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From the Editor

Dear readers,

In the third issue of 2021, we have prepared articles that we think are interesting for you. In this issue, you will find 15 original researches, and 2 case reports.

As we announced in our previous issue, the process we started to take place in Scopus and other internationally respected indexes continues. For this reason, we have decided to accept only articles in English as of August 15, 2021. With our first issue of 2022, we are planning to publish articles only in English.

As always, your interest is our greatest source of motivation to carry our quality to a higher level.

Please stay tuned for the next issue.

Assoc. Prof. Dr. Ahmet Keskin

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THE RELATIONSHIP BETWEEN HEALTHY LIFESTYLE BEHAVIORS AND BODY COMPOSITIONS IN UNIVERSITY STUDENTS

ÜNİVERSİTE ÖĞRENCİLERİNDE SAĞLIKLI YAŞAM BİÇİMİ DAVRANIŞLARI İLE VÜCUT KOMPOZİSYONLARI ARASINDAKİ İLİŞKİ

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Öz

Amaç: Sağlıklı yaşam tarzı davranışları, "sağlıklı bir zihin durumunu sürdürmek ve sağlıklı aktivite davranışları geliştirmek" anlamına gelir. Bu çalışmanın amacı üniversite öğrencilerinde sağlıklı yaşam tarzı davranışları ile vücut kompozisyonları arasındaki ilişkiyi incelemektir.

Materyal ve Metot: Kesitsel tipteki bu çalışmanın evrenini Beslenme ve Diyetetik Bölümü'nde okuyan öğrenciler oluşturdu. Katılımcıların demografik verileri toplandı ve "Sağlıklı Yaşam Biçimi Davranışları Ölçeği-II" uygulandı.

Bulgular: Öğrencilerin ortalama Sağlıklı Yaşam Biçimi Davranışları Ölçeği II puanı 130,15±15,07 olarak belirlendi. Vücut kitle indeksine göre normal olan öğrencilerin fiziksel aktivite puanları, zayıf ve fazla kilolu olanlara göre istatistiksel olarak anlamlı düzeyde daha yüksekti. Vücut kitle indeksine göre normal olan öğrencilerin beslenme puanları zayıf olanlara göre istatistiksel olarak anlamlı derecede daha yüksekti. Vücut yağ yüzdelerine göre obez olan öğrencilerin fiziksel aktivite puanları atlet, fit veya normal olanlara göre istatistiksel olarak anlamlı derecede düşüktü. Bel çevresine göre fazla kilolu olan öğrencilerin sağlık sorumluluğu ve fiziksel aktivite puanları normal olanlara göre istatistiksel olarak anlamlı derecede düşüktü.

Sonuç: Bu çalışma, daha sağlıklı ve daha zinde bir vücuda sahip öğrencilerin beslenmelerine daha fazla önem verdiklerini, daha fazla fiziksel aktivitede bulunduklarını ve daha yüksek sağlık sorumluluklarına sahip olduklarını göstermiştir.

Anahtar Kelimeler: Vücut kompozisyonu, sağlıklı yaşam tarzı davranışı, öğrenci.

Abstract

Objectives: Healthy lifestyle behaviors refer to "maintaining a healthy state of mind and developing healthy activity behaviors." The aim of this study was to investigate the relationship between healthy lifestyle behaviors and body composition in university students.

Materials and Methods: The population for this cross-sectional study consisted of students from the Nutrition and Dietetics Department. Demographic data were collected, and the "Health Promoting Lifestyle Profile II" (HPLP-II) was administered.

Results: The mean HPLP-II score of the students was 130.15 ± 15.07. The physical activity score of the students was normal according to body mass index (BMI), and it was significantly higher than that of those who were underweight and overweight. According to BMI, the nutrition scores of normal students were statistically significantly higher than those who were underweight. The physical activity scores of the students who were obese according to their body fat percentage were statistically significantly lower than those of those who were athletes, fitness, or average. According to their waist circumference, the health responsibility and physical activity scores of the overweight students were statistically significantly lower than those of those who were normal.

Conclusion: In this study, it was shown that students who have healthier and fitter bodies pay greater attention to their nutrition, take part in more physical activity, and have higher levels of health responsibility.

Keywords: Body composition, healthy lifestyle behavior, students.

Introduction

For individuals in the community to maintain good health, they must create a healthy lifestyle. A healthy lifestyle comprises controlling one's actions and choosing attitudes and behaviors that improve health by maintaining daily activities. On the other hand, healthy lifestyle behaviors refer to "maintaining a healthy state of mind and developing healthy activity behaviors." Healthy lifestyle behaviors include adequate and balanced nutrition, stress management, regular exercise, not smoking or drinking alcohol, hygienic measures, spiritual development, healthy interpersonal relationships, and the responsibility for protecting and improving one's health.[1]

The first steps toward creating healthy lifestyle behaviors are taken in the family and society and are followed by development through education. According to World Health Organization estimates, 70–80% of deaths in developed countries and 40–50% of deaths in underdeveloped countries are from diseases that occur due to unhealthy lifestyles. For this reason, the health services provided should be in the direction of protecting, maintaining, and improving health this direction.[2-4]

University life is a period during which people experience significant changes. For the first time, most students who start university leave their families and attain some personal freedom. Therefore, during this period, students can develop unhealthy lifestyle behaviors, such as unhealthy nutrition, which can cause significant body composition changes.[5] There are a few studies in the literature examining the relationship between healthy lifestyle behaviors and body mass index (BMI). Nonetheless, in none of them, the relationship between healthy lifestyle behaviors and body composition, such as body fat percentage, waist circumference, and waist-to-hip ratio, were developed or identified in English literature.[6-9] The aim of this study was to investigate the relationship between healthy lifestyle behaviors and body composition in university students.

Materials and Methods

This questionnaire-based cross-sectional study considered 127 students from the Faculty of Health Sciences, Department of Nutrition and Dietetics at Trakya University in 2017.

The data were collected by asking demographic information questions, making anthropometric measurements, and administering the "Health Promoting Lifestyle Profile-II" (HPLP-II). Demographic data included questions related to descriptive characteristics (e.g., age, gender, place of residence, place of eating, grade level, smoking, and presence of chronic disease) of the participants and their families. The HPLP-II total and subgroup scores were evaluated according to demographic characteristics and body compositions.

Anthropometric Measurements

The weight, height, and waist and hip circumferences of the participants were measured. Body fat percentage was assessed using a bioimpedance analyzer (Tanita MC 780 MA, Tanita Corporation, USA), considering age, gender, and height. Participants were divided into four groups according to the American Council on Exercise (ACE) body fat chart: athletes (14-20%), fitness (21-24%), average (25-31%), and obese (higher than 32%).[10] Body mass index was calculated using the weight/height^2 formula. Body mass index scores are categorized into four groups: underweight (≤ 18.5), normal weight (18.6-24.9), overweight (25-29.9), and obese (≥ 30).[11] The waist-to-hip ratio was calculated using the waist circumference/hip circumference formula. A waist circumference greater than 80 cm in women and 90 cm in men is considered overweight.[12] Waist-to-hip ratio should generally be less than 0.7. Values above 0.8 in women and above 1.0 in men indicate abdominal obesity.[13] Before beginning the study, the aim of the research was verbally discussed with the participants. The questionnaire forms were administered at appropriate times without disrupting the lessons of the students.

Health Promoting Lifestyle Profile II

The Health Promoting Lifestyle Profile was developed in 1987 by Walker et al.[14] The first version consisted of 48 items and six sub-factors. Walker et al. reorganized the scale in 1996 and renamed it "Health Promoting Lifestyle Profile II."[15] A Turkish validity and reliability study was conducted by Bahar et al.[16] in 2008. The scale consists of 52 items and six sub-factors. All the items are positive, and marking is based on a 4-point Likert-type scale. Each of the four sub-factors with nine items (e.g., health responsibility, nutrition, spiritual development, and interpersonal relationships) provides a score from nine to 36 points. The sub-factors with eight items (e.g., physical activity and stress management) provide a score from eight to 32 points each. The lowest possible total score is 52 points, and the highest possible total score is 208 points. High scores in the subscales mean more frequent health-promoting behaviors. Cronbach's alpha coefficient of the HPLP-II original version is 0.94, and the coefficient in the Turkish version is 0.92.[15,16]

In the HPLP-II, the following sub-factors are considered: 1. Spiritual development: It determines the personal life goals, the ability to perform oneself individually, and to what extent the participants know and are satisfied with themselves; 2. Health responsibility: determines the level of responsibility for the health of the individual and to what extent the person is involved in health; 3. Physical activity: shows the level of physical activity of the individual; 4. Nutrition: determines the values of the person in choosing, organizing, and choosing food; 5. Interpersonal relationships: determines the communication and continuity of communication with the immediate environment of the person; 6. Stress management: determines the level of recognition of stress mechanisms and stress sources of the person.[15]

Statistical Analysis

Statistical evaluation was performed using SPSS (version 22.0; SPSS Inc., 2016). After examining the suitability of the quantitative data obtained due to the research to the normal distribution, the Student t-test was used in two independent groups, and the one-way ANOVA test was used in three or more independent groups to compare variables that fulfill the parametric test assumptions. Pearson test was used for correlation analysis. Descriptive statistics are given as mean ± standard deviation, numbers, and percentages. $P < 0.05$ was taken as the limit of significance.

Results

In 2017, 237 students were studied at Trakya University Faculty of Health Sciences, Department of Nutrition and Dietetics, who were potentially eligible participants in a questionnaire-based cross-sectional study. One hundred fifty (63.30%) of them were contacted and invited to participate in the study. One hundred thirty-five (56.96%) of them agreed to participate in the study, and the questionnaires were distributed to them to fill out. One hundred twenty-seven (53.58%) of them filled out the questionnaires completely, and their data were analyzed for the study (Figure 1). The mean age of the participants was 20.38 ± 2.22, with 44 (34.64%) under the age of 20. There were 108 (85.03%) females. It was determined that 12 (9.44%) students had a chronic disease. Thirteen (10.23%) stated that they smoked. Thirty-nine (30.70%) students lived at home, 51 (40.15%) lived in a state dormitory, and 37 (29.15%) lived in a private dormitory. Regarding the eating location of the participants, 38 (29.92%) ate at home, 79 (62.20%) ate at school/dormitory, and 10 (7.88%) ate at restaurants. Forty-eight (37.79%) were in the first grade, 36 (28.34%) were in the second grade, 22 (17.32%) were in the third grade, and 21 (16.55%) were in the fourth grade (Table 1).

According to BMI, 50 (39.37%) students were underweight, 67 (52.75%) were normal weight, and 10 (7.88%) were overweight. According to body fat percentage, 39 (30.70%) were athletes, 38 (29.92%) were fit, 40 (31.49%) were normal, and 10 (7.89%) were obese. According to waist circumference, 118 (92.91%) students were of normal weight, and nine (7.09%) were overweight. The waist-to-hip ratio was normal in 118 (92.91%) students and abnormal in nine (7.09%).

The mean HPLP-II score was 130.15 ± 15.07. The two subgroups with the highest scores were spiritual development and interpersonal relationships, while the two with the lowest scores were physical activity and stress management (Table 2).

According to the demographic characteristics of the students, the mean HPLP-II for each subgroup and total scores are presented in Table 2. The nutrition scores of students aged 20 years and over were statistically

significantly higher than those under 20 years of age (p=0.042). It was found that the physical activity scores of males were statistically significantly higher than females (p=0.048). There was no statistically significant difference between the accommodations of the students, their eating places, their grade levels, smoking habits, chronic disease states, or the mean HPLP-II subgroup and total scores.

The mean HPLP-II subgroup and total scores according to body compositions are shown in Table 3. According to BMI, the physical activity scores of the normal students were statistically significantly higher than those who were underweight and overweight (p=0.015). According to the BMI values, the nutrition scores of the normal students were statistically significantly higher than those who were underweight (p=0.023). It was revealed in a Pearson correlation analysis that as the nutrition subgroup scores of the students increased, the BMI increased (Figure 2, p=0.02, r=0.206). According to their body fat percentage, the physical activity scores of the students who were obese were statistically significantly lower than those who were athletes, fitness, or average (p=0.046). According to waist circumference, the health responsibility (p=0.048) and physical activity (p=0.044) scores of overweight students were statistically significantly lower than normal ones. No statistically significant difference was found between normal and abnormal waist-to-hip ratios in terms of HPLP-II subgroup scores.

Table 1. Participants' Demographic Characteristics (n=127)

Demographic data	**n (%)**
Gender	
Female	108 (85.03)
Male	19 (14.97)
Chronic disease	
Yes	12 (9.45)
No	115 (90.55)
Smoking	
Smoker	13 (10.24)
Non-smoker	114 (89.76)
Living location	
Home	39 (30.70)
State dormitory	51 (40.15)
Private dormitory	37 (29.15)
Chronic disease	
Yes	12 (9.45)
No	115 (90.55)
Eating location	
Home	38 (29.92)
School / dormitory	79 (62.20)
Restaurant	10 (7.88)
Academic grade	
1	48 (37.79)
2	36 (28.34)
3	22 (17.32)
4	21 (16.55)

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Table 2. Health Promoting Lifestyle Profile II Scores of students' characteristics (n=127)

	Health Responsibility	Physical Activity	Nutrition	Spiritual Development	Interpersonal Relations	Stress Management	Total HPLP-II Score
HPLP-II Scores	20.21 ± 3.66	17.14 ± 4.18	21.32 ± 3.28	26.59 ± 3.67	25.67 ± 4.00	19.20 ± 3.00	130.15 ± 15.07
Age							
< 20	20.13 ± 4.23	17.00 ± 3.16	20.54 ± 2.90	26.61 ± 3.74	25.84 ± 3.97	19.52 ± 3.28	129.65 ± 14.85
≥ 20	20.25 ± 3.34	17.21 ± 4.64	21.73 ± 3.41	26.59 ± 3.66	25.59 ± 4.03	19.03 ± 2.85	130.42 ± 15.27
p value	0.875	0.757	**0.042** *	0.973	0.737	0.409	0.786
Gender							
Female	20.34 ± 3.82	16.75 ± 3.87	21.13 ± 3.27	26.54 ± 3.49	25.93 ± 4.02	19.18 ± 2.93	129.89 ± 15.22
Male	19.47 ± 2.50	19.36 ± 5.18	22.36 ± 3.23	26.89 ± 4.67	24.21 ± 3.61	19.31 ± 3.46	131.63 ± 14.50
p-value	0.211	**0.048** *	0.140	0.760	0.071	0.878	0.638
Place to stay							
Home	20.33 ± 3.40	17.94 ± 5.17	21.71 ± 3.46	26.51 ± 4.03	24.87 ± 4.25	19.02 ± 3.09	130.41 ± 15.70
State Dormitory	20.33 ± 3.97	16.90 ± 3.53	21.43 ± 3.03	26.43 ± 3.31	26.07 ± 4.10	19.23 ± 2.87	130.41 ± 14.93
Private Dormitory	19.91 ± 3.56	16.62 ± 3.81	20.75 ± 3.42	26.91 ± 3.84	25.97 ± 3.53	19.35 ± 3.16	129.54 ± 14.98
p-value	0.848	0.337	0.426	0.818	0.320	0.892	0.958
Place to eat							
Home	20.26 ± 3.51	17.42 ± 5.17	21.42 ± 3.26	26.57 ± 3.61	25.18 ± 3.77	18.84 ± 3.07	129.71 ± 15.91
School cafeteria	20.34 ± 3.77	16.97 ± 3.66	21.34 ± 3.23	26.84 ± 3.46	26.16 ± 4.03	19.46 ± 3.07	131.13 ± 14.93
Outside	19.00 ± 3.39	17.40 ± 4.27	20.80 ± 4.04	24.70 ± 5.22	23.70 ± 4.16	18.50 ± 2.06	124.10 ± 12.49
p-value	0.552	0.848	0.867	0.221	0.123	0.429	0.374
Class							
1	19.93 ± 4.07	17.02 ±3.84	20.56 ± 3.14	26.64 ± 3.95	25.70 ± 4.16	19.58 ± 3.29	129.45 ± 14.80
2	20.38 ± 3.19	18.08 ± 4.77	22.33 ± 3.56	26.88 ± 3.46	26.11 ± 3.70	19.30 ± 3.19	133.11 ± 15.39
3	19.95 ± 2.78	16.81 ± 3.68	21.13 ± 2.31	26.50 ± 2.85	24.77 ± 3.13	19.31 ± 1.78	128.50 ± 8.08
4	20.80 ± 4.34	16.14 ± 4.30	21.52 ± 3.66	26.09 ± 4.30	25.80 ± 4.94	18.04 ± 2.88	128.42 ± 20.23
p value	0.800	0.366	0.104	0.889	0.670	0.269	0.572
Smoking							
Yes	20.00 ± 2.58	17.61 ± 6.21	21.97 ± 3.94	25.61 ± 2.93	26.23 ± 3.67	19.38 ± 3.42	129.92 ± 17.40
No	20.35 ± 3.75	17.07 ± 3.96	21.36 ± 3.25	26.74 ± 3.76	25.64 ± 4.08	19.19 ± 3.00	130.38 ± 15.01
p-value	0.666	0.763	0.801	0.219	0.601	0.854	0.928
Chronic illness							
Yes	21.75 ± 3.84	16.50 ± 3.65	22.25 ± 3.86	27.50 ± 2.74	26.83 ± 4.13	18.58 ± 2.39	133.41 ± 14.11
No	20.05 ± 3.62	17.20 ± 4.24	21.22 ± 3.22	26.50 ± 3.75	25.55 ± 3.98	19.26 ± 3.06	129.81 ± 15.18
p-value	0.166	0.539	0.392	0.268	0.325	0.373	0.418

* Student's t-test, HPLP-II: Health Promoting Lifestyle Profile II

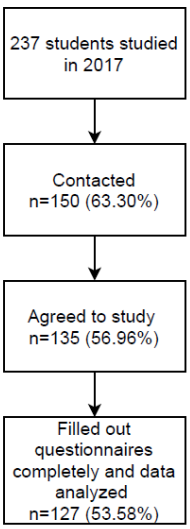

Figure 1. The flow diagram of the participants

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Table 3. Students' Health-Promoting Lifestyle Profile-II Scores According to Body Compositions (n=127)

Body Compositions	Health Responsibility	Physical Activity	Nutrition	Spiritual Development	Interpersonal Relations	Stress Management	Total Score
BMI							
Underweight	19.58 ± 3.73	15.96 ± 3.80	20.36 ± 2.96	26.52 ± 3.72	25.80 ± 3.96	19.08 ± 3.40	127.30 ± 15.42
Normal	20.53 ± 3.65	18.14 ± 4.41	22.02 ± 3.43	26.58 ± 3.63	25.67 ± 4.07	19.35 ± 2.80	132.32 ± 14.91
Overweight	21.20 ± 3.19	16.30 ± 2.75	21.32 ± 2.75	27.10 ± 4.09	25.10 ± 4.04	18.80 ± 2.29	129.90 ± 13.14
p-value	0.255	**0.015** &	**0.023** &	0.902	0.882	0.804	0.204
Body Fat Percentage							
Athletes	20.21 ± 3.87	17.15 ± 5.74	21.21 ± 3.63	26.63 ± 4.35	25.68 ± 4.55	19.42 ± 3.83	130.31 ± 18.91
Fitness	19.47 ± 2.42	17.47 ± 3.16	21.71 ± 2.81	25.76 ± 3.38	24.57 ± 2.88	19.10 ± 2.63	128.10 ± 10.57
Average	20.95 ± 4.11	17.20 ± 3.48	21.12 ± 3.54	27.50 ± 3.02	26.60 ± 4.21	19.07 ± 2.73	132.45 ± 15.15
Obese	20.09 ± 4.63	15.72 ± 3.37	21.09 ± 2.77	26.09 ± 3.98	26.09 ± 4.13	19.27 ± 2.00	128.36 ± 13.76
p-value	0.368	**0.046** &	0.859	0.206	0.164	0.958	0.622
Waist circumference							
Normal	20.38 ± 3.56	17.34 ± 4.22	21.40 ± 3.28	26.64 ± 3.63	25.77 ± 3.98	19.26 ± 3.03	130.82 ± 15.12
Overweight	17.88 ± 4.31	14.44 ± 2.40	20.22 ± 3.23	26.03 ± 4.41	24.44 ± 4.24	18.44 ± 2.55	121.44 ± 11.84
p-value	**0.048** *	**0.044** *	0.299	0.615	0.340	0.433	0.072
Waist/Hip Ratio							
Normal	20.27 ± 3.60	17.10 ± 4.23	21.27 ± 3.29	26.62 ± 3.64	25.72 ± 3.97	19.24 ± 3.05	130.23 ± 14.96
Abnormal	19.44 ± 4.58	17.66 ± 3.60	22.00 ± 3.24	26.22 ± 4.32	25.11 ± 4.53	18.66 ± 2.29	129.11 ± 17.43
p-value	0.516	0.698	0.523	0.752	0.662	0.580	0.830

& One-way ANOVA, * Student's t-test, BMI: Body mass index

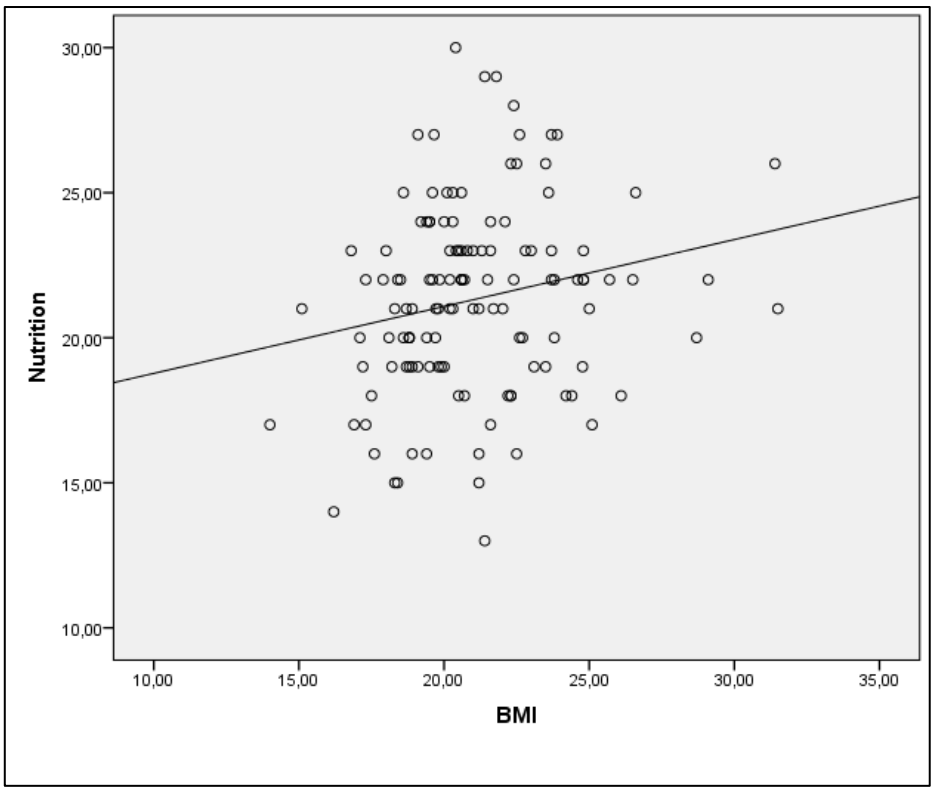

Figure 2. Correlation between the nutrition subgroup scores and the BMI scores in the students (p=0.02, r=0.206).

Discussion

In our study, in which the highest possible total HPLP-II score was 208, the total mean score for the students was 130.15 ± 15.07. Aksoy and Uçar conducted a study on nursing students and found that their HPLP-II total mean score was 136.12 ± 19.16. A survey by Unalan et al. in health college students reached 127.81 ± 17.52.[1-17] A study of nurses by Özkan and Yilmaz[18] found that the total mean score was 125.96 ± 16.99, and in a survey by Uz and Kitiş[19] of healthcare workers, it was 132.87 ± 12.47. The study results conducted on the same scale in health workers in Turkey are similar, and usually mean total scores HPLPS II is moderate levels.[18] In a study conducted by Al-Kandari and Vidal[20] with nursing students in Kuwait, the total mean score was 128.16, and it was 125.76 in a study conducted by Hawks et al.[21] with Japanese nursing students in the USA. In Hui's survey of nursing students in Hong Kong, the total mean score was 116.28 ± 16.82, which is considerably lower than in our study.[22]

In studies conducted by Aksoy and Uçar[1] of nursing students and by Türkol and Güneş[23] in assistants practicing at İnönü University Medical Faculty Hospital, the highest scores were in the spiritual development and interpersonal relationships sub-dimensions of HPLP-II. In this same study, the lowest scores were related to physical activity and stress management. In the research conducted by Cürcani et al.[24] on nurses, the highest mean score was in the spiritual development sub-dimension, and the lowest average score was in the physical activity sub-dimension. Similarly, Özkan and Yilmaz[18] determined that the highest score for nurses was for spiritual development, and the lowest score was for the physical activity sub-dimension. In our study, the two subgroups for which the participants received the highest scores were spiritual development and interpersonal relationships of HPLP-II, while the two subgroups with the lowest scores were physical activity and stress management. In other studies with nurses, as in our study, the spiritual development sub-dimension mean score was the highest, and the physical activity sub-dimension mean score was the lowest.[4] In line with the findings, it can be said that healthcare professionals do not have a habit of exercising regularly.

In a study conducted on physical education and sports students, the mean scores of the physical activity and nutrition HPLP-II sub-dimensions were higher for male students than for female students. The mean scores for fourth-grade students were more elevated in four of the six sub-dimensions compared to the other grades.[25] In the study conducted by Aksoy and Uçar[1] on nursing students, the age group with the highest HPLP-II score was 24 years old and older. It was determined that there was an increase in the mean scores with increasing age. In our study, while the mean score of the HPLP-II physical activity subscale of male students was significantly higher than that of female students, there was no difference between the grade levels. In addition, the mean score of the nutrition subscale for students aged 20 years and older was significantly higher than the score for those under the age of 20. These results indicate that male students attach more importance to physical activity, and older students pay more attention to nutrition.

In studies conducted by Aksoy and Uçar[1] in nursing students and Şimşek et al.[5] in Faculty of Medicine students, the HPLP-II mean scores of the students who stayed with their families during their university education were determined to be the highest. In our study, there was no significant correlation between where the students lived and where they ate and the mean scores of the scale and subgroups. In nurse studies by Altay et al.[26] and Aksoy and Uçar[1], it was found that having a chronic disease did not affect HPLP-II scores, which is similar to the findings of our study. According to this result, it can be said that students do not perceive diseases as threats and do not give importance to healthy lifestyle behaviors that play an essential role in disease prevention. In the same study conducted by Aksoy and Uçar[1], no significant relationship was found between smoking and HPLP-II scores similar to our study.

There are a few studies in the literature examining the relationship between HPLP-II scores and BMI, but in none of them, the relationship between HPLP-II scores and body composition, such as body fat percentage, waist circumference, and waist-to-hip ratio were developed or identified in English literature.[6-9] Nacar et al.[6] in Turkish medical students and Lolokote et al.[7] in their work with university students in China did not find a relationship between HPLP-II scores and BMI. In a study conducted by Alzahrani et al.[9] with medical students, a negative correlation was found between the mean interpersonal relations subgroup score of the HPLP-II and BMI. In a study conducted by Al-Kandari et al.[8] in nursing students in Kuwait, a negative correlation was found between HPLP-II total and nutrition subgroup scores and BMI. In our study, the mean scores of the nutrition subgroup of HPLP-II were significantly higher in the group with a normal BMI than for those who were underweight. The mean scores of the physical activity subgroup of the HPLP-II were significantly higher in the group with a normal BMI than the scores of the underweight or overweight participants. According to these results, it appears that students with a normal BMI pay greater attention to physical activity and nutrition. Our study found that the students who were obese according to body fat percentage had significantly lower mean scores in the HPLP-II physical activity subgroup compared to athletes, fit, and normal students. In addition, it was found that the average scores of the HPLP-II health responsibility and physical activity subgroups for students who were normal according to waist circumference were higher than those who were overweight. These results emphasize the importance of physical activity in preventing weight gain and maintaining a healthy weight.

To the best of our knowledge, this cross-sectional study is the first to examine the relationship between healthy lifestyle behaviors and body compositions, such as body fat percentage, waist circumference, and waist-to-hip ratio in English literature. Limitations of this study include our study site and our sample size. Concerning the sample site, we conducted a cross-sectional survey of students from only one university. About the sample size, the number of participants was low, which may affect the results.

In conclusion, in this study, it was determined that students who have healthier and fitter bodies pay greater attention to their nutrition, do more physical activity, and have a higher level of health responsibility. Healthcare professionals have important roles and responsibilities for individuals in the community to develop and maintain healthy lifestyle behaviors within the scope of preventive health services. For this reason, healthcare professionals first need to improve their health-related knowledge and then transform this knowledge into attitudes and behaviors. Further studies are required on this subject.

Ethical considerations

Approval from Trakya University Ethics Committee (26.04.2017/124) was granted, and informed consent was obtained from each participant.

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Research Article

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FIRST-TRIMESTER MATERNAL VITAMIN D LEVELS AND RISK FOR GESTATIONAL DIABETES MELLITUS

İLK TRİMESTER MATERNAL VİTAMİN D DÜZEYLERİ VE GESTASYONEL DİYABET RİSKİ

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Öz

Amaç: Vitamin D eksikliği; artmış advers gebelik sonuçları, fetal neonatal komplikasyonlar ve anne yenidoğanın ilerideki yaşamlarındaki ciddi sağlık sorunları ile ilişkilidir. Bununla birlikte maternal vitamin D statüsünün gestasyonel diyabet (GDM) riski ile ilişkisini araştıran çalışma sonuçları çelişkilidir. Bu çalışma retrospektif olarak maternal vitamin D düzeylerine göre GDM riskini değerlendirmeyi amaçlamaktadır.

Materyal ve Metot: Dışlama kriterleri uygulandıktan sonra 33 GDM ve 164 kontrol toplam 197 gebe kadın çalışmaya alındı. Vitamin D düzeylerine gebeliğin 11-14 haftaları arasında bakıldı. GDM tanısı gebeliğin 24-28 haftaları arasında 75 gram glukozla yapılan oral glukoz tolerans testi ile kondu.

Bulgular: GDM grubunda BMI non-GDM grubundan yüksekti (24,68 [21,72–27,64] kg/m^2 vs. 22,04 [20,51–24,73] kg/m^2, p = 0,004).). Vitamin D düzeyleri GDM grubunda non-GDM grubundan anlamlı olarak daha düşük bulundu (17,2 [15,6–19,2] nmol/L vs. 33,0 [31,2–35,0] nmol/L, p <0,001). Vitamin D eksikliği prevalansı GDM grubunda % 87,88 olup, D vitamini eksikliği GDM riskini 67,06 kat arttırmaktaydı (odds oranı 67,06, 95% güven aralığı 20,90–215,15, p <0,001).

Sonuç: Gebeliğin erken döneminde D vitamini eksikliği ile GDM gelişme riski arasında anlamlı bir ilişki saptanmıştır. Gebelik sırasında özellikle de ilk prenatal vizitte D vitamini eksikliğinin rutin olarak taranması GDM'nin ve GDM'nin anne ve yenidoğandaki olumsuz sonuçlarının daha iyi yönetilmesi bakımından yararlı olacaktır.

Anahtar Kelimeler: Gestasyonel diabetes mellitus, vitamin D eksikliği, gebelik, ilk trimester.

Abstract

Objectives: Vitamin D deficiency is linked to increased risk of adverse pregnancy outcomes, fetal and neonatal complications, as well as serious health consequences later in life for both mothers and offspring. However, studies on maternal vitamin D status and risk for gestational diabetes mellitus (GDM) are controversial. This study aimed to retrospectively evaluate the risk for GDM based on maternal serum vitamin D levels.

Materials and Methods: After applying the exclusion criteria, a total of 197 pregnant women, including 33 GDM cases and 164 controls, were enrolled in the study. Vitamin D levels were measured at 11–14 weeks of gestation. GDM was diagnosed by performing a 75-g oral glucose tolerance test between 24 and 28 weeks of gestation.

Results: BMI was higher in the GDM group than in the non-GDM group (24.68 [21.72–27.64] kg/m^2 vs. 22.04 [20.51–24.73] kg/m^2, p = 0.004). Vitamin D levels were significantly lower in the GDM group than in the non-GDM group (17.2 [15.6–19.2] nmol/L vs. 33.0 [31.2–35.0] nmol/L, p < 0.001). The prevalence of vitamin D deficiency was as high as 87.88% in the GDM group, with a 67.062-fold higher risk for GDM (odds ratio 67.062, 95% confidence interval 20.904–215.150, p < 0.001).

Conclusion: Insufficient vitamin D level in early pregnancy is significantly associated with GDM development. Routine screening for vitamin D deficiency during pregnancy, particularly at the first prenatal visit, may contribute to the identification and better management of GDM and its related adverse outcomes in mothers and offspring.

Keywords: Gestational diabetes mellitus, vitamin D deficiency, pregnancy, first trimester.

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Introduction

Gestational diabetes mellitus (GDM) is a condition characterized by variable severities of glucose intolerance that begins or is first recognized during pregnancy.[1] The prevalence of GDM ranges between 1% and 14% depending on ethnicity, race, and diagnostic criteria, and it increases in parallel with the substantial rise in the prevalence of overweight and obesity in women of childbearing age.[2] GDM is associated with both impaired insulin secretion and resistance, leading to maternal hyperglycemia and an elevated long-term and short-term risk of adverse pregnancy outcomes and fetal and neonatal complications.[3] GDM is also related to serious health consequences later in life for both mothers and their offspring, including obesity, metabolic syndrome, type 2 DM, and cardiovascular disorders.[4] Thus, it is crucial to identify the etio-pathological mechanisms leading to abnormal glycemic regulation in pregnancy, to enhance pre- and antenatal care and management, and to reduce the frequency of adverse pregnancy outcomes.

Vitamin D plays a neurohormone regulating role in cell proliferation and differentiation and bone and calcium–phosphate homeostasis and has a wide spectrum of effects as an antioxidant, anti-inflammatory, antifibrotic, and immunomodulatory agent.[5] Studies have reported that vitamin D deficiency is related to altered glucose metabolism through impaired pancreatic beta-cell function and mass, leading to insulin resistance.[6] Vitamin D deficiency was also shown as a risk factor for obesity and type 2 DM, especially in women of late reproductive age.[7] In addition, insufficiency and deficiency of vitamin D were common among pregnant women. Vitamin D deficiency in pregnant women has significant involvement in the health of the mother and life-long health status of her child, as it is linked to maternal and child infections, preterm delivery, preeclampsia, small for gestational age, and chronic diseases.[8] However, results of studies on maternal vitamin D status and risk for GDM are inconclusive and contradictory, which are mostly due to differences in population features, including ethnicity, geographic location, seasonal variations, gestational age in sampling, and diagnostic criteria for GDM.[9]

This study aimed to retrospectively determine first-trimester serum vitamin D levels in patients with GDM and to investigate the effects of vitamin D levels on the risk for GDM.

Materials and Methods

This retrospective single-center study was carried out from March 2014 to December 2020 in the Obstetrics and Gynecology Department of Bahçeşehir University Göztepe Medikal Park Hospital. A total of 197 women who presented to the outpatient obstetrics clinic for routine antenatal care between 11 and 14 weeks of gestation were included in the study. All participants had singleton pregnancies and had given blood samples for routine first-trimester screening. Women with known or clinically suspected type 1 and 2 DM, history of

GDM, preeclampsia, thyroid, parathyroid or adrenal diseases, alcohol use, smoking, metabolic bone or kidney disease, and hepatic failure and those taking medications that might affect glucose, calcium, and vitamin D metabolism were excluded from the study.

Pregnant women were divided into two groups based on the presence of GDM. GDM was diagnosed by performing a 75-g oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation based on the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG).[10] According to IADPSG recommendations, the diagnosis of GDM is confirmed if one of the following is met: fasting glucose level ≥92 mg/dL, 1-h glucose level ≥180 mg/dL, or 2-h glucose level ≥153 mg/dL.

Demographic characteristics, including age, weight, height, smoking, number of parity and gravidity, history of abortion and polycystic ovarian syndrome (PCOS), delivery type (vaginal or cesarean), and gestational complications (including atony uterine, bilateral hydronephrosis; placental detachment; early membrane rupture; hemolysis, elevated liver enzyme levels, and low platelet level syndrome; intrauterine growth restriction; cholestasis, placenta previa; pancreatitis; preeclampsia; Rh alloimmunization; and small gestational age) were retrospectively obtained from patients' file. Body mass index was calculated as body weight (kilograms) divided by the square of body height (meters). Clinical data of neonates, including weight, sex, gestational age, length of stay in the neonatal intensive care unit, and congenital abnormalities such as ventricular septal defect and cleft lip and palate, were also obtained from hospital records. Gestational age was evaluated according to the last menstruation date and first-trimester obstetric radiologic examination. Fetal anthropometric measurements (body weight) of the neonates were determined immediately after birth by hospital staff following the hospital quality control procedures.

Biochemical Analyses

Blood samples for 25-hydroxy (25-OH) vitamin D test were obtained from the antecubital vein after overnight fasting within 11–14 weeks of gestation. Blood samples were kept at room temperature for 30 min after collection and were centrifuged at 2000 g for 15 min to separate the serum. Serum 25-OH vitamin D levels were determined with chemiluminescent enzyme immunoassay on the UniCel DxI 800 (Beckman Coulter Inc., CA, USA). Serum 25-OH vitamin D level >50 nmol/L was considered as sufficient, 30–49.9 nmol/L insufficient, and <30 nmol/L deficient. Since vitamin D levels show seasonal variations, only patients whose blood samples were taken to evaluate vitamin D status during the summer season were included in the study.

An OGTT was conducted in all participants with a glucose load of 75 g after overnight fasting between 24 and 28 weeks of gestation. Serum glucose levels were measured at 0, 60, and 120 min after glucose intake. During OGTT, serum HbA1c levels were also measured in all participants. Serum glucose and HbA1c levels were determined by a photometric method using an Olympus AU 2700 autoanalyzer (Beckman Coulter Inc., CA,

USA). All blood samples were examined within <1 h after sampling. All biochemical analyses, which are routinely checked every day, were performed with the same analyzers in the central laboratory of our hospital, depending on the test type.

Statistical Analyses

Power analysis was performed using PASS 11 software. Using the mean values of Vitamin D from the study conducted by Vijay et al., the minimum sample size should be 32 with a power level of 0.80 and 0.05 alpha error. Data from the hospital records were entered in the SPSS Statistics version 26 software (IBM Corp., Armonk, NY, USA), where all statistical analyses were carried out. Histogram and Q-Q plots were used to determine whether variables are normally distributed. Data are expressed as mean ± standard deviation for normally distributed variables and as median (1^{st}–3^{rd} quartiles) for skewed variables. Categorical variables are reported as frequency (percentage). For continuous variables, the independent samples t-test was used to test the significance of differences between groups to normally distributed variables, and the Mann–Whitney U test was used to test the differences between groups in terms of skewed variables. The chi-square test or Fisher's exact test was used to test the differences between groups for categorical variables. Multiple logistic regression analysis (forward conditional method) was performed to determine significant risk factors of GDM, and $p < 0.05$ values were accepted as significant results.

Results

A total of 33 patients with GDM (GDM group) and 164 individuals without GDM (non-GDM group) were enrolled in the study. The mean age was 31.80 ± 3.98 years in the GDM group and 30.99 ± 3.92 years in the non-GDM group ($p = 0.278$). BMI values were higher in the GDM group than in the non-GDM group (24.68 [21.72–27.64] kg/m^2 vs. 22.04 [20.51–24.73] kg/m^2, $p = 0.004$). Smoking was present in 8 (24.24%) patients in the GDM group and 13 (7.93%) patients in the non-GDM group ($p = 0.011$). No significant differences in the number of parity and gravidity, history of abortion and PCOS, delivery type, and gestational complications were observed between the two groups (all, p > 0.05) (Table 1). Neonatal clinical data, including weight, sex, gestational age, length of stay in the neonatal intensive care unit, and congenital abnormality, were similar between the two groups (all, p > 0.05) (Table 1).

Vitamin D levels were significantly lower in the GDM group than in the non-GDM group (17.2 [15.6–19.2] nmol/L vs. 33.0 [31.2–35.0] nmol/L, $p < 0.001$) (Figure 1). The prevalence of vitamin D deficiency was as high as 87.88% in the GDM group compared with 9.76% in the non-GDM group ($p < 0.001$). Fasting blood glucose levels were higher (90 [87–96] mg/dL) in the GDM group than in the non-GDM group (82 [79–87) mg/dL; $p < 0.001$). The mean blood glucose levels with OGTT were 195.73 ± 25.66 mg/dL at 60 min and 154.03 ± 35.38

mg/dL at 120 min in the GDM group, which were significantly higher than that in the non-GDM group ($p < 0.001$). Serum HbA1c levels were 5.52 ± 0.25% in the GDM group and 5.21 ± 0.18 in the non-GDM group ($p < 0.001$). The biochemical characteristics of the participants are shown in Table 2.

Table 1. Demographic characteristics of participants and neonates

	Gestational Diabetes Mellitus		
	Present (n=33)	**Absent (n=164)**	***p* value**
Age (years)	31.80 ± 3.98	30.99 ± 3.92	0.278
Weight (kg)	65 (57 - 73)	60 (55 - 68)	**0.028**
Height (cm)	162.73 ± 5.27	164.30 ± 5.39	0.127
Body mass index (kg/m^2)	24.68 (21.72 - 27.64)	22.04 (20.51 - 24.73)	**0.004**
Smoking (*n*)	8 (24.24%)	13 (7.93%)	**0.011**
Gravidity			
1	24 (72.73%)	121 (73.78%)	0.971
2	7 (21.21%)	33 (20.12%)	
3	2 (6.06%)	9 (5.49%)	
4	0 (0%)	1 (0.61%)	
Parity			
0	28 (84.85%)	133 (81.10%)	0.701
1	5 (15.15%)	28 (17.07%)	
2	0 (0%)	3 (1.83%)	
The history of Aborts (*n*)			
0	29 (87.88%)	144 (87.8%)	0.148
1	2 (6.06%)	18 (10.98%)	
2	2 (6.06%)	2 (1.22%)	
The history of Polycystic ovarian syndrome (*n*)	12 (36.36%)	49 (29.88%)	0.597
Other gestational complications (*n*)	5 (15.15%)	20 (12.20%)	0.578
Type of delivery			
Vaginal	1 (3.03%)	15 (9.15%)	0.481
Cesarean section	32 (96.97%)	149 (90.85%)	
Weight at birth (g)	3260 (3150 - 3520)	3215 (3075 - 3395)	0.083
Gestational week at birth	39 (38 - 39)	39 (38 - 39)	0.219
Gender			
Boy (*n*)	18 (54.55%)	81 (49.39%)	0.727
Girl (*n*)	15 (45.45%)	83 (50.61%)	
The length of stay in neonatal intensive care unit (days)	1 (3.03%)	10 (6.10%)	0.695
Congenital abnormality (*n*)	1 (3.03%)	1 (0.61%)	0.308

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. A *p*-value of <0.05 was considered significant.

Moreover, multiple logistic regression analysis was performed to determine significant risk factors of GDM (Table 3). Patients with vitamin D deficiency (<30 nmol/L) have 67.062-fold higher risk for GDM than other patients (odds ratio [OR] 67.062, 95% confidence interval [CI] 20.904–215.150, $p < 0.001$). Other variables included in the model, namely, age ($p = 0.862$), gravidity ($p = 0.767$), BMI ($p = 0.061$), smoking status ($p = 0.063$), history of PCOS ($p = 0.525$), and sex of neonates ($p = 0.717$), were non-significant.

Table 2. Biochemical characteristics of participants

	Gestational Diabetes Mellitus		
	Present (n=33)	**Absent (n=164)**	***p***
Vitamin D (nmol/L)	17.2 (15.6 - 19.2)	33.0 (31.2 - 35.0)	**<0.001**
< 30 (*n*)	29 (87.88%)	16 (9.76%)	**<0.001**
≥ 30 (*n*)	4 (12.12%)	148 (90.24%)	
Fasting blood glucose (mg/dL)	90 (87 - 96)	82 (79 - 87)	**<0.001**
Blood glucose levels at 60 min with OGTT	195.73 ± 25.66	136.65 ± 25.87	**<0.001**
Blood glucose levels at 120 min with OGTT	154.03 ± 35.38	110.19 ± 19.57	**<0.001**
HbA1c (%)	5.52 ± 0.25	5.21 ± 0.18	**<0.001**

OGTT: Oral glucose tolerance test; HbA1c: Glycosylated hemoglobin. Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. A *p*-value of <0.05 was considered significant.

Table 3. Significant risk factors of the gestational diabetes mellitus with multiple logistic regression analysis

	β coefficient	**Standard Error**	***p* value**	**Exp(β)**	**95.0% CI for Exp(β)**	
Vitamin D deficiency (< 30 nmol/L)	4.206	0.595	**<0.001**	67.062	20.904	215.150
Constant	-3.611	0.507	**<0.001**	0.027		

Dependent Variable: Gestational DM; Nagelkerke R2=0.575; Correct prediction=89.85%. CI: Confidence Interval

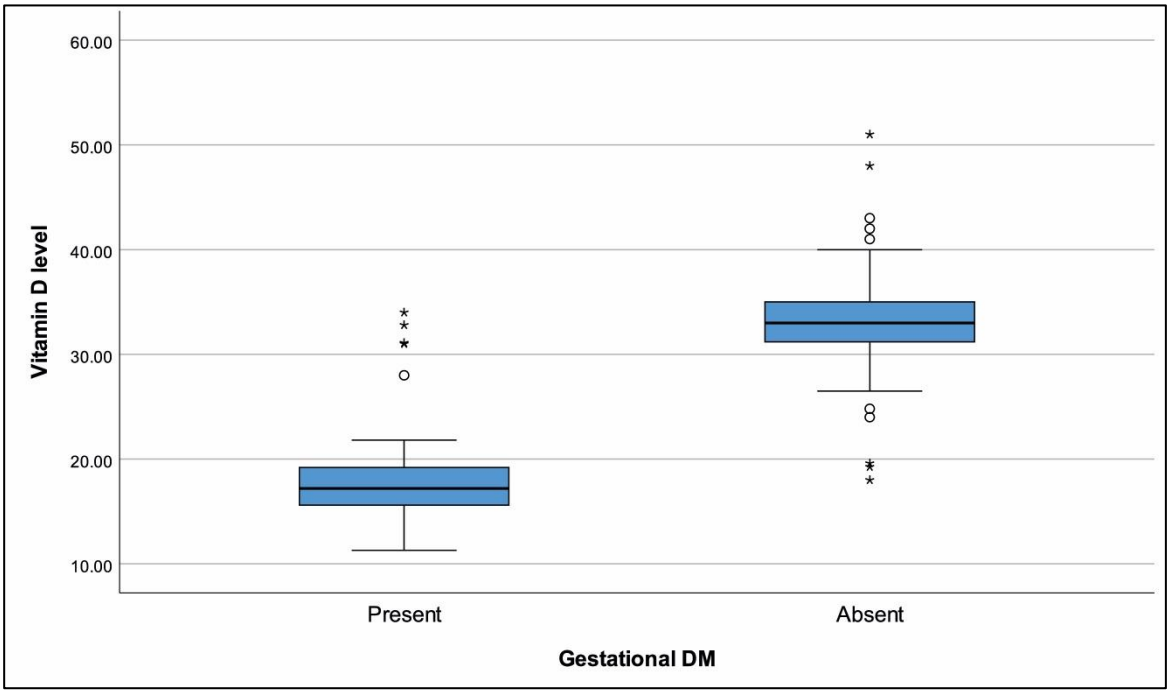

Figure 1. Vitamin D levels in pregnant women with regard to the presence of Gestational diabetes mellitus

Discussion

This study aimed to examine the relationship between maternal vitamin D levels in the first trimester and the risk for GDM. As main study findings, vitamin D levels were lower in women with GDM than in healthy individuals. In addition, the rate of first-trimester vitamin D deficiency was higher in patients with GDM, with a value of 87.88%. Moreover, the risk for GDM development was significantly higher among patients with vitamin D deficiency than among those without vitamin D deficiency. Finally, GDM was not associated with age, BMI, gravidity, smoking, and history of PCOS.

Vitamin D is a secosteroid with various biological effects on multiple mechanisms, including bone formation and mineralization, neuromuscular function, immunomodulatory functions, glucose homeostasis, and placental function.[11] A high prevalence of vitamin D deficiency among pregnant women has been reported.[12] Vitamin D deficiency has been associated with an elevated risk of adverse pregnancy outcomes such as placental implantation, preterm birth, preeclampsia, postpartum depression, maternal hypocalcemia, urinary tract infections, the cesarean section in mothers, as well as increased susceptibility to low-birth-weight, small for gestational age, respiratory diseases, autoimmune diseases, cardiovascular disease, and type 2 DM in neonates and offspring development.[13,14] However, the relationship between vitamin D level and GDM is still controversial. Some studies have demonstrated a relationship between vitamin D deficiency and GDM

development in pregnant women, but others reported no significant difference in healthy normoglycemic individuals. Savvidou et al. conducted a study with three groups of complicated pregnancies, including 50 patients with type 2 DM, 50 individuals without DM who subsequently delivered large-for-gestational-age neonates, and 100 women who subsequently developed GDM and 1000 healthy individuals without DM (control group), and they found no significant differences in the maternal serum vitamin D levels at 11–13^{+6} weeks of gestations in the three groups compared with the control group.[15] In a study of 25 patients with GDM and 208 healthy individuals, Ateş et al. showed that vitamin D levels at 11–14 weeks of gestation and prevalence of first-trimester vitamin D deficiency were comparable between the two groups.[16] Baker et al. did not find a relationship between maternal serum vitamin D levels at 11–14 weeks of pregnancy and GDM development in 60 patients with GDM and 120 ethnicity-matched healthy women from an overall cohort of 4225 pregnant women.[17] By contrast, Lacroix et al. evaluated 54 patients who subsequently developed GDM and 601 control participants and found that a low vitamin D level at the first trimester is an independent risk factor for GDM development.[18] Xu et al. demonstrated lower vitamin D levels at the first trimester in 101 women with GDM than in 726 healthy individuals.[19] Moreover, in their multivariate model analysis, vitamin D levels in the first and second quartiles were related to late development of GDM, and the risk for GDM increased by 24% and 48%, respectively. These differences may be explained by methodological issues, including study design, sample size, gestational age at sampling (first or second trimester), diagnostic criteria, the definition of vitamin D deficiency, and ethnic and genetic features of the participants.

In the present study, vitamin D levels were lower among patients with GDM than among women without GDM. Our results indicate that vitamin D may affect pancreatic beta-cell function and insulin sensitivity and secretion and that vitamin D deficiency may contribute to glucose intolerance during pregnancy. In addition, patients with vitamin D deficiency had a 67 times higher risk for GDM. Our results demonstrated that vitamin D levels at the first prenatal visit were related to an elevated risk of GDM. Various mechanisms may elucidate the observed relationship between vitamin D levels and risk for GDM. Vitamin D exhibits significant role in glucose homeostasis through different mechanisms. First, pregnancy has been an insulin-resistant condition with improved beta-cell function and proliferation that occurs in response to increased insulin secretory demand.[20] Beta cells exhibit vitamin D receptors, and studies have reported that vitamin D increases insulin sensitivity of target cells (i.e., adipose tissue, skeletal muscle, and liver) by increasing the insulin response to glucose transport.[21] Vitamin D also increases the function of beta cells and prevents them from deleterious immune attacks by acting on immune cells, including T cells, dendritic cells, and macrophages.[5] Furthermore, vitamin D promotes intestinal calcium absorption, while low serum calcium levels cause secondary hyperparathyroidism, which is independently related to abnormal glucose homeostasis during pregnancy.[22] Our results support the hypothesis that vitamin D deficiency was a risk factor for GDM. General screening for vitamin D deficiency during pregnancy, especially at the first prenatal visit, may contribute to the identification and management of GDM and its related adverse consequences in mothers and offspring. Previous studies have reported numerous

risk factors for GDM, including ethnicity, maternal age, history of GDM, high BMI, weight gain during pregnancy, multiparity, macrosomia, preeclampsia, family history of DM, history of abortion, and preterm delivery, and congenital anomalies.[23] In this study, although vitamin D deficiency was found to be the only risk factor for GDM, no relationship was observed between risk for GDM and age, BMI, gravidity, smoking, and history of PCOS. This may be related to the relatively small sample size, study design, lack of or uneven adjustments for confounding factors, and inclusion of a single ethnic group of patients. Further large-scale, well-designed prospective studies are warranted to identify risk factors and etiopathogenetic mechanisms on the onset and progression of GDM.

