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Journal article on the Internet

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Website

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 Jul 2002]. Available from: www.cancer-pain.org

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Acknowledgements

The source of financial grants and the contribution of colleagues or institutions should be acknowledged.

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Original Article / Orijinal Araştırma

Evaluation of the Hemoglobin A1c Test in Detecting Pediatric Prediabetes

Pediatrik Prediyabetin Tespitinde Hemoglobin A1c Testinin Değerlendirilmesi

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Abstract

Aim: It was aimed to evaluate the diagnostic performance of the hemoglobin A1c (HbA1c) test in pediatric prediabetes, and to determine the cut-off value for the adolescent.

Material and Method: This study was carried out by retrospectively evaluating the data of 379 adolescents aged between 10 and 18 years. Prediabetes was diagnosed based on glucose criteria, either the fasting glucose value or the 2-hour (2h) glucose value during a 75 g oral glucose tolerance test (OGTT), or HbA1c criteria. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for fasting, OGTT 2h glucose, and HbA1c. The area under the curve (AUC) was calculated for each test by receiver-operating characteristic analysis.

Results: 2.1% of individuals were assigned to the diabetes mellitus group, 21.9% to the prediabetes group, and 76.0% to the normoglycemia group. When 5.7 was used as the threshold value for HbA1c in prediabetes, the sensitivity was 53.0%. The AUC was 0.83 for the HbA1c test. An HbA1c threshold of 5.55% was determined as the optimal cut-off for diagnosing prediabetes, with 62.7% sensitivity and 93.0% specificity.

Conclusion: Although the use of adults' HbA1c criteria for the diagnosis of prediabetes in the pediatric ages is controversial due to the differences between the results of glucose and HbA1c-based tests, prediabetes screening is still important. HbA1c≥5.55 will be useful to follow up on adolescents with prediabetes in terms of risk and to screen them with blood glucose.

Keywords: HbA1c, pediatric prediabetes, diagnostic performance

Öz

Amaç: Hemoglobin A1c (HbA1c) testinin pediatrik prediyabet açısından tanısal performansının değerlendirilmesi, adolesan yaş grubu için cut-off değer belirlenmesi amaçlandı.

Gereç ve Yöntem: Çalışma, yaşları 10-18 yıl arasında değişen toplam 379 çocuğa ait verinin retrospektif değerlendirilmesiyle gerçekleştirildi. Prediyabet vakaları glukoz [açlık ve 75 g oral glukoz tolerans testi (OGTT) 2. Saat (2. sa)] ve Hba1c kriterlerine göre belirlendi. Sensitivite, spesifite, pozitif prediktif değer (PPV), negatif prediktif değer (NPV) ve ROC (receiver-operating characteristic) analiziyle AUC (area under the curve); açlık ve OGTT 2 sa glukozu, HbA1c testlerinin her biri için hesaplandı.

Bulgular: Bireylerin %2.1'i diabetes mellitus, %21.9'u prediyabet, %76.0'ı ise normoglisemi grubuna atandı. Prediyabette HbA1c testi için 5.7 değeri cut-off olarak alındığında sensitivite %53.0 olarak hesaplandı. HbA1c testi için AUC 0.83 olarak hesaplandı. HbA1c opimal cut-off değeri %5.55 olarak belirlendi. Bu değerde sensitivite %62.7, spesifite ise %93.0 olarak hesaplandı.

Sonuç: Pediatrik yaşlarda prediyabet tanısında erişkin HbA1c kriterlerinin kullanımı glukoz ve HbA1c temelli test sonuçları arasındaki farklılıklar nedeniyle tartışmalı olsa da prediyabet taraması önemini korumaktadır. HbA1c ≥ 5.55 değerinin prediyabetli adolesanların risk açısından takip edilmesi ve kan glukoz düzeyiyle taranması konusunda faydalı olacağı kanaatindeyiz.

Anahtar Kelimeler: HbA1c, pediatrik prediyabet, tanısal performans

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INTRODUCTION

Diabetes mellitus (DM), a disorder characterized by hyperglycemia resulting from impaired insulin secretion and/or insulin activity, is one of the most common chronic diseases in children.[1] Conditions in which plasma glucose and hemoglobin A1c (HbA1c) levels are higher than normal but do not reach the diagnostic limits of diabetes are called prediabetes.

Fasting plasma glucose and oral glucose tolerance test (OGTT) 2-hour (2h) plasma glucose are accepted as the conventional tests in the diagnosis of DM. However, these tests require fasting and preliminary preparation. The HbA1c test, on the other hand, is a simpler and more applicable test that does not require fasting. It can also be used as an indicator of chronic hyperglycemia.[2]

HbA1c is a subfraction of glycohemoglobin that is formed non-enzymatically due to glucose exposure. It is continuously produced in vivo by glucose forming a ketoamine at the beta chain N-terminus of hemoglobin. For this reason, HbA1c is used to monitor glucose levels because it is correlated with extracellular glucose levels and provides an estimate of average glucose levels for the last 120 days.[3]

An HbA1c of 5.7-6.4%, provided it was obtained by a standardized analysis, indicates prediabetes.[4] In addition to the differences in its standardization of HbA1c, the use of the same values in the pediatric age groups is highly controversial, since the cut-off values of the HbA1c test are mostly used in adults.[5,6] This study aimed to evaluate the diagnostic performance of the HbA1c test in prediabetes and to determine the cut-off value for adolescents.

