changes (47). Among the positive changes in PTG are improved relationships, a greater appreciation of life, a gratitude for life, and reaching a deeper spiritual meaning (48).

The vulnerability of disaster survivors profoundly shakes their assumptions about the safety, controllability, and predictability of the world (49). Individuals may question their beliefs about a fair world or the idea that "good things happen to good people and bad things happen to bad people" (50). With these interrogations, disaster survivors need to construct a new hypothetical world containing their post-disaster life's realities. Survivors can increase their self-efficacy and personal strength by becoming aware of their ability to survive without the living conditions they were used to before this disaster they never expected (50). In these new living conditions, spiritual and religious changes may occur. After the disaster, survivors may frequently use religious coping methods and forge to bond with God or create new life purposes. Finally, disasters can bring individuals, families, and communities together in ways previously unimaginable and offer many opportunities for changes in relationships with others. Relationships can gain new meanings due

to increased social values, connecting with others, and gains associated with PTG (50).

CONCLUSION

Experiences during and after natural disasters such as earthquakes can cause various psychological effects on the individuals who experienced the disaster and the helpers who work in the region. It is important to make psychosocial assessments for both groups after disasters to see their needs and to apply appropriate treatments. Although major disasters negatively affect many individuals' perceptions of a fair and safe world, it should not be forgotten that individuals and the community can also become stronger after traumatic events and that there is always hope.

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CASE REPORT / OLGU SUNUMU
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TRANSIENT BENIGN HYPERPHOSPHATASEMIA DUE TO ROTAVIRUS GASTROENTERITIS

ROTAVİRÜS GASTROENTERİTİNE BAĞLI GEÇİCİ BENİGN HİPERFOSFATAZEMİ

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ABSTRACT

Transient benign hyperphosphatasemia (TBH) is a benign condition characterized by transiently elevated serum alkaline phosphatase (ALP) levels by 3-50 times normal values. It can sometimes be seen in connection with different clinical disorders such as respiratory tract infections, gastrointestinal diseases, congenital metabolic disorders, malignancies, congenital anomalies, anemia, and neurological disorders. In this report, we describe three children who had TBH after rotavirus-associated gastroenteritis and in whom there was no evidence of liver or bone disease. We aim to raise awareness and draw attention to TBH in this case report.

Keywords: Transient hyperphosphatasemia, alkaline phosphatase, rotavirus, gastroenteritis, children

ÖZET

Geçici benign hiperfosfatazemi (TBH), serum alkalen fosfataz (ALP) düzeylerinin normalin 3-50 katı kadar geçici olarak yükselmesi ile karakterize ve bazen de gastrointestinal hastalıklar, solunum yolu enfeksiyonları, doğumsal anomaliler, doğumsal metabolik bozukluklar, anemi, maligniteler, nörolojik bozukluklar gibi farklı klinik bozukluklarla birlikte görülebilmektedir. Bu çalışmada, karaciğer veya kemik hastalığı olmayan, rotavirüs ile ilişkili gastroenterit sonrası TBH'li üç çocuk sunuldu. Bu olguların sunulması ile TBH konusuna dikkat çekilmesi ve farkındalık yaratılması amaçlandı.

Anahtar Kelimeler: Geçici hiperfosfatazemi, alkalin fosfataz, rotavirüs, gastroenterit, çocukluk evresi

INTRODUCTION

Alkaline phosphatase (ALP) is present in different concentrations in many tissues such as the placenta, ileal mucosa, kidney, bone, and liver. In healthy individuals, more than 80% of ALP in serum is released from the liver and bone. Levels of serum ALP are high during childhood and adolescence, mainly due to bone growth and development (1, 2). Transient benign hyperphosphatasemia (TBH) is a benign condition characterized by above normal levels of serum alkaline phosphatase (ALP), transiently elevated by 3-50 times the normal value. This disease can be seen in connection with different clinical disorders such as respiratory tract infections, gastrointestinal diseases, congenital metabolic disorders, malignancies, congenital anomalies, anemia, and neurological disorders (3).

The characteristic features of TBH have previously been described in the literature: a) no signs of liver or bone disease on laboratory findings or physical examination, b) serum ALP elevation, c) return to normal levels of serum ALP within four months, d) age of presentation less than five years (4).

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In this report, we describe three children who had TBH after rotavirus-associated gastroenteritis. This study aims to raise awareness and draw attention to TBH.

CASE PRESENTATIONS

A two and half-year-old female, a three-year-old boy and a four and a half-year-old boy were admitted to our pediatric emergency department with the complaint of acute diarrhea. All three cases had been born full term, and their neuromotor developments were compatible with their peers. They had no history of illness and were not on any medication. Their physical examinations were normal except for increased bowel sounds. Their growth parameters were normal for their age. When rotavirus antigen was tested in fresh stool specimens of the patients, all samples were positive. The initial blood test results of the patients are shown in Table 1. Their laboratory examinations also revealed high ALP activity.