Some limitations should be considered. First, participants were recruited from a tertiary care hospital and from the Turkish pregnancy population and thus did not represent the general population. Second, data on clinical characteristics and vitamin D supplementation were obtained from the hospital data system, which could lead to under-or over-reporting. Third, as selection bias is also a concern in retrospective studies, it is difficult to control all potential covariates, and there may be unmeasured differences between the two study groups. Fourth, we did not provide information on dietary habits, lifestyle, sun exposure, use of fat-derived hormones, and other parameters that could theoretically affect vitamin D status. Fifth, serum vitamin D levels were evaluated by a single measurement during the early period of pregnancy, which did not allow for a time-integrated measure to demonstrate vitamin D status throughout pregnancy. Finally, the study uses a retrospective design, so we could not determine the effect of adequate vitamin D replacement on GDM and any causal relationship.

In conclusion, this retrospective analysis of first-trimester vitamin D levels in Turkish pregnant women demonstrated lower vitamin D levels in pregnant women with GDM than in healthy subjects. Moreover, the multiple regression analysis revealed that insufficient vitamin D level during pregnancy is associated with GDM. Thus, routine screening for vitamin D deficiency before and during early pregnancy may contribute to better management of the adverse outcomes associated with GDM in mothers and offspring.

Ethical considerations

All research procedures were evaluated and accepted by the Research Ethics Committee of İstanbul Medeniyet University, Göztepe Training and Research Hospital (date: 13.01.2021, decision number: 2021/0007) and were conducted in agreement with the ethical standards specified in the Declaration of Helsinki. Written informed consent was obtained from patients before they participated in this study.

Conflict of interest

The authors declare no conflict of interest.

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ERİŞKİN AŞILAMASINDA NEREDEYİZ? TÜRKİYE'DE ÜÇÜNCÜ BASAMAK BİR ÜNİVERSİTE HASTANESİ'NDE ERİŞKİN AŞI ÜNİTESİ'NE BAŞVURAN 65 YAŞ VE ÜZERİ ERİŞKİNLERİN AŞILANMA DURUMLARININ DEĞERLENDİRİLMESİ

WHERE ARE WE IN ADULT VACCINATION? EVALUATION TO VACCINATION STATUS OF ADULTS AGED 65 AND OVER WHO APPLIED TO THE ADULT IMMUNIZATION UNIT OF A TERTIARY UNIVERSITY HOSPITAL IN TURKEY

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Öz

Amaç: Türkiye'de 65 yaş ve üzeri bireyler için zorunlu olarak yapılan aşı uygulaması olmaması nedeniyle bu yaş grubunun immunizasyon durumları hakkında net veriler bulunmamaktadır. Bu nedenle hem ulusal hem uluslararası literatüre katkı sağlamak amacıyla çalışmamız planlanmıştır. Çalışmamızda Türkiye'de üçüncü basamak bir Üniversite Hastanesi erişkin aşı ünitesine başvuran 65 yaş ve üzeri bireylerde aşılanma durumlarının değerlendirilmesi amaçlanmıştır.

Materyal ve Metot: Çalışmamızda Hacettepe Üniversitesi Tıp Fakültesi Hastanesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı bünyesinde bulunan Erişkin Aşı Birimi'ne Haziran 2020 ile Haziran 2021 tarihleri arasında başvuran 65 yaş ve üzeri bireylerin yaş-cinsiyet dağılımı ve influenza-pnömokok-tetanoz-difteri aşıları ile aşılanma durumu/oranları değerlendirilmiştir.

Bulgular: Toplamda 1194 kişiye (kadın %53,4) ulaşılmıştır. Yaş gruplarına göre ikiye ayrılan bireylerin, 830'u (%69,5) 65-75 yaş aralığında iken; 364 'ü (%30,5) 75 yaş üstünde saptanmıştır. Polikliniğimizde yapılan aşıların %76,72'sini Prevenar 13 oluştururken 2. sırada tetanoz-difteri aşısı (%15,41), 3. sırada ise influenza aşısı bulunmaktadır (%7,03).

Sonuç: 65 ve üzeri erişkinlerde gelişebilecek enfeksiyon hastalıkları ve bunlara bağlı komplikasyonların önlenmesinde, böylece morbidite ve mortalitenin azaltılmasında etkin aşılamanın önemi tartışılmazdır.

Anahtar Kelimeler: Aşılama, erişkin bağışıklama, yaşlı bireyler.

Abstract

Objectives: There is no compulsory vaccination for individuals aged 65 and over in Turkey, there is no precise data about the immunization status of this age group. For this reason, our study is planned to contribute to both national and international literature. The study aimed to evaluate to vaccination status of individuals aged 65 and over who applied to the adult immunization unit of a Tertiary University Hospital in Turkey.

Materials and Methods: In our study, age-gender distribution and vaccination status of individuals aged 65 and over who applied to the Adult Vaccination Unit within the Infectious Diseases and Clinical Microbiology Department of Hacettepe University Faculty of Medicine between June 2020 and June 2021, and vaccination status with influenza-pneumococcal-tetanus vaccines rates were evaluated.

Results: A total of 1194 persons (53.4% of women) were reached. 830 (69.5%) of the individuals divided into two according to age groups were in the 65-75 age range; 364 (30.5%) of them were over 75 years old. Prevenar 13 constitutes 76.72% of the vaccines administered in our outpatient clinic, while the tetanus-diphtheria vaccine is in the second place (15.41%), and the influenza vaccine is in the third place (7.03%).

Conclusion: In preventing infectious diseases and related complications in adults aged 65 and over; thus, the importance of effective vaccination in reducing morbidity and mortality is indisputable.

Keywords: Vaccination, adult immunization, elderly people.

Giriş

Dünya Sağlık Örgütü'ne (DSÖ) göre 65 yaş üstü insanlar yaşlı kabul edilmektedir. 65 yaş ve üzeri nüfus tüm dünyada giderek artmakta, ortalama yaşam süresi uzamakta ve buna bağlı olarak da bu yaş grubunda takip ve tedavi edilen hastalıklar süregen bir hal almaktadır. Bu nedenle bu yaş grubuna ait sağlık sorunları iyi yönetilmeye ve çözülmeye muhtaç birer klinik antite olarak karşımıza çıkmaktadır. Tüm dünyada olduğu gibi ülkemizde de DSÖ verilerine göre 2015-2050 yılları arasında tüm dünyada 65 yaş ve üzeri nüfusun %12'den %22'ye çıkacağı tahmin edilmektedir. 2015 yılında 900 milyon olan 65 yaş ve üzeri nüfusun 2050 yılında 2 milyara ulaşması beklenmektedir.[1]

Ülkemizde ise Türkiye İstatistik Kurumu (TÜİK) verilerine göre 65 yaş ve üzeri yaştaki nüfus, 2015 yılında 6 milyon 495 bin 239 kişi iken son beş yılda %22,5 artarak 2020 yılında 7 milyon 953 bin 555 kişi olmuştur. Yaşlı nüfusun toplam nüfus içindeki oranı ise 2015 yılında %8,2 iken, 2020 yılında %9,5'e yükselmiştir. Nüfus projeksiyonlarına göre yaşlı nüfus oranının 2025 yılında %11,0, 2030 yılında %12,9, 2040 yılında %16,3, 2060 yılında %22,6 ve 2080 yılında %25,6 olacağı öngörülmektedir.[2] Buna göre ileriki günlerde sayısı daha da artacak olan geriatrik hasta popülasyonu için koruyucu sağlık hizmetlerine önem ve öncelik verilmesi oldukça gereklidir. Bu sayede önlenebilir hastalıkların önüne geçilebilmesi ve sağlıklı-bağımsız yaşlılık hedefine ulaşılabilmesi sağlanabilecektir. Koruyucu sağlık hizmetleri içerisinde en önemli ve başarılı halk sağlığı stratejisi şüphesiz aşılama programlarıdır.

65 yaş ve üzeri hasta grubunda tüm sistemlerde meydana gelen değişikliklere bağlı olarak koroner arter hastalıkları, serebrovasküler olaylar, diabetes mellitus, hipertansiyon, kronik böbrek yetersizliği gibi sık görülen hastalıklar dışında immun yaşlanmaya ve immun sistem değişikliklerine bağlı olarak artmış enfeksiyon riski de karşımıza çıkmaktadır. İmmun sistemde artmış yaşa bağlı olarak ortaya çıkan değişiklikler immunosens olarak adlandırılmaktadır. Yaşın ilerlemesinden hem edinsel hem de doğal immun yanıt etkilenirken edinsel immun yanıtta meydana gelen değişiklikler daha belirgindir. Edinsel immün sistem değişiklikleri T lenfosit fonksiyonunda azalma, B lenfosit uyarılması-immünglobulin üretiminin azalması ve aşı yanıtının zayıflaması olarak sayılabilmektedir.[3,4] Yaşlılık döneminde immun sistemde meydana gelen bir diğer değişiklik ise hafıza T ve B hücrelerinin sayı olarak artması ve bu durumun artmış otoantikor yapımı gibi istenmeyen bir sonuç doğurmasıdır.[5] Bu değişiklikler de klinik olarak artmış enfeksiyon riski, otoimmunite ve malignitelere sebep olmaktadır.[6] Bu yüzden yaşlılarda zaten artmış olan enfeksiyon riski ve bu enfeksiyonlara karşı oluşturulan zayıf immun yanıt nedeniyle en önemli koruyucu sağlık hizmeti olan aşılama daha da büyük bir önem kazanmaktadır.

Gelişebilecek enfeksiyon hastalıkları ve bunlara bağlı komplikasyonların önlenmesinde; böylece morbidite ve mortalitenin azaltılmasında etkin aşılamanın önemi tartışılmazdır. Yaşlılarda aşı ile önlenebilecek hastalıkların

başında influenza (mevsimsel grip), pnömokokal enfeksiyonlar (pnömoni, menenjit, plörit, artrit), tetanoz, herpes zoster gelmektedir ve bu enfeksiyonlara karşı aşılama dünyada birçok ülkede olduğu gibi ülkemizde de önerilmektedir.[7] Ancak ülkemizde erişkin aşılama bilinci ve oranı maalesef istenen düzeylere ulaşamamıştır. Hedeflenen düzeylere ulaşmak öncelikle yolun neresinde bulunduğumuzu belirlemek ve sorunları ortaya koymak ile mümkündür. Sağlıklı her erişkine zorunlu aşılar dışında özel durumlarda (gebelik, immunsupresyon, kronik hastalıklar (diabetes mellitus (DM), kalp hastalığı, kronik akciğer-karaciğer-böbrek hastalığı, son dönem böbrek yetmezliği-hemodiyaliz, seyahat, askerlik, sağlık çalışanı olmak) farklı aşılar önerilmektedir.

Ayrıca farklı yaş gruplarında ve durumlarda farklı aşılama protokolleri bulunmaktadır.[8] Erişkinde yaş gruplarına göre önerilen aşılar şu şekildedir:

- 18-24 yaş grubuna bağışık olmadıkları takdirde uygulanacak aşılar: TdaP, KKK(MMR), su çiçeği
- 25-64 yaş: Td, kızamıkçık (sadece kadınlar), influenza, su çiçeği
- 60 yaş ve üzeri: Zona
- 65 yaş ve üzeri: Td, influenza, pnömokok, su çiçeği.

65 yaş ve üzeri bireyleri aşılama programları ülkeler arasında büyük farklılıklar göstermektedir. Gelişmiş ülkeler içerisinde erişkin aşılama oranı en yüksek olan Avrupa ülkeleri Hollanda ve Birleşik Krallık'tır.[9] Aşılama programları şartlara göre güncel olarak düzenlenmektedir, örneğin İngiltere'de boğmaca aşısı önceden sadece yenidoğan döneminde uygulanırken 2008-2012 yılları arasında boğmacanın insidansının %50 oranında artması üzerine yetişkin aşılama programına dahil edilmiştir.[10] Ayrıca boğmaca aşısı yeni doğan döneminde yapıldığında yeterli immünite sağlayamadığı için ergen ve yetişkinlerle birlikte sağlık çalışanları ve gebelerin aşılanmasını öneren çalışmalar bulunmaktadır.[11] Ülkemizdeki erişkin aşılama programına bakacak olursak; 2018 yılında erişkin bağışıklama oranını göstermeyi amaçlayan bir çalışmada bu oran %35,4 olarak bulunmuştur ve ülke olarak hedefimizin oldukça uzağındadır.[12] Bu durumun en önemli sebepleri bireylerin aşı ile önlenebilecek hastalıklar hakkında yeterli bilgiye sahip olmaması, aşıları güvenilir bulmaması ve aşıların etkinliğinden şüphe duyması olarak sayılabilir. 65 yaş ve üzeri bireylerde aşı ile önlenebilir hastalıklar içerisinde çalışmamıza konu olan aşılar şu şekildedir;

1) İnfluenza
2) Pnömokok
3) Tetanoz
4) Herpes Zoster

İnfluenzaya bağlı solunum yetmezliği yaşlılarda gençlere göre 10-30 kat daha fazla görülmektedir. 65 yaş ve üzeri bireylere sadece inaktive influenza aşısı her yıl tek doz olarak uygulanmalıdır.

Pnömokokkal hastalık insidansı ve mortalitesi 50 yaş, belirgin olarak da 65 yaş üzerinde artış göstermektedir. Bu nedenle 65 yaş ve üzeri bireylere pnömokok aşısı yapılması önerilmektedir. Mümkünse, önce konjuge aşı (PCV13) ve daha sonra polisakkarid aşının (PPSV23) ardışık olarak uygulanması önerilmektedir. 65 yaşından sonra tek doz PCV13 ve tek doz PPSV23 uygulanması yeterlidir, rapel dozlara gerek yoktur. Konjuge ya da polisakkarid pnömokok aşısı, ayrı bölgelere olmak koşulu ile inaktive influenza aşısı ile eş zamanlı olarak uygulanabilir.

Yeni bir aşı olan herpes zoster aşısı 60 yaş üzerindeki immünokompetan erişkinlere (herpes öyküsü olup olmamasına bakılmaksızın) herpes zoster ve post-herpetik nevraljiden koruma amacıyla tek doz olarak önerilmektedir. Ciddi immün yetmezliği olanlarda ise kontrendikedir. Gerektiği zaman yaşlılara, erişkin dönemde olduğu gibi başka aşıların (tetanoz, difteri, boğmaca, suçiçeği, hepatit, meningokok, kuduz, tifo, kolera) yapılması da önerilebilir.

Çalışmamızda Hacettepe Üniversitesi Tıp Fakültesi Hastanesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı bünyesinde bulunan Erişkin Aşı Birimi'ne Haziran 2020 ile Haziran 2021 tarihleri arasında başvuran 65 yaş ve üzeri bireylerin yaş-cinsiyet dağılımı ve influenza-pnömokok-tetanoz-difteri aşıları ile aşılanma durumları, aşılanma oranları ve eşlik eden komorbiditeler gibi demografik verileri retrospektif olarak değerlendirilerek erişkin aşılamasında yolun neresinde olduğumuzu görerek gelecekteki çözüm önerilerine ışık tutmak amaçlanmıştır.

Materyal ve Metot

Bu çalışma Hacettepe Üniversitesi Tıp Fakültesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Bölümü tarafından retrospektif olarak dizayn edilmiştir. Hacettepe Üniversitesi Tıp Fakültesi Hastanesi Erişkin Aşı Birimi'ne Haziran 2020 ile Haziran 2021 tarihleri arasında başvuran 65 yaş ve üzeri 1194 bireyin demografik özellikleri, ilgili birime hangi bölümlerden yönlendirildikleri ve influenza-pnömokok-tetanoz-difteri aşıları ile aşılanma durumları, aşılanma oranları ve eşlik eden komorbiditeler değerlendirilmiştir. Ayrıca hastane personeli olarak değerlendirilen bireyler Hacettepe Üniversitesi Tıp Fakültesi Hastanesi'nde halihazırda çalışmakta olan kişiler ile aynı hastaneden emekli olan ve aşılarını yaptırmak için merkezimize başvuran kişilerdir.

Veriler SPSS 22.2 programında analiz edilmiş olup verilerin sıklık ve yüzdelik dağılımları saptanmıştır. Ayrıca bağımlı ve bağımsız değişkenler karşılaştırılmıştır.

Bulgular

Hacettepe Üniversitesi Tıp Fakültesi Hastanesi Erişkin Aşı Birimi'nde gerek çocukluk döneminde aşılama takvimi dahilinde bulunan aşıları eksik kalmış bireyler gerekse de aşıların pekiştirilmesi amacıyla ek aşılamalara ihtiyacı olan bireyler ile gebeler, yaşlılar, kronik hastalığı olanlar, immun yetmezliği bulunanlar ve diğer risk gruplarındaki erişkinlerin enfeksiyon hastalıklarından korunması hedefleri doğrultusunda aşılama çalışmaları yürütülmektedir. Bu kapsamda Haziran 2020 ile Haziran 2021 tarihleri arasında ünitemizde verilmiş olan aşılama hizmetini retrospektif olarak değerlendirdiğimizde 1194 yaşlı bireyin %53,43 'ü (n:638) kadın, %46,61'sı (n:556) erkek olarak bulunmuştur. Yaş ortalamaları 72,58±6,43 (ortanca: 72,0, minimum:65,0, maksimum: 92,0) yıl olup yaş gruplarına göre ikiye ayrılan bireylerin, 830' u (%69,51) 65-75 yaş aralığında iken; 364 'ü (%30,49) 75 yaş üstündedir. Aşılama hizmeti alan bireylerin büyük çoğunluğu %95,91 oranı ile dahili ve cerrahi polikliniklerden yönlendirilen hastalar iken doktorlar (%2) ve hastane personeli (%2) ise oldukça geri planda kalmaktadır. Polikliniğimizde yapılan aşıların %76,72'sini Prevenar 13 oluştururken 2. Sırada tetanoz-difteri aşısı (%15,41), 3. Sırada ise Influenza aşısı bulunmaktadır (%7,03) (Tablo 1). Aşılama hizmeti alan erişkinlerin büyük çoğunluğu aşılanmaya hastanemize başvurduğu sırada doktor önerisi ile karar verirken (%72,78), %22,20'si takibinde bulunduğu aile hekiminin yönlendirmesi ile aşı olmaya karar vermiştir. Kendi kararı ile aşı polikliniğine başvuran hastaların oranı ise sadece %5,02'dir (Tablo2). Polikliniğimizde Haziran 2020-Haziran 2021 tarihleri arasında İnfluenza aşısı olan 84 kişinin %52,38'i kadın %47,62'si erkek olup ve aşı olanların tamamı hastaneye başvurusu sırasında doktorunun önerisi ile aşı olmaya karar vermiştir. Aşı önerisinde bulunan doktorların bölümlerine bakıldığı zaman ilk sırada Geriatri gelirken 2. Sırada Göğüs Hastalıkları bulunmaktadır. Bu bölümleri Enfeksiyon Hastalıkları, diğer dahili bölümler ve son olarak da cerrahi bölümler takip etmektedir. İnfluenza aşısı olan bireylerin komorbiditeleri değerlendirildiğinde ilk sıralarda DM ve KOAH bulunurken sonraki sıralarda solid maligniteler, kronik böbrek hastalığı, hematolojik maligniteler ve Hipertansiyon (HT) gelmektedir. Ayrıca bu kişilerin sigara kullanma durumu değerlendirildiğinde %46,42'sinin 10 yıldan uzun süre sigara kullandığı ancak bıraktığı; %42,86'sının 10 yıldan uzun süredir sigara kullandığı ve kullanmaya devam ettiği; %10,72'sinin ise hiç sigara kullanmadığı görülmüştür. İnfluenza aşısı olan kişilerin sadece %33,33'ü sağlık çalışanıdır (Tablo 3).

Polikliniğimizde pnömokok aşısı olanların sayısı 926 olup bu bireylerin %98,9'u konjuge pnömokok aşısı (Prevenar 13) yaptırmıştır. Bu kişilerin %55,94'ü kadın olup influenza aşısında olduğu gibi büyük kısmı hastaneye başvurusu sırasında doktor önerisi ile aşısını olmuştur (%70,95). Yine influenza aşısı ile benzer şekilde aşıyı öneren doktorların büyük çoğunluğu Geriatri bölümü doktorları olup onları sırası ile Enfeksiyon Hastalıkları ve Göğüs Hastalıkları izlemektedir. Pnömokok aşısı olan bireylerin komorbiditeleri incelendiğinde ilk sırada KOAH bulunurken sonrasında kronik böbrek hastalığı ve HT gelmektedir. Pnömokok aşısı olan bireylerin sadece %1,60'ı (n:15) sağlık çalışanıdır (Tablo 4).

Aşı Polikliniği'nde tetanoz-difteri aşısı olan kişi sayısı 184 olup bu kişilerin %41,30'u kadındır. İnfluenza ve pnömokok aşılarında olduğu gibi aşı olmaya hastaneye başvuruları sırasında doktorlarının önermesi ile karar vermişlerdir (%69,56). Ayrıca yine influenza ve pnömokok aşıları ile benzer olarak aşılanmayı öneren doktorların büyük kısmı Geriatri Bölümü doktorları olup onları sırası ile Enfeksiyon Hastalıkları ve Göğüs Hastalıkları takip etmektedir. Aşı olan bireylerin komorbiditeleri incelendiğinde ilk 3 sırada KOAH, DM ve HT bulunmaktadır. Ayrıca bireylerin %79,90'ı 10 yıldan uzun süre sigara kullanmış ancak sigarayı bırakmış olan kişilerdir. Bu aşı grubundaki sağlık çalışanı oranı ise %3,27'dir (Tablo 5).

Polikliniğimizde aşı olan 1194 kişi 65-75 yaş arası ve 75 yaş üzeri olmak üzere 2 gruba ayrıldıktan sonra bu 2 grupta yapılmış olan aşılar değerlendirildiğinde; ilk gruptaki toplam 830 kişinin 655'i pnömokok aşısı olurken 107'si tetanoz-difteri ve 68'i influenza aşısı olmuştur. 75 yaş üzeri grupta bulunan 364 kişinin ise 271'i pnömokok aşısı olurken 77'si tetanoz-difteri, 16'sı ise influenza aşısı olmuştur. Her 2 grup da benzer şekilde hastanemize başvurdukları sırada doktorlarının önerisi ile aşı olurken yine her 2 grupta da en sık görülen komorbidite KOAH'tır. 65-75 yaş arası grupta KOAH'tan sonra sırası ile kronik böbrek hastalığı, DM ve HT görülürken 75 yaş üzeri grupta ise KOAH'ı sırası ile HT, kronik böbrek hastalığı ve DM takip etmektedir (Tablo 6). Kombine aşı olma oranı 65-75 yaş arası grupta daha yüksek bulunmuş olup influenza-pnömokok ve tetanoz-difteri aşılarının tümünü olan hasta sayısı bu grupta 11 iken 75 yaş üzeri grupta sıfırdır (Tablo 7).

Tablo 1. Aşıların tiplerine göre dağılımı

Aşı tipi	**n (%)**
Grip (İnfluenza)	84 (7,03)
Pnömokok (PPSV23)	10 (0,84)
Prevenar 13	916 (76,72)
Tetanoz, Difteri	184 (15,41)
Toplam	1194 (100)

Tablo 2. Aşılanma endikasyonu kararında etkenler

Aşı yaptırması gerekliliğine nasıl karar verdi?	**n (%)**
Aile hekiminin önerisiyle	265 (% 22,20)
Hastanemize başvurusu sırasında doktor önerisi ile	869 (% 72,78)
Sosyal medya üzerinden öğrenip kendi isteği ile	60 (% 5,02)
Toplam	1194 (%100)

Tablo 3. İnfluenza aşısı olan bireylerin demografik özellikleri

İnfluenza aşısı (n=84)	**n (%)**
Cinsiyet (Kadın /Erkek)	44 (%52,38) / 40 (%47,62)
Yaş (median,yıl)	68 yıl
Aşı yaptırması gerekliliğine nasıl karar verdi?	
Hastanemize başvurusu sırasında doktor önerisi ile	84 (%100)
Aşı Önerisinde Bulunan Branşlar	
Dahili Branşlar	
Geriatri Polikliniği	31 (%36,90)
Göğüs Hastalıkları Polikliniği	18 (%21,43)
Enfeksiyon Hastaliklari Polikliniği	16 (%19,05)
Diğer Dahili Poliklinikler	14 (%16,66)
Cerrahi Branşlar	5 (%5,95)
Eşlik Eden Komorbiditeler	
Konjestif Kalp Yetmezliği (KKY)	5 (%5,95)
Hipertansiyon (HT)	20 (%23,8)
Diabetes Mellitus (DM)	37 (%44)
Kronik Obstruktif Akciğer Hastalıkları (KOAH)	34 (%40,5)
Kronik böbrek hastalığı	28 (%33,33)
Kronik Karaciğer hastalığı	5 (%5,95)
Hemodiyaliz	13 (%15,47)
Kronik nörolojik hastalık	5 (%5,95)
Solid malignite	29 (%34,52)
Hematolojik malignite	24 (%28,57)
Romatolojik hastalık	9 (%10,71)
Obezite	10 (%11,90)
Spelenektomi	18 (%21,42)
Sigara Kullanım Öyküsü	
Hiç kullanmamış	9 (%10,72)
>10 yıl kullanmış ve bırakmış	39 (%46,42)
>10 yıl süreli, halen kullanmaya devam ediyor	36 (%42,86)
Sağlık çalışanı mı?	
Evet	28 (%33,33)
Hayır	56 (%66,67)

Tablo 4. Pnömokok aşısı olan bireylerin demografik özellikleri

Pnömokok Aşısı (n: 926)	**n (%)**
Cinsiyet (Kadın /Erkek)	518 (%55,94) / 408 (%44,06)
Yaş (median,yıl)	71 yıl
Pnömokok aşı tipi	
Polisakkarid pnömokok aşısı (PPSV23)	10 (%1,08)
Konjuge pnömokok aşısı (Prevenar 13)	916 (%98,92)
Aşı yaptırma gerekliğine nasıl karar verdi ?	
Hastanemize başvurusu sırasında doktor önerisi ile	657 (%70,95)
Aile hekiminin önerisiyle	209 (%22,57)
Sosyal medya üzerinden kendi isteği ile	60 (%6,48)
Aşı Önerisinde bulunan branşlar	
Dahili branşlar (845) (%91,25)	
Geriatri Polikliniği	329 (%35,50)
Enfeksiyon Hastaliklari Polikliniği	234 (%25,27)
Göğüs Hastalıkları Polikliniği	69 (%7,45)
Genel Dahiliye Polikliniği	35 (%3,78)
Nefroloji Polikliniği	31 (%3,34)
Hemato-Onkoloji Polikliniği	29 (%3,13)
Gastroenteroloji Polikliniği	23(%2,48)
Kardiyoloji Polikliniği	22(%2,37)
Diğer Dahili Poliklinikler	73 (%7,88)
Cerrahi Branşlar (81) (%8,75)	
Genel Cerrahi Polikliniği	28 (%3,02)
Üroloji Polikliniği	25 (%2,70)
Diğer Cerrahi Poliklinikler	28 (%3,02)
Eşlik eden komorbiditeler	
Konjestif Kalp Yetmezliği (KKY)	141 (%15,22)
Hipertansiyon (HT)	294 (%31,74)
Diabetes Mellitus (DM)	250 (%26,99)
Kronik Obstruktif Akciğer Hastalıkları (KOAH)	425 (%45,89)
Kronik Böbrek hastalığı	306 (%33,04)
Kronik Karaciğer hastalığı	146 (%15,76)
Hemodiyaliz	60 (%6,47)
Kronik nörolojik hastalık	146 (%15,76)
Solid malignite	99 (%10,69)
Hematolojik malignite	157 (%16,95)
Romatolojik hastalık	56 (%6,04)
Geçirilmiş nöroşirürjik operasyon	40 (%4,31)
Obezite	98 (%10,58)
Splenektomi	143 (%15,44)
Sigara Kullanım Öyküsü	
Hiç kullanmamış	117 (%12,63)
>10 yıl kullanmış ve bırakmış	618 (%66,74)
>10 yıl süreli, halen kullanmaya devam ediyor	191 (%20,63)

Tablo 5. Tetanoz-Difteri aşısı olan bireylerin demografik özellikleri

Tetanoz-Difteri Aşısı (n: 184)	**n (%)**
Cinsiyet (Kadın /Erkek)	76 (%41,30) / 108 (%58,70)
Yaş (medyan)	72
Aşı yaptırma gerekliğine nasıl karar verdi ?	
Hastanemize başvurusu sırasında doktor önerisi ile	128 (%69,56)
Aile hekiminin önerisiyle	56 (%30,44)
Sosyal medya üzerinden kendi isteği ile	-
Aşı Önerisinde bulunan branşlar	
Dahili branşlar	
Geriatri Polikliniği	64 (%34,78)
Enfeksiyon Hastaliklari Polikliniği	40 (%21,74)
Göğüs Hastalıkları Polikliniği	16 (%8,70)
Genel Dahiliye polkliniği	13 (%7,07)
Nefroloji Polikliniği	11 (%5,98)
Hemato-Onkoloji Polikliniği	12 (%6,52)
Gastroenteroloji Polikliniği	1(%0,54)
Kardiyoloji Polikliniği	3 (%1,63)
Diğer Dahili Poliklinikler	14 (%7,61)
Cerrahi Branşlar	9 (%4,90)
Eşlik eden komorbiditeler	
Konjestif Kalp Yetmezliği (KKY)	26 (%14,13)
Hipertansiyon (HT)	76 (%41,30)
Diabetes Mellitus (DM)	84 (%45,65)
Kronik Obstruktif Akciğer Hastalıkları (KOAH)	105 (%57,07)
Kronik Böbrek hastalığı	53 (%28,80)
Kronik Karaciğer hastalığı	17 (%9,23)
Hemodiyaliz	52 (%28,26)
Kronik nörolojik hastalık	17 (%9,23)
Solid malignite	34 (%18,47)
Hematolojik malignite	48 (%26,08)
Romatolojik hastalık	23 (%12,50)
Geçirilmiş nöroşirürjik operasyon	3 (%1,63)
Obezite	12 (%6,52)
Splenektomi	2 (%1,08)
Sigara Kullanım Öyküsü	
Hiç kullanmamış	8 (%4,34)
>10 yıl kullanmış ve bırakmış	147 (%79,90)
>10 yıl süreli, halen kullanmaya devam ediyor	29 (%15,76)
Sağlık çalışanı mı?	
Evet	6 (%3,27)
Hayır	178 (%96,73)

Tablo 6. 65-75 yaş ve >75 yaş bireylerin demografik özelliklerinin karşılaştırılması

Yaş Grupları	**65-75 yaş** (n:830)	**>75 yaş** (n:364)	***P***
Grip (İnfluenza)	68 (%8,19)	16 (%4,40)	***0,001***
Pnömokok	**655 (%78,92)**	**271** (%74,45)	
Tetanus,Difteri	107 (%12,89)	77 (%21,15)	
Aşı yaptırma gerekliğine nasıl karar verdi ?			
Hastanemize başvurusu sırasında doktor önerisi ile	607 (%73,13)	262 (%71,98)	*0,732*
Aile hekiminin önerisiyle	184 (%22,17)	81 (%22,25)	
Sosyal medya üzerinden kendi isteği ile	39 (%4,70)	21 (%5,77)	
Eşlik eden komorbiditeler			
Konjestif Kalp Yetmezliği (KKY)	125	47	*0,371*
Hipertansiyon (HT)	274	116	*0,738*
Diabetes Mellitus (DM)	**275**	**96**	***0,021***
Kronik Obstruktif Akciğer Hastalıkları (KOAH)	393	171	*0,950*
Kronik böbrek hastalığı	277	110	*0,314*
Kronik Karaciğer hastalığı	119	49	*0,718*
Hemodiyaliz	85	40	*0,683*
Kronik nörolojik hastalık	139	68	*0,455*
Solid malignite	118	44	*0,359*
Hematolojik malignite	153	76	*0,338*
Romatolojik hastalık	62	26	*0,905*
Geçirilmiş nöroşirürjik operasyon	33	10	*0,399*
Obezite	83	37	*0,917*
Spelenektomi	118	45	*0,411*
Sigara Kullanım Öyküsü			
Hiç kullanmamış	98	36	*0,223*
>10 yıl kullanmış ve bırakmış	546	258	
>10 yıl süreli, halen kullanmaya devam ediyor	186	70	

Tablo 7. 65-75 yaş ve >75 yaş bireylerin kombine aşı olma durumları

Aşı Kombinasyonları	**65-75 yaş**	**>75 yaş**
İnfluenza + pnömokok	24 (%2,89)	6 (%1,64)
İnfluenza+ pnömokok+ TD	11 (%1,32)	0
TD+ pnömokok	29 (%3,49)	1 (%0,27)

(TD; Tetanoz-Difteri)

Tartışma

Polikliniğimizde aşılanan ve çalışmamızda değerlendirdiğimiz 65 yaş ve üzeri 1194 bireye yapılan aşılara bakıldığında %76,72 gibi oldukça yüksek bir yüzde ile ilk sırada pnömokok aşısı bulunmaktadır. Yapılan pnömokok aşılarının da %98,92'si Prevenar 13'tür. Bu yaş grubunda mortalite oranı son derece yüksek olan influenza aşısı yaptırma oranı ise sadece %7,03'tür. Hastaların büyük kısmının aşılanmaya hastane başvuruları sırasında öneride bulunan doktorları aracılığı ile karar verdiği göz önünde bulundurulacak olursa influenza aşılanma oranının düşüklüğü hastaların yetersiz bilgi sahibi olması ile açıklanabilir. Özellikle bu yaş grubu bireylerde influenzanın klinik seyri, mortalite oranları hakkında hastalar bilgilendirilmelidir. İnfluenza aşı grubu içerisinde sağlık çalışanlarının oranı %33,33'tür, pnömokok aşı grubunda bu oran %1,61, tetanoz-difteri aşı grubunda ise %3,27'dir. Bu oranlar sağlık çalışanlarının mevsimsel gribe yakalanma konusunda daha hassas olduklarını göstermektedir.

2020 yılında yayımlanan bir çalışma yaşlı bireylerde mevsimsel grip ve pnömokok aşıları ile COVID-19'a bağlı mortalite oranlarında düşme elde edildiğini ortaya koymuştur.[13] Bu nedenle etkin aşılama özellikle pandemi döneminde risk altında olan yaşlı hasta grubunda daha da önem kazanmaktadır. Merkezimizde aşılanmış olan bireyler yaşlarına göre 65-75 yaş arası ve 75 yaş üzeri olmak üzere 2 gruba ayrıldıktan sonra her 2 grupta yapılmış olan aşılara bakıldığında her 2 grupta da ilk sırada yine pnömokok aşısı bulunurken 2. sırada tetanoz-difteri ve son sırada da influenza aşısı bulunmaktaydı. Ayrıca kombine aşı yaptırma oranları değerlendirildiğinde de her 2 grupta da oldukça düşük olarak bulunmuştur. Ancak 2 grup birbiri ile kıyaslandığında 65-75 yaş arası grupta kombine aşılanma oranları 75 yaş üzeri gruba göre daha yüksek olarak gösterilmiştir. Bu durumun sebebi olarak 75 yaş üzeri bireylerde artan yaş ile birlikte kronik hastalık sayısının, yatağa bağımlılığın artması ve bunlara bağlı olarak da sağlık hizmetine ulaşmada güçlük çekmeleri gösterilmektedir.[14]

Türkiye yaşlı nüfusuna göre merkezimizde 1 yıl süresince aşılanan hasta sayısının hedeflenen sayıya ulaşmadığını söylemek mümkündür. Avrupa'da 24 ülkenin sonuçlarını içeren çok merkezli ADVICE araştırmasında aşı yaptırma oranı medyan değeri %44,7 (minimum: %1, maksimum: %77,4) olarak

bildirilmiştir.[8] Bu araştırmaya göre aşılama oranlarının en yüksek olduğu Avrupa ülkeleri Hollanda ve Birleşik Krallık'tır. Ülkemizde 2020 yılında 65 yaş ve üzeri 147 kişi ile yapılan bir çalışmada influenza/pnömokok/tetanoz-difteri/herpes zoster aşılarından en az biri ile aşılanma oranı %53,7 olarak bulunmuştur.[15] 2014 yılında yayımlanan 18 yaş üzeri erişkin ve yaşlılarda yapılan çalışmada, çalışmaya katılanların %65'inde difteri, %69'unda tetanoz, %90'ında boğmacaya karşı seropozitifliğin olmadığı ve çalışmaya katılanların %78'inin tetanoz, %90'ının boğmaca ve %96'sının ise difteri aşısına ihtiyacı olduğu belirtilmektedir.[16] Yine ülkemizde yapılan ve 2019 yılında yayımlanan geriatrik yaş grubunda yapılan bir çalışmaya göre erişkin dönem aşılarından en az birini yaptırmış olanların oranı %46 olarak ortaya konmuştur. Ayrıca en çok bilinen ve uygulanan aşının influenza aşısı olduğu gösterilmiştir.[17]

Her 3 aşı grubunda da (influenza-pnömokok-tetanoz/difteri) aşı olan bireylerde en sık görülen komorbidite KOAH olup bunu DM, HT ve kronik böbrek hastalığı takip etmektedir. İlk sırada KOAH bulunmasının en muhtemel nedeni pnömokok pnömonisi açısından en riskli olan gruplardan biri olan KOAH hastalarının doktorları tarafından etkin bir şekilde aşıya yönlendirilmiş olması olabilir. Aşılanmış olan hastaların tamamına yakının özgeçmişinde sigara bulunması (10 yıldan uzun süre kullanıp bırakan ve halihazırda kullanmaya devam eden) da KOAH tanılarını desteklemektedir. Ülkemizde yapılan 2 çalışmada KOAH tanısı olan bireylerde influenza aşılanma oranları sırası ile 27,3% ve 14,9% olarak rapor edilmiştir ve hedeften oldukça uzak olduğumuz görülmektedir.[18,19] 2017 yılında ülkemizde yapılan başka bir çalışmada ise KOAH tanısı olan hastalarda pnömokok aşılanma oranı %14,1 olarak gösterilmiştir.[20] Polonya'da diyabetik yaşlı bireylerde yapılmış olan çalışmada komorbidite sayısı; influenza aşısını [Odds oranı =1,351; p=0,004] ve pnömokok aşısını (OR=2,778; p<0,001) yaptırma üzerinde etkili bulunmuştur.[21] Etkin aşılama üzerine etkili diğer bir faktör de bireylerin sağlık personeli tarafından ayrıntılı bir şekilde bilgilendirilmesi, aşılar hakkındaki önyargıların kırılması ve aşı olmaya yönlendirilmesidir.

Tüm bu veriler ışığında ülkemizde 65 yaş ve üzeri nüfusun henüz etkin bir şekilde aşılanamadığı ve aşılanan bireylerin tamamına yakınının aşılanmasını sağlayan sağlık personelinin kendi aşılanması söz konusu olduğunda yeterince hassas davranmadığı söylenebilir. En önemli halk sağlığı hizmeti olan aşılamanın daha verimli bir şekilde yapılabilmesi için hastaların bu konuda daha detaylı bir şekilde bilgilendirilmesi ve sağlık personeli tarafından teşvik edilmesi çok önemlidir.

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Çıkar çatışması

Yazarlar herhangi bir çıkar çatışması olmadığını beyan ve taahhüt ederler.

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CLINICAL EVALUATION OF NON-TRAUMATIC RHABDOMYOLYSIS PATIENTS FOLLOWED IN THE INTERNAL DISEASES CLINIC

İÇ HASTALIKLARI KLİNİĞİNDE TAKİP EDİLEN NON-TRAVMATİK RABDOMİYOLİZ HASTALARININ KLİNİK DEĞERLENDİRİLMESİ

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Öz

Amaç: Rabdomiyoliz, çizgili kas liflerinin yıkımı sonucu hücre içindeki toksik potansiyeli olan maddelerin sistemik dolaşıma katılmasıyla oluşan klinik ve biyokimyasal bir durumdur. Bu çalışmada, non-travmatik rabdomiyoliz tanısı ile takip edilen semptomatik hastaların epidemiyolojik verileri morbidite, mortalite ve hastanede kalış süreleri açısından değerlendirildi.

Materyal ve Metot: Hastanemizde non-travmatik rabdomiyoliz tanısı konduktan sonra iç hastalıkları kliniğine yatırılan ve takip edilen 18 yaş üzeri 95 hastanın serum kreatin kinaz (CK), miyoglobin ve kreatinin (CR) seviyeleri retrospektif olarak değerlendirildi (retrospektif kohort çalışması).

Bulgular: Bu çalışmamızda, hasta grubumuzda, hastalık etiyolojisi ile hastanede yatış süresi arasında istatistiksel olarak anlamlı bir fark saptanmadı. Hastaların kreatinin değerleri ile hastanede yatış süresi arasında pozitif bir korelasyon vardı. Hastanede yatış süresi ile başvuru anında ve yatıştan sonra 24. saatteki kreatinin değerleri arasında istatistiksel olarak anlamlı fark saptandı (p=0,043). Başvuru anındaki CK değerleri ile takip ve taburculuktaki CR değerleri arasında istatistiksel olarak anlamlı fark bulunmadı (p=0,594). Non-travmatik rabdomyoliz tanısı ile yatırılan hastaların başlangıç CK değerinden bağımsız olarak uygun takip ve tedavi ile böbrek fonksiyonlarının izlemde olumsuz etkilenmediği saptanmıştır.

Sonuç: Travmatik olmayan rabdomiyoliz yaygın olmakla birlikte olası komplikasyonlar erken tanı, uygun tedavi ve takip ile en aza indirilebilir. Serum CK ve kreatinin değerleri hastaların takibinde önemli bir prognostik değere sahip olmasına rağmen birçok parametrenin birlikte değerlendirilmesi ve hastalık prognozunun değerlendirilmesini standardize etmek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Rabdomiyoliz, kreatin kinaz, yatış süresi, böbrek yetmezliği.

Abstract

Objectives: Rhabdomyolysis is a clinical and biochemical condition that occurs when substances that have a toxic potential inside of cells enter systemic circulation as a result of the destruction of striated muscle fibers. In this study, the epidemiological data of patients who were symptomatic and followed-up with a diagnosis of non-traumatic rhabdomyolysis were evaluated in terms of morbidity, mortality, and length of hospitalization.

Materials and Methods: The serum creatinine kinase(CK), myoglobin, and creatinine(CR) levels of 95 patients who were over 18 years of age and had been hospitalized and followed up in the Internal Diseases ward after being diagnosed with non-traumatic rhabdomyolysis at the hospital were evaluated retrospectively.

Results: In this study, no statistically significant difference was found between disease etiology and the duration of hospitalization. There was a positive correlation between the CR values and the duration of hospitalization. A statistically significant difference was found between the length of hospitalization and the CR values on admission and at 24h following admission(p=0.043). No statistically significant difference was found between the CK values on admission and the CR values at follow-up and hospital discharge (p=0.594). It was found that patients admitted with a diagnosis of non-traumatic rhabdomyolysis did not negatively affect kidney function with appropriate follow-up and treatment, regardless of the initial CK value.

Conclusion: Although non-traumatic rhabdomyolysis is common, possible complications can be minimized with early diagnosis, appropriate treatment, and follow-up. Although serum CK and creatinine values have an important prognostic value in the follow-up of patients, many parameters need to be evaluated together, and more studies are needed to standardize the evaluation of disease prognosis.

Keywords: Rhabdomyolysis, creatine kinase, length of stay, renal insufficiency.

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Introduction

Rhabdomyolysis is a complex medical condition that occurs when substances that have a toxic potential inside of cells enter systemic circulation as a result of the destruction of striated muscle fibers. The clinical spectrum of rhabdomyolysis can range from the asymptomatic elevation of muscle enzymes to the development of life-threatening acute renal failure and severe electrolyte disturbance. Rhabdomyolysis is classified according to traumatic or non-traumatic causes. Although rhabdomyolysis is mostly due to traumatic causes, there are a significant number of non-traumatic rhabdomyolysis cases among admissions to internal medicine clinics. Infections, drugs, muscle diseases, and rheumatic diseases are among the causes of non-traumatic rhabdomyolysis.[1–4] The classic symptoms of rhabdomyolysis are myalgia, weakness, and tea-colored urine. Although there are no consensus diagnostic criteria for rhabdomyolysis, an increase in serum creatinine kinase (CK) levels five times above the normal level is sufficient for diagnosis. In some studies, a 10-fold increase is the desired reference value for diagnosis.[5] In this study, the epidemiological data of patients who were symptomatic and followed-up with a diagnosis of non-traumatic rhabdomyolysis were evaluated in terms of morbidity, mortality, and length of hospitalization.

Materials and Methods

The serum CK and myoglobin levels of 95 patients who were over 18 years of age and had been hospitalized and followed up in the Internal Diseases ward after being diagnosed with non-traumatic rhabdomyolysis at the hospital, between January 2016 and December 2018, were evaluated retrospectively (retrospective cohort study). Patients with test values five times the normal value or higher were included in the study. Patients with kidney disease, hypertension, diabetes mellitus, muscular dystrophy, neuromuscular disorder, and those with creatine kinase elevation who were using statin class drugs were excluded from the study. Demographic data, laboratory test values, organ failure, and prognosis of the patients were evaluated. For all of the patients, age, gender, creatine kinase levels, complaints, etiology, development of acute renal failure, hospitalization and discharge status, and patient clinic were evaluated.

Statistical Analysis

The IBM SPSS 21.0 statistical software package for Windows was used for the statistical analysis of the data. For all data, the normality assumption was evaluated via the Shapiro-Wilk test. Numerical data are indicated by median (minimum-maximum), and categorical data are indicated by numbers (percentage). The Mann-Whitney U test was used to compare numerical data between two groups, and the Kruskal-Wallis test was used to compare more than two groups. Values of $p<0.05$ were considered statistically significant.

Results

Included in the study were 95 patients who had been hospitalized with the diagnosis of non-traumatic rhabdomyolysis. The demographic data and laboratory findings of the patients are shown in Tables 1 and 2. Of the patients, 63 (66,31%) had proteinuria. The number of patients with myoglobinuria was 38 (40%). Muscle biopsy was performed in 9 patients (9,47%) (Table 3). The patients with the longest hospitalization according to etiology were those with bleeding/disseminated intravascular coagulation (DIC). In these patients, the median hospital stay was 6,50 days. The patients requiring the shortest hospitalization were those with a drug/herbal/alcohol etiology (Table 4). However, no statistically significant difference was found between disease etiology and the duration of hospitalization (p=0,053). There was a positive correlation between the creatinine values and the duration of hospitalization (Table 4). A statistically significant difference was found between the length of hospitalization and the creatinine values on admission and at 24 h following admission (p=0,043). No statistically significant difference was found between the CK values on admission and the CR values at follow-up and hospital discharge (Table 5). It was found that the renal function of patients hospitalized with a diagnosis of rhabdomyolysis was not affected by appropriate follow-up and treatment, regardless of the CK value on admission. According to the CR values on admission, there was no difference between patients with a CR value >1,45 and those with a CR value <1,45 (Table 6).

Table 1. Demographic, etiological, treatment, and length of stay data of the patients.

		n	(%)
Gender	Women	34	35.78
	Men	61	64.21
Age [Median(Min-Max)]		52 (17 - 72)	
Complaint on Application	Pain	40	42.10
	Nausea and vomiting	10	10.52
	Change of consciousness	14	14.73
	Decrease in urine	8	8.42
	Shortness of breath	21	22.10
	No	2	2.10
Etiology	Pharmaceuticals/herbal/alcohol/poison	20	21.05
	Infection	34	35.78
	Ischemia/Convulsion	15	15.78
	Exercise	18	18.94
	Bleeding/DIC	8	8.42
Treatment	Oral hydration	8	8.42
	IV hydration	72	75.78
	Dialysis	15	15.78

Table 2. Laboratory findings of the patients.

	Median (Min-Max)
AST (U/L)	98 (19 - 198)
ALT (U/L)	41 (19 - 82)
Ca (mg/dL)	8.80 (4.50 – 11.10)
P (mg/dL)	4.20 (1.30 – 14.80)
K (mEq/L)	4.60 (2.10 – 7.50)
pH	7.33 (7.26 – 7.38)
GFR (CKD-EPI) (ml/dk/1.73m²)	88 (15 - 123)
Uric acid (mg/dL)	6.90 (4 – 9.20)
Myoglobin (mcg/L)	1106 (95 - 8751)
CK1 (U/L)	2352 (647 - 203766)
Creatine kinase MB (mcg/L)	10.50 (1.70 - 903)
CR (mg/dL)	1.20 (0.40 – 9.00)
LDH (U/L)	422 (192 - 6521)
Troponin (ng/L)	5 (1.50 - 18)
Urea (mg/dL)	63 (6 - 225)

(AST: aspartat aminotransferaz, ALT: alanin aminotransferaz, Ca: calcium, P: phosphorus, K: potassium, pH: Power of Hydrogen, GFR: Glomerular Filtration Rate, CK: creatine kinase, CR: Creatinine, LDH: Lactate dehydrogenase, CKMB: Creatine Kinase MB Isoenzyme)

Table 3. Evaluation of the urine findings and muscle biopsies of the patients

Variables		**n**	**%**
Myoglobinuria	**Yes**	38	40
	No	57	60
Proteinuria	**Yes**	63	66.31
	No	32	33.68
Muscle Biopsy	**No**	86	90.52
	Yes	9	9.47

Table 4. Hospitalization according to the etiology and creatinine levels of the patients

Variables		Duration of hospitalization (Day)	p
		Median (Min-Max)	
Etiology	Pharmaceuticals/herbal/alcohol/poisoning	2.50 (0 - 63)	0.053
	Infection	5 (0 - 40)	
	Ischemia/Convulsion	3 (0 - 98)	
	Exercise	3 (0 - 20)	
	Bleeding/DIC	6.50 (3 - 19)	
CR		1.20 (0.40 - 9)[a]	0.043
CR 24		1.10 (0.30 – 8.60)[b]	
CR 48		1.10 (0.30 - 9)	
CR 72		1.10 (0.30 - 9)	

(CR: Creatinine; a-b: groups that make the difference)

Table 5. CK and CR values on admission, follow-up, and hospital discharge

Variables		CK1	CR	CR24	CR48	CR72	CR at discharge
CK1	Correlation Coefficient	1.000	-0.018	-0.105	-0.068	-0.100	-0.063
	p-value	-	0.863	0.313	0.515	0.337	0.594

Table 6. Follow-up and discharge CR values according to the basal CR values

	CR 24th hour		CR 72nd hour		CR at discharge	
CR Baseline	<1.45	>1.45	<1.45	>1.45	<1.45	>1.45
<1.45	60	2	61	0	57	4
>1.45	1	32	2	31	1	32
p-value	1		0.5		0.375	

(CR: Creatinine)

Discussion

Similar to the literature in this study, rhabdomyolysis frequency was higher in males than in females.[6,7] The frequency of etiological causes varies according to age. Similar to the current study, the most common non-traumatic causes in adults are infections and drugs.[8] In a study with 8610 patients in which drug-related rhabdomyolysis cases were evaluated, it was reported that statin-associated rhabdomyolysis constituted 45% of all cases.[9] Atorvastatin, one of the commonly used statins in Turkey, is metabolized through CYP3A4 and is relatively risky in terms of drug-related rhabdomyolysis. Rosuvastatin metabolized via CYP2A9 seems to have a lower risk of rhabdomyolysis, and the risk of statin-related severe CK elevation is less than 1%.[10,11] Among the drug-related rhabdomyolysis patients in the current study, there were no patients who used a statin. It was believed that this was caused by these patients being admitted to the emergency department mostly due to symptomatic cases. Statin-associated rhabdomyolysis may be more asymptomatic and diagnosed in outpatient settings. Due to etiological reasons, it was seen that the patients with the longest hospitalization were those with DIC/bleeding-induced-rhabdomyolysis. The reason for this may have been the need for additional treatment other than hydration and a tendency towards hypovolemia, hypoperfusion, and ischemia.