MATERIAL AND METHOD

This study was carried out by retrospectively evaluating the data of 379 children aged between 10 and 18 years who applied to Yüzüncü Yıl University Dursun Odabaş Medical Center and underwent OGTT. Individuals with Hb<11 mg/dL and/or who were determined to have any hemoglobinopathy were not included in the study. Fasting glucose levels were measured in blood taken after at least 8-10 hours of fasting. Two-hour data after a 1.75 g/kg (maximum 75 g) oral glucose load were used to evaluate OGTT 2h glucose levels. Normoglycemia was determined at a fasting serum glucose of less than 100 mg/dL and an OGTT 2h serum glucose of less than 140 mg/dL and an HbA1c of less than 5.7%. Prediabetes was diagnosed based on glucose criteria, either the fasting glucose value or the 2h glucose value during a 75g OGTT, or HbA1c criteria. An HbA1C of 5.7-6.4% and/or fasting serum glucose of 100-125 mg/dL and/or an OGTT 2h serum glucose of 140-199 mg/dL resulted indicating prediabetes. Diabetes was diagnosed when the fasting serum glucose level was greater than or equal to 126 mg/dL, the OGTT 2h serum glucose level was greater than or equal to 200 mg/dL, and the HbA1c level was greater than or equal to 6.5%.[4] Serum glucose levels were analyzed by the hexokinase method, and HbA1c levels were analyzed by the high-performance liquid chromatography (HPLC) method.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for HbA1c, fasting, and OGTT 2h glucose tests. The area under the curve (AUC) was calculated for each test by receiver-operating characteristic (ROC) analysis. The Youden index was used to determine the optimal cut-off values ["J=maximum (sensitivity+specificity −1)"].[7] The Mann-Whitney U test was used to evaluate the difference in HbA1c and glucose levels according to gender. A Spearman correlation analysis was performed to determine the correlation between HbA1c and blood glucose values. Analyses were performed using Microsoft Excel v2019 and IBM SPSS Statistics 22 programs. p-value < 0.05 was considered statistically significant.

RESULTS

59.6% (226) were female, and 40.4% (153) were male. The mean age was 14.0±2.5 years. Eight (2.1%) of 379 individuals were assigned to the DM, 83 (21.9%) to prediabetes, and 288 (76.0%) to normoglycemia groups. Since the number of patients with DM was small, they (n=8) were not included in the statistical analysis. The median (min-max) values of tests are summarized in **Table 1**. When grouped according to gender, fasting glucose levels were found to be higher in males compared to females (p=0.002). There was no difference between OGTT 2h glucose and HbA1c levels in terms of gender (p=0.096, 0.385).

The sensitivity, specificity, PPV, and NPV for HbA1c, fasting, and OGTT 2h glucose tests are shown in **Table 2**. When 5.7 was used as the threshold value of HbA1c in prediabetes, the sensitivity was 53.0%. An HbA1c threshold of 5.55% was determined as the optimal cut-off for diagnosing prediabetes, with 62.7% sensitivity and 93.0% specificity. Since each of the three tests was used as the gold standard, specificity and PPV were 100% as expected (**Table 2**). The AUC values analyzed by the ROC curve were 0.86, 0.72, and 0.83 for fasting glucose, OGTT 2h glucose, and HbA1c tests, respectively (**Figure 1**).

Table 1. Data for groups and tests.

	Number (%)	Fasting serum glucose (mg/dL)	OGTT 2h serum glucose (mg/dL)	HbA1c (%)
All	379 (100)	92.0 (62.0-158.0)	103.0 (50.0-245.0)	5.3 (4-8.7)
Normoglycemia	288 (76.0)	90.0 (62.0-99.0)	99.0 (50.0-136.0)	5.3 (4.0-5.6)
Prediabetes	83 (21.9)	102.0 (76.0-125.0)	114.0 (75.0-187.0)	5.7 (4.7-6.4)
Diabetes Mellitus	8 (2.1)	132.0 (100.0-158.0)	187.5 (113.0-245.0)	6.1 (5.1-8.7)

The test results for each group were expressed as a median (min-max).

Table 2: Diagnostic performance values of tests for diagnosing prediabetes.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
HbA1c (≥%5,7)	53.0	100	100	88,1	0,83
Fasting glucose (≥100 mg/dL)	60.2	100	100	89.7	0,86
OGTT 2h glucose (≥140 mg/dL)	18.1	100	100	80.9	0,72

OGTT: Oral glucose tolerance test, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve.