Levels of 25-hydroxy vitamin D, parathormone, phosphorus, and calcium were all within normal values. Skeletal radiographs were checked, and they were all normal as well. Liver function tests, albumin, total and direct bilirubin and prothrombin time were all within normal values. Abdominal ultrasonography for possible hepatic disorders were normal. The results of examinations carried out on the parents were within normal levels. After excluding bone and liver diseases in the differential diagnosis, we thought that the high ALP levels might be due to rotavirus gastroenteritis. Serial levels of ALP were checked during follow-up of the patients (Table 2). Alkaline phosphatase levels decreased and returned to normal levels at 3 months. As a result of all these findings, the patients were diagnosed with TBH due to acute rotavirus infection.

Informed consent was obtained from the families of the patients for the publication of the case report.

DISCUSSION

Alkaline phosphatase is a widely used biochemical marker to screen for hepatic or skeletal disorders. Therefore, patients with high ALP levels are potentially referred to tertiary care centers for further evaluation. Transient benign hyperphosphatasemia is a benign condition typically caused by viral infections such as Epstein-Barr virus, enterovirus, and rotavirus. However, it is certainly difficult to diagnose TBH in children (5-8). Behulova et al. reported a wide variety of clinical disorders associated with TBH (9). The most common diseases associated with TBH are gastrointestinal diseases (24%), respiratory infections (21%), congenital anomalies and metabolic diseases (15%) (9). Zemer et al. reported that the three leading diagnoses noted with hyperphosphatasemia included fever (28%), gastroenteritis or diarrhea (25%) and acute otitis media (11%) (10). Suzuki et al. reported that the four most common infectious diag-

Table 1: Initial blood test results of patients

	Case-1	Case-2	Case-3	Reference range
ALT (IU/L)	10	24	31	5-45 IU/L
AST (IU/L)	10	23	39	15-55 IU/L
GGT (U/L)	16	28	24	5-32 U/L
D bil (mg/dl)	0.21	0.40	0.35	0-0.5 mg/dl
ALP (IU/L)	1846	2423	1958	145-420 IU/L
LDH (U/L)	348	284	326	180-345 U/L
Ca (mg/dl)	9.2	9.6	10.2	8.8-10.8 mg/dl
P (mg/dl)	4.0	4.3	4.8	3.7-5.6 mg/dl
PTH (pg/dl)	38	41	31	9-65 pg/dl
25 (OH) Vit. D (ng/ml)	36	28	34	7.4-53.3 ng/m

ALP: Alkaline Phosphatase, Ca: Calcium, P: Phosphorus, PTH: Parathormone, LDH: Lactate dehydrogenase, 25 (OH) vit. D: 25-Hydroxy Vitamin D, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase, D bil: Direct bilirubin

Table 2: Serial ALP (IU/L) measurements

	1st day	3rd day	7th day	1st month	2nd month	3rd month	4th month
Case 1	1846	2284	2784	1946	454	401	345
Case 2	2423	2372	2057	1155	427	354	320
Case 3	1958	1848	1764	978	357	368	290

noses observed in TBH cases were bronchitis, pneumonia, diarrhea, and fever (11). The pathogenesis of TBH is not fully understood. The presence of diarrhea may lead either to impaired clearance of ALP from the circulation or to increased production of ALP secondary to hyperactivated osteoblasts (6). In our cases, TBH was associated with diarrhea or rotavirus infection.

The prevalence of TBH is difficult to estimate because it is usually discovered incidentally in laboratory tests requested for other reasons (12). Its prevalence in patients whose age falls between 6 months and 5 years ranges between 2-6% depending on the ALP values used for the diagnosis (13-17). In one study, 2.8% of patients had a transient and unexplained elevation of the ALP level among 321 healthy infants and toddlers aged 8-24 months (13). A study in Israel reported that 87% of patients with TBH between the ages of one day and 18 years consisted of children under the age of 2 years (10). This condition is not common in older children or adults (15). All three patients in our case report were under 5 years old, which is consistent with the literature.

An evaluation of the patient with a detailed history, basic laboratory tests, and accurate physical examination are usually sufficient to exclude possible bone or liver disease. We found 25-hydroxy vitamin D, parathormone, phosphorus and calcium levels within normal values, therefore we excluded increased bone turnover. High levels of serum ALP (3-50 times above the normal value of serum ALP levels) return to normal levels within an average of four months in TBH. It is recommended that the diagnosis of TBH according to age criteria should be considered in children younger than five years old (4). Although there is no clear information on the timing to check the ALP levels in the follow-up of patients with TBH, a conservative approach recommending testing again in 2-3 months has been reported to be safe and cost-effective (17). In our patients, the time it took for ALP levels to normalize again was within four months, and all children with TBH were under five years of age, consistent with both Kraut's criteria and previous reports (4, 5, 17). In the follow-up of our patients, their growth and development were normal, and no additional pathology was observed. According to these findings, our patients met all the diagnostic criteria of TBH.

Transient benign hyperphosphatasemia is associated with a marked but transient benign elevation of ALP without any other abnormality and it does not have any specific treatment (7). No special treatment was applied to our patients except symptomatic treatment. The clinical course of our patients showed an event-free improvement in the expected time, consistent with previously reported cases.

CONCLUSION

Transient benign hyperphosphatasemia is a self-limited clinical condition, and no treatment is required. For patients with elevated ALP for any reason, if there is no known chronic disease nor evidence of bone or liver diseases, outpatient follow-up will be sufficient until their ALP values decrease. Awareness of this condition among pediatricians will reduce expensive and unnecessary investigations.

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