The most common symptoms in rhabdomyolysis patients are pain, especially in the proximal muscles, darkening of the urine color, and weakness.[12] In this study, the most common symptom on presentation was muscle pain, followed by shortness of breath. The reason for this may have been the involvement of the proximal muscle group, which is the most commonly involved muscle group, and the presence of severe pain. The most basic laboratory test for the diagnosis of rhabdomyolysis is the serum CK level. The CK level can be between 1500–100,000 IU/L. In a study in which rhabdomyolysis cases with different etiologies were evaluated, the mean CK peak level was reported to be between 10,000–25,000 IU/L.[13] In the current study, there was an increase in serum aminotransferase levels, especially the aspartate transaminase (AST) level, due to muscle cells. In a study in which rhabdomyolysis patients with serum CK levels above 1000 IU/L were evaluated, it was reported that 93,10% of the patients had elevated AST levels.[14] Myoglobin is a heme-containing monomer that is released from damaged muscle cells. When the plasma concentration exceeds 1,50 mg/dL, it passes into the urine, and the urine concentration must be 100–300 mg/dL in order to give the urine its characteristic color.[15,16] In this study, proteinuria was detected in 66,31% of the patients, but myoglobinuria was found in only 40%. The myoglobin half-life is much shorter than that of CK, and it can regress to normal serum levels within 6–8 h. For this reason, myoglobinuria may not be seen in rhabdomyolysis patients, even though the CK level is high.[16] In more than half of rhabdomyolysis patients, myoglobinuria cannot be detected by a dip-stick test in urine.[12] In this study, the difference between the frequency of myoglobinuria and proteinuria may have been caused by this fact. Hemoglobinuria may be detected in rhabdomyolysis patients. Hemoglobinuria may be the cause of this condition in patients with proteinuria detected independent of myoglobinuria.

Acute kidney injury (AKI) is a common complication in rhabdomyolysis patients, with a rate of 10%–50%.[17,18] Patients with a CK level below 15,000–20,000 IU/L on admission have a low risk of AKI, and dehydration, sepsis, and acidosis increase the risk of AKI in these patients.[19] In a study in which patients with serum CK levels above 5000 IU/L were evaluated, a scoring system was created for the risk of developing AKI in rhabdomyolysis patients. The patients were evaluated in terms of serum creatinine, CK, calcium, phosphate, bicarbonate values on admission, age, gender, and underlying predisposing factors. Patients with scores of 5 or less were considered to be at low risk for developing AKI.[20] According to this scoring, patients with a serum CK level above 40,000 IU/L on admission were given 2 points, while those with a serum creatinine level of 1,40–2,20 mg/dL were given 1,5 points, and those with a serum creatinine level of 2,20 or above were given 3 points. In this study, no correlation was found between the serum CK levels on admission and serum creatinine levels at follow-up and discharge. Patients with serum CK levels below 5000–10,000 IU/L have been reported to have a low risk of developing AKI.[21] In a meta-analysis by Safari et al., it was stated that the importance of the serum CK level in predicting the risk of AKI changed, and there was a correlation between the serum CK value and the risk of developing AKI in traumatic rhabdomyolysis patients.[22] When evaluated in this respect, serum CK values alone could not predict the risk of developing AKI in non-traumatic rhabdomyolysis patients and should be evaluated together with other factors. Considering the serum creatinine values on admission, there was no significant difference in the risk of developing AKI between the patients with a serum creatinine value >1,45 and those with a serum creatinine value <1,45. In this respect, it is suggested that the serum creatinine value alone cannot predict the risk of AKI and should be evaluated together with other factors. There was a positive correlation between the serum creatinine levels of the patients on admission and the duration of hospitalization. When the serum creatinine levels on admission were compared with the serum creatinine levels 24 h following admission, a significant difference was found in terms of the duration of hospitalization, which revealed the importance of appropriate treatment and follow-up of the patients.

Of the patients, 9 had muscle biopsy indications. Muscle biopsy was performed on patients whose etiology was unclear. Muscle biopsies of 2 patients were found to be compatible with dermatomyositis. No enzyme deficiency or pathology was found to suggest rhabdomyolysis in the muscle biopsies of 7 patients. It was believed that the herbs used by these patients may have played a role in the etiology.[23]

Rhabdomyolysis has a wide spectrum, from mild increases in serum CK levels to a severe, life-threatening syndrome. Although non-traumatic rhabdomyolysis is common, possible complications can be minimized with early diagnosis, appropriate treatment, and follow-up. Although serum CK and creatinine values have an important prognostic value in the follow-up of patients, many parameters need to be evaluated together, and more studies are needed to standardize the evaluation of disease prognosis.

Ethical Considerations

The study was approved by the ethics committee of the local hospital on 25.11.2020 with number E1-20-1311. The authors declared that this study is in accordance with the Helsinki Declaration. In addition, informed consent was obtained from patients during their application to the hospital.

Conflict of Interest

The authors declare no conflict of interest.

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ONKOLOJİ HASTALARININ GELENEKSEL VE TAMAMLAYICI TIP (GETAT) YÖNTEMLERİ HAKKINDAKİ TUTUMLARI

ATTITUDES OF ONCOLOGY PATIENTS ON TRADITIONAL AND COMPLEMENTARY MEDICINE (T&CM)

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Öz

Amaç: Bu çalışmada Ankara Şehir Hastanesi Onkoloji Polikliniklerine başvuran hastalarda GETAT (Geleneksel ve Tamamlayıcı Tıp) hakkında literatür taranarak oluşturulan anket sorularına verdikleri yanıtlar değerlendirilerek, GETAT kullanan grubun prevalansı, sosyodemografik özellikleri, hangi kanser tanısı ve tedavisi aldığı, GETAT hakkındaki tutumları ve bunları etkileyen faktörlerin saptanması amaçlanmıştır.
Materyal ve Metot: Çalışma, 1 Kasım 2019 ile 31 Aralık 2019 tarihleri arasında Ankara Şehir Hastanesi Tıbbi Onkoloji Polikliniklerine başvuran kanser tanısıyla izlenen hastaların Geleneksel ve Tamamlayıcı Tıp kullanım durumları, nedenleri, etkileyen faktörleri araştırmak amacıyla yapılan tanımlayıcı ve kesitsel bir çalışmadır.
Bulgular: Çalışmamızda hastaların %57,66'sının kanser tanısı öncesi GETAT kullandığı, %33,66'sı ise kanser tanısı aldıktan sonra GETAT kullandığı saptanmıştır. Erkeklerin kadınlara göre daha yüksek oranda doktora gittiği bulunmuştur(p=0,022). Hastaların sosyodemografik özelliklerine bakıldığında; yaş, cinsiyet, meslek, öğrenim durumu, aylık gelir durumu, medeni hali ve aile tipi ile GETAT kullanımı arasında istatistiksel olarak anlamlı ilişki saptanmamıştır. Hastaların yaşadıkları yerleşim yeri ile GETAT yöntemlerini kullanma sıklıklarına bakıldığında il merkezinde yaşayan hastalar ilçe/köy de yaşayan hastalara göre GETAT yöntemlerine daha sık başvurmuşlardır (p=0,034). Kanser tanısı sonrası GETAT yöntemleri arasında en sık başvurulan yöntem fitoterapi (%90,90), ikinci sırada hacamat uygulaması (%5,45), üçüncü sırada ise sülük uygulaması (%3,63) gelmektedir. Fitoterapinin içinde ilk sırada bitkisel çaylar (%52), ikinci sırada ise ısırgan otu (%30) yer almaktadır.
Sonuç: Hastaların GETAT hakkındaki bilgi düzeylerinin yetersiz olduğu görülmüştür. GETAT yöntemleri hakkında hastaların bilgi ve farkındalıklarını artırmaya yönelik çalışmalar yapılması faydalı olacaktır.

Anahtar Kelimeler: Geleneksel ve tamamlayıcı tıp (GETAT), onkoloji, aile hekimliği.

Abstract

Objectives: This study aims at determining the prevalence, socio-demographic features, the type and treatment of cancer, the attitudes towards the T&CM (Traditional and Complementary Medicine), and the factors influencing these attitudes of the patients at Ankara City Hospital, Oncology Polyclinics.
Materials and Methods: This is a descriptive and cross-sectional study aiming at the research on the use of, the rationale for and the influential factors leading to the utilization of T&CM on cancer patients at Ankara City Hospital, Oncology Polyclinics between the periods of November 1, 2019, and December 31, 2019.
Results: The study had found that 57.66% of the patients used T&CM before diagnosis, while 33.66% begun using them after the diagnosis. Male patients have sought the doctor's help more than female patients (p=0,022). As for socio-demographic findings, there was no significant statistical correlation between the use of T&CM and age, gender, occupation, educational background, monthly income, marital status, or family type. In terms of location, the patients residing in city centers utilized T&CM more than those living in smaller regions such as counties or villages (p=0,034). Among the post-diagnosis T&CM practices, phytotherapy was the most popularly applied (90.90%), followed by phlebotomy (5.45%), and leech therapy (3.63%). Amongst phytotherapy were the consumption of herbal teas (52%) and the use of Urtica urens (30%).
Conclusion: It was observed that the knowledge level of the patients about T&CM was insufficient. It would be beneficial to carry out studies to increase the knowledge and awareness of patients about T&CM methods.

Keywords: Traditional and Complementary Medicine (T&CM), oncology, family medicine.

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Giriş

Dünya Sağlık Örgütü; "Geleneksel ve Tamamlayıcı Tıp" ı; 'fiziksel ve ruhsal hastalıklardan korunma, bunlara tanı koyma, iyileştirme veya tedavi etmenin yanında sağlığın iyi sürdürülmesinde de kullanılan, farklı kültürlere özgü teori, inanç ve deneyimlere dayalı, izahı yapılabilen veya yapılamayan bilgi, beceri ve uygulamaların bütünüdür' şeklinde tanımlamıştır.[1]

GETAT (Geleneksel ve Tamamlayıcı Tıp)'ın en sık kullanıldığı hastalıklar; kanser, kronik hastalıklar ve ağrıdır. ABD'de hastalar en sık eklem ağrısı, kas-iskelet sistemi rahatsızlıkları nedeniyle GETAT uygulamalarını tercih etmektedirler.[2] Avrupa ve Türkiye'de ise kullanılan rahatsızlıklar arasında kanser ön sıralarda bulunmaktadır.[3]

GETAT kullanılmasının sebepleri araştırıldığında; modern tıpta hastalara az süre ayrılması, hasta tatminsizliği ve maddi yetersizlikler, çeşitli hastalıklarda modern tıbbın çaresiz kalması ve en önemlisi ise GETAT yöntemlerinin tamamen doğal ve yan etkisinin çok az olduğuna inanılması olarak görülmüştür.[4]

Geleneksel ve Tamamlayıcı Tıp Uygulamaları Daire Başkanlığı'nın çalışmaları neticesinde "Geleneksel ve Tamamlayıcı Tıp Uygulamaları Yönetmeliği" 27 Ekim 2014 tarihli ve 29158 sayılı Resmi Gazete'de yayımlanmıştır. Bu yönetmeliğin amacı; insan sağlığına yönelik GETAT uygulama yöntemlerini belirlemek, bu yöntemleri uygulayacak kişilerin eğitimi ve yetkilendirilmeleri ile bu yöntemlerin uygulanacağı sağlık kuruluşlarının çalışma usul ve esaslarını tertip etmektir. Geleneksel ve tamamlayıcı tıp yöntemleri; bakanlıkça yetkisi olan uygulama merkezlerinde, uygulama sertifikası bulunan tabip ve diş tabibi tarafından uygulanabilir.[5] Bu yönetmelikte 15 adet GETAT yöntemi bulunup bunlar; fitoterapi, kupa uygulaması, larva uygulaması, sülük tedavisi, proloterapi, müzik terapi, mezoterapi, homeopati, ozon uygulaması, osteopati, hipnoz, akupunktur, kayropraktik, refleksoloji, apiterapidir.[5,6]

Bu çalışmada Ankara Şehir Hastanesi Onkoloji Polikliniklerine başvuran hastalarda GETAT hakkında literatür taranarak oluşturulan anket sorularına verdikleri yanıtlar değerlendirilerek, GETAT kullanan grubun prevalansı, sosyodemografik özellikleri, hangi kanser tanısı ve tedavisi aldığı, GETAT hakkındaki tutumları ve bunları etkileyen faktörlerin saptanması amaçlanmıştır.

Materyal ve Metot

Bu araştırma Ankara Şehir Hastanesi Tıbbi Onkoloji Polikliniklerine başvuran kanser tanısıyla izlenen hastaların Geleneksel ve Tamamlayıcı Tıp yöntemlerini kullanım durumları, nedenleri, etkileyen faktörleri araştırmak amacıyla yapılan tanımlayıcı ve kesitsel bir çalışmadır.

Çalışmanın evrenini; 2019 yıl ortası onkoloji polikliniklerine başvuran bir yıldaki toplam hasta sayısı hesaplanarak 41,600 kişi oluşturmaktadır. Bu evrenden %95 güven oranı ve %6 etki genişliği ile rastgele seçilerek ve gönüllülük esasına dayalı olarak 300 kişiye ulaşıldı. Çalışmaya katılanlara herhangi bir kimlik bilgisi sorulmadı.

Etik kurul onayı alındıktan sonra 1 Kasım 2019 ile 31 Aralık 2019 tarihleri arasında çalışmaya katılan kişilerden sözlü onam alınarak, anketler yüz yüze görüşme şeklinde yapıldı. Ankara Şehir Hastanesi onkoloji polikliniklerine başvurmuş ve çalışmaya katılmayı kabul etmiş olmak çalışmaya katılma kriterleri olarak belirlendi. Gönüllülük esasına dayalı olarak yapılan anketlere katılmayı kabul etmeyenler çalışmaya dahil edilmedi. Katılımcıların, çalışmaya katılmayı reddetme ve cevaplandırmaya başladıktan sonra anketi yarıda bırakma hakkı mevcuttu.

Veriler araştırmacı tarafından hazırlanan bir anket yardımıyla toplandı. Anket katılımcıların sosyodemografik özellikleri ve tıbbi durumlarıyla ilgili 13 soru, literatür taranarak oluşturulan geleneksel ve tamamlayıcı tıp hakkındaki tutumlarını, kanser tedavisi almadan önce ve aldıktan sonraki dönemde kullanım sıklıklarını, en sık kullanılan GETAT yöntemlerini ve kullanmaya yönlendiren nedenlerini, GETAT yöntemleri hakkında bilgi düzeylerini, kimin tavsiyesi ile bu yönteme başvurduğunu, bu yöntemlere toplamda ne kadar para harcadıklarını, bu yöntemlerden yan etki görüp görmediklerini ve doktorlarına bu konuda danışıp danışmadıklarını belirlemeye yönelik 16 soru olmak üzere toplam 29 sorudan oluşmaktadır.

İstatistiksel Analizler

Araştırmada elde edilen verilerin istatistiksel analizi SPSS 19 (Statistical Package for the Social Sciences, version 19) istatistik programı kullanılarak yapıldı. İstatistik yöntem olarak Ki-kare analiz testi kullanıldı. İstatistiksel anlamlılık düzeyi (p) ilgili testlerle birlikte gösterildi. $p<0,05$ düzeyi anlamlı kabul edildi.

Bulgular

Hastaların %66,33'ü (n=199) kadın olup yaş ortalamaları 59,26±13,32 (19-90) yıl olarak bulundu. Hastaların saptanan demografik özellikleri Tablo 1'de gösterilmiştir.

Tablo 1. Hastaların demografik özellikleri

		n	%
Meslek	Ev hanımı/İşsiz	171	57
	Emekli	89	29,67
	Memur	18	6
	İşçi	4	1,33
	Diğer	18	6
Gelir durumu	Gelirim giderimden az	182	60,67
	Gelirim giderime eşit	114	38
	Gelirim giderimden çok	4	1,33
Medeni durum	Evli	236	78,67
	Bekar	11	3,67
	Boşanmış	8	2,67
	Dul	45	15
Aile yapısı	Çekirdek aile	249	83
	Geniş aile	37	12,33
	Parçalanmış aile	14	4,67

Hastalar %62,66'sı (n=188) ilk ve orta öğretim mezunu olup %73,33'ü (n=220) il merkezinde yaşamaktaydı. Hastaların kanser dışında en az bir kronik hastalığı sahip olma oranı %54 (n=162) olup %53,33'ünün (n=160) onkoloji polikliniğine başvuru sıklığı ayda birden az - yılda en az bir kez idi. Kanser tanıları incelendiğinde ilk dört sırada meme (%29,66), kolon (%12), mide (%8,33) ve akciğer kanseri (%6,33) tanısı olduğu saptandı. Hastaların doktor tarafından bilgilendirilme durumları incelendiğinde doktoru tarafından yüksek oranda yeterli bilgilendirme yapıldığı belirtildi (Tablo 2).

Tablo 2. Hastaların doktor tarafından bilgilendirilme durumu

Bilgi Verilme	**n**	**%**
Yeterli bilgilendirme yaptı.	233	77,66
Yetersiz bilgilendirme yaptı.	62	20,66
Bilgilendirme yapmadı.	5	1,66

Hastaların %97,33'ü kanser tanıları nedeniyle medikal onkolog tarafından verilen tedavi seçeneklerinden birini almaktaydı. Hastaların tanı öncesi ve tanı sonrası GETAT kullanım durumları ve kullanılan GETAT yöntemleri Tablo 3'de belirtilmiştir. Tanı öncesi fitoterapi de ilk sırada bitkisel çaylar (%57,60), tanı sonrası ilk sırada bitkisel çaylar (%52), ikinci sırada ise ısırgan otu (%30) yer almaktaydı.

Tablo 3. Hastaların tanı öncesi ve tanı sonrası GETAT yöntemlerini kullanma dağılımları

		Tanı Öncesi		Tanı Sonrası	
		n	%	n	%
GETAT Kullanımı	Evet	173	57,66	101	33,66
	Hayır	127	42,33	199	66,33
GETAT Yöntemi	Fitoterapi	165	90,16	100	90,90
	Hacamat	11	6,01	6	5,45
	Sülük	7	3,82	4	3,63

Tanı sonrasında GETAT uygulaması kullanmama nedenleri incelendiğinde ilk sırada, tavsiye eden doktora güven duyulması saptandı (Tablo 4). Tanı sonrasında GETAT yöntemini hastaların %26,05 'i başlangıç aşamasında, %30,28'i tedavi sürecinde, %43,66'sı tedavi olup süreç bittikten sonra kullanmıştı. Hastalara GETAT yöntemini tavsiye edenler incelendiğinde ilk iki sırada kendi araştırmam, aile/arkadaş yer alıp; yalnızca 8'inin (%5,44) sağlık personeli tarafından önerildiği saptanmıştı.

Tablo 4. Hastaların GETAT yöntemlerini kullanmama nedenleri

		n	%
Nedeni	Doktorumun tavsiyesine güveniyorum, gerek duymuyorum.	137	28,36
	Yeterli bilgim yok.	136	28,15
	Doktor tavsiye ederse kullanırım.	115	23,80
	Kullanmadım ama kullanmayı düşünüyorum.	32	6,62
	Yararı olduğuna inanmıyorum.	25	5,17
	Tedavi sürecindeki etkileşimlerinden dolayı kullanmadım.	25	5,17
	Günümüzdeki GETAT uygulayıcılarına güvenmiyorum.	11	2,27
	Diğer	2	0,41
Toplam		483*	100

* Birden fazla yanıt verilebilmiştir.

Hastaların GETAT yöntemlerini kullanış nedenlerine baktığımızda ilk sırada kansere karşı vücudun direncini arttırma (%27,73; n:66), ikinci sırada ise hastalıkla direkt savaş (%23,94; n:57) yer almaktaydı. Tanı sonrası 101 hastanın bu yöntemlere başvurma sıklıkları incelendiğinde %42,57'si (n=43) ayda bir ve daha sık, %45,54'ü (n=46) ayda birden az ve en az yılda bir kez, %11,88'i ise (n=12) yılda birden daha seyrek GETAT yöntemini kullanmıştı.

GETAT yöntemlerinden fayda görme dağılımlarına bakıldığında hastaların %22,77'si (n:23) hiçbir yarar görmediğini, %25,74'ü (n:26) daha sonucu almadığını, %23,76'sı (n:24) beklediği sonucu aldığını, %27,72'si (n:28) tedavi olmadan kısmi rahatlama olduğunu belirtti. Tanı sonrası GETAT yöntemi kullanan 101 hastanın 9'unun (%8,91) yan etki gördüğü saptandı. Hastaların büyük çoğunluğunun GETAT yöntemleri hakkında bilgi düzeyi yetersizdi (%56,43; n:57). Hastaların sadece %5'ine GETAT yöntemini sağlık personeli uygulamıştı. Tanı sonrası GETAT yöntemi kullanan 101 hastanın 97'si GETAT yöntemine para harcama miktarını belirtti.

Hastaların 13'ü (%12,87) hiç para harcamamış, 68'i (%67,32) 500 TL altında 20'si (%19,80) 500 TL üstünde para harcamışlardı.

GETAT yöntemi kullanan hastaların %62,37'si (n=63) onkoloji hekimine danışmadıklarını ve büyük çoğunluğu (%71,42; n=45) gerek duymadığı için onkoloji hekimlerine söylemediklerini ifade ettiler. Çalışmamızda GETAT yöntemlerini hastaların büyük kısmı bir başka hastaya tavsiye etmemekle (%37,62; n:38) birlikte bu yöntemleri uygulayan kişiler tarafından istismar edilmediklerini düşünmekteydiler (%27,72 n:28). Tanı sonrası GETAT yöntemi kullanan hastaların %35,64'ü (n=36) bu yöntemlerin tıbbi tedavi kadar etkili olmadığını, %38,61'i ise (n=39) etkili veya bazen etkili olduğunu belirttiler.

Ki-kare analiz testinde; hastaların cinsiyetleri ile doktora gitme sıklıkları karşılaştırıldığında erkeklerin kadınlara göre daha yüksek oranda doktora gittiği istatistiksel olarak anlamlı bulundu (p=0,022). Hastaların sosyodemografik özelliklerine bakıldığında; yaş, cinsiyet, meslek, öğrenim durumu, aylık gelir durumu, medeni hali ve aile tipi ile GETAT kullanımı arasında istatistiksel olarak anlamlı ilişki saptanmadı (Tablo 5).

Hastaların yaşadıkları yerleşim yeri ile GETAT yöntemlerini kullanma sıklıkları arasında istatistiksel olarak anlamlı ilişki olduğu gösterilmiş olup il merkezinde yaşayan hastalar ilçe/köy de yaşayan hastalara göre GETAT yöntemlerine daha sık başvurmuştu (Tablo 6).

Tablo 5. Hastaların cinsiyetleri ile doktora gitme sıklıkları, kanser hakkında bilgilendirme ve GETAT ile ilgili soruların karşılaştırılması

Cinsiyet		**Kadın n(%)***	**Erkek n(%)***	**x^2**	**P**
Doktora Gitme Sıklığı	Haftada En Az Bir Kez	33(16,58)	29(28,71)	7,668	**0,022**
	Hafta-Ay 1	50(25,13)	28(27,72)		
	1ay-1yıl	116(58,29)	44(43,56)		
Doktorun Kanser Bilgilendirmesi	Yeterli Bilgilendirme Yaptı.	153(76,88)	80(79,21)	0,346	0,556
	Yetersiz Bilgilendirme Yaptı/ Bilgilendirme Yapmadı.	46(23,12)	21(20,79)		
Tanı Öncesi GETAT	Hayır	83(41,71)	44(43,56)	0,095	0,759
	Evet	116(58,29)	57(56,44)		
Tanı Sonrası GETAT	Hayır	128(64,32)	71(70,30)	1,071	0,301
	Evet	71(35,68)	30(29,70)		
GETAT Sıklığı	Haftada En Az Bir Kez	34(47,89)	9(30)	2,882	0,237
	Hafta-Ay 1	29(40,85)	17(56,67)		
	1ay-1yıl	8(11,27)	4(13,33)		
GETAT Bilgisi	Yetersiz	36(50,70)	21(70)	3,879	0,144
	Kısmen Yeterli	31(43,66)	8(26,67)		
	Tamamen Yeterli	4(5,63)	1(3,33)		
Yan Etki Görme	Yetersiz	62(87,32)	30(100)		0,055
	Tamamen Yeterli	9(12,68)	0(0)		
GETAT Tavsiye Eder misiniz?	Hayır	23(32,39)	15(50)	3,183	0,204
	Evet	24(33,80)	9(30)		
	Kararsızım	24(33,80)	6(20)		
GETAT İstismar Edildiğini Düşünme	Hayır	21(29,58)	7(23,33)	1,046	0,790
	Evet	14(19,72)	6(20)		
	Bilmiyorum	25(35,21)	10(33,33)		
	Bazen	11(15,49)	7(23,33)		
GETAT'ın Klasik Tedavi Kadar Etkili Olduğunu Düşünme	Hayır	23(32,39)	13(43,33)	1,195	0,752
	Evet	10(14,08)	4(13,33)		
	Bazı durumlarda evet	19(26,76)	6(20)		
	Fikrim yok	19(26,76)	7(23,33)		

*Sütun yüzdeleri verilmiştir.

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Tablo 6. Hastaların ikamet ettikleri yerleşim yeri ile doktora gitme sıklığı, kanser hakkında bilgilendirme durumu ve GETAT ile ilgili soruların karşılaştırılması

İkametgâh		**Köy/ilçe n(%)***	**İl n(%)***	**x^2**	**P**
Doktora Gitme Sıklığı	Haftada En Az Bir Kez	16(20)	46(20,91)	0,135	0,936
	Hafta-Ay 1	22(27,50)	56(25,45)		
	1ay-1yıl	42(52,50)	118(53,63)		
Doktorun Kanser Bilgilendirmesi	Yeterli Bilgilendirme Yaptı.	59(73,75)	174(79,09)	0,965	0,203
	Yetersiz Bilgilendirme Yaptı/ Bilgilendirme Yapmadı.	21(26,25)	46(20,91)		
Tanı Öncesi GETAT	Hayır	34(42,50)	93(42,27)	0,001	0,972
	Evet	46(57,50)	127(57,73)		
Tanı Sonrası GETAT	Hayır	53(66,25)	146(66,36)	0,001	0,985
	Evet	27(33,75)	74(33,64)		
GETAT Sıklığı	Haftada En Az Bir Kez	6(22,22)	37(50)	6,474	**0,034**
	Hafta-Ay 1	16(59,26)	30(40,50)		
	1ay-1yıl	5(18,52)	7(9,50)		
GETAT Bilgisi	Yetersiz	13(50)	44(58,67)	3,327	0,189
	Kısmen Yeterli	10(38,50)	29(38,67)		
	Tamamen Yeterli	3(11,50)	2(2,66)		
Yan Etki Görme	Hayır	23(88,46)	69(92)	-	0,691
	Evet	3(11,54)	6(8)		
GETAT Tavsiye Eder misiniz?	Hayır	8(30,77)	30(40)	0,810	0,667
	Evet	10(38,46)	23(30,70)		
	Kararsızım	8(30,77)	22(29,30)		
GETAT İstismar Edildiğini Düşünme	Hayır	8(30,77)	20(26,67)	1,510	0,680
	Evet	3(11,54)	17(22,67)		
	Bilmiyorum	10(38,46)	25(33,33)		
	Bazen	5(19,23)	13(17,33)		
GETAT'ın Klasik Tedavi Kadar Etkili Olduğunu Düşünme	Hayır	8(30,77)	28(37,33)	3,274	0,351
	Evet	5(19,23)	9(12)		
	Bazı durumlarda evet	4(15,38)	21(28)		
	Fikrim yok	9(34,62)	17(22,67)		

*Sütun yüzdeleri verilmiştir.

Tartışma

Çalışmamızda hastaların kanser tanısı aldıktan sonra GETAT yöntemlerini kullanım sıklığı %33,66 olarak gösterildi. Molassiotis ve arkadaşlarının aralarında Türkiye'nin de olduğu 14 Avrupa ülkesinde kanser hastalarının TAT yöntemlerini kullanmalarıyla ilgili oranın %14,8 ile %73,1 arasında ve ortalamanın da %35,9 olduğu çalışmada gösterilmiştir.[7] 2010 yılında Dicle Üniversitesi Tıp Fakültesi Tıbbi Onkoloji Bölümü'nde yapılan bir çalışmada en az bir TAT yöntemi kullanan hasta oranı %62 olarak gösterilmiştir.[8] 2018 yılında Haydarpaşa Numune Eğitim ve Araştırma Hastanesi Palyatif Bakım Merkezi'nde yapılan bir çalışmada hastaların %29,7'si GETAT uyguladıklarını ifade etmiştir.[9] 2018 yılında Hindistan'ın altı şehrinde 2614 onkoloji hastasına yapılan çalışmada TAT yöntemini kullanım oranı %46,2 olarak gösterilmiştir.[10]

Çalışmamızda GETAT yöntemlerini uygulama sıklığı ile istatistiksel olarak anlamlı çıkan tek nokta yerleşim yeriydi. İl merkezinde ikamet edenlerin köy/ilçede ikamet edenlere oranla daha sık GETAT yöntemine başvurdukları görüldü. Hastaların sosyodemografik özellikleri ile GETAT yöntemleri arasında istatistiksel olarak anlamlı ilişki saptanmamış olup yapılan çalışmalara baktığımızda; Molassiotis ve arkadaşlarının TAT yöntemlerini kadınların, gençlerin ve yüksek eğitimlilerin daha fazla kullandığını saptamışlardır.[7] 2010 yılında Dicle Üniversitesi Tıp Fakültesi Tıbbi Onkoloji Bölümü'nde yapılan bir çalışmada; hastaların özellikle 60 yaşına kadar TAT kullanımı yaş ile birlikte artmakta ve üniversite mezunlarının lise mezunlarına kıyasla daha fazla oranda TAT kullandığı gösterilmiştir.[8] 2018 yılında palyatif bakım merkezinde yapılan çalışmada ise; hastaların GETAT uygulama durumu ile yaş, cinsiyet, eğitim durumu ve kanser evresi arasında anlamlı bir ilişki bulunmamıştır.[9]

Çalışmamızda hastalarımızın büyük çoğunluğu ilk ve ortaokul mezunuydu. Hastaların lise, lisans ve lisansüstü oranının düşüklüğü göze çarpmakta olup; bu grubu kapsayan GETAT yöntemlerinin kullanım durumunu araştırmaya yönelik çalışmalar yapılabilir. Çalışmamızda hastaların kanser tanılarına baktığımızda %29,66 ile ilk sırada meme kanseri yer almaktaydı.

GETAT yöntemi kullanan hastalarda fitoterapi %90,90 ile ilk sırada gösterilmişti. Fitoterapi içinde bitkisel çaylar %52 ile ilk, ısırgan otu oranımız ise %30 ile 2.sırada yer almaktaydı. Molassiotis ve arkadaşlarının çalışmasında en sık kullanılan yöntemlerin bitkisel tedavilerdi.[7] 2018 yılında palyatif bakım merkezinde onkoloji hastalarına yapılan çalışmada ise; fitoterapinin hastaların en fazla uyguladıkları GETAT yöntemi olduğu gösterilmiştir.[9] Onkoloji hastalarında fitoterapi kullanımı çok fazla olup, sağlık çalışanları bu konuda yeterli bilgi düzeyine sahip olmalı ve hastalara gerekli bilgilendirmeleri açık bir şekilde yapmalıdırlar.

Isırgan otu literatürdeki çalışmalarda fitoterapi içinde ilk sırada yer alarak bu sonucun çalışmamızla uyumlu olmadığı saptanmıştır.[3,11,12] Literatür ile kıyaslandığında ısırgan otundaki düşük saptanan oranın sebebine

baktığımızda; Ankara Şehir Hastanesinde çalışan onkoloji hekimlerinin uyarılarının hastalar üzerinde etkili olduğunu ve bu nokta da hastaların hekimlere güvendiklerini söylemek mümkündür. Ama buna rağmen hala yüksek oranda ısırgan otu tüketimi mevcuttur ve hekimlerin bu konuda daha dikkatli olmaları gerektiği düşünülmektedir. Bilinen diğer GETAT yöntemlerinin oranı düşük olup; bunun sebebi olarak hastalarımızın düşük gelire sahip olması ve daha az eğitimli olması düşünülmekteydi. Fitoterapinin yüksek oranda olmasında ise kullanım kolaylığının ve maliyetindeki düşüklüğünün etkili olduğunu söyleyebiliriz.

Hastalara GETAT yöntemini tavsiye edenlerin dağılımına baktığımızda ilk sırada kendi araştırmam, aile/arkadaş; en son sırada ise onkoloji doktoru (%0,68) ve aile hekimi (%0) gelmekteydi. Bunun dışında sadece 7 hastaya GETAT yöntemleri sağlık personeli tarafından tavsiye edilmişti. Molassiotis ve arkadaşlarının TAT hakkında bilgi kaynaklarının yaptıkları çalışmada %56,5'inin hastaların arkadaşları olduğu görülmektedir.[7] 2010 yılında Dicle Üniversitesi Tıp Fakültesi Tıbbi Onkoloji Bölümü'nde yapılan çalışma da; sağlık çalışanı (doktor, hemşire) tavsiye etme oranı %7,5, medya ise %14,8 oranında olduğu saptanmıştır.[8] 2018 yılında palyatif bakım merkezindeki çalışmada ise; hastalara GETAT yöntemlerini kullanma önerisinde bulunanların büyük çoğunluğunun arkadaşlar ve akrabalar olduğu gösterilmiştir. Doktorların tavsiye etme oranı %13,6 saptanmıştır.[9] 2018 yılında Hindistan'ın altı şehrinde 2614 onkoloji hastasına yapılan çalışmada hastaların %67,9'u TAT yöntemlerini aile üyeleri ve arkadaşlarının önerisi ile kullanmaktadırlar.[10]

Hastaların kanser tedavileri sürecinde GETAT yöntemlerini kullanma oranı %30,28 olarak tespit edilmişti. Mevcut durum kemoterapik ajanların etkilerini değiştirebileceğinden ve ciddi toksisitelere neden olabileceğinden her hastada bu yöntemlerin kullanımı dikkatlice sorgulanmalıdır. Çalışmamızda hastalara GETAT yöntemi %86,13 oranında sağlık personeli tarafından uygulanmamıştı. Yani bu yöntemler yetkili olmayan kişiler tarafından hastalara uygulanmaktaydı. Hastalar bu yöntemlerin faydalı olduğunu düşünerek bu insanlara güvenmekte ve belki de bu yöntemlerin yararından ziyade zararına maruz kalmaktadırlar. Bu konu da gerekli hukuki düzenlemelerin yapılıp Sağlık Bakanlığı tarafından yetkili olamayan bu kişilere gerekli cezai işlemler uygulanmalıdır.

Çalışmamızda GETAT yöntemini uygulayan hastaların %62,37'sinin hekimine danışmadığı sonucu saptandı. Nedenine baktığımızda ilk sırada %71,42 ile 'gerek duymadım' seçeneği gelmekteydi. Bu konuda hekimin bilgili olmayacağını düşünen hasta oranı ise %9,52 ile hiç az sayılmayacak bir düzeydeydi. Hekimler bu konuda hastalara hem uyarı hem öneri de bulunmalı ve bu konuda bilgili olduklarını göstermelidirler. Ayrıca hastalara her durumda bu yöntemleri uygulamadan önce hekimlerine danışmaları gerektiğini açık bir şekilde ifade etmek gerekmektedir. 2018 yılında palyatif bakım merkezindeki çalışmada; hastaların GETAT yöntemi uygulamadan önce %63,6 oranında doktorlarına danıştığı gösterilmiştir. Doktorlara danışan bu hastaların ise %64,2 oranında doktorlarının onayladıklarını söyledikleri saptanmıştır.[9]

Sonuç olarak; hastaların GETAT hakkındaki bilgi düzeylerinin yetersiz olduğu görülmüştür. GETAT yöntemleri hakkında hastaların bilgi ve farkındalıklarını artırmaya yönelik çalışmalar yapılması faydalı olacaktır. Bu konuda toplumda farkındalık oluşturmak açısından halka yönelik eğitimlere yer verilmesi önerilebilir. Hastaların GETAT yöntemlerini kullanım durumu mutlaka sorgulanmalıdır. Onkoloji polikliniklerindeki yoğunluğa bağlı olarak hastalar kısıtlı bir sürede muayene olmaktadırlar. Burada esas önem vermemiz gereken nokta birinci basamak sağlık hizmetlerini sağlayan aile hekimleridir. Çünkü hastaların bu süreçteki her türlü tıbbi probleminde ilk temas noktasını aile hekimleri oluşturur. Hastaların aile hekimlerine istedikleri her zaman ulaşabilme kolaylığı olup, GETAT yöntemleri hakkında hastaları bilgilendirme açısından özellikle aile hekimlerine gerekli eğitimler verilip bu konuda bilgi düzeylerinde artış ve farkındalık sağlanmalıdır. Günümüzde GETAT yöntemlerinin birinci basamak sağlık hizmeti veren aile sağlığı merkezlerinde uygulanmasına izin verilmemektedir. Bu konuda gerekli düzenlemelerin yapılması önerilmektedir.

Dünya genelinde GETAT yöntemlerine ilgi giderek artmaktadır. Tüm sağlık çalışanlarının GETAT yöntemleriyle ilgili bilgili olması ve hastalarına açıklama yapması gerekmektedir. Bu nedenle sağlık çalışanlarının GETAT yöntemleri hakkında bilgi düzeyi ve farkındalığının arttırılmasına yönelik çalışmalar yapılmalıdır. Bunun sonucunda hastaların hekimleri ile bu konudaki paylaşımları ve bilgi düzeyleri artacaktır.

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Research Article

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PLATELET HYPERREACTIVITY RELATED WITH COVID-19 DISEASE SEVERITY

COVID-19 HASTALIK ŞİDDETİ İLE İLİŞKİLİ TROMBOSİT HİPERREAKTİVİTESİ

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Öz

Amaç: SARS-CoV-2 enfeksiyonunda bir hiperkoagulasyon durumu rapor edilmiştir. Trombositler geleneksel rollerinin yanı sıra bağışıklık hücreleri olarak da adlandırılır. Çalışmanın amacı, COVID-19'da trombosit aktivasyonunu ve agregasyonunu incelemekti.

Materyal ve Metot: Bu vaka-kontrol çalışması SARS-CoV-2 enfeksiyonu olan 61 hasta ve 18 sağlıklı bireyden oluşmuştur. Hastalar yoğun bakım ünitesinde (YBÜ) tedavi ihtiyacına göre gruplara ayrıldı. Tüm gruplarda CD41, CD61, CD42a ve CD42b saptandı ve trombosit agregasyon testleri incelendi.

Bulgular: Trombosit CD41, CD61, CD42a ve CD42b ekspresyonları, YBÜ hastalarında sağlıklı donörlere YBÜ olmayan hastalara kıyasla önemli ölçüde yüksekti. YBÜ grubundaki hastalar, YBÜ olmayan hastalar ve kontrollere göre trombosit agregasyonlarında artışa sahipti. Ek olarak, trombosit aktivasyonu ve trombosit fonksiyon testleri, C-reaktif protein, interlökin-6, nötrofil-lenfosit oranı, trombosit-lenfosit oranı, monosit-lenfosit oranı, D-dimer ve fibrinojeni içeren inflamatuar ve pıhtılaşma belirteçleri ile korelasyon göstermiştir.

Sonuç: YBÜ COVID-19 hastalarında artmış trombosit aktivitesi ve daha hızlı trombosit agregasyonu gözlendi. Trombosit hiperreaktivitesinin SARS-CoV-2 enfeksiyonunun ilerlemesine katkıda bulunması olasıdır. Trombosit aktivasyon ve fonksiyon testlerinin inflamatuar ve pıhtılaşma belirteçleri ile arasındaki ilişkiler, sistemik inflamasyonun ve sitokinlerin YBÜ'deki COVID-19 hastalarında hiperkoagulasyonu tetikleyebileceğini veya hiperaktif trombositlerin inflamasyonu artırabileceğini göstermektedir.

Anahtar Kelimeler: COVID-19, inflamasyon, trombosit aktivasyonu, trombosit agregasyonu, SARS-CoV-2.

Abstract

Objectives: A hypercoagulability status has been reported in SARS-CoV-2 infection. Beside their traditional roles, platelets are referred to as immune cells. The purpose of the study was to examine platelet activation and aggregation in COVID-19.

Materials and Methods: This case-control study comprised 61 patients with SARS-CoV-2 infection and 18 healthy individuals. The patients were separated into groups with respect to the need for treatment in the intensive care unit (ICU). CD41, CD61, CD42a, and CD42b were determined as platelet activation markers, and platelet aggregation tests were analyzed in all groups.

Results: Platelet CD41, CD61, CD42a, and CD42b expressions were significantly elevated in ICU patients compared to non-ICU patients and healthy donors. Patients in the ICU group had increased platelet aggregations than those in non-ICU patients and controls. Additionally, platelet activation and platelet function tests correlated with inflammatory and coagulation markers involving C-reactive protein, Interleukin-6, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte to lymphocyte ratio, D-dimer, and fibrinogen concentrations.

Conclusion: Enhanced platelet activity and faster platelet aggregation were observed in ICU COVID-19 patients. It is possible that platelet hyperreactivity may contribute to the progression of SARS-CoV-2 infection. The relationships between platelet activation and functions tests with inflammatory and coagulation markers show that systemic inflammation and cytokines may trigger the hypercoagulability in COVID-19 patients in ICU, or hyperactivated platelets could augment the inflammation.

Keywords: COVID-19, inflammation, platelet activation, platelet aggregation, SARS-CoV-2.

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Introduction

Coronaviruses are a group of primary pathogenic RNA viruses that target the respiratory tract in humans. At the end of 2019, a group of cases of pneumonia with unfamiliar etiology was identified. The novel pathogenic agent was designated as acute respiratory syndrome coronavirus-2 (SARS- CoV-2).[1]The infection created by the SARS-CoV-2, commonly recognized coronavirus disease-2019 (COVID-19), has at full speed proceeded overspread throughout the world. The signs and symptoms of COVID-19 range from asymptomatic to severe infection among individuals. [1-2]

Traditionally, platelets have physiologic and pathophysiologic features in hemostasis and thrombosis. Besides this, platelets induct cellular functions that get involved in the immune and inflammatory network system.[3] Activated platelets have essential thromboinflammatory features in the link between coagulation and immune responses in various infections. Platelets are increasingly being accepted as immune cells.[4,5] In addition, platelets interact with a wide variety of immune cells and thus help regulation of the immune response to injury, infections, and inflammatory responses.[3-6] Pathophysiological mechanisms comprising thrombocyte responses in HIV infection, dengue fever, and influenza pneumonia have been reported in naturally infected patients and experimental infection models. [4,7]

The interaction between virus and platelets causes alterations in both innate and adaptive immunity.[4] Viruses can increase platelet production at various phases.[5] Also, they have an impact on the cytokine profile of the host, arriving at the conclusion of altered thrombopoietin production in the liver.[5] Thrombocytopenia, which is rapidly stimulated in response to viral infections, is intermediated by enhanced platelet disruption.[4,5] The fastest metabolic pathway of platelet destruction arises from directly the interaction through platelets and viruses.[5] These immediate interactions frequently end up platelet activation and afterward platelet degranulation, and adherence of activated platelets to leukocytes.[3, 5, 8] Activation of platelets and connection of platelets to neutrophils raises the clearance of platelets in the spleen and liver.[5, 8] The interaction of platelets with B lymphocytes enhances the generation of antiviral IgG. Moreover, platelets trigger the differentiation of T lymphocytes and monocytes. [5, 8]

With the increase in the number of studies performed in COVID-19, obtained data emphasizes that thrombotic complications are closely related to the SARS-CoV-2 infection.[9, 10] Patients suffering severe COVID-19 are observed to have a hypercoagulable state, which is associated with the progression of multiple organ injury.[10] Increased acute phase reactants in severe COVID-19 may also involve in the COVID-related hypercoagulability.[11, 12]

The aim of the study was to investigate platelet aggregation and activation in patients affected by COVID-19 and to evaluate the platelet homeostasis of the patients with respect to the disease severity. The correlation between inflammatory markers and platelet functions was also investigated in order to discuss the pathophysiological mechanisms related to the coagulation status of COVID-19 patients. Although there are currently very few studies examining platelet activation in SARS-CoV-2 infection, to our knowledge, it is the first study that detects CD41, CD 61, CD42a, and CD42b surface molecules that we investigated.

Materials and Methods

Study design

This study was conducted at Ankara City Hospital, which is one of the main pandemic hospitals for COVID-19 in Turkey. Clinical diagnosis and classifications were made in accordance with the directory of WHO for COVID-19. Patients with existing clinical symptoms, the indication of COVID-19 pneumonia with respect to computed tomography, and/or positive RT-PCR test results of oro-nasopharyngeal swab samples for SARS-CoV-2 were enrolled in the study. Patients having an unverified diagnosis of COVID-19 and receiving previously anticoagulants, anti-inflammatory, and antiplatelet drugs were excluded. A group of healthy subjects without existing respiratory diseases and not being under anticoagulant treatment were included. None of the volunteers in the control group had cancer or any other systemic, inflammatory, or infectious disease, and none were taking medication. All the controls had negative RT-PCR test results for SARS-CoV-2. All participants underwent a comprehensive physical examination, oro-nasopharyngeal swab sampling, chest CT and standard clinical laboratory tests. As well as the routine clinical examinations and blood tests, all participants had platelet activation and aggregation tests. Blood samples were taken from all patients within 24 hours of hospitalization after diagnosis with SARS-CoV-2 infection. Demographic and clinical features and radiological and laboratory test results were gained from both electronic laboratory information systems and case report forms.

Routine Laboratory Tests

Complete blood cell counts were measured on Siemens Advia 2120 Hematology Analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany). C-reactive protein (CRP) tests were detected on Advia Chemistry- XPT systems (Siemens Healthcare Diagnostics, Erlangen, Germany) with an immunoturbidimetric method. The Interleukin-6 (IL-6) tests were determined on an Atellica IM analyzer with chemiluminescence. D-dimer and fibrinogen tests were analyzed on The Sysmex CS-5100 coagulation analyzer. Siemens commercial kits were used in the analysis of routine laboratory tests.

Flow Cytometry

Venous blood samples for flow cytometry were collected in Vacuette® Blood Collection Tubes containing sodium citrate as anticoagulant and studied according to the manufacturer's instructions. In brief, plasma samples (100 uL) were incubated in the dark at room temperature for 15 min with 5 uL of anti-CD41-PC5 (platelet glycoprotein GPIIb; IIb integrin), 5 uL anti-CD42a-FITC (platelet glycoprotein GPIX), 5 uL anti-CD42b-PE (platelet glycoprotein GPIbα), 5 uL anti-CD61-PC7 (platelet glycoprotein GPIIIa) after the centrifugation at 4000 rpm for 10 minutes. After 15-min incubation, a washing procedure was performed according to the instructions of the supplier. The stained samples were analyzed for their immunofluorescence content. A combination of SSC (Side Scatter Channel) and FSC (Forward Scatter Channel) was used to differentiate the platelets, and the antibody expressions on the gated platelets were calculated.

Analyses were performed by using a 10-color flow cytometer (Beckman Coulter, Navios, Miami, FL, USA) within one hour after the sample preparation. In order to perform daily verification of the flow cytometer optical alignment and fluidics system, Flow Check Pro Fluorospheres (Beckman-Coulter) were used. For calibration and standardization of fluorescence detectors, Flow Set Pro Fluorospheres (Beckman-Coulter) were utilized. Settings were optimized, and fluorescence overlap compensation was calculated using single labeling, isotype controls, and Full Minus One (FMO) procedure.

Platelet Function Analyze

Platelet function tests were performed by using Innovance PFA-200 System (Siemens Healthcare Diagnostics, Erlangen, Germany). Citrated blood samples were transferred to disposable cartridges coated with adenosine diphosphate (ADP) and coated with epinephrine (EPI). If platelets were activated, blood plugs were formed, and blood flow in the analyzer was occluded. The closure times were determined for each activator. Platelet reactivity under two different conditions was recorded. The upper detection limit of the closure time was 300 seconds. When the time exceeded the limit, it was counted as 300 seconds.

Statistical analysis

Variables were tested with respect to their distribution via The Kolmogorov-Smirnov test. Normally distributed data were stated with mean and standard deviation. The categorical variables were represented as a number and percentage (%). The significance of difference through categorical variables was assessed by the chi-square or Fisher's exact test (when proper). A one-way ANOVA with a Bonferroni posthoc test was used to identify the differences of parameters among groups. Correlation analyses were conducted by Pearson's correlation for data following a normal distribution. A p-value less than 0.05 was noted as pointing to a significant difference.

The Statistical Package for Social Sciences (SPSS) software program (v.26; IBM, Armonk, NY) was performed for statistical utilizations.

Results

The study included 61 patients who were infected with SARS-CoV-2. The patients were divided into groups regarding the requirement of treatment in the intensive care unit (ICU). Twenty-one (15 male/6 female) of the patients needed ICU support. There were 40 cases (22 male/18 female) in the non-ICU group. The control group consisted of 18 subjects (10 male/8 female). The mean age of the patients who required ICU support was significantly higher than other study groups ($p < 0.001$, for both). Moreover, patients in the ICU group had almost two-fold more comorbidities. The characteristics of participants with COVID-19 are presented in Table 1.

As shown in Table 2 and Figure 1, patients in ICU group displayed increased platelet surface expressions of CD41, CD61, CD42a, CD42b when compared to non-ICU group and controls ($p = 0.013$, $p = 0.012$, $p = 0.009$, $p = 0.011$, respectively). When evaluated based on the platelet function tests, closure times in response to both epinephrine and ADP (agonists) were significantly lower in patients in the ICU group than those of subjects in the non-ICU group and healthy group ($p = 0.007$, $p = 0.004$, respectively). Also, patients had increased platelet aggregations (with epinephrine and ADP agonists) in non-ICU group than control group ($p = 0.650$ and $p = 0.712$, respectively)(Figure 2). There was no significant difference between the non-ICU group and control group in terms of platelet surface expressions of CD41, CD61, CD42a, CD42b. Patients in the ICU group had significantly increased D-Dimer and fibrinogen levels than those in other groups ($p < 0.001$, for both). With regard to inflammatory parameters, C-reactive protein (CRP), Interleukin-6 (IL-6), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR) were significantly higher in the ICU group than non-ICU group and controls ($p < 0.001$, for all). Considering in the way of platelet number and size, platelet counts were lower in the ICU group than those of other study groups; mean platelet volume (MPV) and plateletcrit (PCT) levels were significantly higher in ICU patients with COVID-19 than non-ICU patients and controls ($p < 0.001$, $p = 0.002$ respectively). There were no differences in terms of platelet count and platelet distribution width (PDW) among groups.

The associations of platelet activation and aggregation tests with other parameters were evaluated and shown in Table 3, there were correlations between the platelet surface markers (CD41, CD61, CD42a, CD42b) and inflammatory markers (CRP, IL-6, NLR, PLR and MLR). Also, platelet activation tests had significant relationships with D-dimer and fibrinogen concentrations. Like the platelet activation tests, platelet function tests also had relationships with inflammatory indicators, D-dimer and fibrinogen levels. Additionally, there were associations between MPV and CRP, IL-6, NLR, PLR and MLR ($r = 0.41$, $r = 0.48$, $r = 0.44$, $r = 0.33$, $r = 0.41$

respectively; $p < 0.001$, for all). In addition, significantly positive correlations were found between PCT and CRP, IL-6, NLR, PLR and MLR ($r = 0.35$, $p = 0.012$; $r = 0.34$, p =0.036; $r = 0.31$, p = 0.011; $r = 0.26$, p= 0.042; $r = 0.45$, p < 0.001 respectively).

Table 1. Demographic characteristics of patients with COVID-19

	Non-ICU COVID-19 cases (n = 40)	**ICU COVID-19 cases (n = 21)**	***p***
Age, mean ±SD	47.4 ± 12.48	68.13 ± 15.38	< 0.001
Sex			
Male	22 (55)	15 (71.42)	0.039
Female	18 (45)	6 (28.57)	0.005
Comorbidities	17 (42.50)	17 (80.95)	0.951
Diabetes	7 (17.50)	8 (38.09)	0.754
Hypertension	8 (20)	10 (47.61)	0.042
Cardiovascular disease	6 (15)	5 (23.80)	0.859
Chronic lung disease	6 (15)	5 (23.80)	0.859
Cancer	1 (2.50)	1 (4.76)	0.965
Signs and symptoms			
Fever	25 (62.50)	6 (28.57)	0.056
Cough	21 (52.50)	8 (38.09)	0.058
Dyspnea	19 (47.50)	15 (71.42)	0.047
Myalgia	11 (27.50)	4 (19.04)	0.052
Fatigue	18 (45)	2 (9.52)	0.008

ICU, Intensive Care Unit

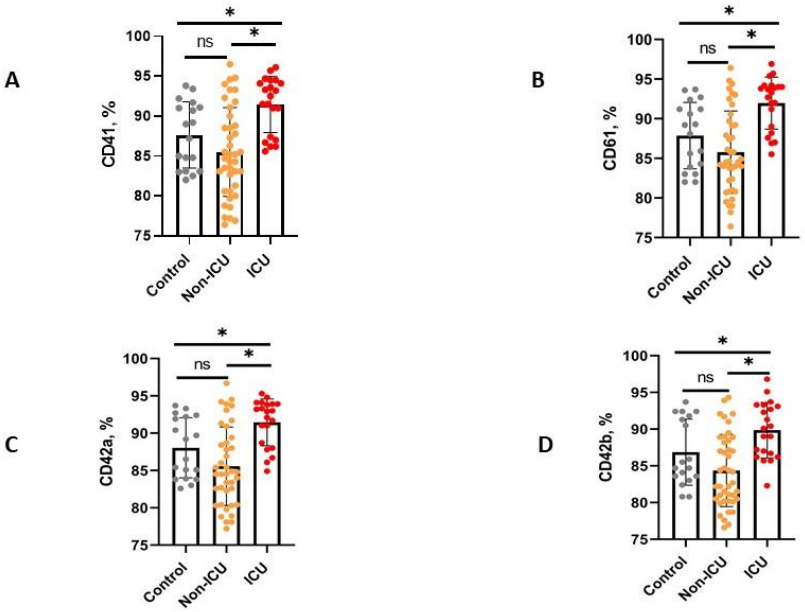

Figure 1 Elevated platelet activation in ICU COVID-19 patients (A-D)
The percentage expressions of CD41 (A), CD61 (B), CD42a (C) and CD42b (D) surface molecules of healthy individuals and patients with COVID-19. The scatter plot with the bar represents the mean with standard deviation. ICU, Intensive Care Unit; * indicates p < 0.05 between selected groups, ns means nonsignificant.