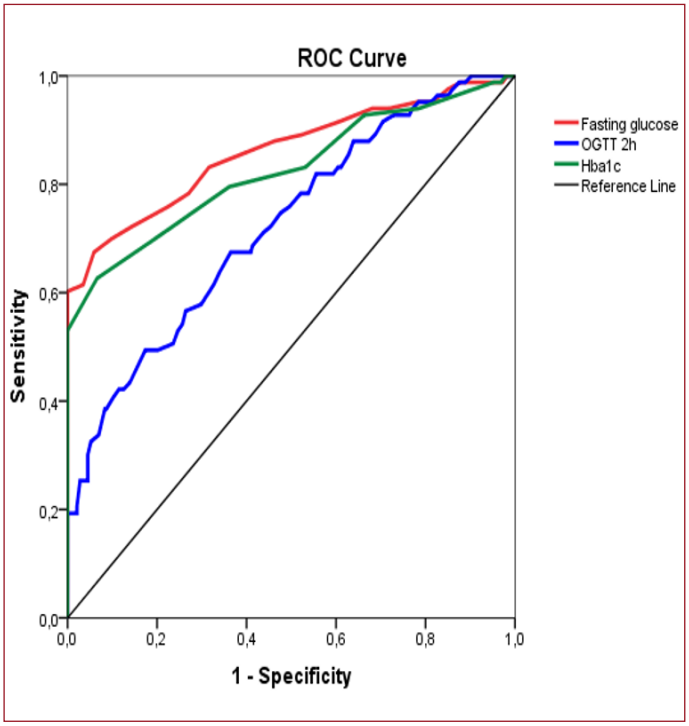

Figure 1. Receiver operating characteristic (ROC) curves comparing serum fasting glucose (red), oral glucose tolerance test (OGTT) 2 hour (2h) glucose (blue), and HbA1c (green) for the detection of prediabetes. The AUC (area under the curve) of the tests was calculated as 0.86, 0.72, and 0.83 for fasting glucose, OGTT 2h glucose, and HbA1c, respectively.

According to the HbA1c test, 25 prediabetic cases and one diabetic case did not meet the blood glucose criteria. According to the fasting glucose, 29 prediabetic and three diabetic cases did not meet both OGTT 2h glucose and Hba1c criteria. According to the OGTT 2h glucose, six prediabetic cases, and one diabetic case did not meet both fasting glucose and Hba1c criteria (**Figure 2, 3**). It was determined that HbA1c values were moderately correlated with fasting glucose values (r=0.306; p <0.001), while HbA1c levels were correlated with OGTT 2h glucose at a low degree (r=0.213; p <0.001). Fasting glucose values were moderately correlated with OGTT 2h glucose values (r=0.329; p <0.001).

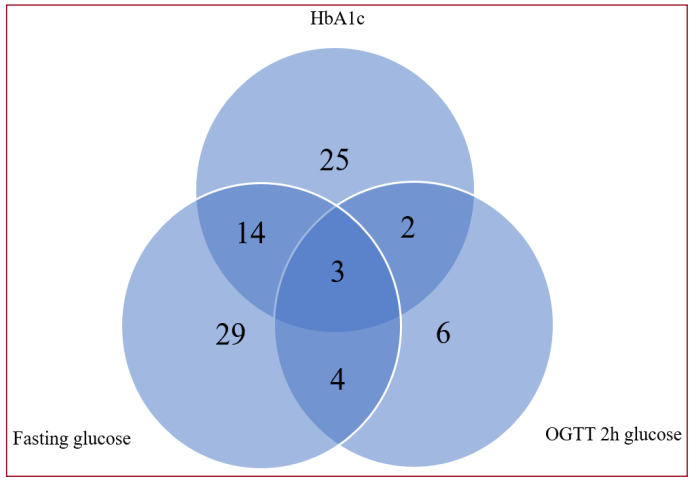

Figure 2. Venn Diagrams for Prediabetes. Prediabetes diagnosed by HbA1c 5.7-6.4% (n=44) or fasting glucose 100-125 mg/dL (n=50) or OGTT 2h glucose 140 mg/dL-199 mg/dL (n=15).

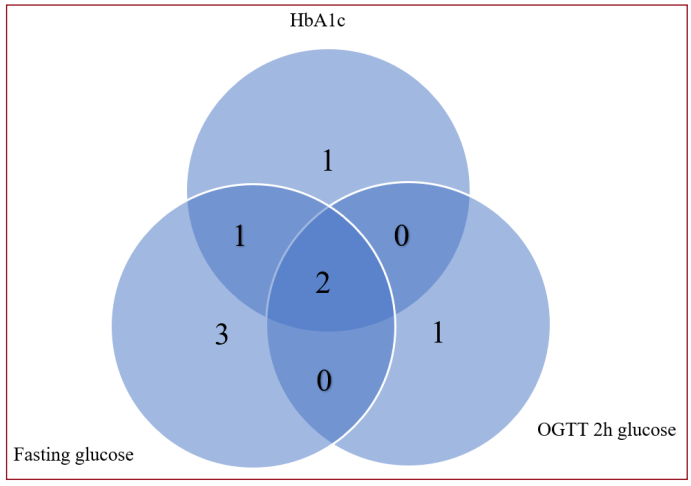

Figure 3. Venn Diagrams for Diabetes mellitus. Diabetes diagnosed by HbA1c ≥ 6.5% (n=4) or fasting glucose ≥ 126 mg/dL (n=6) or OGTT 2h glucose ≥ 200 mg/dL (n=3)

DISCUSSION

In this retrospective study, 21.9% (n=83) of the individuals who underwent OGTT had prediabetes. In the study, it was observed that the HbA1c ≥5.7 criteria had low sensitivity in the diagnosis of prediabetes for adolescents from the Van region of Turkey. We recommend an HbA1c value of 5.55% as an optimal cut-off to screen for prediabetes. This is a unique study evaluating the performance of HbA1c in the diagnosis of prediabetes and its relationship with serum glucose levels in adolescents in the Van region.