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Table 2. Laboratory findings of participants in study groups

	ICU COVID-19 cases (n = 21)	Non-ICU COVID-19 cases (n = 40)	Healthy individuals (n = 18)	p value
CD41, %	91.51 ± 3.37 [b]	85.56 ± 5,57 [c]	87.38 ± 4.12	= 0.013
CD61, %	92.02 ± 3.28 [b]	85.83 ± 5.19 [c]	87.62 ± 4.18	= 0.012
CD42a, %	91.59 ± 3.13 [b]	85.43 ± 5.26 [c]	88.06 ± 4.07	= 0.009
CD42b, %	89.98 ± 3.78 [b]	84.6 ± 4,91 [c]	86.87 ± 4.5	= 0.011
EPI CT, s	93.69 ± 10.62 [a, b]	102.75 ± 9.54 [c]	109.66 ± 8.42 [c]	= 0.037
ADP CT, s	78 ± 8.14 [a, b]	88.31 ± 7.31 [c]	90.53 ± 8.54 [c]	= 0.042
D-dimer, mg/L	1.46 ± 0.59 [a, b]	0.59 ± 0.30 [a, c]	0.28 ± 0.08 [b, c]	< 0.001
FIB, g/L	5.05 ± 1.07 [a, b]	3.93 ± 0.97 [a, c]	3.01 ± 0.52 [b, c]	< 0.001
WBC, x10^9/L	10.03 ± 3.27 [a, b]	6.94 ± 2.25 [c]	5.89 ± 1.26 [c]	< 0.001
NEU, x10^9/L	8.54± 1.95 [a, b]	4.22 ± 1.23 [c]	3.55 ± 0.80 [c]	< 0.001
LYM, x10^9/L	0.72 ± 0.34 [a, b]	1.61 ± 0.43 [c]	1.89 ± 0.5 [c]	< 0.001
NLR	11.61 ± 4.7 [a, b]	3.06 ± 1.12 [c]	2.08 ± 0.31[c]	< 0.001
HGB, g/dL	13.79 ± 1.69	13.4 ± 1.62	14.37 ± 0.7	= 0.078
PLT, x10^9/L	226.11 ± 64.49	229.35 ± 57.71	238.05 ± 33.6	= 0.614
MPV, fL	9 ± 0.55 [a, b]	8.27 ± 0.57 [c]	8.1 ± 0.76 [c]	< 0.001
PCT, %	0.25 ± 0.1 [a, b]	0.19 ± 0.05 [c]	0.20 ± 0.04 [c]	= 0.002
PDW, %	55.56 ± 8.93	51.84 ± 6.9	50.37 ± 7.21	= 0.134
MLR	0.74 ± 0.26 [a, b]	0.26 ± 0.08 [c]	0.19 ± 0.05 [c]	< 0.001
PLR	483.22 ± 89.49 [a, b]	174.96 ± 40.22 [c]	135.76 ± 24.58 [c]	< 0.001
IL-6 pg/mL	106 ± 25.7 [a, b]	20.9 ± 8.3[a, c]	2.72 ± 0.14 [b, c]	< 0.001
CRP, g/L	0.14 ± 0.06 [a, b]	0.030 ± 0.011[a, c]	0.0018 ± 0.0008 [b, c]	< 0.001

(Values are expressed as mean ± SD. p value < 0.05 considered significant. p value*, One-way analysis of variance [ANOVA]. [a] Statistically significant difference between healthy subjects vs. the other groups; [b] Statistically significant difference between the non-ICU(Intensive Care Unit) group vs. the other groups; [c] Statistically significant difference between the ICU vs. the other groups. EPI CT, induced by epinephrin, cloture time; CT, ADP, induced by adenosine, cloture time; FIB, fibrinogen; WBC, white blood cell; NEU, neutrophils count; LYM, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; and MLR, monocyte to lymphocyte ratio; HGB, hemoglobin; PLT, platelet count; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; CRP, C-reactive protein; IL-6, Interleukin-6.)

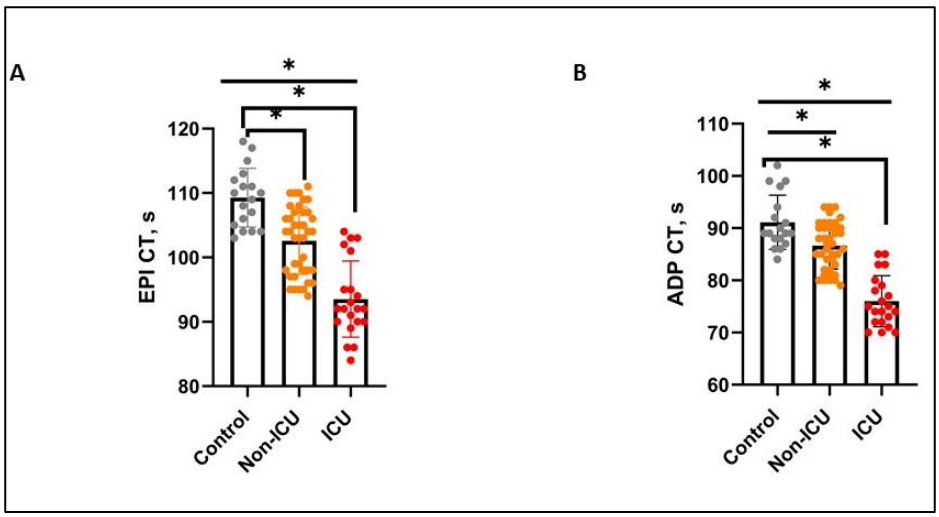

Figure 2. Increased platelet aggregation in COVID-19 patients (A-B)

(Closure times in response to both epinephrine (EPI) and adenosine diphosphate (ADP) (agonist). The scatter plot with the bar represents the mean with standard deviation. ICU: Intensive Care Unit, *indicates p<0.05 between selected groups.)

Table 3. Correlations between the platelet function tests and inflammatory and coagulation factors

n = 79	D-Dimer	FIB	CRP	IL-6	NLR	MLR	PLR
CD41	*r* = 0.33 *p*= 0.035	*r* = 0.30 *p* = 0.024	*r* = 0.40 *p* =0.003	*r* = 0.41 *p* = 0.024	*r* = 0.28 *p* = 0.039	*r* = 0.28 *p* = 0.037	*r* = 0.29 *p* = 0.033
CD61	*r* = 0.31 *p* = 0.047	*r* = 0.31 *p* = 0.021	*r* = 0.44 *p* = 0.001	*r* = 0.42 *p* = 0.021	*r* = 0.31 *p* = 0.022	*r* = 0.32 *p* = 0.017	*r* = 0.31 *p* = 0.018
CD42a	*r* = 0.33 *p* = 0.037	*r* = 0.26 *p* = 0.048	*r* = 0.40 *p* = 0.003	*r* = 0.46 *p* = 0.01	*r* = 0.28 *p* = 0.037	*r* = 0.29 *p* = 0.032	*r* = 0.29 *p* = 0.028
CD42b	*r* = 0.35 *p* = 0.027	*r* = 0.36 *p* = 0.006	*r* = 0.47 *p* = 0.001	*r* = 0.46 *p* = 0.015	*r* = 0.35 *p* = 0.012	*r* = 0.32 *p* = 0.023	*r* = 0.30 *p* = 0.033
CT, EPI	*r* = - 0.31 *p* = 0.045	*r* = - 0.21 *p* = 0.136	*r* = - 0.17 *p* = 0.262	*r* = - 0.23 *p* = 0.069	*r* = - 0.39 *p* = 0.009	*r* = - 0.30 *p* = 0.43	*r* = 0.35 *p* = 0.021
CT, ADP	*r* = - 0.20 *p* = 0.153	*r* = - 0.28 *p* = 0.048	*r* = - 0.22 *p* = 0.084	*r* = - 0.20 *p* = 0.161	*r* = - 0.37 *p* = 0.007	*r* = - 0.34 *p* = 0.01	*r* = - 0.41 *p* = 0.02

(The *r*-value is the Pearson correlation coefficient. The *p*-value is significance. CT, EPI, cloture time, induced by epinephrin; CT, ADP, cloture time, induced by adenosine diphosphate; FIB, fibrinogen; CRP, C-reactive protein; IL-6, Interleukin-6; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; and MLR, monocyte to lymphocyte ratio.)

Discussion

The results of our study not only provide information about the underlying reasons for the tendency to hypercoagulability in ICU patients with various platelet function tests but also verified the relationship between the inflammatory markers and platelet functions for COVID 19. To the best of our knowledge now, very few studies evaluating platelet activation in COVID-19 are present. Thus, our work constitutes the first study in this area to determine CD41, CD61, CD42a, and CD42b surface molecules.

The novel coronavirus has reached pandemic rates leading to notable raised morbidity and mortality all over the world.[13] However, contributing factors to life-threatening situations in patients suffering from COVID-19 are multifactorial, high incidence of thrombotic complications including venous, arterial thromboembolism, ischemic cerebrovascular stroke, and myocardial infarcts may contribute to poor outcomes in these patients.[14] Platelets are recognized to have possible major contributions in hypercoagulation and thrombotic events in SARS-CoV-2 infection.[9-12]

Besides the conventional opinion, platelets are known to express several receptors and surface molecules triggering the cellular functions existing in the inflammatory and immune system network against various pathogens, including viruses.[5, 15] Platelet-virus interaction, antiviral effects of platelets, and activation of platelets in the pathophysiologic mechanisms of viruses were discussed before.[4-6] In recent studies, increased

platelet activations in viral infections such as human immunodeficiency virus (HIV), dengue, and influenza have been reported. [4,7]

Analyzing the activation of platelets by testing the expression of CD41, CD61, CD42a, CD42b in COVID-19 patients, our results showed that the expression of all CD41, CD61, CD42a, and CD42b were significantly higher in ICU COVID-19 patients than in non-ICU patients and controls. CD41 and CD61 are the most abundant surface adhesion molecule of platelets. [3]Upon activation of platelets, this cluster surface molecules take a role in binding adhesion molecules, coherence of platelets, and thrombus growth.[3] Moreover, both CD42a and CD42b are involved in the adhesion of platelets to the proinflammatory endothelium.[15, 16] Platelet surface receptor and molecules and related pathways modulate platelet function.[3, 15, 16] Platelet glycoprotein Ib-IX-V complex including CD42a and CD42b not only triggers platelet adhesion but also mediate in coagulation, arrangement of leukocytes, and be in interaction with viruses.[15, 16] They are recognized as potential risk indicators in several diseases.[16]

Increased platelet aggregations induced by ADP and epinephrine in ICU COVID-19 patients were observed in our study. There were correlations between platelet activation and inflammatory markers, mainly CRP and IL-6. This outcome suggested that inflammation may mediate the platelet activation in SARS-CoV-2 infection. Furthermore, found enhanced D-dimer and fibrinogen levels in ICU patients with COVID-19 represented the activation of coagulation. The relationship found between both the platelet activation and function tests and coagulation factors (D-dimer and fibrinogen) showed that hyperactivated platelets might augment the hypercoagulability in COVID-19 patients. Obtained elevated MPV levels in patients in the ICU group pointed to increased platelet diameter, which can be a reflection of platelet activation. The powerful associations between MPV and PCT levels and inflammatory markers may be a component of the linkage bridge through the circulating platelets and inflammation.

Recent studies have examined platelet activation and aggregation in terms of various molecules.[17-19] Hottz et al. assessed expressions of P-selectin and CD63 surface molecules.[17] They observed elevated P-selectin and CD63 expressions in severe COVID-19 patients than mild group and controls.[17] Also, in the mentioned study, enhanced platelet-monocyte aggregates formation was found in severe COVID-19 patients but not in patients exhibiting mild SARS-CoV-2 infection.[17] Likewise, in this research, Manne et al. evaluated platelet function in COVID-19 patients.[18] Increased P-selectin expressions were obtained in patients with COVID-19 than healthy participants. Additionally, elevated platelet-neutrophil, platelet-monocyte, and platelet- T cell aggregates were determined in COVID-19 patients than controls. The researchers gained faster platelet aggregation in COVID-19 patients.[18] Another study performed by Kalinskaya et al. reported that there was diminished platelet aggregation in patients with SARS-CoV-2 infection at the beginning when compared with the healthy group.[19] After then a significant elevation in platelet reactivity in the course of the disease was observed.[19]

This study has certain limitations. First of all, the study consisted relatively low sample size. Platelet aggregation and activation tests are highly affected by the preanalytical process. Therefore, sample collection for these tests is a somewhat difficult process. In addition, the cost of these tests is high. Although light aggregometry is the gold standard method for platelet aggregation, it could not be used in the study because it is difficult to routinely use in laboratories.

In conclusion, there is rising evidence that hypercoagulability and thrombotic events have a key contribution in the severe SARS-CoV-2 infection. Our outcomes point out that enhanced platelet activation and aggregation are related to the severity of COVID-19. The associations among the markers of platelet activation and aggregation and platelet indices with the indicators of inflammation such as CRP and IL-6 highlight that there is a complex linkage among hyperreactive platelets with inflammation and hypercoagulability, so platelets are probably one of the main participators in immune and inflammatory responses. Our data could be encouraging for improving new therapy approaches targeting platelets in COVID-19.

Ethical Considerations

The study procedure was established in compliance with the basis of the Helsinki Declaration and confirmed by the local ethics board (Number: E1-20-653).

Conflict of Interest

The authors declare no conflict of interest.

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SAMSUN İLİNDEKİ AİLE HEKİMLERİNİN GELENEKSEL VE TAMAMLAYICI TIP HAKKINDAKİ BİLGİ DÜZEYLERİ VE TUTUMLARI

KNOWLEDGE LEVELS AND ATTITUDES OF FAMILY PHYSICIANS IN CITY OF SAMSUN ABOUT TRADITIONAL AND COMPLEMENTARY MEDICINE

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Öz

Amaç: Son yıllarda Geleneksel ve Tamamlayıcı Tıp (GETAT) uygulamalarına ilgi tüm dünyada ve ülkemizde artış göstermektedir. Bu çalışmada Samsun ilindeki aile hekimlerinin GETAT ile ilgili bilgi düzeylerini ve tutumlarını araştırmak amaçlanmıştır.

Materyal ve Metot: Tanımlayıcı, kesitsel türde tasarlanan bu çalışmaya Ocak 2021- Mart 2021 tarihleri arasındaki 3 aylık süre içerisinde, Samsun İl Sağlık Müdürlüğü'ne bağlı aile sağlığı merkezinde çalışan hekimler katılmıştır. Hekimlere literatürden faydalanılarak hazırlanan GETAT ile ilgili bilgi düzeyi ve tutumlarını içeren bir veri toplama formu uygulanmıştır. İstatistiksel analizler SPSS 17.0 paket programı yardımıyla gerçekleştirilmiştir.

Bulgular: Toplamda 213 hekim katılmıştır, yaş ortalaması 45,54±7,68'dir. Hekimlerin en sık duyum ya da bilgisi olduğu uygulama hipnozdur (%89,67). Kendilerine en sık kupa terapisi yaptırdıkları görülmüştür (%8,92). Hekimler hastalarına en sık ozon terapisi tavsiye etmektedir (%27,23). Hastalarına uyguladıkları ve sertifikasyona sahip oldukları en sık uygulama ise kupa terapisidir (sırasıyla %2,35, %1,41). GETAT uygulamalarının faydalı olduğunu ve klasik tıp ile tamamlayıcı tıbbın bir bütünün parçaları olduğunu düşünenler çoğunluktadır. Hekimler GETAT ile ilgili bilgileri %77 oranında sosyal çevre ve medyadan öğrendiklerini belirtmiştir.

Sonuç: Birinci basamak hekimlerinin GETAT hakkındaki bilgi düzeyinin yeterli olmadığı görülmektedir. Kanıta dayalı bilimsel çalışmaların artırılmasıyla GETAT bilinirliği ve doğru kullanımı da yaygınlaşacaktır.

Anahtar Kelimeler: Aile hekimi, bilgi, tutum, tamamlayıcı tıp.

Abstract

Objectives: In recent years, interest in Traditional and Complementary Medicine (T&CM) applications has increased all over the world and in our country. This study, it was aimed to investigate the knowledge levels and attitudes of family physicians in Samsun province about T&CM.

Materials and Methods: Physicians working in the family health center of Samsun Provincial Health Directorate participated in this descriptive, cross-sectional study. A data collection form including the level of knowledge and opinions about T&CM was applied to the physicians using the literature. Statistical analyzes were carried out with the help of the SPSS 17.0 package program.

Results: A total of 213 physicians participated, the average age was 45.54 ± 7.68. Hypnosis is the most common practice that physicians know about (89.67%). It was observed that they mostly applied cupping therapy (8.92%). Physicians most often recommend ozone therapy for their patients (27.23%). The most common practice they apply to their patients and have certification is cupping therapy (2.35%, 1.41%, respectively). Those who think that GETAT applications are beneficial and that classical medicine and complementary medicine are parts of a whole are in the majority. Physicians stated that they learned about T&CM from the social environment and media at a rate of 77%.

Conclusion: It is observed that the knowledge level of primary care physicians about T&CM is not sufficient. With increasing evidence-based scientific studies, T&CM awareness and correct use will also increase.

Keywords: Family physician, knowledge, attitude, complementary medicine.

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Giriş

Klasik batı tıbbındaki çalışmalara ve gelişmelere paralel olarak, özellikle son yıllarda geleneksel ve tamamlayıcı tıp (GETAT) uygulamaları da tüm dünyada ve ülkemizde yükselen bir trend içerisindedir.[1] GETAT'ın popüler hale gelmesinde modern tıbbın talepleri yeterince karşılayamadığı inancı, daha az invaziv ve yan etkilerinin az olduğu düşüncesi, bütüncül tıp anlayışına eğilim olması, insanların dini-kültürel olarak kendilerine yakın hissetmeleri gibi çeşitli nedenler sıralanabilir. Nitekim GETAT'ın birçok ülkede sağlık sigortası kapsamında olmamasına rağmen yaygın olarak kullanılması halk tarafından kabul edildiğini göstermektedir.

T.C. Sağlık Bakanlığı'nca 27/10/2014 tarihinde 29158 sayılı Resmi Gazete'de "GETAT Uygulamaları Yönetmeliği" yayımlanmıştır. Bu yönetmelikle birlikte ülkemizde GETAT uygulamaları yasal hale gelmiştir. Böylece sağlık mensubu olmayan kişilerce uygulanmasının önüne geçilmiş, uygulama yapılabilecek sağlık kuruluşları ve bunların çalışma usul ve esasları belirlenmiştir.[2] Ülkemizde GETAT kendisini etik kurulları, anabilim dalları ve literatür bilgileriyle de ıspatlamaktadır.[2-7]

GETAT uygulamalarının gerekliliği ve etkinliği birçok hekim arasında tartışmalı bir konudur. Bir kısım görüş bu uygulamaların terapide yeri olduğunu savunurken bir kısım görüş konvansiyonel terapiyi geciktirdiğini ve yeterli çalışma olmadığını savunmaktadır.[1,8] Hizmet sağlayıcıların hastalara bütüncül bir bakım vermesi gerekmektedir. Aşırı uzmanlaşmaya bağlı olarak hasta yönetiminin iyileştiği düşünülse de bazen hastalar hangi uzmanlık alanı ile yola devam edecekleri konusunda karmaşa yaşamaktadır. Aile hekimliğinin çekirdek yeterlilikleri arasında olan bütüncül yaklaşım ile hasta bir bütün olarak değerlendirilmekte ve hizmetin sürekliliği ile birinci basamakta hasta yönetimi daha başarılı hale gelmektedir.[9] Birinci basamak sağlık kuruluşlarının hastalarla ilk tıbbi temas noktası olması ve GETAT yöntemlerinin özellikle kronik hastalıkların terapisinde kullanılması nedenleri ile gözler aile hekimlerine çevrilmiştir. Bu çalışmada Samsun'daki aile hekimlerinin GETAT ile ilgili bilgi düzeylerini ve tutumlarını araştırmak amaçlanmıştır.

Materyal ve Metot

Bu çalışma tanımlayıcı, kesitsel türde tasarlanmıştır. Evreni Samsun ilinin bütün ilçelerindeki (17 ilçe: 19 Mayıs, Alaçam, Asarcık, Atakum, Ayvacık, Bafra, Canik, Çarşamba, Havza, İlkadım, Kavak, Ladik, Salıpazarı, Tekkeköy, Terme, Vezirköprü, Yakakent) aile hekimleri (415 kişi) oluşturmuştur. Atakum, Canik, İlkadım ve Tekkeköy ilçeleri merkez ilçe olup diğer 13 ilçe perifer ilçeleri oluşturmaktadır.[10] Veri toplama aşamasında aile hekimleri, uzman olup olmamaları dikkate alınmaksızın araştırmaya dahil edilmiştir. Minimum örneklem büyüklüğü "%5 kabul edilebilir hata ve %95 güven seviyesi ile 200 olarak hesaplanmıştır. Evrenin tamamına ulaşılmaya çalışılmıştır. Bütün aile sağlığı merkezleri (ASM) bizzat araştırıcılar tarafından ziyaret edilmiştir.

Veriler; literatürden yararlanılarak oluşturulan, sosyodemografik özellikleri ve hekimlerin GETAT uygulamaları ile ilgili bilgi ve tutumlarını içeren 17 soruluk veri toplama formu kullanılarak yüz yüze görüşme yöntemi ile Ocak 2021-Mart 2021 tarihleri arasında toplanmıştır. Bir formun doldurulması ortalama 15 dakika sürmüştür. Katılımcıların yaşını sorgulayan soru hariç bütün sorular çoktan seçmeli olacak şekilde oluşturulmuştur. Toplamda 5 soru demografik verileri, 12 soru GETAT ile ilgili konuları içermektedir.

Çalışmaya dahil edilme kriterleri: Samsun'da çalışıyor olmak, aile hekimi olmak, iletişime engel bir sorunu bulunmamaktır.

Verilerin analizi

İstatistiksel analizler SPSS 17.0 paket programı yardımıyla gerçekleştirilmiştir. Değişkenlerin normal dağılıma uygunluğu histogram grafikleri ve Kolmogorov-Smirnov testi ile incelenmiştir. Tanımlayıcı analizler sunulurken ortalama, standart sapma, yüzdelik değerler kullanılmıştır. Kategorik değişkenler Pearson Ki Kare Testi ile karşılaştırılmıştır. Normal dağılım göstermeyen değişkenlerin analizinde gruplar arasındaki veriler değerlendirilirken Mann Whitney U Testi kullanılmıştır. $P<0,05$ değerler istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular

Toplamda 213 hekim (evrenin %51,3'ü) çalışmaya katılmayı kabul etmiş olup yaş ortalamaları 45,54±7,68'dir. Katılımcıların %52,11'i (n=111) merkez ilçelerdeki hekimlerden oluşmaktadır. Diğer sosyodemografik özellikleri Tablo 1'de gösterilmiştir.

Katılımcıların GETAT uygulamaları yönetmeliğindeki uygulamalara karşı bilgi, deneyim ve tutum düzeyleri Tablo 2'te gösterilmiştir. Buna göre; en sık hipnoz hakkında duyum ya da bilgi sahibi olunduğu (n=191, %89,67), kendilerine en sık kupa terapisi yaptırdıkları (n=19, % 8,92), hastalarına en sık ozon terapisi tavsiye ettikleri (n=58, % 27,23), hastalarına en sık kupa terapisi yaptıkları (n=5, % 2,35) ve en sık kupa terapisi sertifikasına sahip oldukları (n=3, %1,41) görülmektedir.

Katılımcıların GETAT yöntemleri ile ilgili bilgilerini en sık sosyal çevre/medyadan (%77, n=164) öğrendiği anlaşılmıştır. GETAT uygulamalarının faydalı olduğunu düşünenler yarıdan fazlasını oluşturmaktadır (%56,34, n=120). Hekimlerin %69,48'i (n=148) hastalarının GETAT kullanma durumu hakkında bilgi sahibi değildir. "GETAT uygulamalarını kimler yasal olarak uygulama hakkına sahiptir?" sorusuna 124 kişi (%58,22) "eğitim almış olan tıp/diş hekimi" cevabını vermiştir. 189 hekim (%88,73) "klasik tıp ve tamamlayıcı tıbbın bir bütünün parçaları olduğunu" düşünmektedir.

Katılımcıların 47'si (%22,07) ülkemizde GETAT yönetmeliği olmadığını, 60'ı (%28,17) GETAT etik kurulu olmadığını, 70'i (%32,86) GETAT anabilim dalı olmadığını, 20'si (%9,39) GETAT literatürü olmadığını düşünmektedir. ASM'lerin GETAT uygulamaları için elverişli olduğunu düşünenler azınlıktadır (%13,62 , n=29). Aile hekimliği deneyimi 5 yıl ve altında olanlarda maggot terapisini duyma / bilgisi olma oranı ve osteopatiyi, homeopatiyi, ozon terapisi hastalara tavsiye etme oranı, aile hekimliği deneyimi beş yılın üzerinde olan hekimlere göre daha yüksektir (sırasıyla p=0,012; p=0,031; p=0,024 ve p=0,026). Uzman veya sözleşmeli aile hekimliği uzmanlık eğitimi (SAHU) asistanı olanların apiterapi, hirudoterapi, homeopati, kupa uygulaması, maggot terapi, mezoterapi ve ozon terapi uygulamalarını pratisyen hekimlere kıyasla daha sık tavsiye ettiği görülmüştür (sırasıyla p=0,002; p=0,012; p=0,030; p=0,016; p=0,035; p=0,002 ve p=0,011).

Hekimlerin merkez ilçelerde veya perifer ilçelerde çalışma durumlarına göre GETAT uygulamalarını duyma/ bilme, kendine yaptırma, hastalarına tavsiye etme, hastalarına uygulama, sertifika sahibi olma durumları karşılaştırılmıştır ve herhangi bir fark saptanmamıştır. Yine, merkez/ perifer ilçeler arasında ASM'lerin GETAT için elverişliliği düşüncesinde fark bulunmamıştır.

Tablo 1. Katılımcıların sosyodemografik özellikleri (n=213)

		n	**%**
Cinsiyet	Kadın	73	(34,27)
	Erkek	140	(65,73)
Kaç yıllık hekimsiniz?	0-5	4	(1,88)
	6-10	26	(12,21)
	11-15	28	(13,15)
	15 ve üstü	155	(72,77)
Kaç yıllık aile hekimisiniz?	0-5	38	(17,84)
	6-10	39	(18,31)
	11-15	136	(63,85)
Uzman veya SAHU asistanı mısınız?	Evet	45	(21,13)
	Hayır	168	(78,87)

Tablo 2. Katılımcıların GETAT uygulamaları için "Duydum /Bilgim var, Kendime yaptırdım, Hastama tavsiye ederim, Hastama uyguladım ve Sertifikam var" deme oranları

	Duydum / Bilgim var		Kendime yaptırdım		Hastama tavsiye ederim		Hastama uyguladım		Sertifikam var	
	n	%	n	%	n	%	n	%	n	%
Akupunktur	175	(82,16)	18	(8,45)	53	(24,88)	3	(1,41)	2	(0,94)
Apiterapi	135	(63,38)	3	(1,41)	31	(14,55)	2	(0,94)	1	(0,47)
Fitoterapi	175	(82,16)	8	(3,76)	43	(20,19)	2	(0,94)	2	(0,94)
Hipnoz	191	(89,67)	2	(0,94)	26	(12,21)	1	(0,47)	1	(0,47)
Hirudoterapi	181	(84,98)	8	(3,76)	28	(13,15)	2	(0,94)	1	(0,47)
Homeopati	133	(62,44)	2	(0,94)	20	(9,39)	1	(0,47)	0	(0)
Kayropraktik	105	(49,30)	3	(1,41)	14	(6,57)	1	(0,47)	1	(0,47)
Kupa Uygulaması	184	(86,38)	19	(8,92)	36	(16,90)	5	(2,35)	3	(1,41)
Maggot Tedavisi	117	(54,93)	1	(0,47)	17	(7,98)	0	(0)	0	(0)
Mezoterapi	149	(69,95)	11	(5,16)	34	(15,96)	1	(0,47)	0	(0)
Müzik Terapisi	151	(70,89)	4	(1,88)	30	(14,08)	3	(1,41)	0	(0)
Osteopati	110	(51,64)	1	(0,47)	16	(7,51)	1	(0,47)	0	(0)
Ozon tedavisi	169	(79,34)	10	(4,69)	58	(27,23)	1	(0,47)	1	(0,47)
Proloterapi	99	(46,48)	1	(0,47)	18	(8,45)	0	(0,00)	1	(0,47)
Refleksoloji	124	(58,22)	2	(0,94)	23	(10,80)	1	(0,47)	0	(0)

Tartışma

Bu çalışma aile hekimlerinin GETAT'a ilgisini değerlendiren güncel bir çalışmadır. Birinci basamak sağlık hizmeti, şifa arayan herkese kapsamlı bir bakım vermeyi hedefler ve bu doğrultuda hastaların hizmet alımı için ilk başvuru noktasıdır. Kişi merkezli ve bütüncül bir yaklaşımın benimsendiği aile hekimliği disiplininde hastalıkların erken tanı ve terapisinin yanı sıra sağlığın devamı ve iyileştirilmesi de sağlanmaktadır.[9] Tüm bu özellikler GETAT'ı birinci basamak ile ilişkilendirebilmektedir.

Yüksel ve ark.'nın yürüttüğü bir çalışmada hekimlerin çoğunun GETAT uygulamaları hakkında bilgi düzeylerinin düşük olduğu görülmüştür.[8] Orhan ve ark.'nın aile hekimleri ve pediatristlerle yaptığı başka bir çalışma da hekimlerin büyük çoğunluğunun GETAT hakkında pek bilgisi olmadığını belirtmektedir.[11] Çalışmamızda benzer şekilde hekimler GETAT uygulamaları hakkında kısmen bilgi sahibi olduklarını ya da hiç bilgi sahibi olmadıklarını düşünmektedir.

Mak ve ark.'nın Avusturalya'da hekimlerle yürüttüğü bir çalışmada katılımcılar en sık akupunktura aşina olduklarını belirtmektedir.[12] Kanada'da Verhoef ve ark.'nın yaptığı bir çalışmada hekimlerin en sık kayropraktik hakkında bilgisi olduğu görülmektedir.[13] Çalışmamızda hekimler, diğer çalışmalardan farklı

olarak en sık hipnoz hakkında duyum ya da bilgi sahibi olduklarını belirtmektedir. Sonuçlardaki değişikliklerin nedeni yaşanan bölgedeki toplumun yaklaşımı ile sosyo-kültürel beklentiler olabilir.

Yüksel ve ark.'nın çalışmasına göre hekimler hastalarına en sık akupunktur terapisini tavsiye etmektedir.[8] Norveç ve Danimarka'da beraber yürütülen Salomonsen ve ark.'nın yaptığı çalışmada, hastalara en çok önerilen yöntem akupunkturdur.[14] Çalışmamızdaki hekimler ise en sık ozon terapisini önermektedir. Ozon terapisinin COVID-19 enfeksiyonuna karşı iyi geldiği ile ilgili haberler hekimlerin hastalarına bu terapiyi tavsiye etme oranlarını arttırmış olabilir.[15] Akupunkturun farklı ülkelerde sıklıkla tavsiye edilmesi bu alanda yapılan kanıta dayalı bilimsel araştırmaların fazla olmasıyla açıklanabilir.

Giannelli ve ark.'nın İtalya'da genel pratisyenlerle GETAT uygulamaları hakkında yaptığı çalışmada hekimlerin en sık homeopati uyguladığı görülmektedir.[16] Özçakır ve ark.'nın çalışmasında ise hekimlerin en sık fitoterapiden yararlandığı gösterilmiştir.[17] Çalışmamızda hekimlerin hastalarına en sık kupa terapisi uyguladığı görülmektedir ancak çalışma birinci basamak hekimleri ile yapıldığından ve aile hekimliği yönetmeliğinde GETAT uygulamaları olmadığından sonuçlar negatif etkilenmiş olabilir.

Patel ve ark.'nın çalışmasında hekimlerin %35'i tıp eğitimi sırasında GETAT hakkında seçmeli ders olduğunu ve % 15'i uzmanlık eğitimi sırasında GETAT öğrendiğini bildirmiştir.[18] Özkaptan ve ark.'nın çalışmasında hekimlerin çoğunluğu GETAT konusunda herhangi bir eğitim almadıklarını bildirmiştir.[19] Çalışmamızdaki sonuçların ülkemizdeki literatürle benzerlik göstermesine rağmen diğer ülkelerden farklı olduğu görülmektedir. Bunun nedeni ülkemizde tıp ve uzmanlık eğitim müfredatında GETAT yöntemlerine yer verilmemesi olabilir. Hekimler ancak tıp eğitimi sonrasında T.C. Sağlık Bakanlığı'nın belirlediği merkezlerde sertifikasyon programlarına katılabilmektedir. Son yıllarda giderek yaygınlaşan bu yöntemler hakkında hastaların doğru yönlendirilmesi hem iyilik haline ulaşma süresini kısaltma hem de sağlık harcamalarını azaltmada önemlidir. Bu nedenle kanıta dayalı bilimsel çalışmaların artması ve bu sayede GETAT yöntemlerinin ülkemizdeki tıp eğitim müfredatına dahil edilmesi sağlanabilir.

Katılımcılara GETAT yöntemlerinin faydası konusundaki düşünceleri sorulduğunda çoğunluğun faydalı olduğunu düşündüğü cevabı alınmıştır. Ayrıca hekimlerin büyük kısmı klasik tıp ile tamamlayıcı tıbbı bir bütünün parçaları olarak düşünmektedir. Elbi ve ark.'nın araştırmasına göre hekimlerin çoğunluğu GETAT uygulamalarının faydalı olduğunu düşünmektedir.[20] Yüksel ve ark.'nın çalışmasında katılımcı hekimlerin çoğu GETAT yöntemlerinin faydalı olduğunu belirtmiştir.[8] Gana'da Ameade ve ark.'nın çalışmasına göre tıp fakültesi öğrencilerinin çoğu GETAT uygulamalarının faydalı olduğunu düşünmektedir.[21] Çalışmamız bu konuda literatürdeki çalışmalarla benzerlik göstermektir.

Katılımcılarımız büyük oranda hastalarının GETAT kullanma durumu hakkında bilgi sahibi değildir. Shelley ve ark.'nın çalışmasına göre birçok hasta birinci basamak hekimi ile GETAT kullanımı hakkında neredeyse hiç

konuşmadığını bildirmiştir.[22] Samancı ve ark.'nın yaptığı çalışmada hekimlerin büyük çoğunluğunun hastalarına GETAT yöntemlerine başvurma durumunu sorgulamadığı görülmüştür.[23] Çalışmamızın bulguları da literatürdeki diğer çalışmalarla benzerlik göstermektedir.

'GETAT uygulamalarının yasal uygulayıcısı kimdir?' sorusuna katılımcıların yarıdan fazlası 'eğitimini alan tıp ve/veya diş hekimleri' olarak cevap vermiştir. Esen de çalışmasında benzer bir sonuca ulaşmıştır.[24] Bu terapilerin yalnızca sertifikalı sağlık profesyonelleri tarafından uygulanabileceği hastalar tarafından öğrenildikçe, merdiven altı uygulamalar son bulabilir.

Çalışmamızda tamamlayıcı tıp yöntemlerinin medyada sıklıkla olumlu haberlerde duyulduğu belirtilmiştir. Ayraler ve ark.'nın tıp fakültesi öğrencileri ile yaptığı çalışmada GETAT uygulamalarını medyada olumlu haberlerde duyanların oranı %59,3'tür. Akademik olmayan personele yapılan başka bir çalışmada ise olumlu duyma oranı %54,2'dir.[25,26] Medyada çıkan olumlu haberlerin hem hekimlerin GETAT'ı önermesine hem de hastaların tercihine katkı sunduğu düşünülebilir.

Katılımcı hekimlerimizin yarıdan fazlası ASM'lerin GETAT uygulamaları için elverişsiz olduğunu düşünmektedir. Hekimlerin bu düşüncesini merkez ya da perifer ilçede çalışıyor olmanın etkilemediği görülmüştür. Işık'ın bir eğitim ve araştırma hastanesinde yaptığı çalışmaya göre katılımcıların çoğunluğu birinci basamak sağlık kuruluşlarında GETAT uygulanabileceği ve böylece üçüncü basamak sağlık kuruluşlarında yoğunluğun azalacağı görüşündedir.[27] Bizim çalışmamızla karşılaştırıldığında sonuçlar ters düşmektedir. Ülkemizde hekimlerin günlük hizmet verdiği hasta sayısı düşünüldüğünde mevcut şartlarda ASM'lerde GETAT uygulamalarına vakit ayırmak, hizmetin kalitesini düşürebilir. Bunun yanı sıra yönetmelikteki uygulama alanı fiziki şartlarının da karşılanıyor olması gerekir ki bu her ASM için mümkün olmayabilir ancak hizmet verilen nüfus oranı daha düşük olan ve yönetmeliğe uygun fiziki şartları karşılayabilen birinci basamak sağlık kuruluşlarında GETAT uygulamaları ile ilgilenen hekimler hastalarına sadece farmakolojik terapi değil bütünleştirici bir yaklaşımda da bulunabilir.

Barikani ve ark.'nın çalışmasına göre hekimlik yılı ile GETAT uygulamaları arasında anlamlı fark saptanmamıştır.[28] Elbi ve ark.'nın çalışmasına bakıldığında çalışma süresi 10 yıl üzerinde olan aile hekimlerinin GETAT kullanma oranı, 10 yıl ve altı olanlara göre daha fazla bulunmuştur.[20] Çalışma sonuçlarımız literatürdeki diğer çalışmalardan farklı bulunmuştur. GETAT yönetmeliğinin henüz 7 yıllık olduğu düşünüldüğünde daha genç hekimlerde daha fazla kabul görmesi anlaşılabilir.

Aile hekimliği uzmanları ya da SAHU asistanı katılımcılarda bu uygulamaları duyma ve tavsiye etme oranları yüksek bulunmuştur. Bu hekimler eğitimleri sırasında GETAT merkezlerini daha yakından gözlemlemiş ve bilgi sahibi olmuş olabilir.

GETAT uygulamalarının faydalı olduğunu düşünen katılımcıların hastalarına daha fazla GETAT önerdikleri görülmektedir. Yüksel ve ark.'nın çalışmasında GETAT yöntemlerinin faydalı olduğunu düşünenlerin hastalarına önerme oranı daha yüksektir.[8] Bir grup aile hekimiyle yapılan bir çalışmada GETAT yöntemlerinin faydalı olduğunu düşünenlerin %95,7'si bu yöntemleri hastalarına tavsiye ederken, faydalı olmadığını düşünenlerin %30,8'i tavsiye etmektedir.[20] Çalışmamız literatürdeki diğer örneklerle uyumludur.

Çalışmamızda "GETAT yönetmeliği", "literatürü", "etik kurulu" ve "anabilim dalı" vardır diyenlerin hastalarına bu uygulamaları daha çok tavsiye ettiği görülmektedir. Akademik zemindeki GETAT çalışmalarının ve dolayısıyla bilinirliğinin artması ile hastalara daha kaliteli hizmet sunumu sağlanabilir.

Çalışmanın kısıtlılıkları

Evrenin bir ildeki aile hekimleri ile sınırlı olması, sonuçların ülkeye genellenmesini kısıtlayacaktır. Bütün evrene ulaşılmaya çalışılmasına rağmen hekimlerin bir kısmının çalışmaya katılmayı kabul etmemesi ya da COVID-19 pandemisi sebebiyle iştirak edememesi bir kısıtlılık olarak karşımıza çıkmaktadır. Hekimler üzerinde GETAT bilinirliği ile ilgili geçerlilik ve güvenilirliği olan, aynı zamanda Türkiye'deki yönetmeliği karşılayan bir anket çalışmasına ulaşılamadığı için literatür derlenmesiyle oluşturulmuş bir veri toplama formu kullanılması da bir kısıtlılık olarak değerlendirilebilir. Hastaların hekimler tarafından GETAT yöntemlerine başvurma durumlarının sorgulanmamasının, hekimlerin ASM'de GETAT hizmeti vermek istememesinin ve hekimlerin GETAT literatürünü ne kadar takip ettiğinin irdelenmemesi de bu çalışmanın diğer kısıtlılıklarıdır.

Sonuç olarak, aile hekimleri çoğunlukla GETAT uygulamaları hakkında duyum ya da bilgisi olduğunu ifade etmekte fakat daha az sıklıkla hastalarına tavsiye etmektedir. Hekimlerin çoğu bu uygulamaların faydalı olduğunu ve klasik tıp ile beraber kullanılması gerektiğini düşünmektedir. Genç hekimler GETAT uygulamaları hakkında daha sık duyum ya da bilgiye sahiptir. Gün geçtikçe kullanımı artan GETAT'a günümüz tıp eğitim müfredatında yeterince yer verilmediğini düşünmekteyiz. Kanıta dayalı çalışmaların artırılması ve bu uygulamaların eğitim müfredatına entegre edilmesi ile danışanlara yeterli ve gerekli bilgilendirilme sağlanarak GETAT yönetmeliğinde belirlenen hastalıkların terapi süresi ve tıbbi maliyetleri azaltılabilir.

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Research Article

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Family Medicine Through the Eyes of Final Year Medical Students; A University Example in South of Turkey

Tıp Fakültesi Son Sınıf Öğrencilerinin Gözüyle Aile Hekimliği: Türkiye'nin Güneyinde Bir Üniversite Örneği

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Öz

Amaç: Türkiye'nin de dahil birçok ülkede birinci basamakta kariyer yapmayı düşünen öğrenci sayısı az olmakla birlikte, birinci basamak hekimine duyulan ihtiyaç artmaktadır. Türkiye'de bu konuda yapılan çalışmalar sınırlıdır. Bu çalışmanın amacı, öğrencilerin aile hekimliği hakkındaki bilgi ve tutumlarını değerlendirmek ve aile hekimliği uzmanlığı tercihi ile düşüncelerini incelemektir.

Materyal ve Metot: Tanımlayıcı kesitsel çalışma 2020 Kasım ayında yapılmıştır. Veriler çevrimiçi bir anket yoluyla toplanmıştır

Bulgular: Toplam 225 öğrenci anketi tamamladı (Cevap oranı: %82,72; kadın oranı: % 58,66; ortalama yaş: % 24,43 yıl). Uzmanlık eğitimi yapmadan pratisyen aile hekimi olarak çalışmayı isteyenler %17,77 (n=40), geçici bir süre pratisyen aile hekimi olarak çalışabileceğini belirtenler %49,33 (n=111) olarak bulundu. Aile hekimliği uzmanlığını kariyer tercihleri arasında planlayanların oranı %27,55 (n=62) olarak saptandı. Öğrencilerin büyük çoğunluğu aile hekimlerinin iş-yaşam dengesinin diğer hekimlere göre daha iyi olduğunu (%92,88), aile hekimliğinin tedavinin yanında hastalıktan korunmaya da odaklandığını (%92), aile hekimliğinde uzun süreli hekim hasta ilişkisi olduğunu (%88,00), aile hekimliğinin tıbba önemli katkı sağladığını (%85,77) onayladı. "Aile hekimliğindeki sağlık hizmetleri diğer uzmanlık alanları kadar heyecan vericidir" (%16,44) ve "aile hekimlerine toplumda gereken saygı gösterilir" (%27,55) ez az onaylanan ifadelerdi. "Aile hekimleri diğer uzmanlardan daha az kazanır", "aile hekimliği teşhis açısından zordur" en yaygın kararsız kalınan ifadeler olarak saptandı.

Sonuç: Öğrencilerin büyük çoğunluğunun aile hekimliğini koruyucu hekimlik, uzun süreli hekim hasta ilişkisi ve tıbba önemli katkı sağlama özelliklerini bilmesine rağmen üçte birisinden daha azının aile hekimliği uzmanlığına ilgisi olduğu bulundu. Aile hekimliğindeki sağlık hizmetlerinin heyecan verici olmadığı ve toplumda gereken saygı gösterilmemesi en yaygın olumsuz düşüncelerdi.

Anahtar Kelimeler: Aile hekimliği, tıp öğrencileri, kariyer tercihi, bilgi, tutum.

Abstract

Objectives: In many countries, including Turkey, the number of students considering a career in primary care is low, although the need for primary physicians increases. Studies on this subject in Turkey are scarce. The aim of this study was to evaluate students' knowledge and attitudes about family medicine (FM) and to examine their intentions to enter the FM specialty.

Materials and Methods: The descriptive cross-sectional study was conducted in November 2020. The data was collected via an online questionnaire.

Results: A total of the 225 students (response rate: 82.72%; female rate: 58.66%; mean age: 24.43 years) completed the survey. It was found that 27.55% (26 males, 36 females) of the students would include FM specialty among their specialty preferences. The most important factors for the specialization choice of these students were comfort/work-life balance and personal interest. There was no significant relationship between gender, income, place of residence, and preferring FM specialty ($p > 0.05$). The majority of students approved that the work-life balance of family physicians was better than that of other physicians (92.88%), that FM had protective properties besides treatment (92.00%), that long-term physician-patient relationship (88.00%). "FM is as exciting as other specialties" (16.44%) and "family physicians are given the necessary respect in society" (27.55%) were the least approved statements.

Conclusion: Less than a third of students were found to have an interest in an FM specialty. The most common negative thoughts about FM are that FM is not exciting and is not properly respected in society.

Keywords: Family medicine, medical students; career choice; knowledge, attitude.

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Introduction

In the 21st century, the increasing burden of chronic diseases and the need to strengthen primary health care services arising from the changing nature of diseases have revealed the importance of developing the family medicine (FM) program as a strategy.[1] With its feature of providing appropriate healthcare services to individuals without discriminating between age, gender, or disease, FM constitutes the cornerstone of the healthcare system.[2] It has been documented that healthcare systems where strong primary health care services are provided have better population health by ensuring equality, decreasing costs, and increasing service quality.[3, 4]

Primary care physicians meet the basic needs of a country's healthcare infrastructure.[5] However, in many countries, including Turkey, the number of students considering a career in primary care is low, although the need for primary physicians increases.[6,7] According to current trends, it is estimated that there will be a shortage of 52,000 primary care physicians in the United States (US) by 2025.[8] However, it has been reported that less than 20% of medical faculty graduates in the US will choose a career in primary care.[9] The problem of the workforce in primary care is not only a problem in the US, but the rate of family physicians/practitioners in many countries, including Oman, Canada, and France, is decreasing or already low.[10] In a study conducted in Turkey, it was reported that FM specialty was not included in the career options of medical students, and they considered it as an uninteresting branch of medicine.[11]

Although FM specialty education has been provided in Turkey since 1985, certified practitioners who have not received specialty education in primary care can work as family physicians.[6] According to the 2018 data of the Ministry of Health, a total of 24,082 family physicians, works in Turkey, including 1814 specialists and 22,268 practitioners. The number of family physicians is 15.7% of the total number of physicians (153,128), and the average population per family physician is 3,124.[12] However, the Ministry of Health has aimed for the average population of a family physician to be 2,000 by 2023.[13] This indicates that there is a need for more family physicians in Turkey.

In Turkey, studies evaluating medical students' preferences for FM as a career and their knowledge and attitudes about FM are limited. The aim of this study was to evaluate students' knowledge and attitudes about FM and to examine their intentions to enter the FM specialty.

Materials and Methods

Study population and design

This descriptive cross-sectional study was conducted between November 1 and December 1, 2020 at Gaziantep University Faculty of Medicine. The target population was all students in the 6th year (272 students). A web-based questionnaire was prepared using Google forms. The link to the questionnaire was also shared with groups of all 6th year students on WhatsApp Messenger.

Questionnaire

The questionnaire consisted of two parts. In the first part, the students' socio-demographic characteristics, career preferences, and their desire to work as a family physician in the future were questioned. In the second part of the survey form, knowledge and attitudes about FM were evaluated with 12 questions scored on a five-point likert-type scale. These questions were taken from the survey used in another study and were translated into Turkish.[14]

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences software (SPSS), version 22.0 (IBM Inc., Chicago, IL, USA). Mean and standard deviation, number, and percentage values were used for descriptive statistics, and the chi-square test was used to compare analytically expressed data. $P < 0.05$ was considered statistically significant.

Results

A total of 225 students completed the survey (response rate is 82.72%). The average age of students was 24.43±1.16 (range 22-28), and 132 (58.66%) of them were women. Those who wanted to work as a practicing family physician without specializing have been 17.77% (n=40) and 49.33% (n=111) who stated that they could work as a practicing family physician temporarily. The most desired specialties were 48.44% (n=109) surgical sciences, 45.33% (n=102) internal sciences, 2.22% (n=5) basic sciences.

It was found that 27.55% (26 males, 36 females) of the students would include FM specialty among their specialty preferences. There was no significant relationship between gender, income, place of residence, and preferring FM specialty. It was determined that the most important factors in the choice of specialty in medicine were personal interest (n=74, 32.88%) and comfort/work-life balance (n=67, 29.77%). It was found that

51.61% (n=32) of the students who stated that they would prefer FM specialization stated comfort/work-life balance as the most important factor, and 20.96% (n=13) stated personal interest. The socio-demographic characteristics and career preferences of the students are shown in Table 1.

Table 1. The socio-demographic characteristics and career preferences of the students

	n	%
Gender		
Male	93	41.33
Female	132	58.66
The most common place of residence		
Village or District	32	14.22
City center	193	85.77
Income status		
Low	22	9.77
Middle	159	70.66
High	44	19.55
Willingness to work as a family physician without specializing		
Yes	40	17.77
No	74	32.88
Temporarily	111	49.33
Preference of family medicine specialty		
Yes	62	27.55
No	101	44.88
Undecided	62	27.55
The most desired area of specialization		
Internal sciences	102	45.33
Surgical sciences	109	48.44
Basic medical sciences	5	2.22
Does not want to specialize	9	4.00
The most important factor for your specialty choice		
Personal interest	74	32.88
Financial gain	20	8.88
Comfort/work-life balance	67	29.77
Prestige	8	3.55
Being beneficial to people	23	10.22
Having an academic career	14	6.22
Influence of family members and friends	2	0.88

59.11% of the students confirmed that more family physicians are needed in Turkey, 85.77% that FM contributes significantly to medicine, 92.00% that FM focuses on prevention of disease as well as treatment, 88.00% that there is a long-term physician-patient relationship in FM, 72.44% that education in other

specialties is more difficult, and 92.88% that family physicians have a better work-life balance than other physicians. It was found that 16.44% of the students thought that healthcare services in FM are as exciting as other specialties and 27.55% of them thought that family physicians are respected by society. The statements that students were most undecided about were "family physicians earn less than other specialists", "FM is difficult in terms of diagnosis" (Table 2).

Table 2. Students' knowledge and attitudes regarding family medicine

	Strongly agree/agree n (%)	**Undecided** n (%)	**Disagree / strongly disagree** n (%)
There is a need for more family physicians in Turkey.	133 (59.11)	54 (24.00)	38 (16.88)
Healthcare services in family medicine contribute significantly to medicine	193 (85.77)	18 (8.00)	14 (6.22)
Family medicine is difficult in terms of diagnosis.	110 (48.88)	71 (31.55)	44 (19.55)
Family physicians focus on prevention of disease as well as treatment.	207 (92.00)	6 (2.66)	12 (5.33)
Family physicians earn less than other specialists.	96 (42.66)	80 (35.55)	49 (21.77)
Healthcare services in family medicine are as exciting as other specialties.	37 (16.44)	57 (25.33)	131 (58.22)
Family medicine is a respected field of application in medicine.	105 (46.66)	66 (29.33)	54 (24.00)
Family physicians take care of all the health problems of patients.	107 (47.55)	57 (25.33)	61 (27.11)
There is a long-term physician-patient relationship in family medicine.	198 (88.00)	13 (5.77)	14 (6.22)
Education in other specialties is more difficult than family medicine specialty education.	163 (72.44)	25 (11.11)	37 (16.44)
Family physicians' work-life balance is better than other physicians.	209 (92.88)	6 (2.66)	10 (4.44)
Family physicians are respected in our society as required.	62 (27.55)	54 (24.00)	109 (48.44)

The knowledge and attitudes of students who would include FM specialization in their preferences and other students regarding FM were compared. A significant difference was found between the students in the statements "There is a need for more family physicians in Turkey" and "Healthcare services in FM are as exciting as other specialties" ($p < 0.001$). While the majority of students (79.03%) who consider FM in their

specialty preferences confirm the statement that more family physicians are needed in Turkey, the majority of students (73.26%) who do not consider FM in their specialty preferences did not confirm the statement that "healthcare services in FM are as exciting as other specialties" (Table 3).

Table 3. Comparison of the knowledge and attitudes of students who would prefer and would not prefer family medicine specialization regarding family medicine

			Preference of Family Medicine Specialty			p
			Yes	No	Undecided	
There is a need for more family physicians in Turkey.	Strongly agree/agree	n	49	47	37	0.001
		%	79.03	46.53	59.67	
	Undecided	n	10	25	19	
		%	16.12	24.75	30.64	
	Strongly disagree/disagree	n	3	29	6	
		%	4.83	28.71	9.67	
Healthcare services in family medicine are as exciting as other specialties.	Strongly agree/agree	n	22	7	8	0.001
		%	35.48	6.93	12.90	
	Undecided	n	19	20	18	
		%	30.64	19.80	29.03	
	Strongly disagree/disagree	n	21	74	36	
		%	33.87	73.26	58.06	

Discussion

The results of our study revealed that the vast majority of students want to be specialists, and less than one-third include FM in their specialty preferences. Studies conducted in Turkey have shown that the majority of medical faculty students want to work as specialists after graduation.[15-16] In another study, it was reported that medical students did not see FM as an attractive option in career planning.[11] Dikici et al. reported that the preference rate of FM was 0.9% in a study they conducted with first-year students from four different universities.[6] The results of our study suggested that interest in FM has increased in Turkey compared to the previous years.

Students' desire for FM as a career was found to be 2.6% in Saudi Arabia, 4% in Pakistan, 4.7% in Egypt, 6.4% in Morocco.[17-20] In a study conducted in South Africa, it was reported that FM was in sixth place in the specialty preference.[21] In a study conducted in Germany, it was reported that 49.3% of the students were interested in working as family physicians, and FM specialty was ranked 2nd among the most popular specialty preferences.[22] It has been shown that 19% of students in Israel and 31.4% of clinical students in Canada are interested in FM.[7,23] These results show that there are great differences between countries in terms of inclusion of FM in career plans by the students.

In a study conducted in Brazil, it was reported that a controllable lifestyle, financial factors, and leisure time were important factors for specialty selection for medical students and physicians.[24] In a study conducted in Spain, it was reported that working conditions in FM were an effective factor for specialty selection.[25] Kawamoto et al. reported in their study that work-life balance was an important factor in choosing FM as a career.[26] In a study conducted in Turkey, it was reported that a flexible lifestyle and acceptable working hours were important factors for specialty selection for medical students.[27] Almost all of the students (92.9%) confirmed the statement in this study that family physicians' work-life balance is better than other physicians. In addition, it was found that half of the students who stated that they would prefer the FM specialization stated the comfort/work-life balance as the most important factor for their specialization preference.

The focus of FM on a holistic approach to patients with preventive, curative, and rehabilitative services ensures that high-quality and cost-effective healthcare services are provided to communities.[28] In the study conducted by Alshammari et al., it was shown that the majority of Saudi students agreed that FM has the characteristics of preventive medicine, long-term physician-patient relationship, and focusing on patient holistically and contributes significantly to medicine.[15] Similarly, in our study, almost all of the students confirmed the protective feature of FM, the long-term physician-patient relationship, and its important contribution to medicine.

In their nationwide study in Spain, Zurro et al. reported that less than 20% of students thought that FM has a high status within the medical profession, has a scientific prestige similar to other specialties, or is an interesting medical specialty in terms of research.[25] In this study, it was found that nearly half of the students considered FM to be a respected field of application in medicine but thought that family physicians are not respected in society. In addition, it was determined that the majority of students did not consider healthcare services in FM as exciting as other specialties.

Conducting the study with a limited number of students in a single-center is the limitation of our study. Therefore, the results of the study cannot be generalized. Working with more students at different universities in the future will provide better enlightenment on the subject. In addition, the validity and reliability analysis of the scale used in the study was not performed, which is another limitation of the study.

As a result, although the vast majority of the students know that FM has the characteristics of preventive medicine, long-term physician-patient relationships, and important contributions to medicine, it has been found that less than a third of them are interested in specializing in the field of FM. It was determined that the most common negative thoughts have been that healthcare services in FM are not exciting and that they are not respected in society as required. The preference of FM as a career should be increased by explaining the

importance of FM and primary healthcare services in medical faculty education and increasing the prestige of FM in society.

Ethical considerations

Approval was obtained from Gaziantep University Clinical Research Ethics Committee for the study. (Decision number: 333 Date: 21.10.2020) Informed consent of all the students who participated in the study was obtained.

Conflict of interest

The authors declare no conflict of interest.

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Research Article

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CLINICAL SIGNIFICANCE OF PLATELET PARAMETERS IN THE DIFFERENTIAL DIAGNOSIS OF THROMBOCYTOPENIA

TROMBOSİTOPENİNİN AYIRICI TANISINDA TROMBOSİT PARAMETRELERİNİN KLİNİK ÖNEMİ

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Öz

Amaç: Hipoprodüktif (örn: AA, AML, ALL, MDS) ve hiperdestrüktif trombositopeninin (örn: ITP) ayrımında en geçerli tanı yöntemi kemik iliği incelemesidir. Ancak kemik iliği incelemesi oldukça invaziv bir yöntem olup ITP gibi hiperdestrüktif trombositopeninin tanısında yapılması bazı çalışmalarda önerilmemektedir. Son yıllarda yapılan bazı çalışmalarda MPV, PCT ve PDW gibi platelet parametrelerin trombositopeninin ayırıcı tanısında kullanılabileceği ileri sürülmüştür. Bu çalışmada amacımız, bu parametrelerin trombositopeninin ayırıcı tanısındaki etkinliğini araştırmaktır.

Materyal ve Metot: Çalışmaya trombositopenisi olan 164 hasta dahil edildi. Hastalar tanısına göre hiperdestrüktif (75 ITP) ve hipodestrüktif(25 AA, 25 MDS, 24AML, 15 ALL) trombositopeni olarak iki gruba ayrıldı. Hastaların tanısı güncel hematoloji, patoloji rehberleri ve kromozom analizleri kullanıldı. K3EDTA'lı tüplere alınan kan örnekleri Beckman-Coulter otomatik cihazlarda çalışıldı.

Bulgular: Trombosit sayısı açısından iki grup arasında herhangi bir farklılık yoktu. Cinsiyet, yaş ve PDW açısından iki grup arasında herhangi bir farklılık izlenmedi. Bununla birlikte MPV, hiperdestrüktif grupta hipodestrüktif gruptakilere göre belirgin olarak daha yüksekti. Bunun aksine PCT değeri hiperdestrüktif grupta hipodestrüktif gruba göre önemli ölçüde daha düşüktü.

Sonuç: Bu çalışmada; trombosit parametrelerinin kullanımının, ITP hastalarının tanısını güçlendirebileceği, diğer klinik ve laboratuvar testleri ile birlikte faydalı olabileceği saptandı.

Anahtar Kelimeler: MPV, trombosit parametreleri, trombositopeni.

Abstract

Objectives: Bone Marrow (BM) examination is the gold-standard test in discriminating between hyperdestructive thrombocytopenia and hypoproductive thrombocytopenia. However, BM examination is an invasive, time-consuming, and expensive approach. Therefore, BM study is not recommended as the first-line method. Recent studies showed that platelet parameters such as mean platelet volume (MPV), plateletcrit (PCT), platelet size deviation width (PDW) could be used for differential diagnosis of thrombocytopenia. In the present study, accordingly, we aimed to investigate the significance of these parameters in the differential diagnosis of thrombocytopenia.

Materials and Methods: One hundred sixty-four (164) patients with thrombocytopenia were included in the present study. The patients were divided into two groups according to the time of the diagnosis of thrombocytopenia: hyperdestructive (75 ITP) and hypoproductive (25 AA, 25 MDS, 24 AML, 15 ALL). The diagnosis was made based on hematological, pathological, and chromosomal analyses and guidelines. Samples for complete blood counts were collected in K3EDTA tubes and analyzed with an automated hematology analyzer, Beckman-Coulter.

Results: The platelet count was similar in both groups. The present results showed that there were no statistically significant differences between the groups in terms of age, gender and PDW. However, MPV was significantly higher in the hyperdestructive group than the hypoproductive group. By contrast, PCT was considerably lower in the hyperdestructive group than the hypoproductive group.

Conclusion: The results of the present study indicated that these platelet parameters might provide additional contributions to strengthen the diagnosis in patients diagnosed with ITP and would be beneficial to consider the thrombocyte parameters as well as the clinical and other laboratory tests of the patient.

Keywords: MPV, platelet parameters, thrombocytopenia.

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Introduction

Platelets are blood cells that play a fundamental role in primary hemostasis. The normal number of platelets in the circulating blood is about 150-450x 10^9. Thrombocytopenia is shown to be the most common cause of abnormal bleeding in daily health practices.[1] It is critically important to determine whether the thrombocytopenia is primarily owing to the increase in hyperdestruction of platelets or hypoproduction of them after excluding splenic sequestration in defining the etiology of thrombocytopenia or not.[2] Decrease in platelets outside the bone marrow due to platelet destruction and normal or increased platelet-derived megakaryocytes are monitored in bone marrow examinations in the hyperdestructive thrombocytopenia. The best examples that can be cited in this group might be immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP) and disseminated intravascular coagulation syndrome (DIC). On the other hand, reduced or no megakaryocytes are observed in bone marrow examinations in hypoproductive thrombocytopenia. The best examples that can be mentioned in this group might be bone marrow damages leading to acute and chronic leukemia, aplastic anemia (AA), and myelodysplastic syndrome (MDS), chemotherapy and drug use.[2] Examination of bone marrow aspirations and various biochemical tests are used to differentiate the type of thrombocytopenia. Although invasive bone marrow aspiration is the gold standard and technically not difficult in the discrimination of the thrombocytopenia, but it is a painful, uncomfortable, time-consuming, and expensive approach. Therefore this method is not recommended in the diagnosis of hyperdestructive thrombocytopenia such as ITP.[3,-6] Overall, these studies do not suggest the use of bone marrow aspiration as first-step approach in the management of the thrombocytopenic patients.[5,6] Nonetheless, bone marrow examination is mandatory and necessary for diagnosis in other patient groups, except for ITP and several clinics continue to use the examination of it in the differential diagnoses of thrombocytopenia type.

Rapid advances in automated hematology analyzers have allowed easy and rapid measurements of several blood parameters. Among these, platelet parameters such as MPV, PDW, and PCT can provide important information regarding the kinetics of platelets.[7-13] These tests are inexpensive, non-invasive, requiring no additional blood samples and they can be performed using an automated hematology analyzer in each health center. In addition, some studies suggest that these platelet parameters can be used in the differential diagnosis of thrombocytopenia.[14-24] Nonetheless, these parameters are not currently used in the differential diagnosis of thrombocytopenia. In the present study, we aimed to investigate the usefulness of the platelet parameters in the differential diagnosis of thrombocytopenia based on the hyperdestructive or hypoproductive nature of thrombocytopenia.

Materials and Methods

Study design and participants

The patients at ages between 18-85 years old with platelet counts <100x10^9 were enrolled in the present study, but those patients diagnosed with splenic sequestration, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), chronic systemic diseases, thrombocytopenia due to use of drug or chemotherapy were excluded from the current study.

Data screening process

The data pertaining to the patients were evaluated prospectively. The distribution of the patients enrolled in the present study based on their diagnosis was as follow 75 patients with idiopathic thrombocytopenic purpura (ITP), 24 with acute myeloid leukemia (AML), 15 with acute lymphoblastic leukemia (ALL), 25 aplastic anemia (AA) and 25 myelodysplastic syndrome (MDS) patients (Figure 1). Diagnoses of the impairment of the patients were determined using hematological, pathological, chromosomal analyses and other guiding tests. The bone marrow aspiration and biopsy examination were carried out for all of the patients enrolled in the present study. Of the entire patients, 75 patients were classified in the hyperdestructive group and 89 patients were classified in the hypoproductive group. The samples for complete blood counts were collected in K3EDTA tubes and analyzed with an automated hematology analyzer, Beckman-Coulter.

Statistical Analysis

IBM SPSS 20 was used for statistical analyses of the data obtained from the present study. Continuous variables were expressed as mean ± SD and they were compared using Shapiro Wilk normality test. Mann-Whitney U test was used to compare non-normally distributed continuous variables. Median (Quartiles) values were provided for descriptive statistics. Finally, categorical variables were defined as percentages and they were analyzed via Fisher's Exact Chi-Square and Continuity Correction.

Results

No differences were noted regarding the effectiveness of the platelet parameters in the differential diagnosis of thrombocytopenia between the groups in terms of age (p=0.974). Serum hemoglobin and white blood cell levels were found to be lower in the hypoproductive group than in the hyperdestructive group (p <0.001). The platelet counts were similar between the groups (p=0.444). Moreover, while MPV was 7.4 fl in the hypoproductive group, it was 10.7 fl in the hyperdestructive group. The difference in the level of the MPV

between the groups was statistically significant (p<0.001). In addition, the PCT level was lower in the hyperdestructive group than in the hypoproductive group (p=0.039). There was also no difference in PDW between the groups (p=0.907) (Table 1). Furthermore, levels of leukocytes and hemoglobin were markedly reduced in the hypoproductive group with respect to the hyperdestructive group (p<0.001).

Table 1. Features pertaining to the groups

	Hyperdestructive Group (n=75)	**Hypoproductive Group (n=89)**	**p**
Hemoglobin (gr/dl)	13.5(13.025-14.10)*	7.9(6.42-9.25)*	<0.001
Leucocyte (10^3 /□l)	6800 (5900-8475)*	2200 (1400-4225)*	<0.001
Platelet (10^3 /□l)	24 (9.25-49.75)*	18 (9.0-39.25)*	0.444
MPV (fl)	10.7 (10.0-11.75)*	7.4 (7.1-7.9)*	<0.001
PCT (%)	0.02 (0.0052-0.05)*	0.024 (0.011-0.0462)*	<0.039
PDW	16.99±1.08 #	16.97±1.19 #	0.907

#: Values expressed as mean ± Standard Deviation
*: Values expressed as median (25-75%)

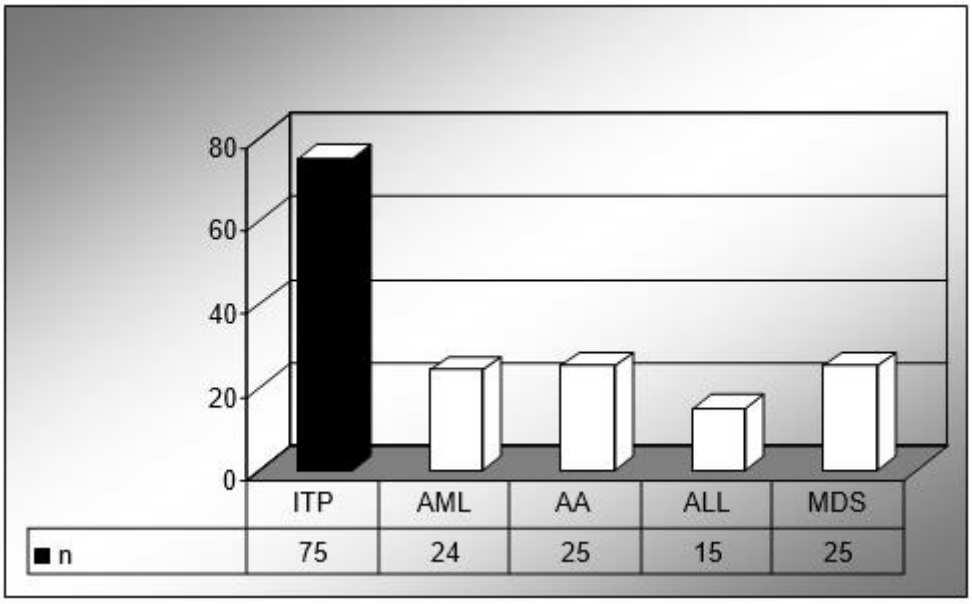

Figure 1: Causes of thrombocytopenia

Discussion

Differential diagnosis of thrombocytopenia is intricate since there are many factors playing a role in the platelet etiology. It is crucially vital to determine whether thrombocytopenia is developed owing to platelet shortage or surplus for the proper differential diagnosis of thrombocytopenia. Inspection of bone marrow aspiration and various biochemical tests are used for differential diagnosis. Even though bone marrow aspiration is the gold standard in the discrimination of thrombocytopenia, it is invasive, time-consuming, expensive, demanding an experienced hematologist and detailed examination. In addition, this method is not recommended in the diagnosis of hyperdestructive thrombocytopenia (e.g., ITP).[3-6] Studies indicate that bone marrow aspiration should not be performed on thrombocytopenic patients as the first-line method[5,6]; therefore, a novel, easy and non-invasive method is required for the diagnosis of thrombocytopenic patients. Several studies assert that particular platelet parameters such as MPV, PDW, and PCT can be useful as the first-line method for managing thrombocytopenic patients.[10-28] Besides, previous studies indicate that while levels of MPV and PDW are higher in the hyperdestructive group but lower in the hypoproductive group.[12,13,29,30] Present results concerning the levels of MPV are consistent with the literature. Accordingly, current results showed that the levels of MPV were 10.7 fl in the hyperdestructive group and 7.4 fl in the hypoproductive group ($p<0.001$).

The results of the current study suggest that the platelet parameters such as MPV and PCT can be used in the differential diagnosis of thrombocytopenia as first-line methods. They are cheaper, easily available, reliable, require no additional blood sample, and can be performed in health centers in addition to the clinical and other laboratory tests of the patient. We think that although the platelet parameters alone are not considered to be thoroughly effective in uncovering the etiology of thrombocytopenia, they are useful as a first-line approach and can play a critical role in determining the direction of the etiological investigation for the diagnosis of thrombocytopenia.

Ethical considerations

Our study was designed in accordance with the principles of the Helsinki Declaration and regulation of patient rights and approved by the clinical research ethics committee of Eskişehir Osmangazi University with the date of 28.07.2020 and the number of 08.

Conflict of İnterest

The author declares no conflict of interest.

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OXIDATIVE STRESS IN PATIENTS WITH CARBON MONOXIDE POISONING

KARBON MONOKSİT ZEHİRLENMESİ OLAN HASTALARDA OKSİDATİF STRES

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Öz

Amaç: Oksidatif stres, hücresel savunma mekanizmalarıyla (antioksidanlar) elimine edilenden daha fazla reaktif oksijen türü (ROS) oluşumunu ifade eder. Bu çalışmanın amacı, CO zehirlenmesinde gelişen oksidatif stresi belirlemek, oksidan ve antioksidan parametreleri ölçmek ve normobarik oksijen (NBO9 ve hiperbarik oksijen (HBO) tedavilerinin bu parametreler üzerindeki etkilerini incelemektir.
Materyal ve Metot: Acil servise başvuruda ve oksijen tedavisi sonrası 24. saatin sonunda toplam oksidan durum (TOS) oksidatif stres parametresi, total antioksidan durum (TAS), paraoksonaz (PON), serum paraoksonaz (SPON), arilesteraz (ARES) ve tiol (TTL) seviyeleri, antioksidan kapasite göstergesi olarak ölçüldü.
Bulgular: Hasta grubunda kontrol grubuna göre TAS, TTL ve ARES düzeyleri anlamlı olarak düşük bulundu. Hiperbarik tedavi ve normobarik tedavi alan hastalar arasında oksidatif stres parametrelerinin hem başlangıç hem de 24. saat düzeylerinde farklılık yoktu.
Sonuç: TAS, PON, SPON, ARES ve TTL'de devam eden düşüş, antioksidan kapasitenin henüz değiştirilmemiş olmasından veya reperfüzyon iskemisinin tedaviden kaynaklanmasından kaynaklanıyor olabilir. Çalışmamızın sonuçları CO zehirlenmesi vakalarında oksidatif dengenin antioksidanlara ters döndüğünü desteklemektedir.
Anahtar Kelimeler: Karbon monoksit zehirlenmesi, oksidatif stres, hiperbarik oksijen tedavisi.

Abstract

Objectives: Oxidative stress refers to formation of more reactive oxygen species (ROS) than that are eliminated by cellular defense mechanisms (antioxidants). The aim of this study is to determine oxidative stress developed in CO poisoning, to measure oxidant and antioxidant parameters and to study the effects of the NBO and HBO treatments on these parameters.
Materials and Methods: On admission to emergency department and at the end of 24th hour after the oxygen therapy, total oxidant status (TOS) was measured as an oxidative stress parameter, total antioxidant status (TAS), paraoxonase (PON), serum paraoxonase (SPON), arylesterase (ARES), and thiol (TTL) levels were measured as indicators of antioxidant capacity.
Results: TAS, TTL and ARES levels were found to be significantly lower in the patient group when compared to control group. There were no differences in both inital and 24th hour levels of oxidative stress parameters between the patients who received hyperbaric therapy and normobaric therapy.
Conclusion: Continuing decrease of TAS, PON, SPON, ARES, and TTL may be because the antioxidant capacity has not yet been replaced or reperfusion ischemia is caused by treatment. The results of our study support that oxidative balance turns against antioxidants in cases of CO poisoning.
Keywords: Carbon monoxide poisoning, oxidative stress, hyperbaric oxygen therapy.

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Introduction

Carbon monoxide (CO) is a tasteless, colorless, odorless, and nonirritant gas, which produced by incomplete combustion of carbon-based fuels and other substances. CO is the leading agent causing death due to poisoning.[1]

Early symptoms of CO poisoning are first seen in oxygen-dependent organs such as the brain and heart; the symptoms are usually headache, vomiting, palpitations, and confusion.[2] Clinical suspicion is very important in the diagnosis of CO poisoning, but definitive diagnosis is made by measurement of carboxyhemoglobin (COHb) levels.[3]

Both normobaric oxygen (NBO) and hyperbaric oxygen (HBO) therapies are accepted methods of treatment for CO poisoning. Patients with mild poisoning symptoms should undergo NBO treatment. For patients who have coma, altered mental status, seizures, focal neurological deficits, acute myocardial ischemia findings, COHb level > 25% (or for pregnant women COHb level > 15%), HBO therapy should be considered.[1]

CO has a 200 times higher affinity for hemoglobin (Hb) than oxygen. Therefore, it leads to the formation of COHb even at low concentrations. The oxygen dissociation curve is shifted to the left, and as a result, tissue hypoxia develops.[4] In addition, CO also causes the formation of free oxygen radicals, directly by cellular damage and by affecting oxidative metabolism.[5,6] Oxidative stress refers to the formation of more reactive oxygen species (ROS) than that is eliminated by cellular defense mechanisms (antioxidants).[6,7]The increase in reactive oxygen species and free radicals in cells is a major cause of cell damage. Reperfusion after ischemia also increases cellular damage produced by the ischemia due to increased ROS.

There are various opinions on the mechanism of long-term harm of carbon monoxide poisoning. There is no consensus on who should be given hyperbaric oxygen therapy.

The aim of this study is to determine oxidative stress developed in CO poisoning, to measure oxidant and antioxidant parameters, and to study the effects of the NBO and HBO treatments on these parameters.

Materials and Methods

This study was conducted in a Training and Research Hospital. The number of patients admitted to the emergency department annually is approximately 144,000. The study was designed as a prospective observational study. Patients over the age of 18 years who were admitted to our emergency department and diagnosed with CO intoxication during the study period were included in the study. The definitive diagnosis of

CO poisoning was made according to the COHb level in the venous blood gas analysis. Blood gas analysis was made with the analyzer Roche COBAS b221© (Germany) that is available in the emergency department laboratory. COHb levels were measured in patients suspected to be poisoned according to the clinical findings. Patients who had serum COHb levels above 10% in smokers and above >5% in non-smokers were diagnosed with CO poisoning. These patients were informed about the research study. Patients who accepted to participate were included in the study. The patients who are younger than 18 years of age, who didn't accept to participate or who resigned from the study, patients with a history of malignancy, with a diagnosis of an acute inflammatory disease or active infection were excluded from the study. The control group consisted of 50 healthy volunteers that work in our hospital. Informed consent was obtained from all participants.

Firstly demographic data of the patients, date, time, and type of transportation used to come to the emergency department (ambulance or non-ambulance) were recorded in the study form. Then the patient's history (previous diseases, drugs used) and smoking habits were recorded. The source of CO (stove, combi-boiler, water heater, water pipe, exhaust gases, etc.) and exposure time were asked and recorded. The patients' complaints on admission were also recorded (seizures, headache, dizziness, nausea, vomiting, syncope, changes of consciousness, and chest pain). The patients' vital signs, physical examination and detailed neurological examination findings, laboratory results, the type of treatment (NBO or HBO), total duration of treatment, and consultations were recorded in the study forms. The clinician responsible for the treatment of the patient decided on the need for HBO therapy. For patients who have coma, altered mental status, seizures, focal neurological deficits, acute myocardial ischemia findings, COHb level > 25% (or for pregnant women COHb level > 15%), HBO therapy was chosen. All patients who have been treated with HBO have also received NBO during the time they spent in ER.

Routine laboratory tests and peripheral venous blood samples of 5 mL were collected on admission to the emergency department and at the end of the 24th hour after the oxygen therapy. The samples were kept at room temperature for 10-15 minutes in the emergency laboratory and then centrifuged at 3000 rpm for 10 minutes. The obtained sera were placed into a second tube and stored at -80 ° C freezer until the time of analysis.

The oxidative stress parameters total oxidant status (TOS), total antioxidant status (TAS), paraoxonase (PON), serum paraoxonase (SPON), arylesterase (ARES), and thiol (TTL) levels were analyzed.

Measurement of the total oxidant status (TOS)

The TOS of plasma was measured using a novel automated colorimetric method described by Erel (2005). The results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Eqv./L).[8]

Measurement of the total antioxidant status (TAS)

Serum TAS was measured using a novel automated colorimetric measurement method developed by Erel. The results are expressed as millimolar Trolox equivalent per liter.[9]

Measurement of PON-SPON and Arylesterase

Paraoxonase and arylesterase activities were measured using commercially available kits (RelassayR, Gaziantep, Turkey).[10] Paraoxonase activity was expressed as U/L serum. Phenylacetate was used as a substrate to measure arylesterase activity. One unit of arylesterase activity was defined as 1 µmol phenol generated / min under the above conditions and expressed as KU/L serum.[11]

Thiol analysis

Serum total thiol concentration or sulfhydryl groups (SH) were measured by the methods originally described by Ellman (1979) and modified by Hu (1994). The result was expressed in µmol/L.[12,13]

Statistical Analysis

The normal distribution of continuous variables in the study was assessed by the Shapiro-Wilks test. The descriptive statistics for continuous variables with normal distribution are expressed by mean± standard deviation, and the descriptive statistics of the variables not normally distributed or discrete are expressed by the median, interquartile range (IQR), and minimum-maximum values. The categorical variables obtained in the study were expressed as numbers (n) and percentages (%). In the comparisons of the continuous and discrete quantitative data of two independent groups Mann-Whitney U test or independent samples, t-test was used. In the comparison of 3 or more independent groups, Kruskal-Wallis test or Analysis of Variance (ANOVA) was used. In the comparison of continuous and discrete quantitative data in dependent groups, paired Wilcoxon Signed Rank test and two paired-samples t-tests were used. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 were used for statistical analysis and calculations. A value of $p< 0.05$ was considered statistically significant.

Results

Approximately 72,000 patients were admitted to the emergency department of Training and Research Hospital during the study period. 1270 (1,76%) of these patients were admitted because of poisoning and, 108 (0.15%) of them were diagnosed with CO poisoning. CO poisoning (n = 108) constituted 8.50% of all poisoning cases (n = 1270). The study group consisted of 71 patients who agreed to participate in the study, and the control group consisted of 50 healthy volunteers among our hospital employees, and a total of 121 people were included in the study. The remaining 37 of 108 patients diagnosed with CO poisoning were excluded from the study because 17 of them did not accept to participate, 5 of them had malignancy or active infection, 10 of them were under the age of 18, and 5 of them resigned during the study.

The study group included 71 patients (58.67%), and the control group included 50 healthy individuals (41.32%). The gender distribution of the individuals was similar in the groups (p=0.656). The mean age of individuals in the patient group was 41.3±12.9 years (range 18-65), and the mean age of the individuals in the control group was 30.5±10 years (range 18-53). The average age of individuals in the patient group was older than the control group (p <0.001). There was no significant difference between the study and control groups in terms of conditions that may affect the oxidative stress parameters such as coronary artery disease, hypercholesterolemia, hypertension, neurological disorders, diabetes, liver and kidney disease, peripheral vascular disease, lung disease, multiple sclerosis, iron deficiency anemia, and smoking status.

The mode of transportation was an ambulance for 24 (33,80%) of the patients. Time of admission was between 8-16 in 15 (21,12%) patients, 16-24 in 13 (18,30%) patients, and 24- 8 in 43 (60.56%) patients. The Source of CO exposure was combi boiler in 56 (78,87%) patients, whereas stove was responsible in 14 (19.71%) patients. In 1 (1.40%) patient, the source was unidentified. HBO treatment was used in 11 (15.49%) patients.

The mean duration of exposure to CO was 5.0 hours (IQR= 2.0; min= 1.0; max= 12.0). One of the patients was pregnant (1.40%). Sixty-two patients had a headache (87.32%), 40 patients had nausea (56.33%), 35 patients had dizziness (49.29%), 21 patients had vomiting (29.57%), 16 patients had a syncope (22.53%), eight patients had altered mental status (11.26%), eight patients had chest pain (11.26%), and one patient had a seizure (1.40%) at the time of admission. The mean COHb levels of those patients presenting with syncope were found to be 28.54± 8.5, and those presenting with a symptom other than syncope were found to be 21.7± 5.8; the difference is statistically significant (p = 0.001). For symptoms other than syncope, there was no statistically significant difference in mean COHb levels between patients who have the particular symptom and patients who don't have the symptom.

Physical examination was normal in 69 patients (97.18%), trauma signs were present in one patient (1.40%), and agitation was observed on neurological examination in one patient (1.40%). Venous blood gas analysis results of the patient group were as follows: Median (IQR) value of Ph in the patient group was 7.38 (0.7) (Min-Max 7.2-7.6). The Median (IQR) value of HCO3 was 22.3 (3.7) (Min-Max 9.2- 29.5). Median (IQR) value of COHB was 23.2 (7,1) (Min-Max 10.0- 50.0). Median lactate level (IQR) was 3 (2,3) (Min- Max 0.4-14).

The most frequently consulted departments were cardiology for 18 patients (25.35%), neurology for five patients (7.02%), and gynecology for one patient (1.40%), respectively. There were no significant differences between those who received hyperbaric therapy and those who did not, in terms of initial lactate levels ($p = 0.135$). A comparison between oxidative stress parameters and antioxidant parameters of the patient and control groups when they were first presented to the emergency department is shown in Table 1.

There were no significant differences between the patients with or without a history of DM, hypertension, CAD, and smokers and non-smokers in terms of TOS, TAS, PON, SPON, ARES, and TTL variable values of the patients on admission.

Blood samples were collected from 33 of the 71 patients, for repeated tests, after 24 hours, and oxidative stress and antioxidant capacity parameters were measured. These 24^{th}-hour measurements could not be obtained for 38 patients, either because follow-up in the emergency department lasted shorter than 24 hours or patients did not accept follow-up for 24^{th} hours. The patients' basal and 24-hour values are presented in table 2.

There was no statistically significant difference between admission and 24^{th}-hour values of TOS, PON, SPON, ARES, and TTL obtained from 33 patients (receiving HBO treatment or not) (Table 2). Mean values of TAS were found to be significantly lower at the 24^{th} hour when compared to admission ($p = 0.044$).

There was no difference between the admission oxidative stress parameters of the patients who have received HBO and NBO. Furthermore, we did not found any significant differences when we compared the 24^{th}-hour oxidative stress parameters of those who received NBO and those who received HBO (Table 3).

COHb values of the patients who were consulted with cardiology were found to be significantly higher ($p <0.001$). Similarly, mean troponin and CK-MB values of the patients who were consulted with cardiology were found to be significantly higher ($p <0.001$ and $p = 0.010$, respectively).

Table 1. Oxidative stress and antioxidant parameters of the patient and control groups

	Patient		Control		
	Min; max	**Mean±SD**	**Min; max**	**Mean±SD**	**p**
TOS	0-7.8	2.18-1.73	0-0.89	2.81-2.38	0.177
TAS	1.5-3	2.29-0.30	1.8-3.6	2.46-0.33	**0.006**
PON	50.3-471.2	171.9-95.2	43.9-506.1	193.3-106.6	0.238
SPON	101.9-1423.5	467-297.5	92.5-1457.3	539-340.1	0.213
ARES	40.7-286.7	151.8-53.9	60-382.4	195.8-62.7	**<0.001**
TTL	103.8-343.3	191.1-44	155.8-273.5	209.1-23.3	**0.01**

Table 2. The comparison of basal and 24-hour values (n = 33)

	Time of Measurement				p
	Admission 0. hour		24. hour		
	Min; max	**Mean±SD**	**Min; max**	**Mean±SD**	
TOS	0.0; 8.9	2.4 ± (2.1)	0.1; 7.6	1.44± (1.8)	0.160
TAS	1.5; 3.6	2.3± (0.32)	1.1; 2.7	2.1± (0.38)	**0.044**
PON	43.9; 506.1	180.7± (100.2)	49.1; 513.4	175.1 ±103.8)	0.329
SPON	92.5; 1457.3	496.8 ± (316.4)	106.2; 1427.6	486 (322)	0.142
ARES	40.7; 382.4	170±61.4	18.6; 267.0	158.8±63.4	0.949
TTL	103.8; 343.3	198.2±37.8	38.6; 263.0	177.3±43.3	0.098

Table 3. Comparison of oxidative stress parameters after 24 hours who receive NBO or HBO

	NBO n=27 Mean±SD	**HBO n=6 Mean±SD**	**p**
TOS	1.1± 1.4	2.6±2.9	0.072
TAS	2.2± 0.41	2.2±0.22	0.869
PON	173.1±109.3	186.4±81.3	0.782
SPON	475.8±336	531.8±271	0.706
ARES	155.3±66.3	183.2±17.8	0.334
TTL	179.4±40.6	183.8±17.8	0.799

Discussion

Although CO poisoning has been reported at different frequencies depending on different socio-economic and climatic conditions, it is the most important cause of admissions due to poisoning to emergency departments, especially in the winter. Avşaroğulları et al. reported that approximately 1.2 % of all admissions to emergency departments are cases of poisoning, and CO poisonings consist of 9.5% of these cases.[14] In another study conducted in Turkey, 49 of 623 patients who were admitted to the emergency department because of poisoning (7.9%) were diagnosed with carbon monoxide poisoning.[15] In our study, CO poisonings constituted 8.5% of all poisoning cases; this finding is consistent with the literature.

The ratio of women was 54% in patients with CO poisoning in the study of Sahin et al. and 64% in the study of Keles et al.[16,17] In our study the ratio of women was 60.7%.

In our study, there was no statistically significant difference between the patient and control groups in terms of diseases that may affect the oxidative stress parameters. The mean age of the control group was lower than the patient group because the control group consisted of volunteers working in the hospital.

Non-specific symptoms of CO intoxication include headache, nausea, vomiting, palpitations, dizziness, and confusion. Oxygen-dependent organs (brain and heart) are affected earlier than the other organs.[19] In our study, the most common complaints of the patients, were headache (87.32%), nausea (56.33%), dizziness (49.29%), and vomiting (29.57%), respectively. In another study conducted with 483 patients who were admitted to the emergency department with headaches, non-invasive measurement of COHb was found to be >10% in 6.4% of the patients.[18] The similarity of the symptoms with many other diseases often leads to a missed diagnosis. Therefore, the patients presenting with these symptoms should be suspected in terms of CO poisoning, especially in the months when CO poisoning cases are seen in emergency departments most frequently. Our study was conducted between September and March. During this period, COHb levels were measured in patients who were admitted to the emergency department with symptoms such as headache, dizziness, nausea, vomiting, and syncope to avoid missed diagnoses.

CO poisoning can be diagnosed with a history of exposure, but measuring the COHb level supports the diagnosis. COHb levels may not always be compatible with the severity of poisoning. Some publications suggest that there is a strong correlation between blood COHb levels and the severity of poisoning, whereas others suggest that this correlation is available just in mild poisoning cases.[20-22] In our study, the mean COHb levels are found to be significantly higher in only the patients presenting with syncope when compared to patients who do not present with syncope.

In a study conducted with 80 patients, it is reported that increased lactate levels reflect the severity of CO poisoning in the early period.[23] In our study, the initial median lactate level was found to be 3 in the emergency department. There were no significant differences between those who received hyperbaric therapy and those who did not, in terms of lactate levels (p= 0.135).

The deleterious effects of CO poisoning occur by several different mechanisms: binding of CO to hemoglobin and development of functional anemia, direct cellular toxicity, heme-containing proteins binding, the increase of the oxidants[2,] and late changes that are similar to reperfusion injury.[24]

There is a balance between the oxidant and antioxidant defense systems in the body. Oxidative stress is defined as increased levels of oxidants or a reduction of antioxidant capacity and consequent exposure of the cells to oxidative damage. The organism isn't affected as long as there is a balance between the formation and removal rate of free radicals.[25,26] Oxidative stress plays a role in CO poisoning as well as in the pathophysiology of many other diseases.[26] Oxidative stress plays an important role in both the progression of tissue damage induced by CO and during the ischemic-reperfusion phase.[27,28]

There are only a few studies showing the relationship between CO poisoning and sub-parameters of antioxidants. In our study, TOS was measured as an oxidative stress parameter, and TAS, PON, SPON, ARYL, and TTL levels were measured as indicators of antioxidant capacity. We compared pre and post-treatment levels of oxidative stress parameters of patient and control groups. For this purpose, we also studied the sub-parameters of antioxidants.

Kavaklı et al., in their study conducted with 88 patients with CO poisoning, evaluated total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI) of patients at the time of admission. TOS and OSI levels of the patient group were found to be significantly higher than the control group. They stated that oxidative stress parameters might be important as early biomarkers of CO poisoning. There were no significant differences between patient and control groups in terms of TAS levels.[29] In the study of Zengin et al. PON, ARES and -SH levels were found significantly lower in the patient group.[2]

In our study, TAS, TTL, and ARES levels were found to be significantly lower in the patient group when compared to the control group ($p = 0.006$, $p = 0.01$, and $p < 0.001$, respectively). Our findings are consistent with the study of Zengin et al. Average SPON and PON levels were also lower in the patient group, but the difference was not statistically significant. We believe that the low levels of antioxidants in patients are due to consumption. The results of our study support that oxidative balance turns against antioxidants in cases of CO poisoning.

In our study, there were no statistically significant differences between patient and control groups in terms of the TOS levels. We attribute the TOS levels of the patients not being as high as expected to CO poisonings being diagnosed earlier.

In the study of Kavaklı et al., the TOS and OSI levels significantly decreased 6 hours after treatment, but no change was observed in TAS levels. In the study of Zengin at al. PON, ARYL, and -SH levels of patients increased in 90th and 180th minutes.[30] In our study, the average TOS, PON, SPON, ARES, and TTL levels of the patient group were lower at the 24th hour when compared to initial values, but the difference was not statistically significant. In the patient group, TAS levels were found to be statistically significantly decreased at the 24th hour when compared to the basal values ($p = 0.044$).

The decrease in the TOS levels suggests that the effect of oxidative stress due to CO intoxication ameliorates at the 24th hour after treatment. On the other hand, the continuing decrease of TAS, PON, SPON, ARES, and TTL maybe because the antioxidant capacity has not yet been replaced or reperfusion ischemia is caused by treatment. In our study, we weren't able to measure the 24th-hour values of many patients. The reason for the lack of expected increase in antioxidant levels may also be a result of the patients' profile because the patients who agreed to stay for 24 hours might be the ones who are clinically worse (better patients might have left the study earlier)

The principal method of treatment in CO poisoning is NBO. The indications of HBO therapy are controversial. Several publications suggest HBO therapy for preventing delayed neurological sequelae. However, further studies are needed to support HBO.[30] In our study, 11 patients received HPO treatment. There were no differences in both initial and 24th-hour levels of oxidative stress parameters between the patients who received hyperbaric therapy and normobaric therapy. According to the results of our study, it is not possible to suggest superiority HBO or NBO in terms of oxidative stress in the treatment of CO poisoning.

The aim of oxygen therapy in CO poisoning is to stop the tissue hypoxia despite COHb elevation by increasing O2 saturation in the blood as rapidly as possible. However, it should be noted that hyperoxygenation might also cause a similar situation to reperfusion injury by facilitating the production of ROS. Given that antioxidant levels decrease due to CO poisoning, antioxidant replacement therapy may be effective in addition to oxygen therapy. Several other studies suggest consideration of various antioxidant therapies (e.g., vitamin C, hydrogen gas) in addition to oxygen therapy to prevent reperfusion injury as well as the initial damage.[24] In the study of Zengin et al., it was observed that antioxidant capacity is improved in the course of treatment.[2]

There is not an exact correlation between the COHb levels and the clinical status of the patients. Oxidative stress parameters, together with COHb levels, can be used as early biochemical markers in the assessment of severity and prognosis of poisoning. However, further studies are needed to support this idea.

Limitations of the study

The small number of our sample group is a limitation of our study. The small number of patients who received hyperbaric therapy is another limitation.

Ethical considerations

Ankara Atatürk Training and Research Hospital's institutional ethical review board approved the study protocol on 25/7/2012 (approval number B.30.2.YBÜ.0006.06.01/20).

Conflict of interest statement

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ADÖLESAN İDİYOPATİK SKOLYOZLU HASTALARDA POSTERİOR SPİNAL FÜZYON VE VERTEBRA CİSİM GERDİRME CERRAHİSİNİN SONUÇLARININ VE YAŞAM KALİTESİNİN DEĞERLENDİRİLMESİ

OUTCOMES OF POSTERIOR SPINAL FUSION AND VERTEBRAL BODY TETHERING IN PATIENTS WITH ADOLESCENT IDIOPATHIC SCOLIOSIS AND EVALUATION OF QUALITY OF LIFE

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Öz

Amaç: Adölesan idiopatik skolyoz'un (AIS) cerrahi tedavisinde standart yaklaşımı posterior enstrümentasyon ve füzyon (PEF) oluşturur. Tedaviye alternatif, füzyonsuz cerrahi yöntem olan vertebra cisim gerdirme (VBT) ise giderek daha sık kullanılmaktadır. Bu çalışmayla, PEF ve VBT yöntemleri ile ameliyat edilmiş AIS hastalarının düzelme miktarları ve yaşam kalitelerinin karşılaştırılması amaçlanmıştır.

Materyal ve Metot: Eşleşmiş kohortlar, 2 yıl takipli 40^0-70^0 eğriliği olan AIS hastaları incelenerek elde edildi. Lomber eğriliğin cerrahiye dahil edildiği hastalar çalışmadan çıkartıldı. Hastaların demografik verileri, perioperatif ve takip radyografik ölçümleri ve hasta tarafından bildirilen SRS-22 skorları karşılaştırıldı.

Bulgular: Çalışmaya, 16 PEF ve 18 VBT hastası (30K, 4E) dahil edildi. Kohortun ortalama yaşı 13,4 (10-17) yıl ve takip süresi 25,7 (24–32) aydı. Grupların preoperatif üst torasik, ana torasik (MT) ve torakolomber (TL) skolyoz açıları benzerdi. PEF grubunda MT eğrilikte cerrahi düzelme oranı daha fazla (%84–%53, p<0,001) iken, 2. yılda toplam düzelme oranları gruplarda benzerdi (%80–%76, p=0,616). 2. yılda PEF ve VBT gruplarında kendi imaj/görüşünde ve ara toplamda anlamlı iyileşme olduğu saptandı (p<0,001–p=0,037 ve p<0,001–p=0,016). PEF grubunda, fonksiyon/ aktivite alt başlığındaki skorlar 6. ayda ve 2. yılda (p=0,027) ve ağrı, ara-toplam skorları 2. yılda, VBT grubuna göre düşüktü (p=0,020, p=0,036).

Sonuç: PEF ve VBT cerrahisi takibinde MT ve TL eğriliklerde 2. yılda benzer oranda düzelme görülmektedir. SRS22 skorlarında iki cerrahi ile benzer iyileşme elde edilirken, VBT'de bu iyileşme dinamik olarak seyretmektedir. İki grup arasında fonksiyon/aktivite, ara-toplam ve ağrı skorlarının VBT grubunda erken dönem ve takipte füzyona kıyasla daha iyi olması, daha uzun takipli geniş hasta serilerinde incelenmelidir.

Anahtar Kelimeler: Adölesan idiopatik skolyoz, posterior enstrümentasyon ve füzyon, vertebra cisim gerdirme, yaşam kalitesi.

Abstract

Objectives: Posterior instrumentation and fusion (PEF) is the standard surgical approach and vertebral body tethering (VBT) emerged as an alternative non-fusion technique in the treatment of idiopathic scoliosis. The aim of this study was to compare the correction and health-related life quality of the patients who have undergone PEF and VBT.

Materials and Methods: Matched cohorts were obtained among patients whose curves ranged between 40^0-70^0 who had >2 years follow-up. Patients with a lumbar curve included in surgery were excluded. Patients' demographic data, perioperative and follow-up radiographic measurements, and SRS-22 scores were compared.

Results: 16 PEF and 18 VBT patients (30F, 4M) were included. The mean age and follow-up were 13.4 (10-17) years and 25.7 (24–32) months. Preoperative upper thoracic, main thoracic (MT), and thoracolumbar (TL) curves were similar among groups. The surgical correction percentage in the MT curve was greater in the PEF group (84%–53%, p<0.001), while the overall correction percentage at two years was similar (80–76%, p=0.616). There was an improvement in self-image and subtotal scores at two years in PEF and VBT groups (p<0.001–p=0.037 and p<0.001–p=0.016). In the PEF group, function scores at six months and two years (p=0.027), pain and sub-total scores at two years (p=0.020, p=0.036) were found to be lower compared to VBT.

Conclusion: Following PEF and VBT surgeries, a similar improvement was observed in MT and TL curves. While similar improvement is achieved in SRS22 scores, this improvement is dynamically progressed in VBT. Whether SRS22 scores are better in the VBT group should be examined in larger patient series with longer follow-up.

Keywords: Adolescent idiopathic scoliosis, posterior instrumentation and fusion, vertebral body tethering, quality of life.

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Giriş

Adölesan idiopatik skolyoz (AIS) sagital, aksiyel ve koronal düzlemde dizilim ve şekil değişiklikleri ile karakterize, omurganın 3 boyutlu deformitesidir.[1] 10-18 yaş arasında görülen AIS'in tedavi seçenekleri hastanın eğriliğinin büyüklüğü, yerleşimi, kalan büyüme potansiyeli ve konservatif tedaviye cevabına göre değişiklik göstermektedir.[2] Cerrahi torasik Cobb açısının 40^0 üzerinde olduğu, iskelet olgunluğuna ulaşmamış veya eğriliği ilerlemeye devam eden hastalarda önerilmektedir.[3] Deformitenin zaman içinde daha iyi anlaşılmasıyla geliştirilen çok segment, 3 kolon fiksasyon sağlayan pedikül vidalarının kullanımı kısa sürede yaygınlık kazanmıştır. Bu sayede skolyoz hastalarında yeterli düzeltme ve dengeli bir omurga dizilimi sağlandığı bildirilmiş ve posterior enstrümentasyon ve füzyon (PEF) tedavide standart yaklaşımı oluşturmuştur.[4]

Son yıllarda füzyona alternatif olarak omurga biyomekaniğini koruyan füzyonsuz cerrahi yöntem, vertebra cisim gerdirme (VBT), giderek daha sık kullanılmaktadır.[5] VBT, Hueter- Volkmann kanunu kullanarak ve kalan büyümeden faydalanarak, eğriliklerin kendiliğinden düzelmesini sağlayan bir büyüme yönlendirme yöntemidir.[6,7] VBT ile mevcut deformiteyi tedavi ederken, daha fazla deformite oluşması engellenmekte ve hareket kısıtlılığı minimumda tutularak estetik bir görünüm sağlanmaktır. Sadece skolyozun doğal seyrini değiştirilmediği, deformite düzeltmesinin de yapılabildiği bir yöntem olan VBT'de, farklı hasta serilerinde, aşırı düzelme, düzelmede kayıp, ipin kopması veya akciğer ile ilgili problemler gibi cerrahinin ve yöntemin sonuçları ve komplikasyonları hakkında bilgi verilmiştir.[7-11]

Adölesan idiopatik skolyozun farklı tedavi yöntemleri ile amaçlanan sadece anatomik düzeltme değil aynı zamanda hastaların iyilik hallerinin arttırılmasıdır. Skolyozlu hastalarda yaşam kalitesi ve sağlık sonuçlarının değerlendirilmesinde en sık kullanılan hastalığa özgü anket, skolyoz araştırma cemiyeti (Scoliosis Research Society) tarafından geliştirilmiş olan SRS-22 anketidir.[12,13] Türkçe versiyonunun geçerliliği ve güvenirliliği de Alanay ve ark. tarafından gösterilmiştir.[14] AIS hastalarında sağlıkla ilişkili yaşam kalitesi kavramının, gözlem ve korse gibi konservatif tedavilerle, posterior enstrümentasyon ve füzyon cerrahisi veya farklı cerrahi teknikler ile erken veya geç dönem ilişkileri çeşitli çalışmalarla gösterilmiştir.[15-19] Ancak tedavide standart yaklaşım olan ve füzyon ile giderek popülerliği artan füzyonsuz vertebra cisim gerdirme yöntemlerini benzer cerrahi yaklaşım uygulanmış hasta gruplarında karşılaştırarak hastalar tarafından nasıl algılandığını ortaya koyan çalışma bulunmamaktadır.

Bu çalışma ile amaçlanan adölesan idiopatik skolyoz nedeniyle posterior enstrümentasyon ve füzyon ve vertebra cisim gerdirme yöntemleri ile ameliyat edilmiş, preoperatif benzer deformitelere sahip hasta kohortlarının, postoperatif düzelmeleri ve sağlıkla ilişkili yaşam kalitelerinin değerlendirilerek karşılaştırılmasıdır.

Materyal ve Metot

Etik kurul onayının alınmasını takiben 2014-2019 tarihleri arasında tek merkezde VBT ve PEF cerrahileri uygulanmış prospektif olarak takip edilen adölesan idiopatik skolyoz hastaları retrospektif olarak incelendi. Hastaların demografik verileri, preoperatif, erken postoperatif ve takip radyografik ölçümleri ve hasta tarafından bildirilen sonuç anketleri "SRS-22 skorları", sağlıkla ilgili yaşam kalitesini değerlendirmek için kullanıldı.

İki farklı cerrahi grubunda eşleşen kohortlar elde edilebilmesi amacıyla en az takip süresi 2 yıl olan preoperatif deformite büyüklüğü ve deformite tipi benzer hasta kohortları seçildi.

İki grupta, ana torasik eğrilik hakimiyetinde Lenke tip 1 ve 2 deformitesi olan hastalarda cerrahi sınır olan 40 derece üzeri eğriliği olanlar[3] ve VBT için üst ameliyat sınırı olan 70 derece altında eğriliği olan[7] hastalar çalışmaya dahil edildi. PEF'de eşlik eden posterior kolon osteotomisi yapılmış olan, Tip C veya Ar tipi lomber değiştiricisi olan hastalarda alttaki lomber eğriliğin cerrahiye dahil edildiği veya enstrümantasyonun 1. lomber vertebra distaline uzamış olduğu hastalar ve preoperatif ve takip SRS-22 anketleri eksik olan hastalar ile SRS-22 anketi ile aynı takip tarihinde radyografisi olmayan hastalar çalışmadan çıkartıldı.