The prevalence of DM is increasing in both children and adults. Type 1 DM usually has an obvious clinical presentation. Type 2 DM can be asymptomatic for a long time, so tests to screen for Type 2 DM may be needed more frequently.[8] Although fasting plasma glucose and OGTT 2h plasma glucose are the conventional tests for diagnosis, these tests are demanding to apply for both the individual and the institution. On the other hand, HbA1c is relatively simple and feasible. It does not

require fasting and shows less variation.[9] Since it is related to the average glucose level of the last 8-10 weeks, it can provide information about chronic hyperglycemia and complications.[2,3] However, there are also disadvantages. HbA1c may vary according to age and ethnicity.[10] It may show insufficient performance in detecting Type 1 DM, which can develop suddenly. Conditions such as iron deficiency, anemia, and hemoglobinopathy, which change erythrocyte lifespan, may affect HbA1c levels.[11,12]

While fasting and OGTT 2h glucose threshold values were determined in the past, values deviating from the population's normal ranges were used as threshold values; however, currently, it is determined by following diabetes complications.[13] The diagnosis of DM in children is made according to the same criteria used for adults. Although a strong correlation was observed between plasma glucose and HbA1c in adults in many studies, the information on the correlation in children is not clear, since most of these data are based on studies performed on adults.

In the present study, eight (2.1%) individuals were diagnosed with DM. This rate was reported as 1.2% in the previous study, similar to our findings.[8] However, in the study of Kim et al., it was reported as 17.4%.[13] Since the aforementioned study [13] was conducted on individuals who had obesity and/or glycosuria, it is expected that a high rate was found. Some studies conducted in pediatric ages found the diagnostic performance of HbA1c insufficient and was not recommend its use alone.[8,14] In the study by Lee et al.[8] AUC was calculated at a much lower value (0.54) than in the present study to predict dysglycemia (prediabetes or diabetes). Nowicka et al.[14] reported the AUC of Hba1c (0.81) at a similar level to the present study. In the study by Kim et al.[13] the AUCs for each test (fasting glucose, OGTT 2h glucose, and HbA1c) were higher (>0.9) than our findings. However, the performance in the diagnosis of DM, not in the diagnosis of prediabetes, was examined in the aforementioned study.

In prediabetes, the sensitivity of the threshold value of HbA1c≥ 5.7% was low, but it is higher than the sensitivity of OGTT 2h glucose (140 mg/dL), (**Table 2**). In the study of Kim et al.[13] the sensitivities of fasting glucose, OGTT 2h glucose, and HbA1c tests in the diagnosis of pediatric DM were reported as 63.8%, 85.1%, and 89.4%, respectively. In the present study, while the sensitivity of fasting glucose for predicting prediabetes is similar (60.2%), the sensitivities of OGTT 2h glucose and HbA1c tests were much lower (18.1%; 53.0%) than in the mentioned study. In the study of Wallace et al.[15] the sensitivities of Hba1c and fasting glucose were 55.5% and 35.8%, respectively. In this study, 5.7% and 100 mg/dL cut-off values were used, respectively, as in the present study, but it was examined in cases of hyperglycemia (prediabetes or diabetes). Nowicka et al.[14] reported that the optimal threshold of HbA1c was 5.5%, with a specificity of 59.9% and a sensitivity of 57.0%. In the present study, the optimal threshold value was calculated similarly (5.55%), with higher sensitivity and specificity. In previous studies, the sensitivity of blood glucose was reported in the range of 40%-94%.[16,17] The range of these studies using laboratory values of adults is quite wide. The time at which blood is collected (fasting, 1-hour, 2-hour, etc.) may cause differences between studies. Specimen type (serum, plasma, etc.) and type of blood collection tube can affect results. In this study, glucose was analyzed on serum samples. The guideline recommends that glucose be measured in venous plasma if it is used in the diagnosis of diabetes.[18] Although the threshold is determined according to the plasma value, serum samples are also used in many centers. It should be kept in mind that serum glucose values are lower than those of plasma.[19] This means that if glucose is measured in serum, lower values compared to plasma glucose should be used as the cutoff value to achieve similar diagnostic sensitivity. It is also an important issue whether the HbA1c criterion is included when analyses of diagnostic performance are conducted in studies.

In the present study, a low/moderate level of correlation was observed between HbA1c and serum glucose levels. A moderate correlation was observed between fasting and OGTT 2h glucose values. However, Kim et al.[13] and Ogawa et al.[20] reported that glucose levels and the HbA1c test showed a strong correlation. The inconsistencies between the results of the present study and the studies mentioned may be due to the difference in the number of subjects, the difference in ethnicity, and the fact that the studies were conducted on a specific patient group. Because serum glucose levels and HbA1c levels reflect different aspects of glucose metabolism, expecting a one-to-one correlation would be incorrect. For this reason, cases diagnosed according to glucose levels may be missed with HbA1c. The reverse is also possible, meaning that cases diagnosed with HbA1c may be missed by simply looking at glucose levels.

In this study, an HbA1c threshold of 5.55% was determined as the optimal cut-off for diagnosing prediabetes, with 62.7% sensitivity and, 93.0% specificity. An HbA1c threshold of 5.55 can be used for screening prediabetes, and its performance is similar to fasting glucose (≥100 mg/dL). However, the performance of the OGTT 2h glucose (≥140 mg/dL) was as good as neither fasting glucose nor Hba1c. It is not a correct approach to completely exclude the HbA1c test, which is a simple and practically applicable test, in the diagnosis of prediabetes in adolescents. We think that it would be more beneficial to accept HbA1c as a test that can be used together with blood glucose values in prediabetes diagnosis.