Cerrahi teknik

Bütün cerrahi prosedürler bir kıdemli cerrah tarafından uygulandı. Posterior enstrümentasyon ve füzyon cerrahisi, yüzüstü pozisyonda standart posterior orta hat yaklaşım ile gerçekleştirildi. İnferior fasetektomiler yapıldıktan sonra torasik pedikül vidaları yerleştirildi. Rodlar yerleştirildikten sonra translasyon, derotasyon, kantilever ve segmental kompresyon-distraksiyon manevralar ile deformite düzeltildi ve dekortikasyonu takiben graft yerleştirilerek işleme son verildi. Hastaların rutin preoperatif aktivitelerine 6 ay sonra dönmelerine izin verildi (Resim 1). Vertebra cisim gerdirme yöntemi lateral dekübit pozisyonunda, video-yardımlı torakoskopi yöntemi ile 3 görüntüleme, 3-4 işlem portu açılarak gerçekleştirildi. Mono-aksiyel vidalar birkortikal olacak şekilde konveks tarafta vertebra cisimlerine yerleştirildikten sonra translasyon ve derotasyon manevraları altında ip gerdirilerek sabitlendi. Preoperatif planlanan düzeltme, deformitenin miktarı ve kalan büyüme potansiyeline göre hesaplandı ve gerdirme miktarına işlem esnasında disk açılarındaki değişime göre karar verildi. İşlem bir adet göğüs tüpü yerleştirilerek tamamlandı. Hastaların rutin preoperatif aktivitelerine 6 hafta sonra dönmelerine izin verildi (Resim 2).

Hasta verileri

Perioperatif veriler; cerrahi yöntem, cerrahi süre, tahmini cerrahi kanama miktarı, üst-alt enstrümante edilmiş vertebralar ve enstrümante edilen vertebra sayısını içeriyordu. Hastaların kemik olgunluğunun belirteci olarak preoperatif ve son takip olarak 2. yıl Risser işaretleri değerlendirildi.[20] Hastaların cerrahi öncesi (preoperatif), erken postoperatif (6. hafta) ve son takip (2. yıl) ön-arka ve yan skolyoz grafileri incelendi. Radyografik olarak hastaların üst, ana torasik (UT ve MT) ve torakolomber/lomber(TL/L) skolyoz açıları ile torasik kifoz (TK) ve lomber lordoz (LL) açıları Cobb yöntemi ile doğrulanmış bir yazılım kullanılarak (Centricity Enterprise-W version 3.0.10; General Electric, Milwaukee, WI, USA) ölçüldü. Koronal ölçümlerde aşırı düzelme durumu açısal olarak negatif işareti ile belirtildi. Ana torasik eğrilikteki cerrahi düzelme ((preoperatif -6. hafta) / preoperatif), takip düzelme ((6. hafta- 2. yıl) / 6. hafta) ve toplam düzelme ((preoperatif - 2.yıl) / preoperatif) oranları hesaplandı. Preoperatif, erken postoperatif (6. ay) ve takip dönemi (2. yıl) SRS-22 skorları çalışmaya dahil edildi. Skorlar; ağrı, kendi imaj/görüşü, fonksiyon/aktivite, ruh sağlığı, tatmin ve ara-toplam olmak üzere 6 alt başlıkta incelendi. Her alt başlıkta erken dönem ve son takip değişim miktarları hesaplandı. İstatistiksel analizlerde demografik ve perioperatif klinik ve radyolojik veriler iki cerrahi grubu arasında karşılaştırıldı. İstatistiksel analizler SPSS v. 23 (IBM, Armonk, NY, ABD) kullanılarak yapıldı. Sürekli değişkenler ANOVA, Mann-Whitney U testi ve kategorik değişkenler Ki-kare testi ile karşılaştırıldı. İstatiksel olarak anlamlılık $p<0.05$ değerlerinde kabul edildi.

Bulgular

Eşleşmiş kohort kriterlerini karşılayan 16 PEF ve 18 VBT hastası çalışmaya dahil edildi. Çalışma grubu 30 kadın, 4 erkekten oluşmakta ve kohortun ortalama yaşı 13,4 yıl (10-17) idi. Ortalama takip süresi 25,7 (24-32) aydı. 34 hastanın 32'sinde Lenke tip 1, 2 hastada Lenke tip 2 eğrilik bulunmaktaydı. Hastaların lomber değiştiricileri 15 hastada A tipi, 14 hastada B tipi, 2 hastada C tipi, 3 hastada Ar tipi idi. Hiçbir hastada preoperatif nörolojik defisit yoktu.

İki grubun demografik, radyolojik ve cerrahi özellikleri Tablo 1'de yer almaktadır. PEF ve VBT gruplarında preoperatif UT ($28,6^0$–$29,6^0$), MT ($56,8^0$-51^0) ve TL/L ($32,5^0$–37^0) skolyoz açıları benzerdi (sırasıyla; p=0,732, p=0,126, p=0,088). PEF grubunda 6. haftada ana torasik eğrilikte cerrahi düzelmenin VBT grubuna göre daha fazla olduğu (%84-%53, p<0.001) ve 6. hafta MT skolyoz açısının daha az olduğu görüldü ($8,8^0$–$23,9^0$, p<0,001). PEF ve VBT gruplarında 2. yılda ise toplam düzelme oranları (%80–%76) ve ana torasik skolyoz açıları ($11,2^0$–$12,1^0$) benzerdi (sırasıyla; p=0,616, p=0,838). PEF grubunun UT skolyoz açıları, 6. haftada ve 2.yılda VBT grubundan istatiksel olarak anlamlı şekilde düşüktü ($9,8^0$ ve $11,2^0$–$20,6^0$ ve $15,8^0$, p<0,001, p=0,030). UT eğriliğin cerrahi düzelme / toplam düzelme oranları, PEF grubunda (%65–%62) VBT grubuna göre (%29–%46) istatiksel olarak daha yüksekti (p<0,001/p=0,040). TL/L eğriliğin cerrahi düzelmesi PEF grubunda

(%65) VBT grubuna göre (%47) istatiksel olarak anlamlı olarak daha yüksek görüldü (p 0,010). Toplam düzelme oranları iki grup arasında benzer saptandı (%68-%80, p=0,422). İki grup arasında, preoperatif, 6. hafta ve 2. yıl radyografilerinde torakolomber eğriliklerindeki skolyoz, torakal kifoz ve lomber lordoz açılarında anlamlı fark saptanmadı.

Tablo 1. Posterior enstrümentasyon ve füzyon (PEF) ile vertebra cisim gerdirme (VBT) ameliyat kohortlarının demografik, radyolojik, cerrahi karakteristikleri ve karşılaştırmaları

Değişkenler	**PEF**	**VBT**	**P**
	n=16	**n=18**	
Yaş (yıl)	14,4 (12-17)	12,6 (10-15)	**0,001**
Cinsiyet (K/E)	13/3	17/1	0,698
Preoperatif Risser	3,4 (1-5)	1,3 (0-4)	**0,001**
2. yıl Risser	4,2 (3-5)	3,4 (0-5)	**0,036**
Enstrümante Seviye Sayısı	9,3 (8-12)	7,5 (7-9)	**0,001**
Cerrahi Süresi (dakika)	350 (210-500)	239 (123-360)	**0,001**
Kanama Miktarı (ml)	234 (50-450)	79 (40-150)	**0,001**
Skolyoz Açıları			
Üst Torasik Eğrilik			
Preoperatif (°) 6.hafta Postoperatif (°) 2.yıl Postoperatif (°)	28,6 (14-47) 9,8 (3-20) 11,1 (3-28)	29,6 (17-44) 20,6 (8-34) 15,8 (4-36)	0,732 **0,001** **0,030**
Ana Torasik Eğrilik			
Preoperatif (°) 6.hafta Postoperatif (°) Cerrahi Düzelme (%) 2.yıl Postoperatif (°) Toplam Düzelme (%)	56,8 (43-72) 8,8 (1-19) 84 (71-98) 11,2 (1-23) 80 (69-98)	51 (43-68) 23,9 (14-33) 53 (40-71) 12,1 (-16-28) 76 (44-129)	0,126 **0,001** **0,001** 0,838 0,616
Torakolomber Eğrilik			
Preoperatif (°) 6.hafta Postoperatif (°) 2.yıl Postoperatif (°)	32,5 (22-43) 13 (1-28) 11,6 (1-22)	37 (29-52) 17,4 (3-28) 6,9 (-4-31)	0,088 0,135 0,198
Torakal Kifoz (°)			
Preoperatif 6.hafta Postoperatif 2.yıl Postoperatif	32 ± 11,1 27,1 ± 9 31,4 ± 10,8	30,2 ± 7,9 27,5 ± 8,2 28,1 ± 7	0,592 0,884 0,283
LomberLordoz (°)			
Preoperatif 6.hafta Postoperatif 2.yıl Postoperatif	61,6 ± 7,8 51,1± 11,5 57,3 ± 9,5	64,1 ± 11,1 55,1 ± 17,9 56,1 ± 7,3	0,347 0,454 0,659

n: Hasta sayısı; K: Kadın; E: Erkek; ml: Mililitre; °: Açı; %: Yüzde

Tablo 2. Posterior enstrümentasyon ve füzyon (PEF) ile vertebra cisim gerdirme (VBT) ameliyat kohortlarının SRS22 anketlerinin preoperatif, postoperatif 6. ay ve 2. yıl sonuçları ve karşılaştırmaları

SRS22 skorları	PEF	VBT	p
	n =16	n=18	
Ağrı			
Preoperatif	3,85 ± 0,76	4,18 ± 0,67	0,179
6. ay Postoperatif	4,2 ± 0,82	4,62 ± 0,39	0,107
2. yıl Postoperatif	4,3 ± 0,47	4,57± 0,62	**0,020**
Kendi İmajı/ Görüşü			
Preoperatif	3,13 ± 0,61	3,38 ± 0,65	0,259
6. ay Postoperatif	4,15 ± 0,39	3,92 ± 0,84	0,410
2. yıl Postoperatif	4,14 ± 0,56	4,24± 0,61	0,615
Fonksiyon/Aktivite			
Preoperatif	4,33 ± 0,73	4,53 ± 0,69	0,347
6. ay Postoperatif	3,96 ± 0,68	4,51 ± 0,57	**0,027**
2. yıl Postoperatif	4,28 ± 0,55	4,66± 0,40	**0,027**
Ruh Sağlığı			
Preoperatif	3,43± 0,50	3,61 ± 0,51	0,326
6. ay Postoperatif	3,55 ± 0,57	3,54 ± 0,55	0,983
2. yıl Postoperatif	3,43± 0,68	3,87± 0,77	0,091
Tatmin			
6. ay Postoperatif	4,54 ± 0,54	4,58 ± 0,69	0,616
2. yıl Postoperatif	4,34 ± 0,94	4,8 ± 0,34	0,154
Ara-toplam			
Preoperatif	3,68 ± 0,47	3,93 ± 0,49	0,153
6. ay Postoperatif	3,96± 0,37	4,15 ± 0,49	0,291
2. yıl Postoperatif	4,04 ± 0,43	4,35± 0,49	**0,036**

n: Hasta sayısı

PEF ve VBT gruplarında SRS22 skorlarının preoperatif, 6. ay ve 2. yıldaki ağrı, kendi imaj/görüşü, fonksiyon/aktivite, ruh sağlığı, tatmin ve ara toplam skorları ve karşılaştırmaları Tablo 2'de yer almaktadır. Preoperatif dönemde gruplar arasında ağrı, kendi imaj/görüşü, fonksiyon/aktivite, ruh sağlığı ve ara toplam skorlarında fark bulunmadı. PEF grubunda, fonksiyon/ aktivite alt başlığındaki skorların 6. ayda VBT grubundan anlamlı olarak düşük olduğu görüldü (3,96±0,68 – 4,51±0,57, p=0,027). Ağrı, fonksiyon/aktivite, ara-toplam alt başlıklarındaki skorların 2.yılda PEF grubunda istatiksel olarak anlamlı düşük olduğu saptandı (p 0,020, p 0,027, p 0,036). 6.aydaki ve 2.yıldaki diğer SRS22 skorlarının benzer olduğu belirlendi.

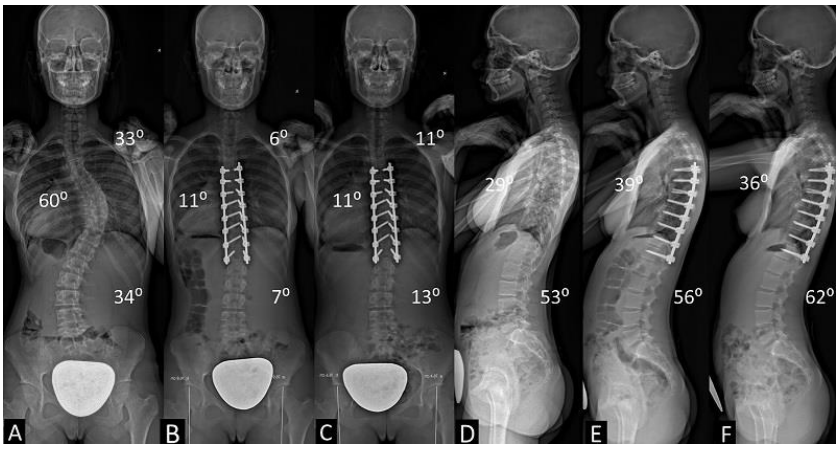
SRS22 skorlarının preoperatif dönemden postoperatif 6. ay ve 2.yıldaki değişimlerinin PEF ve VBT gruplarındaki ayrı ayrı karşılaştırmaları Tablo 3'te gösterilmektedir. Preoperatif döneme kıyasla 6. ayda PEF grubunda kendi imaj/görüşünde ($p<0,001$), VBT grubunda ağrı ve kendi imaj/görüşünde iyileşme olduğu belirlendi (sırasıyla; p=0,028, p=0,044). Preoperatif döneme göre 2. yılda PEF ve VBT gruplarında kendi imaj/görüşünde ve ara toplamda istatiksel olarak anlamlı iyileşme olduğu saptandı (sırasıyla; $p<0,001$, p=0,037 ve $p<0,001$, p=0,016).

Genel kohortta cerrahi süre ve kanama miktarı ile 6. ay ağrı skoru arasında orta-güçlü negatif korelasyon olduğu (r=-0,411, p=0,027 ve r=-0,687, p<0,001), 24. ay UT skolyoz açısı ile tatmin skoru arasında negatif zayıf korelasyon olduğu görüldü (r=-0,346, p=0,045). Takip ve toplam düzelme oranları ile SRS22 alt başlıklarındaki skorlar arasındaki ilişkiye bakıldığında; üst torasik, ana torasik ve torakolomber eğriliklerdeki takip düzelme miktarı ile 2. yıldaki tatmin skorları arasında orta-güçlü korelasyon olduğu görüldü (r=0,572, r=0,712, r=0,733, p<0,001).

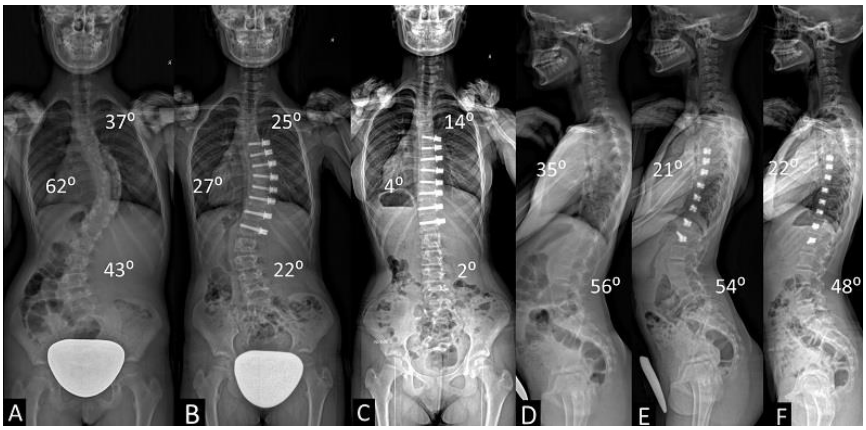
Tablo 3. Posterior enstrümentasyon ve füzyon (PEF) ile vertebra cisim gerdirme (VBT) ameliyat kohortlarında, preoperatif , postoperatif 6. ay ve postoperatif 24. Ayda Ağrı, Kendi İmajı/Görüşü, Fonksiyon/Aktivite, Ruh Sağlığı, Tatmin ve Ara-Toplam skorlarındaki değişimler ve karşılaştırmaları

	Preoperatif	**6.Ay**	**Pre-6**	**24.Ay**	**6-24**	**Pre-24**
SRS22 skorları			**P değeri**		**P değeri**	**P değeri**
PEF						
Ağrı	3,85 ± 0,76	4,2 ± 0,82	0,135	4,3 ± 0,47	0,711	0,054
Kendi İmaj/ Görüşü	3,13 ± 0,61	4,15 ± 0,39	**<0,001**	4,14 ± 0,56	0,961	**<0,001**
Fonksiyon/Aktivite	4,33 ± 0,73	3,96 ± 0,68	0,185	4,28 ± 0,55	0,196	0,829
Ruh Sağlığı	3,43± 0,50	3,55 ± 0,57	0,587	3,43± 0,68	0,651	0,950
Tatmin	-	4,54 ± 0,54	-	4,34 ± 0,94	0,522	-
Ara-Toplam	3,68 ± 0,47	3,96± 0,37	0,103	4,04 ± 0,43	0,652	**0,037**
VBT						
Ağrı	4,18 ± 0,67	4,62 ± 0,39	**0,028**	4,57± 0,62	0,798	0,081
Kendi İmaj/ Görüşü	3,38 ± 0,65	3,92 ± 0,84	**0,044**	4,24± 0,61	0,222	**<0,001**
Fonksiyon/Aktivite	4,53 ± 0,69	4,51 ± 0,57	0,943	4,66± 0,40	0,383	0,489
Ruh Sağlığı	3,61 ± 0,51	3,54 ± 0,55	0,701	3,87± 0,77	0,152	0,232
Tatmin	-	4,58 ± 0,69	-	4,8 ± 0,34	0,244	-
Ara-Toplam	3,93 ± 0,49	4,15 ± 0,49	0,194	4,35± 0,49	0,249	**0,016**

(Pre-6; Preoperatif – postoperatif 6.ay skorlardaki değişimlerin P değeri, 6-24; Postoperatif 6. ay – 24.ay skorlardaki değişimlerin P değeri, Pre-24; Preoperatif- postoperatif 24. ay skorlardaki değişimlerin P değeri)



Resim 1. Posterior enstrümentasyon ve füzyon uygulanmış adölesan idiopatik Skolyoz hastası.
(A-D: Preoperatif ön-arka ve yan grafi, B-E: 6. hafta ön-arka ve yan grafi, C-F: 2. yıl ön-arka ve yan grafi)



Resim 2: Vertebra cisim gerdirme uygulanmış adölesan idiopatik skolyoz hastası (A-D: Preoperatif ön-arka ve yan grafi, B-E: 6. hafta ön-arka ve yan grafi, C-F: 2. yıl ön-arka ve yan grafi)

Tartışma

Mevcut çalışma, adölesan idiopatik skolyozda, selektif olarak torakal bölgeye uygulanmış posterior enstrümetasyon ve füzyon cerrahisi ve vertebra cisim gerdirme cerrahisinin erken dönem sonuçlarını ve sağlıkla ilişkili yaşam kalitesi üzerindeki etkilerini klinik olarak araştıran ilk çalışmadır. Torakal eğriliğin benzer olduğu kohortlarda, SRS22'nin idiopatik skolyozdaki sağlıkla ilişkili yaşam kalitesini anlama kabiliyetine dayanarak, preoperatif, erken postoperatif ve takip radyografik ve SRS22 skorlarının incelendiği çalışmada, 2. yılda ağrı, fonksiyon/aktivite ve ara-toplam skorlarının VBT grubunda daha iyi olduğu belirlendi. Cerrahi yapılan eğrilikteki değişim ile 2. yıldaki tatmin skorları arasında güçlü ilişki olduğu görüldü.

Adölesan idiopatik skolyozda tedavinin temelini periyodik gözlem, skolyoza özgü egzersizler ve korse uygulaması oluşturmaktadır. Ameliyat gerektiren daha az sayıdaki hastalar için, posterior enstrümentasyon ve füzyon standart tedavi yöntemi olmuştur ve hala öyledir.[3] Uzun vadeli iyi sonuçlarla etkinliği kanıtlanmış olsa dahi uygulandığı segmentlerde büyüme ve hareket kalıcı olarak durdurulmakta ve bu da bitişik segmentlerde yük dağılımını değiştirmektedir.[21] Ayrıca AIS, psikososyal işlev ve beden imajı dahil olmak üzere sağlıkla ilgili yaşam kalitesinde kötüleşmeye neden olur.[22] Bu nedenle cerrahi tedavinin birincil hedeflerinden biri, zaman içinde yaşam kalitesinde bozulmasını azaltmaktır. Standart yaklaşım olan füzyon cerrahisi takibinde, normal popülasyona kıyasla, erken dönemde, SRS22 skorlarının benzer olduğu ama 10 yıl ve üzeri takiplerde SRS22 skorlarının düşme eğiliminde olduğu, özellikle diğer alt başlıklara kıyasla hastaların kendi imajı/görüşü'nde ciddi kötüleşme olduğu bildirilmektedir.[23]

Cerrahi tedavide alternatif olarak vertebra cisim gerdirme yöntemi, devam eden spinal ve göğüs kafesi büyümesine müsaade ederken, daha fizyolojik şekilde eğrilikte stabilizasyon ve fonksiyonel hareketin korunmasını sunan ilk umut verici füzyonsuz cerrahi teknik olarak ortaya çıkmıştır.[7-11] Cerrahi düzeltmeyi takiben kalan büyüme potansiyeli kullanılarak takip düzeltmesi elde edilen VBT'de başarı, cerrahi düzeltme

miktarının iyi belirlenmesi, kalan büyüme potansiyelinin iyi hesaplanması gibi faktörlere bağlıdır.[7] VBT cerrahisi ile sağlıkla ilişkili yaşam kalite anketlerinin sonuçlarında iyileşme olduğu daha önce gösterilmiştir; Wong ve ark. 3 yıl takipte preoperatif döneme göre SRS22 skorlarında iyileşme olduğunu bildirirken, Pehlivanoglu ve ark. VBT cerrahisi takibinde, eşleşmiş PEF grubuna kıyasla istatiksel olarak anlamlı yüksek SRS22 skorları olduğunu belirtmektedirler.[11,19] Ancak araştırılan iki kohorttaki cerrahi yaklaşımların homojen olmaması, sonuçları değerlendirmede zayıflık oluşturmaktadır. Çalışmamızda preoperatif döneme kıyasla 6. ayda ve 2. yılda kendi imaj/görüş skorlarında ve 2. yılda ara-toplam skorlarında anlamlı iyileşme olduğu iki kohort içerisinde de benzer şekilde görülmektedir. Ek olarak VBT grubunda 6. ayda ağrı skorunda belirgin anlamlı bir iyileşme saptanmıştır.

Doktorlar için eğriliğin progresyon göstererek oluşturacağı tıbbi sorunları çözmek birincil amaç iken hastalar için en önemli beklentinin estetik kaygıların ortadan kaldırılması ve hayat kalitesinin düzelmesi olduğu bilinmektedir.[24] Füzyon cerrahisi sonrasında yaşam kalitesinde görülen azalmanın, cerrahi sonrasında fiziksel aktivitelere katılmadaki azalma ve sosyal aktivitelerdeki kısıtlanma nedeniyle olduğu gösterilmiştir.[25] Lomber bölgede hareketli segmentlerin korunması ile eklem hareket açıklığının korunduğu ve füzyonun L2 üzerinde sonlanması ile artmış hasta memnuniyeti bildirilmiştir.[26] Selektif torasik füzyonun, hastaların günlük aktivitelerini gerçekleştirme yeteneklerini geliştirerek yaşam kalitesini olumlu yönde etkileyebileceği ve eğriliklerdeki iyileşmenin yanı sıra, yaşam kalitelerinin yıllar sonra normal popülasyona benzer olduğu gösterilmiştir.[27,28] Ohashi ve ark. tarafından selektif torasik füzyona rağmen global spinal hareket açıklığında önemli bir azalma bildirilmiştir ama Hamzaoglu ve ark. selektif füzyon yapılan hastalarda 15 yıl takipte sağlıkla ilgili yaşam kalitesi sonuçlarının, yaş-cinsiyet-vücut kitle indeksi eşleşmiş kontrol grubu ile benzer olduğunu bildirmişlerdir.[15,29] Bu sebeple mevcut çalışmada sadece torakal bölge cerrahisi uygulanmış ana torasik eğriliği olan AIS hastaları değerlendirilerek, cerrahinin yarattığı fonksiyon kısıtlılığından bağımsız, uygulanan cerrahi yöntemin yaşam kalitesi üzerindeki erken ve geç dönem etkisi de incelenmiştir.

Çalışmada hem posterior enstrümentasyon ve füzyon hem de vertebra cisim gerdirme cerrahileri sonrasında hastaların kendi imaj/görüşleri ve ara-toplam skorlarında benzer şekilde iyileşme olduğu görüldü. Preoperatif istatiksel olarak benzer SRS22 skorları olan gruplarda, PEF cerrahisi takibinde hastaların daha uzun cerrahi süre ve kanama miktarına sahip olmalarına rağmen 6. ay SRS22 skorları, fonksiyon/aktivite haricinde VBT grubuna benzer olduğu ama VBT grubunda fonksiyon/aktivite skorlarının hem erken dönem hem de takipte PEF grubundan anlamlı olarak daha iyi olduğu saptandı. İstatiksel olarak anlamlı olmamakla beraber cerrahi düzelme miktarının %84 olduğu PEF grubunda 6. ay kendi imajı/ görüşünün, cerrahi düzelmenin %53 olduğu VBT grubuna göre daha iyi olduğu ancak takipte iki grupta benzer toplam düzelme gerçekleştikten sonra (%80–%76), 2. yılda kendi imajı/görüşü skorlarının benzer (VBT grubunda daha iyi) olduğu belirlendi. Aynı zamanda kanama miktarı-cerrahi süre arttıkça 6. ay ağrı skorlarında kötüleşme olduğu görüldü.

PEF grubundan farklı olarak iyileşmenin dinamik olarak devam ettiği VBT'de radyografik ve klinik sonuçlar kadar yaşam kalite anket sonuçları da süreçten dinamik olarak etkilenmektedir. Dinamik süreç, kendi imaj/ görüşü gibi SRS22 skorlarındaki değişimin, cerrahi düzelme miktarı az ama takip düzelme miktarı fazla olan VBT grubundaki giderek iyileşen skorlarından anlaşılabilir. Bu nedenle büyüme yönlendirme yöntemi olan VBT'de yaşam kalitesinin anlaşılabilmesi için büyüme modülasyonu süreci boyunca, daha uzun dönem takip gerekmektedir.

Çalışmamızda bazı kısıtlılıklar bulunmaktadır. Eğriliğin boyutu ve tipleri üzerinden benzer hasta grupları ve eşleşmiş kohortlar elde edilmiş olsa da hasta kohortları arasında, PEF grubunun VBT grubuna kıyasla hem kronolojik hem de iskelet olgunluk belirteçleri açısından daha matür olması ciddi kısıtlılık yaratmaktadır. Bu durum, endikasyonlar nedeniyle füzyonun teknik olarak iskelet matüritesinin ilerisinde olan çocuklarda gerçekleştirilirken, VBT'nin daha immatür çocuklarda büyüme yönlendirme amacıyla uygulanması nedeniyle görülmektedir. Ancak VBT'nin uygulandığı, erken yaş döneminde, PEF cerrahisinin uygulanmasının komplikasyon riskini arttırdığı, bu nedenle uygulanmadığı ve korse gibi geciktirme taktikleri uygulandığı göz önüne alındığında, iki cerrahi grup için benzer yaş dağılımına sahip kohortlar elde etmenin oldukça zor olduğu bilinmektedir.[30] Diğer bir kısıtlılık ise iki grup içerisindeki hastaların takip protokolleri, skolyoz spesifik egzersiz- korse gibi postoperatif destekleyici tedavilerinin yaşam kalitesi üzerine etkilerinin bilinmiyor olmasıdır. Bu konuda daha geniş hasta kohortlarında, preoperatif ve postoperatif takip protokolleri eşleşmiş çalışma kohortlarında ileri araştırmaya ihtiyaç bulunmaktadır.

Sonuç olarak eğriliğin benzer olduğu adölesan idiopatik skolyoz hastalarında 2. yılda hem ameliyat edilen torakal hem de ameliyat edilmeyen lomber eğriliklerde, posterior enstrümentasyon ve füzyon ile vertebra cisim gerdirme cerrahisinde benzer oranda düzelme görülmektedir. Sağlıkla ilgili yaşam kalitesinde, iki cerrahi yöntem ile, 2. yılda benzer şekilde düzelme elde edilirken, VBT de bu süreç dinamik olarak seyretmektedir. İki grup arasında fonksiyon/aktivite alt skorları VBT grubunda hem erken dönem hem takipte füzyona kıyasla daha iyi olmakla beraber, bu konuda daha geniş hasta kohortlarında, daha uzun takip serilerinde çalışma yapılması gerekmektedir.

Etik onay

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Çıkar Çatışması

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Research Article

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CT-SEVERITY ANALYSIS OF COVID-19 PNEUMONIA IN RHEUMATIC MUSCULOSKELETAL DISEASES

ROMATİZMAL KAS-İSKELET SİSTEMİ HASTALIKLARINDA COVID-19 PNÖMONİSİNİN BT-ŞİDDET ANALİZİ

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Öz

Amaç: Bu çalışma, kas-iskelet sistemi tutulumlu romatizmal hastalıkları (RH) olan hastalarda covid-19 pnömonisinin radyolojik şiddetini vurgulamayı amaçlamaktadır.

Materyal ve Metot: Toplam 342 Polimeraz Zincir Reaksiyonu (PCR) pozitif hasta geriye dönük olarak incelendi. Hastalar RH varlığı açısından iki gruba ayrıldı. Akciğer bilgisayarlı tomografi (BT) şiddet skorları, demografik özellikler, hastaneye yatış, yoğun bakım ünitesi (YBÜ) gereksinimi, hastanede kalış süresi RH ve RH olmayan grup arasında karşılaştırıldı. BT görüntülerinde tipik ve atipik bulgular, her iki hasta grubundaki görülme sıklıkları ile birlikte tanımlandı.

Bulgular: Yaş ve kadın cinsiyet, RH grubunda RH olmayan gruba göre anlamlı olarak daha yüksekti (p=0,001, p=0,041). BT-şiddet skorunun ortalaması RH grubunda RH olmayan gruba göre daha yüksekti, ancak fark istatistiksel olarak anlamlı değildi (p=0,081). YBÜ'ye nakil ve ölüm oranları RH grubunda RH olmayan gruba göre daha yüksek bulunurken, hastanede yatış oranları ve kalış süreleri arasında fark saptanmadı (p=0,002, p=0,036, p=0,280, p=0,168). Her iki grupta da buzlu cam opasiteleri, üst üste bindirilmiş konsolidasyon ve kaldırım desenleri en yaygın tipik bulgulardı. Covid-19 pnömonisi için atipik BT bulguları, RH grubunda RH olmayan gruba göre daha yüksek bulundu.

Sonuç: Kronik inflamasyon ve immünosupresif ilaçların kullanımı RH hastalarında enfeksiyonlara karşı hassasiyete neden olmaktadır. Bu çalışmada, RH'li hastalarda mortalite ve YBÜ gereksinimlerinin daha yüksek olduğu bulundu. Benzer şekilde, RH grubunda atipik akciğer BT bulgularının daha yaygın görülmesi, bu hasta grubunda covid-19 pnömonisinin tanı ve ayırıcı tanısında özellikle önemli olabilir.

Anahtar Kelimeler: Pnömoni, tomografi, koronavirus, romatizmal hastalıklar.

Abstract

Objectives: This study aims to focus on the radiological severity of covid-19 pneumonia in patients with rheumatic musculoskeletal diseases (RMD).

Materials and Methods: A total of 342 Polymerase Chain Reaction positive patients were retrospectively reviewed. The patients were divided into two groups in terms of the presence of RMD. Chest Computed Tomography (CT) severity scores, demographic characteristics, hospitalization, intensive care unit (ICU) requirement, length of stay at the hospital were compared between RMD and non-RMD groups. Typical and atypical findings on CT images were identified with their incidence in both groups of patients.

Results: Age and female gender were significantly higher in the RMD group (p=0.001, p=0.041). The average CT-severity score was higher in the RMD group, but the difference was not statistically significant (p=0.081). ICU transfer and mortality rates were higher in the RMD, whereas no difference was found in hospitalization rates and length of stay (p=0.002, p=0.036, p=0.280, p=0.168). Ground glass opacities, superimposed consolidation, and crazy paving patterns were the most common typical findings seen on both groups. Atypical CT findings for covid-19 pneumonia were found to be higher in the RMD group than in the non-RMD group.

Conclusion: Chronic inflammation and the use of immunosuppressive drugs constitute a vulnerability to infections in RMD patients. In this study, mortality and ICU requirements were found to be higher in patients with RMD. Similarly, the higher rate of atypical chest CT findings in the RMD group may be of particular importance in the diagnosis and differential diagnosis of covid-19 pneumonia in this patient group.

Keywords: Pneumonia, tomography, coronavirus, rheumatic diseases.

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Introduction

Since 2019 December, several cases of covid-19 have been reported in Wuhan, China, then spread worldwide within a few months and became a global public health emergency.[1] Although the most common symptoms of covid-19 infection are fever, cough, dyspnea, and myalgia/fatigue, headache, hemoptysis, sputum production, diarrhea, hemoptysis, chest pain, vomiting, sore throat can also present. Similar to the symptom diversity, clinical severity and prognosis vary from asymptomatic disease to acute respiratory distress syndrome and multiple organ dysfunction.[2] Due to the wide range of presentation and prognosis of the disease, determining the co-morbid diseases' effect on the severity of the covid-19 infection has become one of the most important aims of the studies. In this context, the prevalence of rheumatic diseases who are receiving immunosuppressive medication and determining the radiological severity of pulmonary involvement for covid-19 patients with rheumatic musculoskeletal diseases (RMD) should be clarified. Although there have been several reports concerning the prevalence and clinical severity of RMD among covid-19 patients; the severity and radiological involvement patterns and Chest Computed Tomography (CT) scoring of covid-19 infected patients with RMD have not been clarified yet.[3-5]

Endogenous and exogenous risk factors may exist for the increased infection risk in RMD. The clinicians may consider the patients with RMD might be more prone to covid-19 infection and more severe disease than the general population because of the immune system dysregulation, accompanying co-morbidities, use of immunosuppressive medications, apart from the well-known poor prognostic factors.[3,4] However, some of the anti-rheumatic drugs seemed to be promising on treatment for covid-19 pneumonia (chloroquine, hydroxychloroquine) and the management of the cytokine storm and ARDS at the time of the study (IL-6 inhibitors)[6,7]

Our aim in this study is - beyond determining the prevalence of covid-19 infection in patients with RMD - to compare the clinical course and severity of chest CT scoring and pulmonary involvement patterns in patients with confirmed covid-19 pneumonia between with and without the RMD. We hypothesized that the CT severity scores are higher and intensive care unit (ICU), hospitalization requirements are higher in RMD patients than non-RMD covid-19patients.

Materials and Methods

Patient Selection

In this retrospective study, patients who were diagnosed with covid-19 at our hospital in a five months period between March-July 2020 were reviewed. Real-time reverse transcription-polymerase chain reaction (RT-

PCR) tests for nasopharyngeal/oropharyngeal swabs specimens were used for the diagnosis of covid-19. Medical histories, demographic characteristics, the requirement of hospitalization or not (if yes, length of stay), medication, and the severity of radiological involvement were recorded. Patients were divided into two categories according to the presence of a history of rheumatic musculoskeletal diseases (RMD/non-RMD). Outpatients and the one(s) that did not require antiviral therapy were classified as mild, hospitalized patients as moderate, and those in need of an intensive care unit as severe disease.

Radiological Evaluation

Radiological assessment of patients included unenhanced Chest CT imaging with covid-dedicated scanning protocols in two scanners (128-MDCT Siemens Somatom Definition; 16-MDCT Toshiba Alexion): supine, end-inspiration acquisition; slice thickness, 1.0-1.5 mm; tube voltage, 120 kV; tube current, 200-300mAs; multiplanar reconstructions with mediastinal and lung parenchymal windows settings. All images were evaluated by one European board-certified radiologist with five years of experience and one radiologist with 29 years of experience separately. Radiologists were blinded to clinical data, and discrepancies were resolved with consensus. Multifocal ground-glass opacities (GGO), consolidation, GGO with superimposed consolidation, consolidation predominant pattern, crazy paving pattern, and melted sugar sign were considered as typical; pleural and/or pericardial effusion, cavity, pulmonary nodule, nodular pattern, lymphadenopathy, peribronchovascular distribution, halo and/or reverse halo sign, three-in-bud sign, bronchiectasis, airway secretions, pulmonary emphysema, pulmonary fibrosis, isolated pleural thickening, and pneumothorax were considered as atypical findings for covid pneumonia.[8] Patients were categorized as “normal”, “typical for covid”, “atypical for covid” and “not covid”. A scoring system for typical and atypical categories similar to the Xie et al. was used; each lung was divided into three zones bordered by the levels of the carina and the inferior pulmonary veins.[9] Each zone was scored according to the involvement ratios; 0 for 0% involvement, 1 for <25% involvement, 2 for 25-49% involvement, 3 for 50-74% involvement, and 4 for ≥%75 involvement. A total score between 0 and 24 was obtained per patient. Radiological severity scores were then sub-grouped into mild (1-8), moderate (9-16), and high severity (17-24) classes.[9] These classes were considered as radiological severity of covid-pneumonia, hence correlated with the presence of rheumatic disease, the use of immunosuppressive medication, and clinical severity of the disease. Severity scores were not calculated for “normal” and “not covid” categories; hence they were not correlated with clinical features.

Statistical Analysis

Data analysis was performed by using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY). Continuous variables were expressed as mean ±SD. Student t-test was used for demographic and

continuous variables. Categorical variables were presented as the number and percentage. Categorical variables were

Results

In our cohort, a total of 342 patients were found to have the diagnosis of covid-19 within the timeframe of this study. The patients were aged between 47 and 83 years. Of the 342 PCR confirmed covid-19 patients, 164 (47.95%) were men and 178 (52.04%) were women. RMD represents 2.63% (n=9) of all the confirmed covid-19 patients admitted to our hospital within the timeframe of this study. Five female and one male patient had a history of Rheumatoid Arthritis (RA); 1 female patient had a history of RA+SjS (Sjögren Syndrome); 2 female patients had a diagnosis of gout. Hypertension was the most prevalent concomitant disease (4 out of 9). In order of frequency, hypertension, diabetes mellitus, and congestive heart failure were the most common concomitant co-morbidities. Four patients had stopped their anti-rheumatic medication several years ago, while the other five patients were already receiving their medications. Three patients were receiving conventional synthetic (cs-), whereas no patient was priorly receiving biological (b-) disease-modifying anti-rheumatic drugs (DMARDs). Demographic data, medical histories, RMD types, previous medications, and co-morbid diseases of the patients are summarized in Table 1.

Covid-19 manifestations, hospitalization/ICU requirements, length of hospital stay, radiological-clinical severity, medications they received during this period, and the outcome are summarized in Table 2. Methylprednisolone 4 mg was continued to be administered in case-3 and case-9. All of the patients temporarily withdrew DMARD medication during the entire hospitalization. Eight of the nine patients with RMD (7 with CT-confirmed covid-19 pneumonia and 1 with a normal chest CT scan) required hospitalization (88.90%), and five of them had transferred to ICU due to severe respiratory complications (55.60%). Three of the patients in ICU have died; case-1 had CHF, and chest CT findings were compatible with mild pulmonary involvement, whereas the latter two cases (cases-5 and 6) were of severe and moderate involvement, respectively. Five patients were discharged from the hospital, and none of them required re-hospitalization.

The RMD patients were significantly older and the female gender was significantly higher than non-RMD patients. Although there was no significant difference in hospitalization and length of stay at the hospital; the mean length of stay and hospitalization frequencies were higher in the RMD group than the non-RMD group. ICU requirement and mortality were significantly higher in the RMD group (p=0.002 and 0.036, respectively). The comparison of variables between groups was summarized in Table 3.

Radiological evaluation of the novel-coronavirus disease was performed based on the Chest CT findings. Sixty patients who did not obtain chest CT at hospital admission were not included in the analysis. A total of 402 CT

scans belonging to the remaining 282 patients were retrospectively evaluated (Figure 1). All patients with RMD had chest CT. Seven of them had typical; 2 of them had atypical covid-19 pneumonia findings at chest CT. Chest CT severity scores were calculated for a total of 7 RMD and 166 non-RMD patients within "typical for covid" and "atypical for covid" groups. Although the mean chest CT severity score of RMD patients was found to be higher than non-RMD patients, the difference did not reach the statistical significance level (p=0.081). Amongst the severity score calculated for seven RMD patients, radiological and clinical severity correlate only in two patients (2/7, 28.6%).

Typical and atypical CT features for covid-19 pneumonia were evaluated separately in both groups of patients. Multifocal GGOs and crazy paving patterns are the most common typical findings seen in more than half of the patients in both RMD and non-RMD groups (figure 2). On the other side, atypical CT features for covid are found to be seen more commonly in rheumatic patients; eight of the nine RMD cases compared to only 102 of the 273 non-RMD patients have at least one atypical feature. Peribronchovascular distribution of GGOs, pulmonary nodule, and isolated pleural thickening are the most common atypical CT features in both groups (figure 3). The distribution of CT results and features among RMD and non-RMD patients were summarized in Table 4.

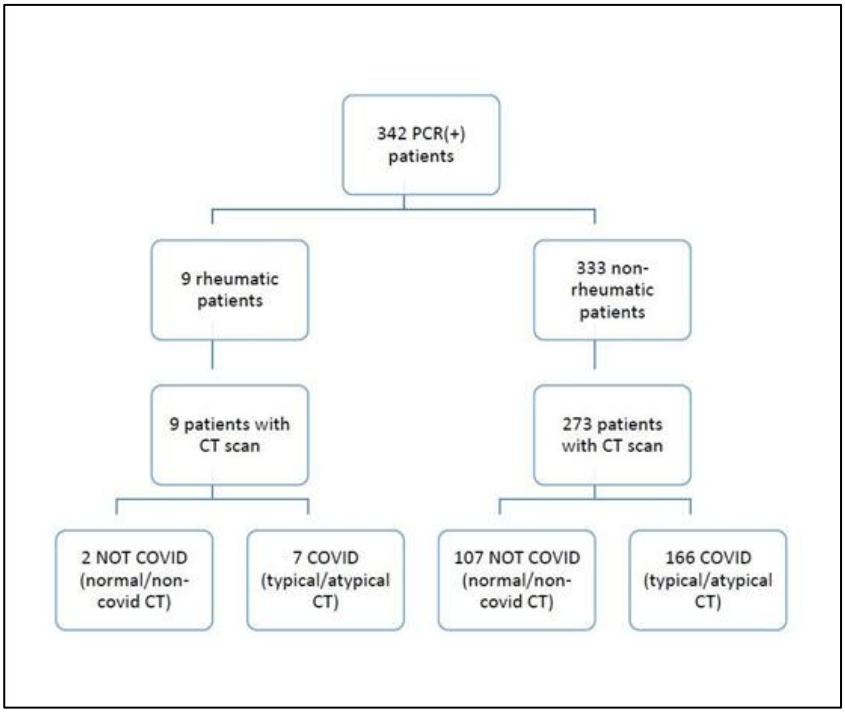
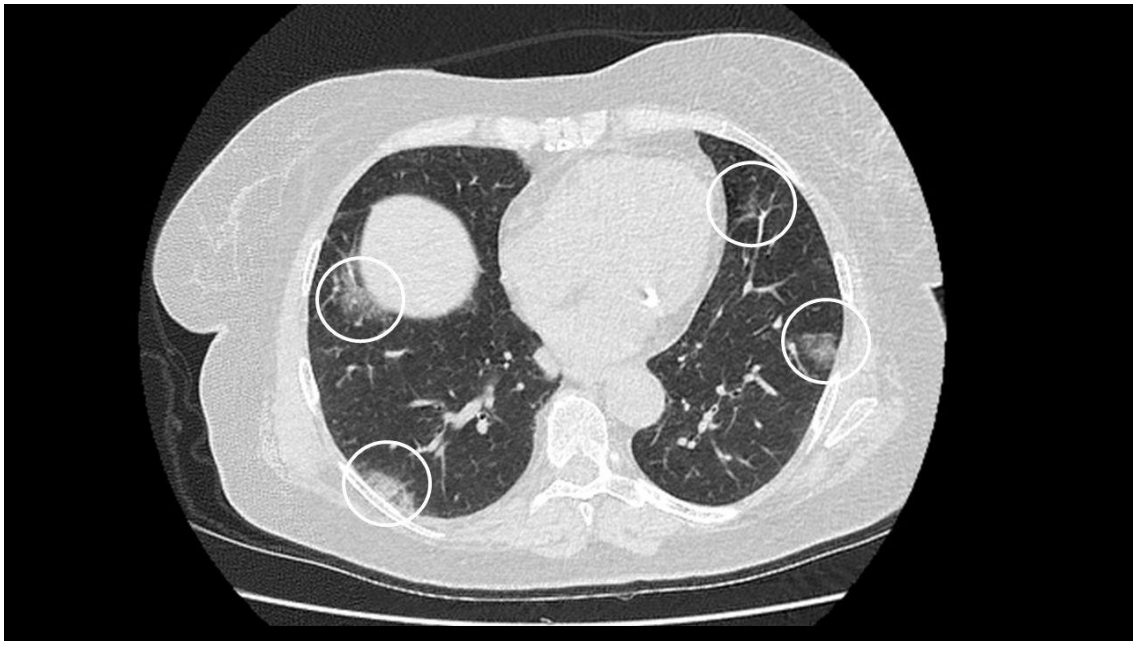
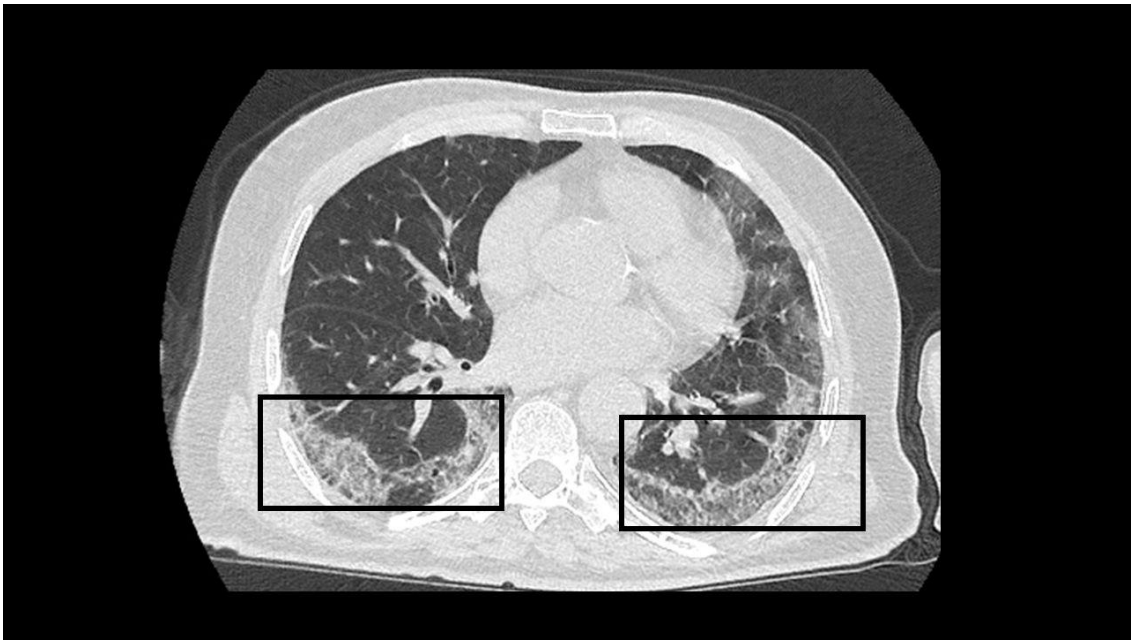


Figure 1. Study flow-chart



2a



2b

Figure 2. Typical CT findings for covid-19 pneumonia. Multifocal ground-glass opacities (circles) are demonstrated in a 68-years old female RMD patient (2a). A crazy paving pattern (rectangles) formed by ground-glass opacities with superimposed interlobular septal thickening and intralobular septal thickening is shown in a 73-years old male non-RMD patient (2b).

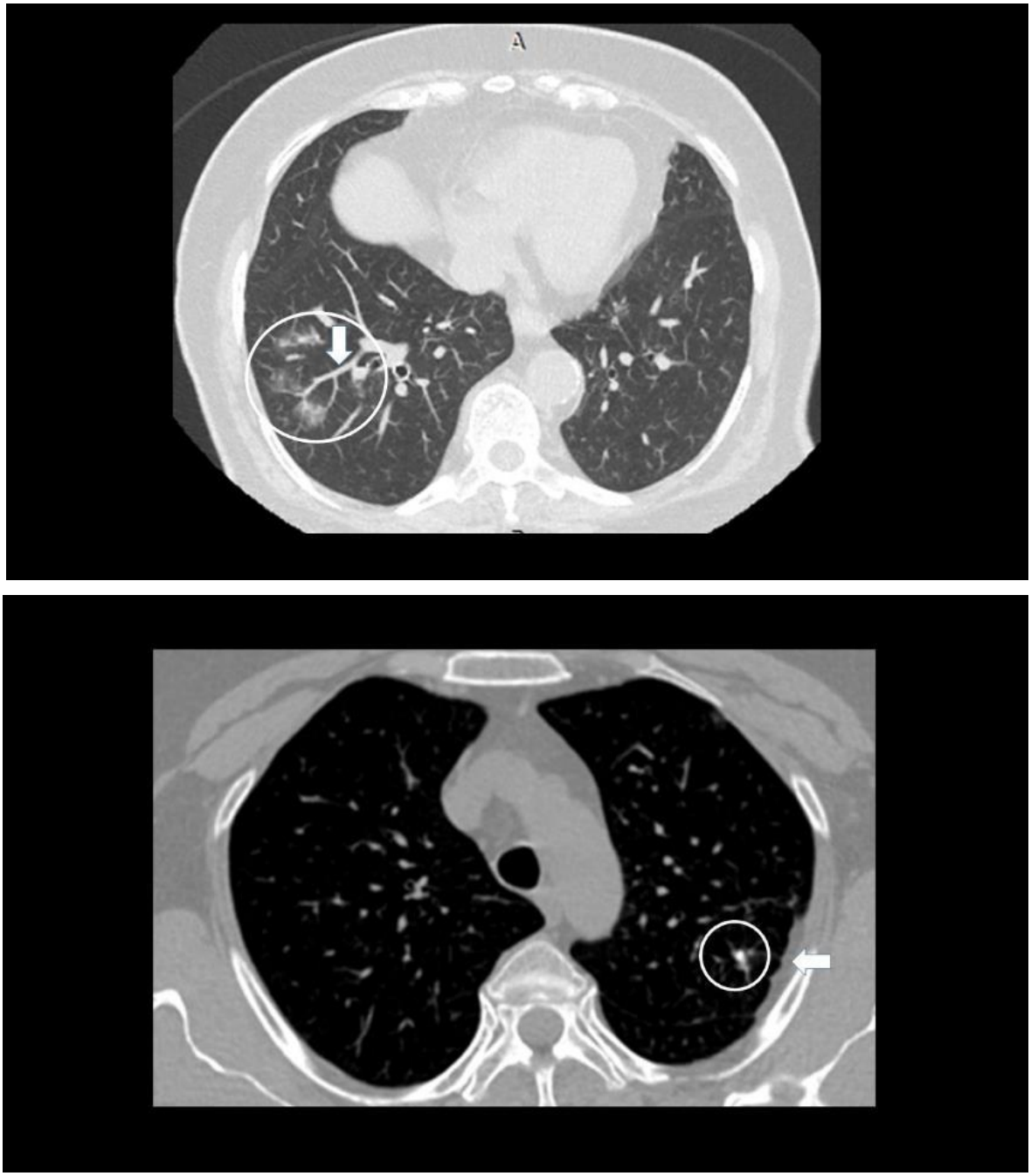


Figure 3. Atypical CT findings for covid-19 pneumonia. Peribronchovascular distribution of ground-glass opacities (circles) and vascular enlargement (thick arrow) is demonstrated in an 83-years old female RMD patient (3a). Isolated pleural thickening (thick arrow) and pulmonary nodule (circle) are shown in a 62-years old female non-RMD patient (3b).

Table 1. Demographic Data and Medical History of Patients with Rheumatic Musculoskeletal Diseases

Cases	Age	Gender	Rheumatic disease	Course of Rheumatic disease	Co-morbid diseases	Rheumatic medicine	Additional medicine
1	79	F	RA	8 years	CHF, AF	None	Rivaroxaban Metoprolol Furosemide
2	83	F	Gout	8 years	CAD, CHF	None	Ranolazine Acetylsalicylic acid Furosemide Atorvastatin
3	62	F	RA	2 years	HT, DM	Leflunomide 10mg/d Methylprednisolone 4mg/d	Gliclazide Perindopril Vildagliptine
4	77	F	RA	6 years	HT, CAD	None	Olmesartan Metoprolol Clopidogrel
5	66	F	RA	>8 years	-	HCQ 2x200 mg Prednisolone 5 mg/d Azathioprine 150 mg/d	-
6	64	F	Gout	3 months	HT, DM, CAD	Colchicum Dyspert 1g/d	Rosuvastatin Nebivolol Clopidogrel Sitagliptin Metformin Insulin aspart Losartan potassium+ Hydrochlorothiazide
7	47	F	RA, SjS	3 years	-	None	-
8	67	M	RA	>8 years	-	Methylprednisolone 4 mg/d	-
9	68	F	RA	>8years	HT	Methylprednisolon 4 mg/d Methotrexate 15 mg/week	Perindopril/indapamide

(F: Female, M: Male, RA: Rheumatoid Arthritis, SjS: Sjögren's Syndrome, CHF: Congestive heart failure, AF: Atrial fibrillation, CAD: Coronary artery disease, DM: Diabetes Mellitus, HT: Hypertension)

Table 2. Clinical Characteristics of Patients with Rheumatic Musculoskeletal Diseases During Covid-19 Infection

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Covid-19 manifestations	Dyspnea, Fever	Asymptomatic	Fever	Diarrhea	Dyspnea	Fever, Diarrhea	Fever, anosmia	Fever	Asymptomatic
RT-PCR	+	+	+	+	+	+	+	+	+
Clinical S.	Severe	Severe	Moderate	Mild	Severe	Severe	Mild	Severe	Moderate
Radiological S.	5 (mild)	N/A	7 (mild)	6 (mild)	19 (severe)	12 (moderate)	N/A	16 (moderate)	5 (mild)
Medication (during covid-19)	HCQ, Oseltamivir, Favipravir, Moxifloxacine, Meropenem, Piperaciline-Tazobactam	HCQ, Oseltamivir, Moxifloxacine, Piperaciline, Ceftriaxone	HCQ, Oseltamivir, Moxifloxacin, Piperaciline, Ceftriaxone, Prednisolone	HCQ	HCQ, Oseltamivir, Moxifloxacine, Piperaciline-Tazobactam, Meropenem, Azitromycine, Ritonavir LMWH	HCQ, Oseltamivir, Moxifloxacine, Piperaciline, Meropenem, Favipravir, Ritonavir	HCQ, Oseltamivir	HCQ Piperaciline-Tazobactam Favipravir, LMWH Moxifloxacine	HCQ, Oseltamivir, Moxifloxacin, Prednisolone
Hospitalization	YES	YES	YES	YES	YES	YES	NO	YES	YES
Length of Stay	30 d	33 d	13 d	2 d	9 d	6 d	-	9 d	4 d
ICU Admission	YES	YES	NO	NO	YES	YES	NO	YES	NO
Outcome	Deceased	Recovery	Recovery	Recovery	Deceased	Deceased	Recovery	Recovery	Recovery

(Clinical/Radiological S.: severity, RT-PCR: Reverse transcription-polymerase chain reaction, HCQ: Hydroxychloroquine, LMWH: Low molecular weight heparin, ICU: Intensive care unit, d: days)

Table 3. Comparison of Radiological and Clinical Severity Between Patients with and without Rheumatic Musculoskeletal Diseases

	RMD (n=9)	**Non-RMD (n=273)**	**p value**
Age*(mean ±SD)*	68.32 ± 10.31	47.74 ± 19.22	**0.001***
Male/Female *(n)*	1/8	129/144	**0.041****
Mean Severity Score (MSS) *(mean ±SD)****	10 ± 5,71	6.25 ± 4,01	0.081*
Hospitalization *(n, %)*	8 (88.89%)	184 (67.40%)	0.280**
ICU *(n, %)*	5 (55.56%)	30 (10.99%)	**0.002****
Mean Total LOS (days) *(mean ±SD)******	13.20±11.23	8.17±8.02	0.168*
Exitus *(n, %)*	3 (33.33%)	22 (8.06%)	**0.036****

(RMD: Rheumatic musculoskeletal diseases, LOS: Length of Stay, ICU: Intensive care unit)
* Student t-test,
** Chi-square test
*** Severity scores were only calculated in "typical for covid" and "atypical for covid" groups (RMD=7, non-RMD=166)
**** Length of Stay (days) was calculated for hospitalized patients (RMD=8; non-RMD=184)

Table 4. Covid-19 Related Chest CT Features of Patients with and without Rheumatic Musculoskeletal Diseases

		RMD (n=9)	**Non-RMD (n=273)**
CT Findings	Normal	1 (11.11%)	94 (34.43%)
	Typical for covid	6 (66.67%)	142 (52,02%)
	Atypical for covid	1 (11.11%)	24 (8.79%)
	Not covid	1 (11.11%)	13 (4.76%)
Typical CT Features for Covid-19	Multifocal GGOs	7 (77.78%)	127 (46.52%)
	Crazy paving pattern	5 (55.56%)	82 (30,04%)
	GGO superimposed with consolidation	4 (44.44%)	79 (28.94%)
Atypical CT Features for Covid-19	Peribronchovascular distribution of GGOs	5 (55.56%)	54 (19.78%)
	Pulmonary nodule	4 (44.44%)	49 (17,95%)
	Isolated pleural thickening	4 (44.44%)	75 (27.47%)

(RMD: Rheumatic musculoskeletal diseases, GGO: Ground glass opacity)

Discussion

In the relevant study, we aimed to evaluate the pulmonary involvement patterns on chest CT in patients with covid-19 infection concomitant with RMD. Secondly, we purposed to compare the chest CT scores, hospitalization, ICU requirement, and mortality of RMD and non-RMD covid-19 patient groups. We reported nine patients with RMD; 7 RA, and two gout arthritis. Of the nine patients with RMD, only one of them was male, whereas the male and female distribution was nearly equal in the whole study population, similar to prevalence reports of previous studies.[10] Hospitalization and chest CT severity scores did not differ among RMD/non-RMD groups, while ICU transfer and mortality rates were higher for patients with RMD than the non-RMD group. Pulmonary involvement patterns on chest CT examination were different between RMD and non-RMD groups regarding atypical CT features for covid-19 pneumonia that is more common in the former one. On the other hand, multifocal GGOs, crazy paving patterns, and GGOs with superimposed consolidation are commonly seen as typical features that are equally seen in both groups.

RA and most of the RMD are known to be associated with the increased risk of respiratory infection and its complications, including viral diseases such as influenza and herpes zoster virus.[11-13] The increased risk of infections is related to disease activity, disease damage, co-morbidity, and treatment.[13-15] On the other hand, there has been no evidence that the risk of respiratory or life-threatening complications from covid-19 is increased in patients with RMD.[16,17] Reports indicate that the prevalence of covid-19 infection is similar to the general population in patient groups with RMD.[18,19] Similar to the previous reports, RA was found to be the most common RMD in our study group.[17] We have found its prevalence was 2.63% among patients with covid-19 infection, which is higher than the estimated prevalence of RA in our country (0.56%) but similar to the RMD prevalence reported by D'Silvia.[20,21]The overestimated the prevalence of the patients with RMD within the covid-19 infected patient group might support the possible facilitative effect of rheumatic diseases regarding covid-19 infection. Similarly, the significantly higher age in RMD patients than the non-RMD group may be related to the higher ICU requirement and the increase in mortality, but the number of patients is insufficient for these comments.

Results regarding the severity and course of covid-19 in people with RMD differ due to the genetic background of study populations, methodology, applied treatments, co-morbidities, disease activities, and undoubtedly the progress of the pandemic. Fredi et al. had compared covid-19 infected patients with RMD with age, gender-matched patients without RMD (n=117) and found no difference regarding the disease symptoms, length of stay in the hospital. The authors reported that poor clinical outcome is related to age and the co-morbidities rather than the presence of RMD.[17] Similar to our results, D' Silva et al have reported a higher percentage of ICU requirement in their study population.[21] Although it's not statistically significant, the rate of hospitalization in the RMD group is higher than the non-RMD group (88.8%-67.4%, respectively; p=0.280) in our study. Cheng

et al. reported one of the first reports about RMD cases with covid-19 which were all hospitalized.[3] Moreover, as a result of the dynamic pandemic process, the hospitalization criteria have been updated along with the spread of the disease and the health care policies. In our study, the mortality rate was found to be ~1/3, which is higher than the previous reports.[21,22] By all odds, it is not possible to isolate RMD from age and other co-morbid diseases with our sample size. Further studies with large cohorts should be required to assess the independent risk and severity of covid-19 infection for RMD.

Covid-19 infection possesses an exaggerated immune system response and cytokine storm resulting in a series of severe respiratory and life-threatening complications. Hence, it is not surprising that the patients receiving b-DMARDs or cs-DMARDs are not at higher risk than the overall general population.[16] Nevertheless, a recent meta-analysis has shown that patients on b-DMARD treatment have a higher risk of infection than those on cs-DMARD.[23] In our case series, three patients were receiving cs-DMARDs and none with b-DMARDs. The severity of the disease was severe in one of them, who is eventually died in ICU. The other two patients had mild-moderate clinical and radiological severity and were discharged after treatment. Due to the low number of patients, we cannot state comment on the medication's effect on the covid-19 disease severity and prognosis. As seen in Table 2, all patients received HCQ treatment. Although chloroquine (CQ) and hydroxychloroquine (HCQ) have been suggested as potential antiviral agents in covid-19, both are not superior to standard care.[14]

Chest X-ray (CXR) is an essential diagnostic tool in pulmonary disorders. Nonetheless, a chest CT scan is recommended in the covid-19 guidelines in patients with multiple symptoms or co-morbidities.[24] Practically, a CT scan of the chest, which is the best diagnostic imaging modality in covid-19 related pneumonia (Lie Bingjie et al.), has become the best available diagnostic tool in covid-19 pandemics.[25] Yet, few papers in the literature evaluate the covid-19 infected patients with RMD, mostly only with CXR. Fredi et al. had scored CXR of covid-19 infected patients with RMD in their case-control study.[17] They have concluded that pulmonary involvement does not differ according to RMD in covid-19 infected patients. Since GGOs are mostly undetectable on CXR, this conclusion may not be sufficient without an evaluation with chest CT. Similarly, in studies of Borghesi et al. and Acharya et al., chest CT was found to be superior to CXR in the diagnosis of covid-19 pneumonia.[26, 27] Moreover, lung complications are common in RMD and mostly cause different patterns of interstitial pneumonia (IP).[28] Thin slice high-resolution CT imaging is the imaging method of choice in the diagnosis of interstitial lung diseases (ILD).[29] Even though a CXR has abnormal findings, it may not be enough to differentiate covid-19 pneumonia from ILDs. Furthermore, radiologists' evaluation of chest CT scans of rheumatic patients, especially with an unknown history of lung involvement, might be challenging. The baseline ILD pattern can hide or replace covid–19 pneumonia-related findings or might worsen the severity of the lung involvement in covid-19 infected patients with RMD.

Radiological findings in patients with RMD might differ from non-RMD ones. This study has shown that most common CT findings "typical for covid" pneumonia does not differ from non-rheumatic ones. Multifocal GGOs followed by a crazy-paving pattern, and GGOs with superimposed consolidation were depicted as the most common CT features in both groups of patients. Although there are only a few articles evaluating patients with RMD for covid-19 pneumonia, this finding has been supported in the study of Ye C, et al.[22.] On the other hand, we have found a higher incidence of atypical CT features for covid-19 in patients with RMD compared to non-RMD ones. Peribronchovascular distribution of GGOs, isolated pleural thickening, and pulmonary nodules were the most common atypical CT features in both groups. The reason for this could be that the involvement of the lungs is due to the chronic inflammatory nature of the RMD. This idea had also been supported in the study of Ye C, et al.[22] with the emphasis on the possibility of interstitial lung disease development in the feature.

It has been an important approach during the covid-19 pandemic to evaluate and report the ratio of pulmonary parenchymal involvement. We have conducted a semi-quantitative evaluation for CT-scoring, but our results did not fit well with clinical severity indices. Tekcan et al. had explained, partly, this difference with an emphasis on the effect of multifactorial parameters, including but not only the percentage of parenchymal involvement on initial chest CT examination on prognosis.[30] Moreover, severity scores of covid-19 pneumonia did not differ among RMD and non-RMD patients in our study. Still, the difference between mean scores might indicate more severe disease progression in patients with rheumatic musculoskeletal diseases.

The small number of RMD patients we detected in our screening greatly limits our data to generalize. We couldn't be able to report the most recent disease activity and previous interstitial lung disease status of our patients. However, we know that 4 of 9 patients were not under any treatment for RMD. This may be one of the reasons, though not all, for our overestimated prevalence of RMD among our cohort. Inevitably, up-to-date reports documenting the covid-19 disease with the co-morbidity of RMD were all case reports or retrospectively designed studies which is the sole option under pandemic conditions. Therefore, these findings should be verified with larger cohorts.

Patients with RMD should be handled as a special patient population regarding chronic systemic inflammation and wide use of anti-inflammatory drugs. It should be kept in mind that these features might affect the diagnostic processes as well as the clinical progress of covid-19 infection. In future studies, a detailed examination of semi-quantitative chest CT involvement patterns in patient populations, such as RMD, will contribute to the literature with a unique nature.

Ethical considerations

Approval from both the Institutional Ethical Committee (issue no: 15345988-7, date: 06/07/2020) and The Government of Health (form no:2020-06-01T21_25_10) was obtained before the study.

Conflict of interest

The authors declare no conflict of interest.

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Research Article

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THE MAGNETIC RESONANCE IMAGING FINDINGS OF MYOCARDIAL MICROVASCULAR CIRCULATORY DISORDER IN PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE

BOZULMUŞ GLUKOZ TOLERANS HASTALARINDA MYOKARDİAL MİKROVASKÜLER DOLAŞIM BOZUKLUĞUNUN MANYETİK REZONANS GÖRÜNTÜLEME BULGULARI

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Öz

Amaç: Bozulmuş glukoz toleransı (BGT) olan hastalarda manyetik rezonans görüntüleme (MRG) ile MRG-perfüzyon ile miyokardiyal kan akımı değerlendirildi. Mikrovasküler obstrüksiyon varlığı ve iskemik kalp hastalığı sıklığı araştırıldı.

Materyal ve Metot: Çalışmamıza IGT'li 20, tip 2 diabetes mellituslu (DM) 16 hasta ve normal MR bulguları olan 15 hasta dahil edildi. Tüm hastalar supin pozisyonda 1.5 Tesla MR ile vücut koili kullanılarak muayene edildi. İlk olarak, duvar hareketlerini görmek, duvar kütlesini ve sol ventrikül ejeksiyon fraksiyonunu hesaplamak için B-TFE sine sekansları elde edildi. Daha sonra diğer kardiyak miyokard hastalıklarını dışlamak için "siyah kan" T2 ağırlıklı ve STIR sekansları alındı. İlk geçiş perfüzyonunu değerlendirmek için 0.2 mmol/kg Gd-DTPA'nın intravenöz uygulanmasıyla bazal, midventriküler ve apikal kısa aks sekansları elde edildi. Ardından "inversiyon recovery GRE" sekansı ile enjeksiyondan 10 dakika sonra geç opaklanma bulguları elde edildi.

Bulgular: Miyokard dokusunda ilk geçiş perfüzyonunda tepe kontrastlanma ve birikmiş kontrastlanma araştırıldığında, BGT ve tip 2 DM'li olgularda benzerlik saptandı. Ancak sağlıklı kontrol grubuna göre anlamlı farklılıklar tespit edildi. İlk geçiş perfüzyonunda; kontrast madde gelme zamanı ile miyokard dokusunda kontrast madde artışının tepe noktası karşılaştırıldığında, bu gruplar arasında fark görülmedi. Ayrıca sol ve sağ ventrikül sistolik fonksiyonları gruplar arasında benzerdi.

Sonuç: BGT'li olgularda miyokardiyal mikrovasküler dolaşım bozuklukları koroner arter hastalığı olmaksızın erken evrelerde ortaya çıkabilir. Bu tür vakalarda kardiyak MRG önemli bir seçim olabilir.

Anahtar Kelimeler: Manyetik rezonans görüntüleme, miyokardiyal mikrovasküler dolaşım bozukluğu, bozulmuş glukoz tolerans.

Abstract

Objectives: Myocardial blood flow was evaluated with magnetic resonance (MR) perfusion in the patients with impaired glucose tolerance (IGT), and the existence of microvascular obstruction and risk for cardiac diseases were researched. In addition, the wall motion, wall mass (gram), and viability of the left ventricle, and the systolic function of both ventricles were evaluated.

Materials and Methods: Twenty patients with IGT, 16 patients with type 2 diabetes mellitus (DM) and 15 patients with normal MR findings were included in our study. All patients were examined in the supine position using a body coil with 1.5 Tesla MR. Firstly, images B-TFE cine sequences to see the wall motions, calculate the wall mass and the left ventricular ejection fraction. "Black blood" T2-weighted and STIR sequences were then taken to exclude other cardiac myocardial diseases. Basal, midventricular, and apical short-axis sequences were obtained by intravenous administration of 0.2 mmol/kg Gd-DTPA to evaluate first-pass perfusion. And late opacification findings were obtained 10 minutes after the injection with the "inversion recovery GRE" sequence.

Results: When peak enhancement and accumulated enhancement in the first pass perfusion of myocardial tissue were investigated, the similarity was found in cases with IGT and type-2 DM. However, significant differences were found compared to the healthy control group. In the first pass perfusion; When contrast agent arrival time and the peak of contrast agent increase in myocardial tissue were compared, no difference was observed between these groups. In addition, left and right ventricular systolic functions were similar between groups.

Conclusion: In the cases with IGT, myocardial microvascular circulation disorders can emerge in early phases without the presence of coronary artery disease. In these kinds of cases, cardiac MRI can be an important choice.

Keywords: Magnetic resonance imaging, myocardial microvascular circulatory disorder, impaired glucose tolerance.

Introduction

Diabetes Mellitus (DM) is an important risk factor for cardiovascular diseases. Silent myocardial ischemia, painless myocardial infarct (MI), and heart failure are more common in diabetic patients when compared to the normal population. DM increases morbidity and mortality by facilitating atherosclerosis with several mechanisms.[1] The patients with impaired glucose tolerance (IGT) are accepted as prediabetic patients, and it was established that the risk of coronary artery disease (CAD) is increased in these patients with coronary angiography.[2, 3, 4] The first finding of CAD is macrovascular obstruction, and this can not be demonstrated with coronary angiography. The microvascular obstruction could be evaluated by cardiac magnetic resonance (MR) imaging with the "first pass" perfusion technique, and as we know, there is no published paper about the evaluation of microvascular obstruction in patients with IGT.[5-7]

In this study, the existence of a microvascular obstruction and the risk for cardiac diseases are searched by evaluating the microvascular blood flow with cardiac MRI in patients with IGT.

Materials and Methods

Study Groups

Forty-three patients who had not any known coronary artery disease, dyspnea, hypertension, or abnormal ECG findings were referred for cardiac MR imaging from endocrinology to radiology department, one obese patient and three patients with claustrophobia were excluded from the study, and three patients did not accept MR imaging. Patients' HbA1c levels, blood pressures, and blood lipid levels were reviewed from past records, and patients with normal values were included in the study. No abnormal findings were found in the echocardiographic examinations of the patients.

Eventually, 16 diabetic patients and 20 patients with IGT were included in the study. For the control group, 15 normal patients who had cardiac MRI for different indications were included. Twelve of the patients with IGT were men, and 8 of them were women; 10 of diabetic patients were men, and 6 of them were women, 9 of control group patients were man and 6 of them were women. The smoking history was asked of the selected patients.

MRI protocol

All of the patients were examined in the supine position by using a body coil (SENSE body coil) with 1.5 Tesla MRI (Philips Achieva, Philips Medical Systems, Best, The Netherlands). The contrast material administration

was done via the right antecubital vein in all study patients. 25 mg beta-blocker (Beloc, metoprolol) was given to the patients in whom heart rate was >80 beats/min before the examination. The heart rate, ECG, and respiration of patients were observed during the process. [8,9]

First, reference images in axial, coronal, and sagittal planes were obtained by the Balanced Turbo Field Echo (B-TFE) sequence. A parallel imaging technique was used for all sequences. The long and short axis of the left ventricle and four-chamber cine images were achieved with ECG triggered and breath-hold B-TFE sequence (TR/TE: 3.2/1.6 flip angle: 60°) to see the wall motions and to calculate the wall mass and ejection fraction. Then, "black blood" T2 weighted (TR/TE: 2000/60, flip angle: 90°) and STIR (TR/TE: 2000/60, flip angle: 90°) sequences were obtained to exclude the other cardiac myocardial diseases.

ECG-triggered and breath-hold "balance" TFE (TR/TE: 2.4/1.2 flip angle: 50°) sequence was obtained by administration of 0.20 mmol/kg Gd-DTPA intravenously to evaluate the first-pass perfusion. Long and short-axis images of basal, midventricular, and apical segments were achieved with ECG-triggered and breath-hold inversion recovery GRE sequence by selecting the optimal "time of inversion" (TI: 220-300ms) of each patient 10 minutes after the injection to suppress the myocardial signals.[5,10,11]

Data analysis

The MR images were transferred to the work station (Philips View Forum Extended MR Workspace), and analytic processes were done with the "Cardiac MR Package" program. The values of EF, SV, cardiac output, cardiac index, and wall mass of left ventricle were obtained by drawing the endocardial and epicardial contour manually on left ventricle short-axis cine images and by analyzing the results automatically (Figure 1).

The values of end-diastolic volume, end-systolic volume, and EF of the right ventricle were obtained by drawing the endocardial contour manually on the four-chamber images and by analyzing the results with the ALEF (Area Length of EF) technique automatically. The viability, cine images, and first-pass perfusion images were evaluated with the short axis 18 segments (left ventricle basis 6, midventricular six, and apical 6) (Figure 2 and 3). The inner and outer parts of each segment were evaluated one by one. The values of time to arrive, time to peak, peak enhancement, and accumulated enhancement were measured quantitatively (Figure 4).

Statistical Analysis

The demographic features of the patients were summarized with fundamental statistics. Mean and standard deviation values were used for numerical parameters, and if necessary, minimum and maximum values were also used. Categorical variables were indicated with the number and percentage of the patients.

P < 0.05 was accepted as statistically significant. The statistical analysis was made with the "SPSS 16.0" program.

Post-hoc analysis

Kolmogorov-Smirnov test was used to determine the distribution of continuous variables, ANOVA test was used to compare the parameters which show a normal distribution, and posthoc Tukey test was used for secondary comparisons. Cross-table statistics were used for the comparison of categoric variables (Chi-square and Fischer tests).

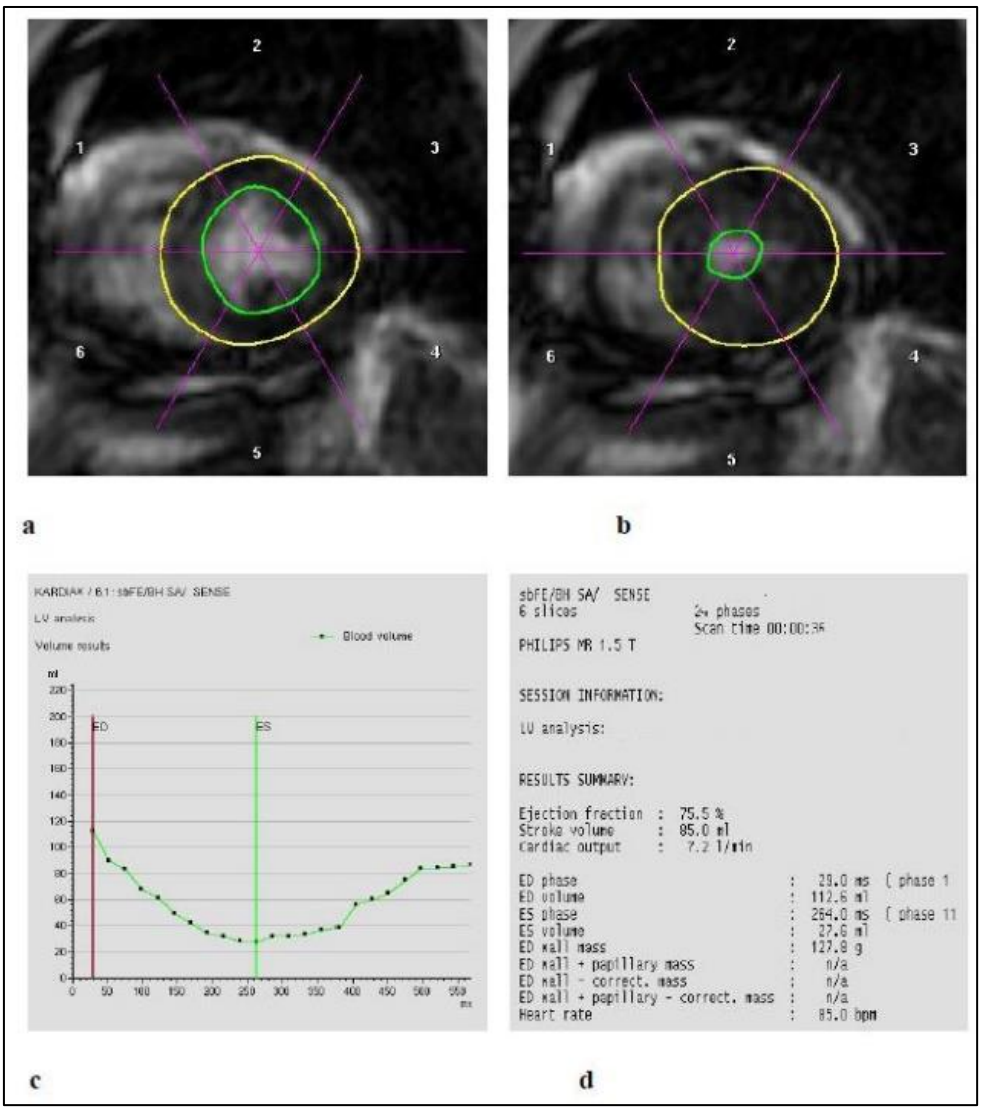

Figure 1. a, b. Contour detection of the left ventricle at systolic and diastolic phase, c. systolic function curve of the left ventricle, d. the values of systolic functions and the wall mass of the left ventricle.

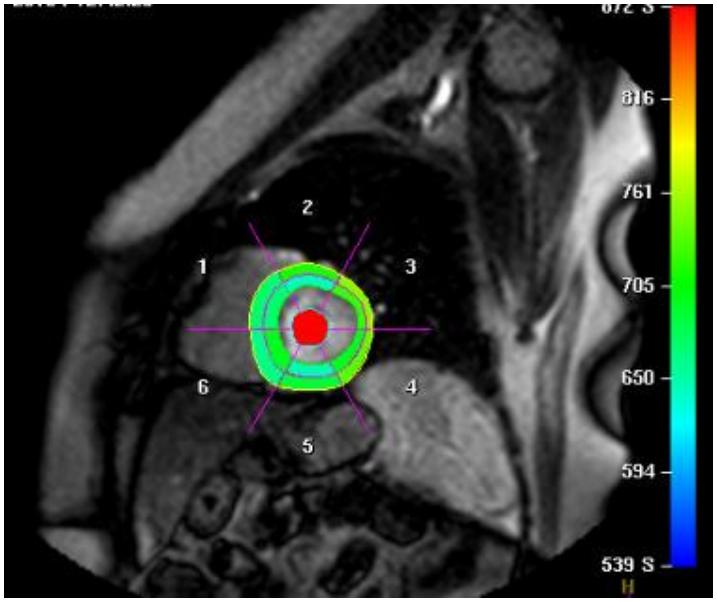

Figure 2. Midventricular perfusion of the healthy individual. (Blue color indicates the perfusion restriction. The red and yellow colors represent normal and near-normal perfusion.) Blue color coding was not seen due to the normal perfusion.

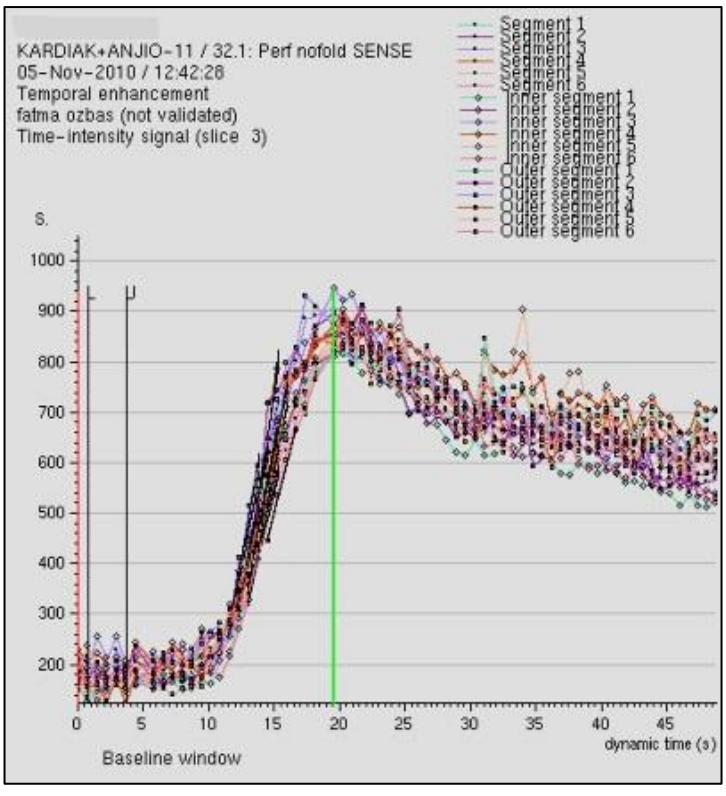

Figure 3. The curve of first-pass perfusion at the midventricular level of a healthy individual. It shows the intensity of contrast material passing through the inner and outer walls of each segment.

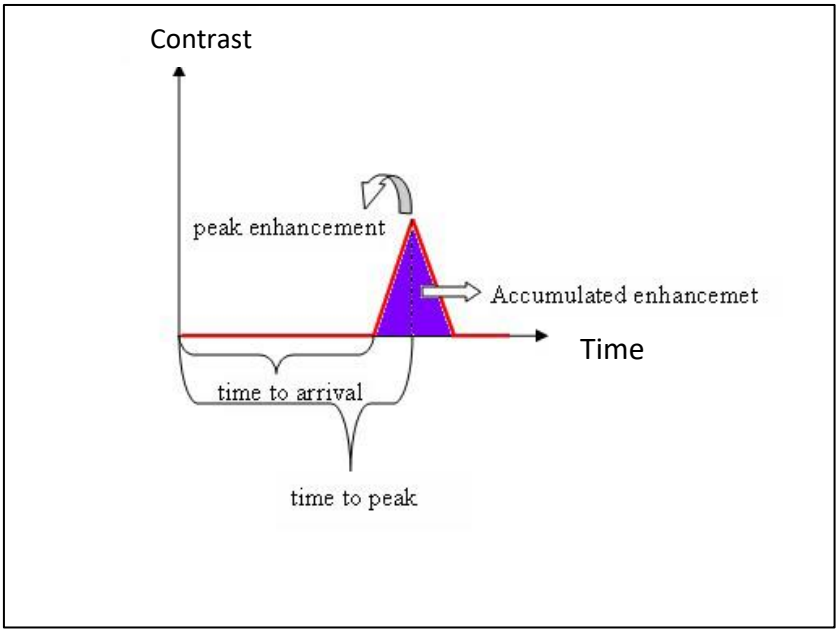

Figure 4. The contrast-time graphic of myocardial tissue on the first pass perfusion examination.

Results

Cardiac MR examination was performed on 20 patients with IGT, 16 diabetic patients, and 15 normal individuals successfully. The mean age was 53.90±7.25 in patients with IGT, 51.69±8.81 in diabetic patients, and 48.60±6.76 in the control group, respectively. The mean BMI value was 29.65±4 in patients with IGT, 30.19±3.51 in diabetic patients, and 30.34±3.07 in the control group, respectively. Male patients consist of 60.78 % (n=31) and female patients consist of 39.22 % (n=20) in study group. The smoking rate was 25% in patients with IGT, 31.25 % in diabetic patients, and 20% in the control group, respectively.

There was no statistically significant difference in terms of the mean age between the groups (p=0.138). The groups were similar in terms of gender distribution (p=0,986). There was no significant statistical difference between the groups in terms of smoking rates (p=0.771). The groups were similar in terms of the mean BMI (p=0.835) (Table 1).

The Value of Peak Enhancement at First Pass Perfusion

When the values of peak enhancement of contrast material at myocardium were evaluated after the first pass perfusion study of the patients, the cut-off signal value was detected as 418s by using the ROC analysis.

When the inner part measures of the apical wall of the patient groups were compared, 6.66% of 120 segments were below the normal values in the IGT group, and this ratio was 6.25% of 96 segments in the DM group.

Table 1. The demographic features of groups (data: mean ± the standard deviation, percent of the case)

	IGT	DM	Control group	p
Age	53.90±7.25	51.69±8.81	48.60±6.76	0.138
Gender (man/woman)	12/8 (60/40)	10/6 (62.50/37,50)	9/6 (60/40)	0.986
Smoking (smoker/non-smoker)	5/15 (25/75)	5/11 (31.25/68.75)	3/12 (20/80)	0.771
BMI	29.65±4	30.19±3.51	30.34±3.07	0.835

Table 2. Comparison of peak enhancement of myocardium (data; percent of the case)

	IGT	DM	The control group	p
Inner apical Wall (normal/patient)	112/8 (93.33/6.66)	90/6 (93.75/6.25)	90/0 (100/0)	IGT- DM=0.902 IGT-C=0.011 DM-C=0.029
Outer apical wall (normal/ patient)	114/6 (95/5)	88/8 (91.66/8.33)	90/0 (100/0)	IGT- DM=0.323 IGT-C=0.039 DM-C=0.007
Inner midventricular wall (normal/ patient)	112/8 (93.33/6.66)	91/5 (94.79/5.20)	90/0 (100/0)	IGT- DM=0.902 IGT-C=0.011 DM-C=0.029
Outer midventric. wall (normal/ patient)	120/0 (100/0)	96/0 (100/0)	90/0 (100/0)	1.000
Inner basal wall (normal/ patient)	110/10 (91.66/8.33)	88/8 (91.66/8.33)	90/0 (100/0)	IGT- DM=1.000 IGT-C=0.006 DM-C=0.007
Outer basal wall (normal/ patient)	110/10 (91.66/8.33)	90/6 (93.75/6.25)	90/0 (100/0)	IGT- DM=0.561 IGT-C=0.006 DM-C=0.029

There was not an abnormal value in any segments of the control group. The difference between the control group and patient group, including DM and IGT groups, was statistically significant since there was not any statistical difference between IGT and DM groups (p=0.011, p=0.029).

There was also not a significant statistical difference between IGT and DM groups in terms of the outer part values of apical walls (p=0.323). The abnormal values of IGT and DM were higher than those of the control group significantly (p=0.039 and p=0.007, respectively).

There was not any statistical difference between IGT and DM groups in terms of the inner part values of midventricular walls since the difference between both of these groups, and the control group was statistically significant (p=0.011 and p=0.029, respectively). There was not any statistically significant difference between the groups in terms of the outer part of the midventricular walls (p=1.000).

When the inner part values of basal walls were evaluated, there was not a significant statistical difference between BGT and DM groups since the difference was statistically significant between both these groups and the control group (p=0.006 and p=0.007, respectively). There was also not any significant statistical difference between the IGT and DM groups in terms of the outer part values of the basal walls since the difference between both these groups and the control group was statistically significant (p=0.006 and p=0.029) (Table 2).

The Value of Accumulated Enhancement at First Pass Perfusion

When the values of peak enhancement of contrast material at myocardium were evaluated after the first pass perfusion study of the patients, the cut-off signal value was detected as 2412s by using the ROC analysis. When the inner part measures of the apical wall of the patient groups were compared, 6.70% of 120 segments were below the normal values in the IGT group, and this ratio was 6.20% of 96 segments in the DM group. There was not an abnormal value in any segments of the control group. The difference between the control group and patient group, including DM and IGT groups, was statistically significant since there was not any statistical difference between IGT and DM groups (p=0.011, p=0.029).

The Value of Accumulated Enhancement at First Pass Perfusion

When the values of peak enhancement of contrast material at myocardium were evaluated after the first pass perfusion study of the patients, the cut-off signal value was detected as 2412s by using the ROC analysis. When the inner part measures of the apical wall of the patient groups were compared, 6.66% of 120 segments were below the normal values in the IGT group, and this ratio was 6.25% of 96 segments in the DM group. There was not an abnormal value in any segments of the control group. The difference between the control group and patient group, including DM and IGT groups, was statistically significant since there was not any statistical difference between IGT and DM groups (p=0.011, p=0.029).

There was also not a significant statistical difference between IGT and DM groups in terms of the outer part values of apical walls (p=0.323). The abnormal values of IGT and DM were higher than those of the control group significantly (p=0.039 and p=0.007, respectively).

There was not any statistical difference between IGT and DM groups in terms of the inner part values of midventricular walls since the difference between both of these groups and the control group was statistically

significant (p=0.031 and p=0.014, respectively). There was not any statistically significant difference between the groups in terms of the outer part of the midventricular walls (p=0.561).

When the inner part values of basal walls were evaluated, there was not a significant statistical difference between IGT and DM groups since the difference was statistically significant between both these groups and the control group (p=0.021 and p=0.002, respectively). There was also not any significant statistical difference between the IGT and DM groups in terms of the outer part values of the basal walls since the difference between both these groups and the control group was statistically significant (p=0.005 ve p=0.003)

Since there was not any significant difference between IGT and DM groups in terms of the outer part values of the basal wall, there was a statistically significant difference between the control group and both of those groups (Table3).

Table 3. Comparison of the accumulated contrast amount values (data, percent of case)

	IGT	**DM**	**The control group**	**p**
Inner apical wall (normal/ patient)	112/8 (93.33/6.66)	90/6 (93.75/6.25)	90/0 (100/0)	IGT - DM=0.902 IGT -C=0.011 DM-C=0.029
Outer apical wall (normal/ patient)	114/6 (95/5)	88/8 (91.66/8.33)	90/0 (100/0)	IGT - DM=0.323 IGT -C=0.039 DM-C=0.007
Inner midventricular wall (normal/ patient)	112/8 (93.33/6.66)	89/7 (92.70/7.30)	90/0 (100/0)	IGT - DM=0.858 IGT -C=0.031 DM-C=0.014
Outer midventricular wall (normal/ patient)	118/2 (98.33/1.66)	92/2 (97.87/2.13)	90/0 (100/0)	0.561
Inner basal wall (normal/ patient)	113/7 (94.16/5.83)	86/10 (89.58/10.41)	90/0 (100/0)	IGT- DM=0,214 IGT-C=0.021 DM-C=0.002
Outer basal wall (normal/ patient)	101/9 (91.81/8.19)	87/9 (90.62/9.38)	90/0 (100/0)	IGT- DM=0.762 IGT-C=0.005 DM-C=0.003

Time to peak and time to arrive at first pass perfusion

When "time to arrival" and "time to peak" were evaluated after the first pass study of patients, there was not a significant statistical difference between the groups.

Delayed Enhancement

There was not any statistically significant difference between the groups in the evaluation of delayed enhancement (10th min) by using the transmural index of the study patients. The enhancement of contrast of more than 50% was adopted as abnormal.

The evaluation of cine images

The left ventricle EF, left ventricle SV, left ventricle cardiac output, left ventricle cardiac index, left ventricle wall mass, right ventricle EDV, right ventricle ESV and right ventricle EF were assessed in study patients by cardiac MR. There was not a significant difference between the groups.

Discussion

Cardiac MR examination provides a comprehensive assessment of the heart since it is non-invasive, has high tissue contrast and spatial resolution, and has no risk of ionizing radiation exposure.[11,12] Cardiac MRI examination allows the characterization of myocardial tissue, evaluation of left ventricle volume and mass, the distinction between the infarct area and the live tissue.[21] It could evaluate the transmural extension of the non-viable tissue, regional wall motion abnormalities, and systolic diastolic wall thickness.[13, 14]

The first pass perfusion is important in ischemic diseases. Al-Saadi et al. studied first-pass perfusion MRI with 15 patients who had coronary artery disease and five normal individuals. According to the study results, first, pass perfusion has high diagnostic accuracy in terms of the diagnosis of coronary artery disease.[7,15,16] To the best of our knowledge, there is not any published report which evaluates microvascular circulation with cardiac MR examination in patients with DM or IGT, and our study will be the first study on this topic.[9,17,18]

Contrast accumulation decreased in some myocardial segments that had perfusion defects due to microvascular obstruction.[7,10] As a result of this condition, contrast enhancement decreased in those segments, and peak enhancement and accumulated enhancement values were below the cut-off values.

However, perfusion defects did not affect the "time to arrival" and "time to peak" values. In our study, there was no significant statistical difference in accumulated enhancement, and peak enhancement values between the patients with IGT and diabetic patients since the difference was significant between the normal group and both of those two groups. These findings indicate a perfusion defect in the early phase due to microvascular obstruction in patients with IGT and in diabetic patients. Thus, myocardial supply could be impaired in patients with IGT before the development of DM, and these patients should be followed up in terms of cardiac risk. Schinner et al. performed coronary angiography in 1,394 patients without the diagnosis of DM. They identified

coronary artery disease (CAD) in 76% of those patients. They detected DM in 15% of patients, impaired fasting glucose (IFG) in 20% of patients, IGT in 13% of them, and both IFG and IGT in 20% of the patients. They indicated that the risk of CAD increase with the rise of fasting and postprandial blood glucose.[2] Sourij et al. performed coronary angiography in 1090 patients with the diagnosis of CAD or with suspicious CAD. Those patients were followed up for 46 months. Three hundred ninety-four of the patients had normal glucose tolerance, 280 of them had the diagnosis of IGT or DM during the follow-up, and 366 of those patients were known as diabetic patients. They demonstrated that the frequency of microvascular diseases is significantly higher in patients with DM or IGT when compared with normal individuals.[3] In a prospective cohort study of Anand et al., 18,990 individuals were followed up in terms of cardiac risk existence during 3.5 years in 21 different countries. As a result, they indicated that 2.52 mmol/l of glucose increase in plasma increases the risk of cardiovascular disease and death by 17%.[4]

Our study has some limitations. Our first limitation was the small number of patients. We could include 16 patients with DM, 20 patients with IGT, and 15 healthy individuals, and it would be proper to study with large series. The second limitation is that we could not use stress agents because monitoring observations could not be done. A study that was made by using stress agents would be more sensitive. Our third limitation is that coronary artery disease was diagnosed just by the anamnesis of angina pectoris and ECG findings. Also, the left ventricle apex could not be evaluated due to technical insufficiency, and it was excluded.

Microvascular circulation failure is developed in the early phase in patients with IGT and in diabetic patients.[23] The changes of peak enhancement and accumulated enhancement which indicate the microvascular obstruction remains parallel in patients with IGT and in diabetic patients.[4,19,20,22] The findings of time to arrive, time to peak, and delayed enhancement were not statistically significant in diabetic patients and in the patients with IGT. Our study indicated that cardiovascular diseases could be seen in the prediabetic stage. Cardiac MRI examination could be used in the assessment of microvascular obstruction when the deterioration of glucose homeostasis begins.

Ethical considerations

Our study was designed in accordance with the principles of the Helsinki Declaration and regulation of patient rights and approved by the clinical research Ethics Committee of Ankara Ataturk Training and Research Hospital Non-interventional Clinical Researches with the date of 30.09.2010 and the number of 2010-09-118.

Conflict of Interest

The authors declare no conflict of interest.

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PREDICTION OF IN-HOSPITAL MORTALITY IN PATIENTS UNDERGOING ENDOSCOPY FOR NON-VARICEAL UPPER GASTROINTESTINAL BLEEDING

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Abstract

Objectives: The aim of this study is to investigate the parameters that may contribute to the prediction of in-hospital mortality in patients who were admitted to the emergency department with non-variceal upper gastrointestinal system (GI) bleeding and underwent endoscopy.

Materials and Methods: Patients with non-variceal upper GI bleeding who were admitted to the emergency department of our hospital between March 2019 and June 2021 were evaluated retrospectively. Surviving and deceased patients were compared. To predict mortality independently, logistic regression analysis was performed with parameters that were significant.

Results: It was shown that there was a relationship between low albumin and T score, older age, high LDH and higher white blood cell count, and mortality. In the ROC analysis, where the diagnostic accuracy of these five factors in predicting mortality was evaluated, the area under the curve was calculated as 0.84.

Conclusion: The evaluation of albumin, age, T score, white blood cell and LDH together may be helpful in predicting the in-hospital mortality of patients with non-variceal upper GI bleeding.

Keywords: Upper gastrointestinal bleeding, mortality, T score, nomogram.

Introduction

Gastrointestinal (GI) system hemorrhages constitute a very important group of diseases because of the high frequency of admissions to the emergency department due to it and the fact that it is associated with both morbidity and mortality.[1] Among GI hemorrhages, upper GI hemorrhages are more common than lower GI hemorrhages.[2] Its occurrence is twice more in men than in women, and studies report figures of 128 and 65 per 100,000, respectively.[3] On inspecting the causes, the most common etiology of non-variceal hemorrhages is peptic ulcer, and gastritis, angiodysplasia, Mallory–Weiss syndrome, malignancies, and drug side effects (vitamin K antagonists, etc.) can also be considered.[3-5]

After evaluation in the emergency department, it is decided whether it is related to varicose veins in patients undergoing endoscopy. Non-variceal hemorrhages also constitute an important part of GI hemorrhages. In studies conducted to date, the patient's age, comorbidities, the diagnosis of the underlying hemorrhagic disease, and the drugs used have been related to the prognosis of the patient.[3,4,6] It is important to predict the course of the disease in these patients, their mortality, and future complications and inform the patients about them for the effective investigation of the underlying disease and making decisions of follow-up in the hospital. This will prove beneficial in guiding the clinician to predict which patient will be followed up for a short time, which patient will need intensive care, and which patient will need a transfusion and additional treatments.

In light of this information, in this study, we aimed to analyze the clinical and laboratory parameters that can provide information about the problems that may occur in the future in patients with upper GIS hemorrhage who were admitted to the emergency department and investigate whether these parameters can predict the prognosis and mortality of these patients.

Materials and Methods

Patients with non-variceal upper GI hemorrhage who were admitted to the emergency department and hospitalized for endoscopy between March 2019 and June 2021 were evaluated retrospectively. The clinical and laboratory data of the patients were obtained from the hospital's registration system. During this period, comorbidities, complete blood count parameters (leukocyte and platelet counts, hemoglobin and hematocrit levels, etc.), biochemical markers, kidney and liver function tests, and albumin levels were recorded in patient follow-up forms.

T-score is a clinical scoring system that includes four parameters in which the patient's general condition, heart rate, systolic blood pressure, and hemoglobin levels and it is previously shown to be associated with poor endpoints in cases of upper GI hemorrhages (Table 1).[6] According to this score, a patient with a poor general

condition, receives 1 point for each parameter and gets a minimum score of 4, whereas a patient with a good general condition receives 3 points from each parameter and gets a maximum score of 12 points. The primary endpoint of this study was in-hospital mortality. The deceased and surviving patients were divided into two groups, and their parameters were compared.

Statistical analysis

All statistical analyses were performed using Stata (version 16.0 MP; StataCorp). The distribution of continuous variables was determined using the Kolmogorov–Smirnov test. Continuous data that showed a normal distribution were presented as mean ± standard deviation, and the data without a normal distribution were presented as median (range). Categorical data were defined as the number of cases and their percentage. The variables with statistically significant differences and normal distribution were compared.

The Student's t-test was used for two different groups with a normal distribution. The Pearson's chi-square test was used for categorical variables. A univariate logistic regression model was constructed for each variable to show significant predictors of in-hospital causes of mortality, and then those with $p<0.10$ were tested using a multivariate logistic regression model. The results of multivariate regression analysis were presented as odds ratios of independent predictors of in-hospital mortality and their 95% confidence intervals.

Receiver operating characteristics (ROC) curve analysis was used to demonstrate the discrimination performance of the final model. Finally, a nomogram containing significant predictors was plotted as a graph. A p-value of <0.05 was considered significant in all the statistical analyses.

Results

During the study period, a total of 82,562 upper endoscopies (all departments including in-patients, out-patients, and emergency department) procedures were conducted in our institute. Eventually, 489 patients who were admitted to the emergency department and underwent endoscopy for upper GI bleeding were included in the study. During this period, 67 patients died while being followed up in the hospital. The mean age of the patients was 64.82±18.39 years, and 66.25% of them were male. On examining the additional morbidities, the most common comorbidities were hypertension (45.81%), coronary artery disease (34.76%), and diabetes mellitus (22.08%). These data are summarized in Table 2**.** When the surviving and deceased patients were compared, the parameters of age, heart failure, arrhythmia, and malignancy were significantly different between the two groups ($p<0.001$, $p=0.007$, $p=0.042$, and $p<0.001$, respectively). When the laboratory values and T-scores were compared, significant differences were found between the two groups in terms of urea, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, lactate

dehydrogenase (LDH), and albumin levels; platelet and neutrophil counts; and T-scores (Table 3). According to the multivariate regression analysis, albumin levels, age, neutrophil count, T-scores, and LDH levels were independent predictors of in-hospital mortality (Table 4). In the ROC analysis in which the diagnostic accuracy of these parameters in predicting mortality was evaluated, the area under the curve was found to be 0.84 (Figure 1). The new nomogram scale created using these parameters is presented in Figure 2.

Table 1. T Score parameters and scoring

Clinical Parameter	**Score**		
	1	**2**	**3**
General Condition	Poor	Intermediate	Good
Heart rate	>110	90-110	<90
Systolic blood pressure (mm/ Hg)	<90	90-110	>110

Table 2. Basal characteristics and co-morbidities of the patients according to the survival status.