CONCLUSION

Although the use of adults' HbA1c criteria for the diagnosis of prediabetes in the pediatric ages is controversial due to the differences between the results of blood glucose and HbA1c-based tests, prediabetes screening is still important.[15] HbA1c

≥ 5.55 will be useful to follow up children in terms of risk and to screen them with blood glucose. The combination of blood glucose and HbA1c tests may reduce the possibility of missing the diagnosis of prediabetes in adolescents.

Due to the retrospective screening of the cases, the inaccessibility of additional disease information that may affect the results and the inability to standardize the preanalytical phase of the tests, especially the OGTT, were among the limitations of the present study.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 10.12.2021, Decision No: 2021/13-15).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Cameron FJ, Wherrett DK. Care of diabetes in children and adolescents: controversies, changes, and consensus. Lancet 2015;385(9982):2096-106.
2. Nakagami T, Takahashi K, Suto C, et al. Diabetes diagnostic thresholds of the glycated hemoglobin A1c and fasting plasma glucose levels considering the 5-year incidence of retinopathy. Diabetes Res Clin Pract 2017;124:20-9.
3. Campbell L, Pepper T, Shipman K. HbA1c: a review of non-glycaemic variables. J Clin Pathol 2019;72(1):12-9.
4. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44(Suppl 1):15-S33. Erratum in: Diabetes Care 2021;44(9):2182.
5. Kapadia CR. Are the ADA hemoglobin A (1c) criteria relevant for the diagnosis of type 2 diabetes in youth? Curr Diab Rep 2013;13(1):51-5.
6. Malkani S, DeSilva T. Controversies on how diabetes is diagnosed. Curr. Opin. Endocrinol. Diabetes Obes 2012;19(2):97-103.
7. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. Biom J 2005;47(4):458-72.
8. Lee JM, Gebremariam A, Wu EL, LaRose J, Gurney JG. Evaluation of nonfasting tests to screen for childhood and adolescent dysglycemia. Diabetes Care 2011;34(12):2597-602.
9. Lippi G, Targher G. A laboratory standpoint on the role of hemoglobin A1c for the diagnosis of diabetes in childhood: more doubts than certainties?. Pediatr Diabetes 2011;12(3pt1):183-6.
10. Vikøren TB, Berg JP, Berg TJ. Feilkilder ved bruk av hemoglobin A1c Tidsskr Nor Laegeforen 2014;134(4):417-21.
11. Tarim O, Kucukerdogan A, Gunay U, et al. Effects of iron deficiency anemia on hemoglobin A1c in type 1 diabetes mellitus. Pediatr Int 1999;41:357-62.
12. Klonoff DC. Hemoglobinopathies and Hemoglobin A1c in Diabetes Mellitus. J Diabetes 2020;14(1):3-7.
13. Kim MS, Jo DS, Lee DY. Comparison of HbA1c and OGTT for the diagnosis of type 2 diabetes in children at risk of diabetes. Pediatr Neonatol 2019;60(4):428-34.
14. Nowicka P, Santoro N, Liu H, et al. Utility of hemoglobin A(1c) for diagnosing prediabetes and diabetes in obese children and adolescents. Diabetes care 2011;34(6):1306-11.
15. Wallace AS, Wang D, Shin JI, et al. Screening and Diagnosis of Prediabetes and Diabetes in US Children and Adolescents. Pediatrics 2020;146(3):e20200265.
16. Kaur G, Lakshmi P, Rastogi A, et al. Diagnostic accuracy of tests for type 2 diabetes and prediabetes: A systematic review and meta-analysis. PloS one 2020;15(11):e0242415.
17. Jagannathan R, Sevick MA, Fink D, et al. The 1-hour post-load glucose level is more effective than HbA1c for screening dysglycemia. Acta diabetologica 2016;53(4):543-50.
18. Kim HS. Blood Glucose Measurement: Is Serum Equal to Plasma? Diabetes Metab J 2016;40(5):365-6.
19. Frank EA, Shubha MC, D'Souza CJ. Blood glucose determination: plasma or serum?. J Clin Lab Anal 2012;26(5):317-20.
20. Ogawa E, Urakami T, Suzuki J, Yoshida A, Takahashi S, Mugishima H. Usefulness of HbA1c to diagnose diabetes among Japanese children detected by a urine glucose screening program in the Tokyo Metropolitan Area. Endocr J 2012;59(6):465-71.

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Original Article / Orijinal Araştırma

Antenatal Factors Affecting the Decision to Have an Oral Glucose Tolerance Test

Oral Glukoz Tolerans Testi Yaptırma Kararını Etkileyen Antenatal Faktörler

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Abstract

Aim: We aimed to investigate the factors that may affect the pregnant's decision to have an oral glucose tolerance test (OGTT) between 24-28 gestational weeks.

Material and Method: This descriptive and cross-sectional study was conducted prospectively with 307 pregnant women. Demographic characteristics of the pregnant women, pregnancy follow-up findings, antenatal tests, and their decision for having an OGTT were questioned and recorded. All the factors were analyzed that may have a possible effect on the OGTT decision.

Results: Fifty-three percent of the participants had OGTT during pregnancy. The rate of positive OGTT was found to be 8.5%. Body mass index, gravida, history of abortion, miscarriage risk, weight gain during pregnancy, the rate of using antenatal folic acid and iron supplementation were similar between the groups that had and did not have OGTT ($p > 0.05$). In the univariate model, age, parity, planned pregnancy, regular follow-up, educational status and physical activity were found to have a significant effect on predicting patients who will have OGTT ($p < 0.05$). Also, antenatal screening tests and level 2 obstetrics ultrasonography were shown to have a significant independent effect in predicting patients who will have OGTT ($p < 0.05$).

Conclusion: By evaluating the factors that may affect the decision of pregnant about OGTT during pregnancy follow-up, we can predict the patients who tend not to have GDM screening and we can increase the screening rate by giving these pregnant women more detailed information. Thus, we have a chance to diagnose and treat more GDM and reduce related mortality and morbidity.

Keywords: Gestational diabetes, oral glucose tolerance test, pregnancy, maternal serum screening tests

Öz

Amaç: Gebelerin 24 - 28. gebelik haftaları arasında oral glukoz tolerans testi (OGTT) yaptırma kararını etkileyebilecek faktörleri araştırmayı amaçladık.

Gereç ve Yöntem: Tanımlayıcı ve kesitsel olan bu çalışma prospektif olarak 307 gebe ile yapılmıştır. Gebelerin demografik özellikleri, gebelik takip bulguları, antenatal testleri ve OGTT yaptırma kararları sorgulanarak kaydedildi. OGTT kararını etkileyebilecek tüm faktörler analiz edildi.

Bulgular: Katılımcıların %53'ü hamilelik sırasında OGTT testi yaptırmayı kabul etti. OGTT sonucunun pozitiflik oranı %8.5 olarak saptandı. OGTT olan ve olmayan gruplar arasında vücut kitle indeksi, gravida, düşük öyküsü, düşük riski, gebelikte kilo alımı, antenatal folik asit kullanımı ve demir kullanımı oranları benzerdi ($p > 0.05$). Tek değişkenli modelde; yaş, parite, planlı gebelik olması, düzenli gebelik takibi yapılması, eğitim durumu ve fiziksel aktivitenin OGTT yaptıracak hastaları öngörmede anlamlı etkisi olduğu bulundu ($p < 0.05$). Ayrıca antenatal tarama testleri ve 2. düzey obstetrik ultrasonografinin OGTT olacak hastaları öngörmede anlamlı bağımsız etkiye sahip olduğu gösterilmiştir ($p < 0.05$).

Sonuç: Gebelerin takipleri sırasında OGTT ile ilgili kararını etkileyebilecek faktörleri değerlendirerek GDM taraması yaptırmama eğiliminde olan hastaları öngörebilir ve bu gebelere daha detaylı bilgi vererek tarama oranını artırabiliriz. Böylece daha fazla GDM tanısı koyarak tedavi etme ve buna bağlı oluşabilecek mortalite ve morbiditeyi azaltma fırsatı bulabiliriz.

Anahtar Kelimeler: Gestasyonel diyabet, oral glukoz tolerans testi, gebelik, anne serumu tarama testleri

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INTRODUCTION

Gestational diabetes mellitus (GDM) is the most common medical complication of pregnancy with a prevalence of 9% to 26% of pregnancies worldwide.[1] The prevalence of GDM increases day by day in parallel with the rise in the prevalence of obesity and type 2 diabetes mellitus (DM).[2] After the 24th week of pregnancy, it is recommended that all pregnant women have a GDM screening test.[3] It is estimated that 70% of women with GDM will have the risk of developing type 2 DM in the following years.[4] Detection of GDM and accordingly a controlled course of blood sugar levels can reduce maternal and infant mortality and morbidity.

The oral glucose tolerance test (OGTT) measures the body's response to glucose. For the test, a glucose solution is drunk after fasting. A blood test is then done to determine if it is metabolizing the glucose properly. There are two different types of OGTT. In the two-step GDM test, the venous glucose level is scanned 1-hour after the administration of 50 g of oral glucose solution. For pregnant women whose glucose levels exceed the screening threshold, a 3-hour 100 g diagnostic test is applied. For the diagnosis of gestational diabetes mellitus, two or more abnormal values must be detected in the 3-hour OGTT. In the one-step GDM test, the venous glucose level is scanned fasting, 1-hour and 2-hour after the administration of 75 g of oral glucose solution.[A] One abnormal result is enough for GDM diagnosis.

Maternal overweight, obesity, previous history of GDM, family history of abnormal sugar metabolism, advanced age, childbearing, cigarette smoking and physically inactive lifestyle before and during pregnancy are major risk factors for GDM.[5] Women with GDM have a higher risk of developing gestational hypertension, pre-eclampsia, eclampsia, polyhydramnios, cesarean section, gestational weight gain, postnatal depression perineal trauma and type 2 diabetes.[6,7]

Fetal hyperinsulinemia may cause respiratory distress by adversely affecting the amount of lung surfactant synthesis, thus increasing the rate of intensive care admission and morbidity in the neonatal period. Children of women with GDM face an increased risk of macrosomia, neonatal hypoglycemia, hyperbilirubinemia, hypocalcemia, birth trauma, shoulder dystocia, respiratory distress syndrome, type 2 DM, cardiovascular disease and unfortunately stillbirth.[8-11]

There are many maternal and fetal complications that may be caused by GDM, and despite this, some pregnant women do not want screening tests. In our study, we planned to investigate the factors that may affect the OGTT decision. In the light of our study, we hope to increase the number of patients who are not expected to have the OGTT test. Thus, since the diagnosis of GDM will increase with the test, it will be more possible to reduce the fetal and maternal morbidity associated with GDM.