	All Patients N=489	**Survivors N=422**	**Non-survivors N=67**	**p-value**
Basal Characteristics				
Age (SD)	64.82 (18.39)	63.23 (18.44)	74.47 (15.31)	<0.001
Male	324 (66.25%)	283 (67.10%)	41 (61.20%)	0.350
Co-morbidities				
Heart failure	55 (11.25%)	41 (9.72%)	14 (20.89%)	0.007
Arrhythmia	88 (17.99%)	70 (16.59%)	18 (26.87%)	0.042
Coronary Artery Disease	170 (34.76%)	143 (33.88%)	27 (40.29%)	0.310
Chronic Kidney Disease	51 (10.42%)	40 (9.48%)	11 (16.42%)	0.084
Cerebrovascular Disease	42 (8.58%)	35 (8.29%)	7 (10.45%)	0.560
Chronic liver disease	7 (1.43%)	7 (1.66%)	0 (0%)	0.290
Hypertension	224 (45.81%)	191 (45.26%)	33 (49.25%)	0.540
Diabetes mellitus	108 (22.08%)	90 (21.33%)	18 (26.86%)	0.310
Gastritis/ulcer	32 (6.54%)	29 (6.87%)	3 (4.47%)	0.460
Chronic lung disease	48 (9.82%)	37 (8.77%)	11 (16.42%)	0.051
Malignancy	58 (11.86%)	36 (8.53%)	22 (32.84%)	<0.001

Table 3. Baseline laboratory markers of patients according to mortality

	All Patients N=489	Survivors N=422	Non-survivors N=67	p-value
Urea, mean (SD), mg/dL	90.62 (63.54)	86.56 (60.72)	115.91 (74.83)	<0.001
ALT, mean (SD), U/L	23.69 (38.37)	21.29 (20.85)	38.46 (89.30)	<0.001
AST, mean (SD), U/L	26.41 (43.19)	23.8 (24.51)	43.83 (99.71)	<0.001
GGT, mean (SD), IU/L	41.26 (76.24)	35.93 (64.41)	76.28 (123.85)	<0.001
Amylase, mean (SD), U/L	64.77 (34.86)	64.03 (31.55)	70.23 (53.49)	0.230
LDH, mean (SD), U/L	227.40 (143.53)	211.01 (98.44)	335.67 (283.55)	<0.001
Albumin, mean (SD), g/L	35.62 (6.28)	36.51 (5.89)	29.77 (6.05)	<0.001
MPV, mean (SD), fL	8.44 (1.10)	8.31 (1.05)	8.60 (1.12)	0.096
PDW, mean (SD), fL	54.20 (11.45)	54.08 (11.43)	55.22 (11.88)	0.460
Platelet, mean (SD), x10^3/mL	283.42 (144.71)	274.52 (121.39)	339.03 (239.09)	<0.001
Neutrophil#, mean (SD)	7928.40 (4757.93)	7440.33 (3992.72)	11002.81 (7387.16)	<0.001
T Score				
4	5 (1.10%)	4 (1%)	1 (1.70%)	<0.001
5	5 (1.10%)	0 (0%)	5 (8.30%)	
6	15 (3.30%)	10 (2.50%)	5 (8.30%)	
7	39 (8.50%)	30 (7.50%)	9 (15%)	
8	71 (15.50%)	55 (13.80%)	16 (26.70%)	
9	99 (21.60%)	88 (22.10%)	11 (18.30%)	
10	97 (21.10%)	88 (22.10%)	9 (15%)	
11	76 (16.60%)	72 (18%)	4 (6.70%)	
12	52 (11.30%)	52 (13%)	0 (0%)	

Table 4. Results of multivariable significant predictors

	Odds Ratio	95% Confidence Interval	p value
Albumin	0.90	0.84-0.96	0.002
Age	1.04	1.01-1.06	0.009
Neutrophil	1.00	1.00-1.00	0.004
T-score	0.79	0.63-0.99	0.036
LDH	1.00	1.00-1.01	0.001

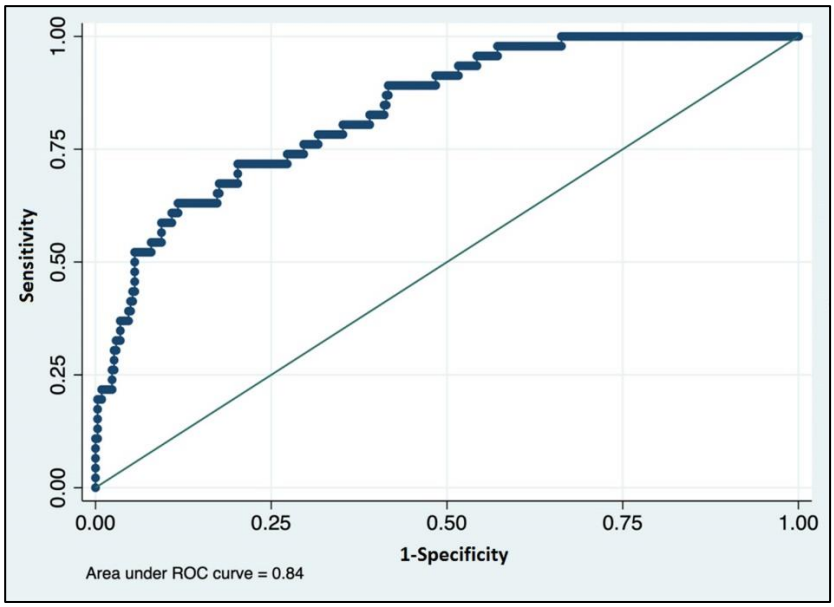

Figure 1. Area under of ROC curve for independently significant predictors of mortality

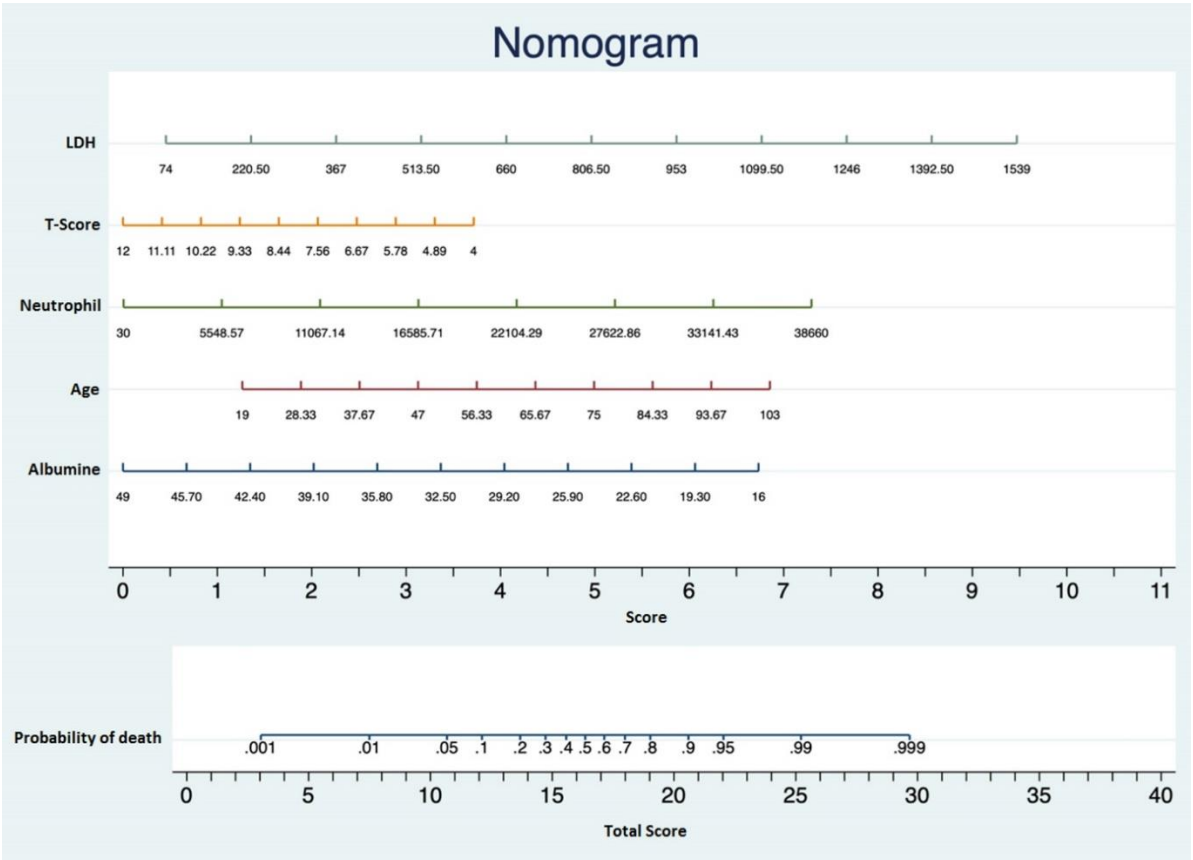

Figure 2. The nomogram of independently significant predictors of mortality

Discussion

In this study, we found that the in-hospital prognosis and mortality of patients admitted to the emergency department with non-variceal upper GIS hemorrhage had an inverse relationship with albumin levels and T-scores and a direct relationship with the neutrophil count, age, and LDH levels. Our study is the first to show these relationships, which provides clinicians essential clues for predicting mortality that may develop in the hospital with the help of easily calculable data such as the results of some biochemical analysis and T-score of patients who were admitted to the emergency department with non-variceal upper GIS hemorrhage. Predicting an important outcome such as mortality using the clues related to these types of diseases that are prone to complications and may progress with additional problems will support the clinician who monitors the patient.

On examining the course of GI hemorrhages over the years, it was observed that the incidence and mortality have decreased over the years. This decrease is consistent with the developments in emergency medicine practice and interventional procedures.[7] Both education provided in the emergency medicine clinics and increased number of trained specialists, as well as the expansion of gastroenterology clinics and specialists in Turkey, has led to improvements in the follow-up and treatment of these patients. In a study by Sezikli et al., non-variceal upper GIS hemorrhages were examined for one year, and ulcer, gastritis, angiodysplasia, and Mallory–Weiss syndrome were found to be the most common causes.[8]

In previous similar studies, the relationship between hematocrit levels and prognosis of patients was investigated, and hematocrit levels <30% were associated with poor prognosis in these patients.[9] In a study by Rao et al., a history of cerebrovascular disease and low albumin levels were found to be associated with 30-day mortality.[10] In another study, hemorrhages due to overdose in patients taking warfarin were analyzed retrospectively. The mortality of the patients within 30 days after endoscopy was predicted using simple laboratory parameters of the patient, and low albumin levels, hypertension, alcohol use, and old age were found to be associated with mortality.[11] Similarly, in a study by Shafaghi et al., low albumin levels were found to be associated with in-hospital mortality.[12] In our study, similar to the results of these studies, low albumin levels and age were found to be associated with mortality.

Some patients included in the current study might have been using anticoagulant drugs and our results might have been affected by this situation. Although there are controversial findings regarding the impact of these drugs on the clinical outcomes, such as duration of hospital stay and risk of re-bleeding, these drugs may lead to poor prognosis. [13-15] Therefore, a closer follow-up of patients using anticoagulants and antiaggregants is required to improve patient management. In addition, in the current study, we have found that albumin level, T-score, neutrophil count, age, and LDH levels should be taken into account. Using the provided nomogram based on these parameters, patients with a higher risk of mortality could be determined, and applications such

as earlier endoscopic evaluation, early admission to the intensive care unit and early blood transfusion could be considered for providing better health care.

The fact that the patients were evaluated retrospectively can be considered as a limitation of our study; however, it can be considered that this aspect of the study has been strengthened by the fact that a sufficient number of patients were analyzed and a large number of patients with GIS hemorrhage were admitted to our hospital. Another limitation of this study is that we were unable to compare mortality rates according to the cause of upper GI bleeding due to a lack of data.

In conclusion, in this study, we found that the mortality of patients with non-variceal upper GI hemorrhage who were admitted to the emergency department is inversely related to albumin levels and T-scores and directly related to neutrophil count, age, and LDH levels. We believe that these findings would be helpful for clinicians in predicting the mortality of patients.

Ethical considerations

This study was confirmed by the local ethics board (Number: E2-21-684) on 14.07.2021.

Conflict of Interest

The author declares no conflict of interest.

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Research Article

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COMPLEMENTARY AND ALTERNATIVE MEDICINE USE IN TYPE 2 DIABETES MELLITUS AND ITS RELATIONSHIP WITH MEDICATION ADHERENCE

TİP 2 DİABETES MELLİTUS'TA TAMAMLAYICI ALTERNATİF TIP KULLANIMI VE TEDAVİ UYUMU İLE İLİŞKİSİ

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Öz

Amaç: Bu çalışmada, Tip 2 Diabetes Mellitus'ta (T2DM) tamamlayıcı ve alternatif tıp (TAT) kullanımını ve bunun uzun süreli medikal tedaviye uyum ile ilişkisini araştırmayı amaçladık.
Materyal ve Metot: Araştırma, tanımlayıcı tipte bir çalışma olarak tasarlandı. En az 1 yıldır oral antidiyabetik kullanan 100 hasta çalışmaya dahil edildi. Katılımcılara, sosyodemografik özellikleri ve TAT kullanımını sorgulayan bir anket; tedaviye uyumu ölçmek için 6 soruluk Türkçe Modifiye Morisky Ölçeği uygulandı.
Bulgular: Hastaların %55'i en az bir TAT yöntemi kullanmıştı. En sık kullanılan yöntem bitkisel ilaçlar (%80(n=44)) idi. TAT yöntemleri başlıca, şikayetleri azaltmak ve tedaviyi destekleyici amaçlı kullanılmış ve hastaların %85,5'i (n=47) bu yöntemlerin kullanımı konusunda doktora danışmamıştı. Bu hastaların %89,4'ü (n=42) danışmama nedenini, 'doktorun olumsuz tepkisinden çekinme' olarak belirtti. TAT kullanımı ile tedaviye uyum arasında istatistiksel olarak anlamlı ilişki bulunmadı.
Sonuç: Hastaların TAT yöntemlerini kullanırken doktora danışmamaları, ilaç-bitki etkileşimlerine bağlı toksikasyonlara ve doz yetersizliklerine karşı dikkatli olmamız gerektiğini göstermektedir. Hekimler hastalarının ilaç öyküsü yanında bu yöntemlerin kullanımını da etkin bir şekilde sorgulamalıdır. Bu bağlamda, tüm hekimler TAT yöntemleri hakkında temel bilgiye sahip olmalı ve bu tedaviler hakkında kanıta dayalı bilgiye nasıl ulaşılabileceklerini de öğrenmelidir.

Anahtar Kelimeler: Tedavi uyumu, diabetes mellitus, tamamlayıcı terapiler, alternatif tıp.

Abstract

Objectives: In this study, we aimed to investigate complementary and alternative medicine (CAM) use and its relationship with adherence to long-term medical therapy in Type 2 Diabetes Mellitus (T2DM).
Materials and Methods: The research was designed as a descriptive study. 100 (a hundred) patients who were using oral antidiabetic for at least one year were included in the study. A questionnaire to determine sociodemographic characteristics and CAM use and a six-item Turkish Modified Morisky Scale for the measure of medication adherence were applied to the participants.
Results: 55% of patients (n=55) used at least one CAM practice. The most commonly used practice was herbal medicine [80% (n = 44)]. The main reasons for using CAM were to relieve complaints and support their conventional treatment, and 85.5% (n=47) of patients did not consult their physicians about the use of these practices. There was no statistically significant relationship between CAM use and medication adherence.
Conclusion: The fact that patients do not consult a doctor while using CAM shows that we need to be careful about toxicities and dose insufficiency due to drug-herb interactions. Physicians should effectively investigate the use of these therapies in addition to the drug history of their patients. Therefore, all physicians should have at least basic knowledge of CAM and learn how to access evidence-based information about these practices.

Keywords: Medication adherence, diabetes mellitus, complementary therapies, alternative medicine.

Introduction

There has been an ever-increasing rise in the use of Complementary and Alternative Medicinal (CAM) practices among general populations during the past few decades. Individuals with diabetes, being prone to an array of related health complications, demand special attention concerning their interest in different CAM practices.[1,2] Since diabetes is a disease resulting in a huge economic burden, physical and mental disability, and all patients should have the privilege of receiving effective therapies with the least adverse effects. According to a study conducted on the prevalence and pattern of complementary and alternative medicine use, individuals with diabetes are approximately 1.6 times more likely to use CAM therapies than people without diabetes.[3] The reasons why patients tend to use CAM practices are widely discussed but not well understood. Moreover, it was observed that patients who were using CAM did not consult their physicians in general.[4] A vast majority of patients opt for CAM therapies as a complement to conventional care rather than as an alternative choice.[5]

Poor treatment adherence is an important problem that increases mortality and morbidity in chronic diseases. Several rigorous reviews have found that, in developed countries, adherence among patients suffering chronic diseases averages only 50%.[6] The magnitude and impact of poor adherence in developing countries are assumed to be even higher given the paucity of health resources and inequities in access to health care. This seriously and adversely affects the treatment efficacy, especially in long-term therapies.[7] Numerous studies have explored potential predictors of adherence to medicine across various conditions. Frequently cited predictors include unmodifiable variables such as age, sex, ethnicity, income, education, and comorbidity.[8] Thus, this study aimed to characterize complementary and alternative medicine (CAM) use and assess its relationship with adherence to long-term oral therapy in the T2DM population.

Materials and Methods

The population of this descriptive study was 435 individuals who applied to the Diabetes Outpatient Clinic of Kocaeli University Faculty of Medicine Hospital in the December 2018- January 2019 period with T2DM who were treated with just oral agents for at least one year. One hundred twenty-three people were invited to the questionnaire; two illiterate, eight hearing-speech problems, and 13 unwilling patients were excluded, and the study was completed with 100 participants. Patients were informed about the study, and their consent was obtained, and the questionnaire was administered face to face with willing patients in the outpatient clinic setting.

The data were collected by a questionnaire comprised four main sections, exploring: (1) sociodemographic characteristics; (2) medication-taking behaviors; (3) Turkish Modified Morisky Scale (TMMS) with six questions to measure treatment adherence; (4) CAM questionnaire contained 15 questions related to CAM

methods used by patients, their sources of information, purposes of use and informing their doctors. The CAM questionnaire has not been carried out for those who stated that they have never used any CAM practices for their diseases.

Morisky scale to measure the patients' adherence to medical treatment in chronic diseases are easily applicable and reliable, which can evaluate motivation and level of knowledge separately. Also, it was concluded that it would be useful to assess adherence to long-term pharmacological treatment of chronic illnesses in primary care.[9] The scale consists of six questions, reflecting five domains: forgetfulness, carelessness; knowledge of long-term therapy; the impact of feeling well on adherence; and the impact of feeling poorly on adherence. Patients with a score of 4 or above were classified as 'treatment adherent; those with a score of 3 or below were classified as 'treatment nonadherent' or 'poor treatment adherent'. Patients who used CAM for chronic diseases at any time were classified as CAM users.

Statistical analyses of the data were carried out using SPSS software (Version 22.0, SPSS Inc., Chicago, IL, USA). Chi-square tests were used for the analysis of the relationships between categorical variables, independent samples t-test, or Mann-Whitney U test (for non-parametric data) for continuous variables. Results are reported as mean±SD or n (%). All statistical tests were two-sided, and differences were accepted as significant at $p<0.05$.

Results

The mean age of the patients included in our study was 58.56 ± 8.88 years, and the age range was 33-84. Fifty of the participants were female (50%), and fifty were male (50%). There were no significant differences in age, gender, education, and duration of diabetes between CAM and non-CAM users (Table 1). 56.36% (n = 31) of the 55 patients who stated that they used at least one CAM practices for any chronic disease used these practices for their diabetes, 69.09% (n = 38) for non-diabetic reasons, 25.45% (n = 14) for both diabetes and non-diabetic reasons (Figure 1). There was no overall difference in treatment adherence between CAM and non-CAM users. When the use of CAM for any reason or diabetes was examined separately, no significant difference was found between the adherence (Table 2). The most common reason cited for using CAM was to relieve complaints. When we investigated these symptoms, the pain was the first, and the high blood glucose level was the second. Another common reason for using CAM was found to support the conventional treatment. These results are summarized in the table below (Table 3).

Table 1. Demographic and clinical characteristics by CAM use status

	CAM (n=55)	No CAM (n=45)	p value
Age [mean ±SD]	57.87±9.23	59.40±8.46	0.395
Gender [n (%)]			
Male	27 (54)	23 (46)	1.000
Female	28 (56)	22 (44)	
Education [n (%)]			
Literate	4 (44.44)	5 (55.55)	0.746
Primary	23 (58.97)	16 (41.03)	
Secondary	7 (63.64)	4 (3.36)	
College-High School	21 (51.22)	20 (48.78)	
Duration of diabetes [n (%)]			
1-5 years	10 (25)	30 (75)	0.716
6-10 years	12 (34.28)	23 (65.72)	
11-19 years	6 (33.33)	12 (66.66)	
20 and +	3 (42.86)	4 (57.14)	

80% (n = 44) of CAM users used at least one of the herbal remedies. Cinnamon (n = 24), herbal teas (n = 15) and black seed (n = 13) were the most commonly used herbal remedies. When we look at the use of traditional practices, it was seen that five people used acupuncture, two people used dry cupping, 15 people used wet cupping (hijamah), and six people used leeches (Table 4). 14.5% (n = 8) of CAM users consulted physicians for the use of these practices; in contrast, 85.5% (n=47) of them did not. 89.4% (n = 42) of these patients stated that the reason for not consulting was 'afraid of the negative reaction of the doctor' (Table 5).

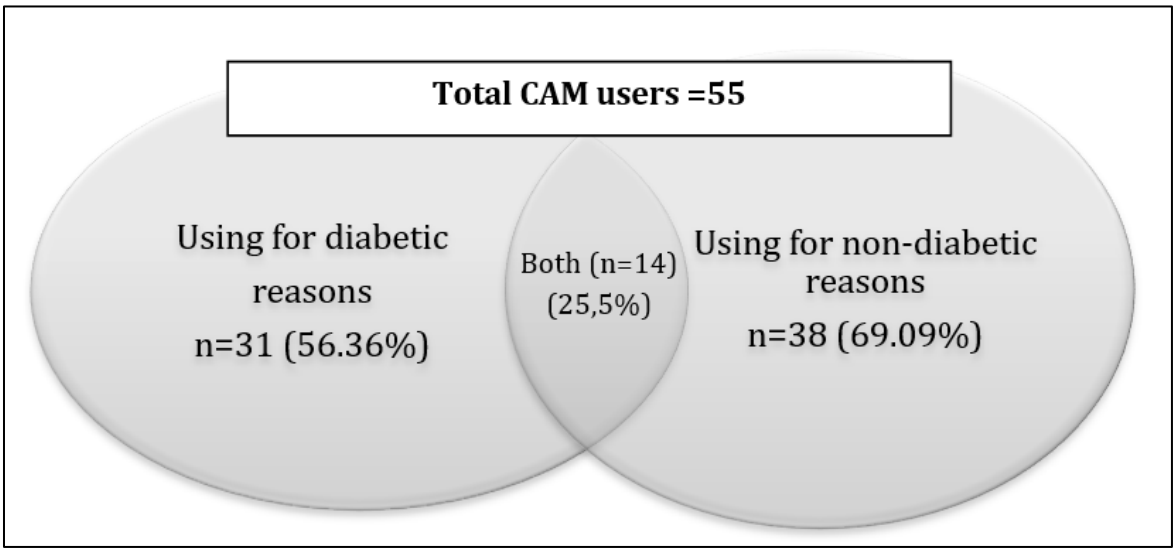

Figure 1. Reasons for CAM usage

Table 2. Adherence to medication by CAM status

CAM use for any reason			
	Yes (n=55)	**No (n=45)**	**p value**
Adherent (n=71)	39 (70.91)	32 (71.11)	1.000
Non-adherent (n=29)	16 (29.09)	13 (28.89)	
CAM use for T2DM			
	Yes (n=31)	**No (n=69)**	**p value**
Adherent (n=71)	21 (67.74)	50 (72.46)	0.630
Non-adherent (n=29)	10 (32.26)	19 (27.54)	

Table 3. Purposes of CAM use

Reason for CAM use	**Yes n (%)**	**No n (%)**	**Total n (%)**
Relieve complaints	38 (69.09)	17 (30.91)	55 (100)
Complaints			
Pain	15 (39.47)	23 (60.53)	38 (100)
High Blood Glucose	11 (28.95)	27 (71.05)	38 (100)
Other	12 (31.58)	26 (68.42)	38 (100)
As supportive treatment	23 (41.82)	32 (58.18)	55 (100)
Reduce to adverse effects of medication	2 (3.64)	53 (96.36)	55 (100)
Support to immunity	8 (14.55)	47 (85.45)	55 (100)
Replace medical treatment	5 (9.09)	50 (90.91)	55 (100)
To relax psychologically	4 (7.27)	51 (92.73)	55 (100)
To do everything against the disease	5 (9.09)	50 (90.91)	55 (100)

Table 4. Used CAM practices

CAM practice	**Users n (%)**
Herbal remedies	44 (80)
Acupuncture	5 (9.09)
Dry cupping	2 (3.64)
Wet cupping (hijamah)	15 (27.27)
Leeches	6 (10.91)
Multivitamins	2 (3.64)
Other (Ozone therapy, honey, probiotics)	3 (5.45)

Table 5. Consultation the use of CAM with the physician

Physician Consultation Status		n (%)	Total n (%)
Yes	Approved my use	4 (50)	8 (14.55)
	Did not approve	1 (12.50)	
	No ideas	3 (37.50)	
No	I was afraid of negative reaction	42 (89.36)	47 (85.45)
	I didn't need it	5 (10.64)	
Total			55 (100)

Discussion

Complementary and Alternative Medicine (CAM) use is increasing worldwide. This increase is thought to be mostly associated with the increase in chronic diseases such as diabetes[10,11]. CAM users with diabetes often think that CAM therapies are safe when used in combination with conventional therapies.[12]

In a review of 13 studies investigating the relationship between diabetes and CAM, the rate of CAM use ranged from 30.5% to 92.9%.[13] The frequency of CAM use in our study was consistent with the literature. In studies, although the use of any CAM method in diabetic patients was found to be significantly higher than in the general population, patients mostly used these practices for non-diabetes conditions.[14,15] Also, in our study, use for non-diabetes purposes was found to be more frequent.

Conflicting results have been reported regarding the relationship between CAM use and adherence to medical treatment. While numerous risk factors for non-adherence have been identified, the role of CAM use and its impact on adherence to conventional medicine is uncertain. It is known that the more medication a patient uses, the less likely the patient is to be adherent to a medication regimen; hence, the addition of CAM could lower medication adherence. [16,17] Our study aimed to investigate this relationship in patients with T2DM. In a study of 196 hypertensive patients in the UK, it was indicated that being a CAM user is significantly associated with imperfect adherence to antihypertensive medication.[18] On the other hand, in a retrospective study of 300 patients at least sixty-five years of age who used at least three medications, no association was found between the use of at least one complementary medicine and adherence to conventional medications.[17] In a study conducted by Bailey et al., it was shown that the use of CAM is one of the less common barriers to medication adherence in patients with diabetes.[19] A study which was conducted with 114 diabetic patients in Indonesia demonstrated that CAM usage significantly decreases adherence to prescribed diabetes medication.[20]

Even in the developed countries, the rate of treatment adherence was reported to be around 50%; this rate in our study was 71%, which was surprisingly higher than expected. Such high rates of patients' adherence may mask the difference between CAM users and non-users. Although the frequency of consultation with physicians

varies between 16.3% and 63.2%, patients often tend to hide that they used CAM.[13,21,22] In 2001, the American Diabetes Association (ADA) issued a position statement on "unproven therapies" encouraging health care providers to ask their patients about alternative therapies and practices, evaluate each therapy's effectiveness, be cognizant of any potential harm to patients, and acknowledge circumstances in which new and innovative diagnostic or therapeutic measures might be provided to patients.[23] In our study, it was noteworthy that the reason for not consulting was 'afraid of the negative reaction of the doctor'. In this context, it is seen that the physician should question the use of CAM in good communication and cooperation. As a consequence of such attitudes, there will not be any problem that the patients are afraid of the negative reaction of the doctor. ADA's advice is also in this sense.

This study is one of the few studies investigating the relationship between CAM use and adherence in T2DM patients. This is a superior aspect of our study. There are several limitations to this study. First, the data were based on the respondents' self-reported medication adherence and CAM usage, thus may have been affected by recall bias. Second, the study did not include patients' clinical data, which could help identify the effect of CAM use on their physiology.

Our results may be interpreted as the majority of patients perceive these practices as complementary and supportive rather than as an alternative to conventional medication. In our study, despite the contrary results, treatment adherence is a multidimensional phenomenon, and it should be kept in mind that it may be affected by many factors, including the use of CAM. Therefore, each patient should be assessed individually. On the other hand, the fact that patients do not consult a doctor while using herbal remedies indicates that we need to be careful about toxicities and dose insufficiency due to drug-herb interactions. All physicians, especially in primary care, should consider CAM practices without any prejudice and should have basic knowledge of these practices at least related to their specialty. This will play a vital role in guiding patients correctly. In this context, courses about complementary and alternative therapies should be added to medicine school curriculums, and these courses should continue even after graduation. Moreover, physicians should be instructed on how to obtain evidence-based information about these therapies.

Ethical considerations

The study was approved by the Kocaeli University Faculty of Medicine Ethics Committee (No: 2018/15.6).

Conflict of interest

The authors declare no conflict of interest.

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Case Report

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GERIATRIC APPROACH IN PRIMARY CARE: CASE REPORTS FROM A RURAL TOWN

BİRİNCİ BASAMAKTA GERİATRİK YAKLAŞIM: KIRSAL BİR BÖLGEDEN OLGULAR

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Öz

Geriatrik hastalar çok sayıda hastalığa sahip olmaya ve yüksek ilaç yükü altında kalmaya yatkındır. Aile sağlığı merkezleri, yaşlıların muayene ve reçete ihtiyaçları için hastanelere kıyasla daha ulaşılabilir yerlerdir. Kırsal bölgelerde, aile sağlığı merkezlerinin bu uygunluğu daha da önemli hale gelir. Bu durumda, aile hekimleri kırsal bölgede yaşayan yaşlıların yaşadıkları problemleri tespit edecek ve ilaçlarını düzeltip doğru ilaç kullanımını sağlayacak tek doktorlar olmaktadır. Bu makalede, kırsal bir bölge olan Bala'da, aile hekimini ziyaret eden üç geriatrik hasta olası uygunsuz ilaç kullanımı yönünden ele alınmıştır.
Anahtar Kelimeler: Birinci basamak, uygunsuz ilaç kullanımı, polifarmasi.

Abstract

Geriatric patients tend to have multiple diseases and a high burden of medication. Primary care centers are more accessible for the elderly to meet their examination and prescription needs compared to hospitals. In rural places, the convenience of primary care centers is far more important. Therefore, family physicians may be the only doctors in rural places to correct and/or supply proper medications as well as detecting ongoing problems of the elderly. In this article, three geriatric patients who visited their family physician in a rural town, Bala, were evaluated in terms of potentially inappropriate drug use.
Keywords: Primary care, inappropriate use of medication, polypharmacy.

Introduction

Life expectancy is rapidly lengthening. Aging is a process in which healthy adults turn into frail people. The physiological capacity of the body decreases with age, and the body becomes vulnerable to diseases. This brings up problems such as polypharmacy and Potentially Inappropriate Use of Medications (PIM).

Three case series are explained below. Each of them has both similar and/or unique features, which aim to show different problems. We also suggested solutions for each case, considering contemporary guidelines. Informed consent was obtained from all patients.

Case Series

Case 1

An 83-year-old male asked his family physician for a repeat prescription. He had no medical complaints. His medical history was vitamin B12 deficiency, which was diagnosed five months earlier, allergy on and off symptoms, and coronary artery disease for which he got a recent coronary stent placement.

His daily medication list included vitamin B12, clopidogrel, loratadine. In addition to these, he was taking amitriptyline occasionally. He had been on vitamin B12 for five months and clopidogrel for 20 days. He said that amitriptyline had been prescribed to him to relieve the feeling of 'restlessness 'by his cardiologist.

While discussing his history of medical use, the patient said that despite having had a recent coronary stent placement, he wasn't feeling well.

Physical examination of the patient showed abnormal cardiac rhythm with tachycardia. An electrocardiogram (ECG) was ordered. The ECG showed Supra-Ventricular Tachycardia (SVT) with Right Bundle Branch Block (RBBB) (Figure 1). He was referred to the emergency department. A follow-up visit was scheduled.

One week later, the patient came for a follow-up visit. He had been hospitalized in a cardiology clinic and had undergone Electrophysiologic Study (EPS). However, source of abnormal electrical activity could not be detected, and the patient was given medical therapy.

In the follow-up meeting, the medication list of the patient was updated to avoid PIM. Since the patient was able to absorb vitamin B12 and was consuming enough meat, 5 months of B12 supplementation was considered to be more than enough and was stopped.

The patient was on amitriptyline; however, according to the American Geriatrics Society (AGS) 2019 Updated Beers Criteria for PIM, Amitriptyline is highly anticholinergic, sedating, and causes hypotension in the elderly. Because of the strong evidence, it is strongly recommended to avoid this drug.[1] In addition to that, amitriptyline has cardiac side effects and should be avoided in treatment for depression in elderly patients.[2-3] Considering the cardiac problems of the patient and lack of depressive symptoms, amitriptyline was stopped. Loratadine is an H2 antihistamine, was found to be safe and proper information was given out.

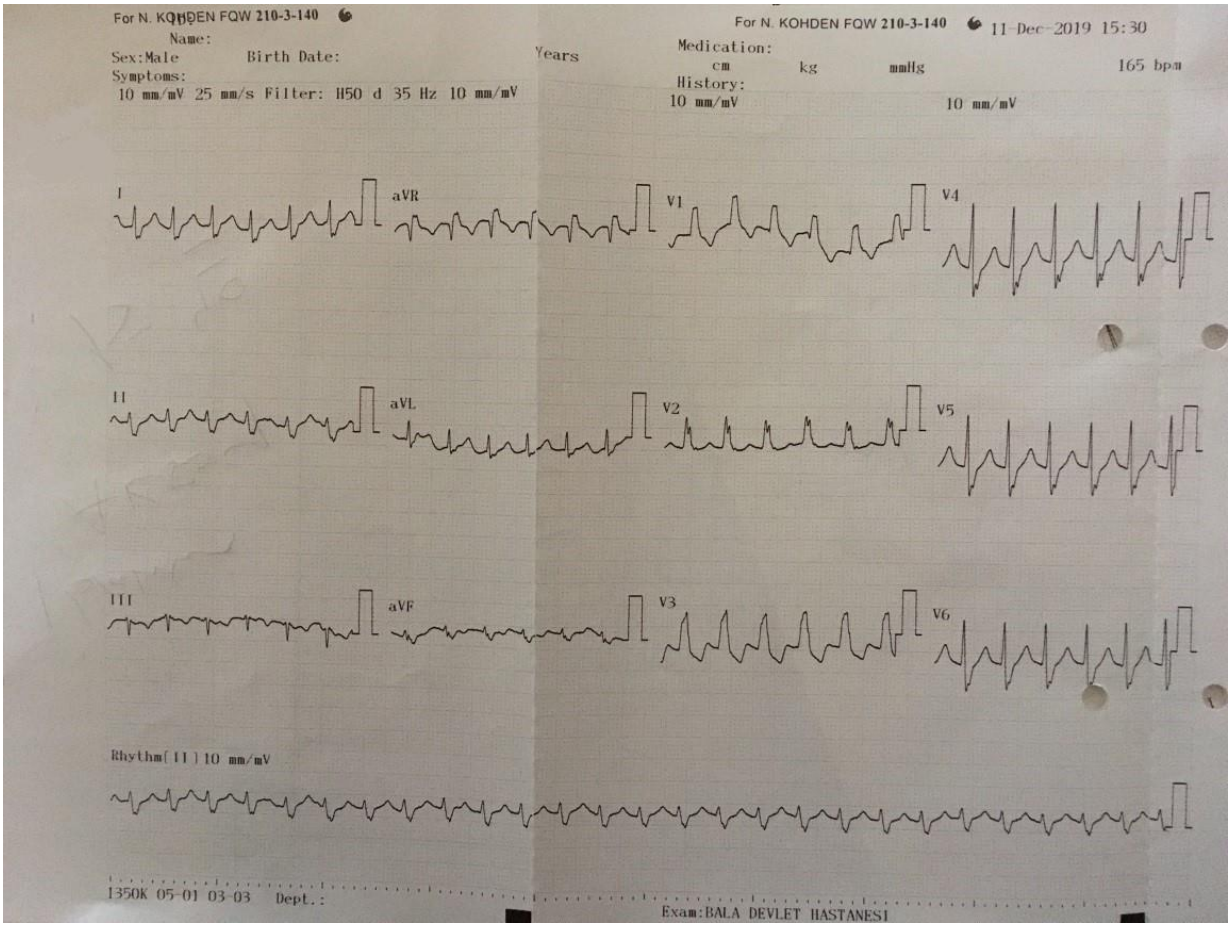

Figure 1. ECG is showing supraventricular tachycardia with right bundle branch block.

Case 2

A 77-year-old female patient came to the primary care center because of flank pain. The pain was in moderate severity and started about three months ago. It was not related to voiding or physical movements. The patient used to take a combination of losartan with thiazide. However, the patient could not find it in her local pharmacy. She was given candesartan combined with Hydrochlorothiazide instead. The patient did not benefit from the new tablet and her blood pressure increased. Hence, perindopril was added as an antihypertensive by another physician. The patient claimed that her flank pain started after she had started taking perindopril.

Her medical history included hypothyroidism, osteoarthritis, and hypertension. She was occasionally on lansoprazole, acetaminophen, and diclofenac in addition to her antihypertensives and L-thyroxin, which she took daily.

Physical examination of the patient was normal except for increased blood pressure which was 180/100 mmHg. Blood and urine analysis was conducted, and both were within the normal limits. The patient was evaluated to detect any PIM. The combination of candesartan and perindopril increases the rate of adverse drug effects and is not recommended.[4-5] Hence, perindopril was stopped. Amlodipine 5 mg daily was started as the third antihypertensive, and home blood pressure measurements were requested from the patient. Thyroid function tests were within the normal range for the patient, so thyroid replacement therapy was found to be effective. Proton Pump Inhibitors (PPI) increase the risk of *Clostridium difficile* infection, bone loss, and fractures; hence are not recommended after eight weeks in geriatric patients according to AGS Beers Criteria 2019.[1] The patient was taking diclofenac and acetaminophen when she had knee pain. Although not recommended routinely in high-risk patients such as patients with chronic NSAID use, PPI treatment could be necessary.[1] The patient was informed about NSAID's side effects, and lansoprazole was stopped. The patient was informed that if the need for NSAIDs increases, she will need to consult her physician in the future.

Case 3

A 78-year-old male patient visited the clinic to get a repeat prescription. He had no medical complaints. His medical history included diabetes mellitus, hypertension, and benign prostate hyperplasia. His medications were metformin (850 mg - three times a day), silodosin, lercanidipine, and acetylsalicylic acid. The patient said his blood glucose levels were high, and he skipped metformin sometimes. The physical examination was normal. Blood and urine samples were ordered, and he was asked to measure home blood glucose and home blood pressure for a week.

HbA1c level of the patient was 7.9%. Creatinine was 1.48 mg/dL. Other blood and urine tests were within normal limits. The glomerular filtration rate (GFR) was calculated as 45 mL/min/1.73m^2.

The mean blood pressure of the patient was 169/91.6 mmHg. The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) suggests 'in the general population aged 60 years or older, treat to a goal systolic blood pressure (SBP) lower than 150 mmHg and goal diastolic blood pressure (DBP) lower than 90 mmHg.'.[6] In order to achieve the goal of blood pressure in our patient, lercanidipine 20 mg daily was found to be insufficient. Lifestyle modifications were explained to the patient. Because the patient also had Diabetes Mellitus, perindopril combined with amlodipine was prescribed, and the patient was asked to perform home blood pressure measurement for the follow-up meeting.

Mean fasting blood glucose was 188 mg/dL with a maximum of 210 mg/dL and a minimum of 153 mg/dL. Mean post-prandial blood glucose was 247 mg/dL. Minimum post-prandial blood glucose was 160 mg/dL and 359 mg/dL maximum. It is recommended by the American Diabetes Association that 'older adults who are otherwise healthy with few coexisting chronic illnesses and intact cognitive function and functional status should have lower glycemic goals (such as A1C <7.5% [58 mmol/mol])' and our patient fitted into that category. Metformin is the first-line agent in the treatment of diabetes mellitus type 2.[7] However, a half dose (1000 mg/day) is recommended in patients with GFR 30-60 mL/min. The metformin dose was lowered to 1000 mg/day.[8] To reach the optimal blood glucose management for the patient, another antidiabetic drug was necessary. Sulfonylureas are known to be hypoglycemic agents. However, gliclazide being the second generation short-acting sulfonylurea causes less hypoglycemia.[7-9] Gliclazide 30 mg daily was added as a second antidiabetic drug.

The patient was on acetylsalicylic acid (300 mg/day) for primary prevention. In the 2019 AGS Beers Update Expert Panel, the age threshold beyond which extra caution is advised for using aspirin for the primary prevention of cardiovascular disease was lowered to 70 years or older for 80 years or older. Considering the age and the GFR of our patient, the risk of gastrointestinal bleeding was considered superior to the benefit of primary prevention, and therefore aspirin was stopped.

Discussion

Geriatric patients tend to have subtle and atypical symptoms.[10] The symptoms of even serious diseases such as SVT may be masked. Regarding our *Case 1*, the family physician assessed the patients' history of medical use. After that, a proper physical examination led the physician to diagnose the ongoing yet hidden emergency. This case is a good reminder to be cautious with geriatric patients who do not even have any complaints. Each and every consultation of geriatric patients should include a reevaluation of the medications. This case report is also an important example of PIM and how to correct it.

In rural places, the transportation of the elderly could be problematic. Such as our patient in *Case 2* whose antihypertensives were changed due to the local pharmacy's lack of stock. While handling geriatric patients' diseases, family physicians in rural areas should also consider local social life conditions. The most suitable drug must be found to achieve treatment compliance.

Resembling our *Case 3*, patients with hypertension, diabetes and/or reduced GFR are very common in daily geriatric practice due to the high incidence rate of these diseases. It is important to avoid PIM while at the same time reaching target goals to reduce cardiovascular risk. This case report is an example of how to handle elderly patients with comorbidities.

These three cases show that elderly people need an attentive evaluation of their medication on every visit. In rural places like Bala, family physicians are responsible for avoiding PIM and polypharmacy in elderly patients. Thus, every geriatric patient who visits a primary care center to get a repeat prescription should be asked about their history of medical use as well as being given a physical examination.

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Olgu Sunumu

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AŞILAR VARYANT COVID-19 HASTALIĞINI ÖNLEMEDE ETKİN Mİ? BİR AŞILI VARYANT COVID-19 VAKASI

ARE VACCINES EFFECTIVE IN PREVENTING VARIANT COVID-19 DISEASE? A CASE OF VACCINATED VARIANT COVID-19

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Öz

SARS-CoV-2 virüsünün neden olduğu COVID 19 hastalığı günümüzün en önemli halk sağlığı sorunudur. Bu virüsün oluşturduğu pandemi tüm dünyadaki yaşam biçimini köklü olarak değiştirdi. Bu virüse karşı geliştirilen aşılar ise elimizdeki en önemli savunma aracımız. Olgumuz iki doz aşılanmasına rağmen varyant COVID 19 hastalığına yakalan bir hastadır. Bu vaka üzerinden aşılanmanın önemi kadar kişisel ve sosyal önlemlere bir süre daha uymanın gereği vurgulanacaktır.
Anahtar Kelimeler: Varyant COVID-19, SARS-CoV-2, pnömoni, aşılama.

Abstract

COVID 19 disease caused by the SARS-CoV-2 virus is the most important public health problem of today. The pandemic caused by this virus has radically changed the way of life all over the world. Vaccines developed against this virus are our most important defense tool. Our case is a patient with variant COVID 19 disease, despite two doses of vaccination. In this case, the importance of adhering to personal and social precautions for a while will be emphasized as well as the importance of vaccination.
Keywords: Variant COVID-19, SARS-CoV-2, pneumonia, vaccination.

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Giriş

2019 yılı sonunda Çin'in Hubei eyaletinin bir şehri olan Wuhan'da bir dizi viral pnömoni vakası saptandı.[1] Bu pnömonilerin etkeni yeni bir tür koronavirüstü. Koronavirüsler hem insan hem de hayvanlar açısından önemi olan büyük, zarflı RNA virüsleridir.[2] Bu virüs öncelikle Çin'de bir salgına neden oldu. Ardından tüm dünyaya yayıldı. Dünya Sağlık Örgütü (WHO) Şubat 2020'de, 2019 koronavirüs hastalığı anlamına gelen COVID-19 hastalığını tanımladı. Bu hastalığa neden olan virüs SARS-CoV-2 virüsü olarak adlandırıldı. Ülkemizdeki ilk vaka 11 Mart 2020'de tespit edildi ve bu tarihten itibaren virüs hızla yayılım gösterdi. 16 Mart 2021 itibari ile tüm dünyada 120 milyondan fazla vaka tespit edildi ve 2,6 milyon hasta bu hastalık nedeniyle hayatını kaybetti.

İlaçların geliştirilmesinde olduğu gibi, aşıların geliştirme süreçleri de preklinik değerlendirme ve üç farklı klinik evrenin faz 1, 2 ve 3 tamamlanmasından oluşur. COVID 19 aşı geliştirme çalışmalarında çok hızlı yol alındı. Farklı aşı üretim platformları kullanılarak birçok aşı üretilmeye çalışıldı. Bu yöntemler arasında inaktive aşılar, canlı zayıflatılmış aşılar, protein rekombinant aşıları olduğu gibi daha yeni yöntemlerden olan vektör aşıları ve nükleik asit (DNA ve RNA) aşıları da bulunmaktadır.

Ülkemizde Ocak 2021 itibariyle inaktive bir aşı olan COVID 19 (Coronovac) aşısı uygulanmaya başlandı. Bu inaktive COVID-19 aşısı Çin'de geliştirildi. Adjuvan olarak alüminyum hidroksit içermektedir.[3] Aşı, 28 gün arayla iki doz şeklinde intramusküler olarak uygulanmaktadır. Aşı insanlarda güvenli ve immünojeniktir.[4] Çin, Brezilya ve Türkiye'de kullanılmaktadır.

Olgu

53 yaşında erkek hasta boğaz ağrısı ve ses kısıklığı şikayetleri ile acil servise 26.01.2021 tarihinde başvurdu. Bilinen Hepatit B taşıyıcılığı ve Hipertansiyon dışında hastalığı bulunmuyordu. Valsartan 160 mg ve tenofovir disoproksil 245 mg dışında düzenli ilaç kullanmıyordu. Fizik muayene bulguları doğal saptanan hastadan COVID 19 PCR testi için nazofarengeal numune alındı. PCR testi pozitif saptanması üzerine numuneye gen analizi yapıldı. İngiliz varyant tip (B.1.1.7) SARS-CoV-2 tespit edildi. Hasta karantina hastanemize yatırılarak filyasyon ekibi tarafından başlanan favipiravir ve hidroksiklorokin tedavisine devam edildi. Tedavisine Enoksaparin sodyum 4000 IU/gün eklendi. Hastanın iki ay önce inaktif koronavirüs aşısının ilk dozunu yaptırdığı, bir ay önce de ikinci dozunu yaptırdığı öğrenildi ve teyit edildi. Hastanın yatışında kan tetkikleri yapıldı. Üre: 32 mg/dL, Kreatinin: 1,1 mg/dL, AST: 34 U/L, ALT: 54 U/L, Fibrinojen: 3,61 g/L, D-dimer: 0,19 mg/L, Prokalsitonin: 0,09 µg/L, Ferritin: 339 µg/L, WBC 4850 /µL, NEU: 1790 /µL, LYM: 2320 /µL, HGB: 15,8 g/dL, PLT: 159 000 /µL, ESR: 5 mm/saat, CRP: 6 mg/L, COVID-19 IgG + IgM: 8,22 (reaktif) saptandı. Hasta kliniğimizde yatarak takip edildi. Vital bulguları düzenli olarak izlendi. Muayeneleri belirli aralıkla tekrarlandı. Genel durumu iyi, vital bulguları stabil seyretti. 1 hafta sonra hastanın oksijen satürasyonunda hafif düşme

izlendi. Kontrol kan tetkikleri yapıldı. Üre: 30 mg/dL, Kreatinin: 1 mg/dL, AST: 72 U/L, ALT: 157 U/L, Fibrinojen: 3,16 g/L, D-dimer: 0,19 mg/L, Prokalsitonin: 0,11 µg/L, Ferritin: 886 µg/L, WBC 6630 /µL, NEU: 3290 /µL, LYM: 2630 /µL, HGB: 17,1 g/dL, PLT: 217 000 /µL, ESR: 3 mm/saat, CRP: 1 mg/L tespit edildi. Hastadan COVID 19 PCR testi için nazofarengeal numune alındı. Test sonucu negatif saptandı. Hastaya bir gün sonra Toraks BT çektirildi. Tomografi sonucunda sağ akciğer üst lob posterior segmentte 3,5 mm çaplı buzlu cam nodül izlendi. Ayrıca her iki akciğer alt lob posterior bazal segmentlerde periferal yerleşimli buzlu cam dansitesinde infiltrasyon mevcuttu. Yine sağ akciğer alt lob superior segmentte de periferal fokal buzlu cam infiltratı izlendi. Hastanın pnömoni kliniği hastada ek bir semptom oluşturmadı. Ertesi gün alınan COVID 19 PCR testi bu kez pozitif saptandı. Hastanın kliniğimizdeki takip ve tedavisine devam edildi. 08.02.2021 tarihinde kan tetkiklerinde Üre: 34 mg/dL, Kreatinin: 1,2 mg/dL, AST: 27 U/L, ALT: 134 U/L, Fibrinojen: 2,54 g/L, D-dimer: 0,2 mg/L, Prokalsitonin: 0,09 µg/L, Ferritin: 814 µg/L, WBC 5790 /µL, NEU: 3070 /µL, LYM: 2040 /µL, HGB: 16,1 g/dL, PLT: 200 000 /µL, ESR: 5 mm/saat, CRP: 0,5 mg/L tespit edildi. Bir gün sonra alınan COVID 19 PCR testi negatif saptandı. Hastadan olgu sunumu için aydınlatılmış onam alındı. Hasta önerilerle taburcu edildi.

Tartışma

COVID 19 pandemisi ile mücadelede koronavirüs aşıları insanlığın elindeki en etkili yöntem konumundadır. İnsan ve hayvanlar üzerinde yapılan çalışmalar SARS-CoV-2 virüsünün reenfeksiyona karşı koruma sağlayan fonksiyonel nötralizan antikorlar oluşturduğunu göstermektedir.[5] Bu gözlem, nötralizan antikorların oluşmasını sağlayan bir aşının hastalığı önleyebileceğini ortaya koymaktadır. COVID-19 aşıları için birincil antijenik hedef, konakçı hücrelerdeki anjiyotensin dönüştürücü enzim 2 (ACE 2) reseptörüne bağlanan ve membran füzyonunu indükleyen geniş yüzeyli spike proteinidir.[6] ACE 2 reseptörleri vücutta yaygın olarak akciğer, kalp, böbrek, barsak ve kan damarlarında bulunur. Virüsün birçok organ sistemini etkileyebilmesinin altında da bu mekanizma söz konusudur. Vücut tarafından oluşturulan antikorların koruyucu olduğu düşünülmektedir. Ancak olgumuzda izlendiği üzere tamamıyla koruma sağlamayabilir. COVID 19 enfeksiyonu (asemptomatik enfeksiyon dahil) aşılamaya rağmen hala ortaya çıkabilir. Aşılanmış bireylere de kişisel koruyucu önlemlere (maske ve mesafe) devam etmeleri hatırlatılmalıdır.

Koronavirüsler zarflı pozitif sarmallı RNA virüsleridir. SARS-CoV-2 genomundaki çoğu mutasyonun viral fonksiyon üzerinde etkisi bulunmamaktadır.[7] Bazı varyantlar toplumda hızlı yayılması ve klinik etki potansiyeli nedeniyle ilgi çekmektedir. B.1.1.7 varyantı Birleşik Krallık'ta 2020 yılının sonunda ortaya çıkıp birçok ülkeye yayıldı. Bizim vakamız da bu varyant ile enfekteydi. B.1.1.7 varyantının daha yüksek bir bulaşma oranına sahip olması daha fazla vakaya yol açacak, genel olarak klinik bakıma ihtiyaç duyan hastaların sayısını artıracak, sağlık sistemi üzerindeki yükü daha da ağırlaştırarak daha fazla ölümle sonuçlanacaktır.[8] Bulaşmayı azaltmak için önlemler almak, B.1.1.7'nin potansiyel etkisini azaltabilir ve aşılama kapsamını artırmak için kritik süre

sağlayabilir. Toplu olarak, aşılama, fiziksel mesafe, maske kullanımı, el hijyeni, izolasyon ve karantina dahil olmak üzere etkili halk sağlığı önlemleriyle SARS-CoV-2'nin yayılması sınırlandırılabilir.[9] B.1.1.7 varyantının immun kaçış ile ilişkili olduğunu gösteren bir durum henüz ortaya konmadı.[10] Ancak unutulmamalı ki varyasyon çeşitliliğinin artması ve pandemide kontrolün sağlanamaması durumunda immün kaçış mekanizmalarına sahip aşılara dirençli suşlar ortaya çıkacaktır.

Ülkemizde de uygulanan Coronavac aşısı hem 18-59 yaş arası hem de 60 yaş üzeri bireylerde etkin ve güvenli bulundu.[3,4] COVID 19 hastalığını %100 önleyen bir aşı henüz bulunmamaktadır. Hastalığı tamamen önleyemese de kritik hastalık ve ölümü önlemesi aşılar için büyük bir başarı sayılmalıdır. Bizim olgumuz çift doz aşısını yaptırdıktan sonra hastalandı. Ancak hafif bir pnömoni kliniği ile hastalığı geçirdi.

Sonuç olarak COVID 19 tüm dünya için bir tehdit olmayı sürdürmektedir. Aşılama, kişisel ve sosyal önlemler SARS-CoV-2 ile mücadelede başarı şansını artıracaktır.

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