MATERIAL AND METHODS

The descriptive, cross-sectional study was carried out prospectively at the department of obstetrics and gynecology of Maltepe University between August 2019 and August 2021. Pregnants between 24 and 28 gestational weeks were included in the study. Those who did not approve to participate in the study, pregnants with pregestational diabetes and women with multiple pregnancies were excluded from the study.

Age, height, weight, gravida, parity, abortion, weight gain up to the 28th week, whether the pregnancy was planned or not, educational status, folic acid support, iron supplement use, and physical activities were questioned. In addition, history of miscarriage risk during pregnancy, whether they had regular antenatal follow-ups, first-trimester screening tests, detailed fetal anatomic sonography in the second trimester, whether they had OGTT and how they got information about OGTT were questioned. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles. Ethics committee approval was obtained for this study. All participants gave written consent for the study.

Statistical Analysis

Mean, standard deviation, median lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov - Smirnov test. The Mann - Whitney U test was used in the analysis of quantitative independent data. The Chi - Square test was used in the analysis of qualitative independent data. The effect level was investigated by univariate and multivariate logistic regression. SPSS 27.0 program was used in the analysis.

RESULTS

A total of three hundred seven pregnant who met the criteria were included in the study. The mean age was 30.9±5.7 (18-48). While 53.4% (n:164) of the participants had OGTT, 46.7% (n:143) did not have a GDM screening test. 47.6% of the participants were university graduates. The rate of those who had at least one anomaly screening test during pregnancy was 67.4%. In our clinic, one step 75 gr or two steps 50 gr OGTT was recommended according to the demographic characteristics of pregnant women and the obstetrician's choice. The screening test was performed with 50 gr (two-step) in 75% and with 75 gr (one-step) in 25% of the pregnant women. The positivity rate of OGTT was found to be 8.5% (**Table 1**).

Body mass index (BMI), gravida, history of abortion, miscarriage risk and weight gain during pregnancy were similar between the groups that had and did not have OGTT ($p > 0.05$) during pregnancy. In addition, the usage rate of antenatal folic acid and iron supplementation was also similar ($p > 0.05$) (**Table 2**).

Table 1. Demographic Characteristics

		n	Median
BMI	<25	53	17.3%
	25-30	145	47.2%
	>30	109	35.5%
Weight Gain	<7 kg	143	46.6%
	>7 kg	164	53.4%
University Graduate	No	161	52.4%
	Yes	146	47.6%
Physical Activity	No	197	64.2%
	Yes	110	35.8%
Planned Pregnancy	No	61	19.9%
	Yes	246	80.1%
Regular Follow-Up	No	31	10.1%
	Yes	276	89.9%
Gravida	Primigravida	138	45.0%
	Multigravida	169	55.0%
Parity	Nulliparous	158	51.5%
	Multiparous	149	48.5%
Abortus Imminens		59	19.2%
History of Abortus		51	16.6%
Folic Acid Supplement		263	85.7%
Iron Supplement		248	80.8%
Antenatal Screening	No	100	32.6%
	Yes	207	67.4%
Level 2 USG	No	117	37.1%
	Yes	193	62.9%
Source of Information	Doctor	77	25.1%
	Media	157	51.1%
	Social Environment	73	23.8%
Reason For Not Doing	Harmful	52	36.4%
	Previously Done	27	18.9%
	Not Recommended	18	12.6%
	Unnecessary	46	32.2%
How Many Gram OGTT	50 gr	123	75.0%
	75 gr	41	25.0%
OGTT Result	(-)	150	91.5%
	(+)	14	8.5%

Table 2. Factors Affecting Decision to Have OGTT

		OGTT (-)		OGTT (+)		
		n	%	n	%	p
BMI	<25	29	20.3%	24	14.6%	
	25-30	66	46.1%	79	48.2%	0.415 X^2
	>30	48	33.6%	61	37.2%	
Weight Gain	<7 kg	66	46.2%	77	47%	0.889 X^2
	>7 kg	77	53.8%	87	53%	
University Graduate	No	97	67.8%	64	39%	0.000 X^2
	Yes	46	32.2%	100	61%	
Physical Activity	No	102	71.3%	95	57.9%	0.015 X^2
	Yes	41	28.7%	69	42.1%	
Planned Pregnancy	No	40	28%	21	12.8%	0.001 X^2
	Yes	103	72%	143	87.2%	
Regular Follow-Up	No	22	15.4%	9	5.5%	0.004 X^2
	Yes	121	84.6%	155	94.5%	
Gravida	Primigravida	56	39.2%	82	50%	0.057 X^2
	Multigravida	87	60.8%	82	50%	
Parity	Nulliparous	64	44.8%	94	57.3%	0.028 X^2
	Multiparous	79	55.2%	70	42.7%	
Abortus Imminens	No	122	85.3%	126	76.8%	0.060 X^2
	Yes	21	14.7%	38	23.2%	
Abortus	No	117	81.8%	139	84.8%	0.490 X^2
	Yes	26	18.2%	25	15.2%	
Folic Acid Supplement	No	25	17.5%	19	11.6%	0.141 X^2
	Yes	118	82.5%	145	88.4%	
Iron Supplement	No	29	20.3%	30	18.3%	0.659 X^2
	Yes	114	79.7%	134	81.7%	
Antenatal Screening	No	85	59.4%	15	9.1%	0.000 X^2
	Yes	58	40.6%	149	90.9%	
Level 2 USG	No	90	62.9%	24	14.6%	0.000 X^2
	Yes	53	37.1%	140	85.4%	
Source of Information	Doctor	49	34.3%	108	65.9%	
	Media	44	30.8%	33	20.1%	0.000 X^2
	Social Environment	50	34,9%	23	14%	

X^2 Ki-kare test

The age of the patients, the rate of university graduates, the rate of physical activity, planned pregnancy rates and regular follow-up rates were significantly higher in the group that had OGTT ($p < 0.05$). In addition, the rate of those who had anomaly screening test and level 2 USG was significantly higher in the group who had OGTT ($p < 0.05$). In the group that had OGTT, the rate of being informed about OGTT from the doctor was significantly higher than the group that did not have OGTT ($p < 0.05$) (**Table 2**).

In the univariate model significant effects of age, parity, planned pregnancy, regular follow-up, educational status, physical activity, anomaly screening test and level 2 USG were observed in predicting patients who will have OGTT ($p < 0.05$). In the multivariate reduced model significant-independent efficacy of antenatal screening test and level 2 USG was observed in predicting patients who will have OGTT ($p < 0.05$) (**Table 3**).

Table 3. Univariate and Multivariate Analysis

	Univariate Model			Multivariate Model		
	OR	%95 GA	p	OR	%95 GA	p
Age	1.075	1.032-1.121	0.001			
Parity	0.603	0.384-0.948	0.028			
Planned Pregnancy	2.644	1.472-4.75	0.001			
Regular Follow-up	3.131	1.391-7.047	0.006			
University Graduate	3.295	2.058-5.275	0.000			
Physical Activity	1.807	1.122-2.911	0.015			
Antenatal Screening	14.557	7.775-27.255	0.000	16.78	8.23-34.20	0.000
Level 2 USG	9.906	5.714-17.172	0.000	11.472	5.99-21.97	0.000

Lojistik regresyon (Forward LR)

DISCUSSION

As a primary outcome, we investigated the rates of pregnant women to have GDM screening tests and possible reasons that may affect their decision to have this test. The rate of having the GDM screening test was found to be 53%, similar to other studies.[12,13] OGTT was positive in 8.5% of 164 people who had the test. In the Basbug et al study, the positivity rate was found to be 7.9%.[13]

While the age of pregnant women was not a factor affecting the OGTT decision in several studies, in our study the pregnant women who decided to have the test were found to be older ages.[12,14,15] We think that this contrast is due to the decrease in pregnancy rates in advanced maternal age and due to the increased maternal and fetal risks in advanced maternal age pregnancies. As the mother's age progresses, pregnant women may want to minimize the risks that may occur by performing antenatal tests.

Hussain et al. and Turkyilmaz et al. stated that the level of knowledge about GDM is related to education, while Shriraam et al. suggested that there is no relationship with education level.[15-17] We found that the rate of university graduates having the screening test was significantly higher in our study. We believe that it would be useful to give a more detailed information about GDM to those who are not university graduates in order to have the OGTT test in the outpatient clinic.

The recommended average weight gain at the end of the second trimester of pregnancy is approximately seven kg. Excess weight gain during pregnancy is associated with adverse perinatal outcomes such as fetal growth, cesarean delivery, preterm birth, hypertensive disorders of pregnancy, GDM and infant mortality.[18] In our study, we observed that weight gain did not affect the decision to have a screening test. Regular exercise during pregnancy helps ensure proper maternal and fetal weight gain. Exercise during pregnancy can also reduce risk of GDM and hypertensive diseases of pregnancy. It is also associated with a shorter first stage of labor and a reduced risk of cesarean section.[19] We investigated whether doing 30 minutes of exercise at least 3 times a week is related to the approach to the screening test.[20] We have ensured that pregnant women who engage in regular physical activity have had diabetes screening test significantly more often. In Basbug et al's study, the rate of those who did a physical activity in the group that had OGTT was 24.8%, while it was 15.8% in the group that did not have OGTT.[13]

For a healthy pregnancy, the prenatal standard follow-up frequency is once a month for the first 28 weeks, every 2 weeks between 28 and 36 weeks and once a week after 36 weeks. We found that pregnant women who had their pregnancy follow-up at recommended intervals had a more positive approach to the screening test.

We determined that the rate of having OGTT in nulliparous pregnant women was found to be significantly higher than in multiparous women. On the contrary Yaprak et al., showed that the rate of having OGTT in those who had their first pregnancies was lower.[14] This difference between the two studies may be due to the fact that pregnant women with their first pregnancy are more compliant with the recommendations of their doctors. Another possible reason is that multiparous pregnant women may have had the test before and did not want to be screened again because it was found to be negative.

Daily iron (30-60 mg) and folic acid (400 µg) supplementation are recommended for every pregnant woman to prevent neural tube defects and anemia.[21] No correlation was found between the regular folic and iron use habits of pregnant women and the rates of having OGTT in our study.

The American Congress of Obstetricians and Gynecologists recommends that all pregnant women be screened or tested for aneuploidy.[22] Screening options include; traditional serum analysis scans such as first-trimester screening, triple marker test, quadruple marker test, neural tube defect screening and cell-free DNA. Level 2 obstetric ultrasound performed around the twentieth week of pregnancy is also a comprehensive assessment of fetal anatomy and development. We detected that the women who had an antenatal genetic screening in the first trimester or level 2 obstetric ultrasound were more prone to do also OGTT test ($p < 0.05$). We thought that this result would be related to the fact that those who are sensitive to the risk of a possible anomaly are also sensitive to the risk of GDM (**Figure 1, 2**).

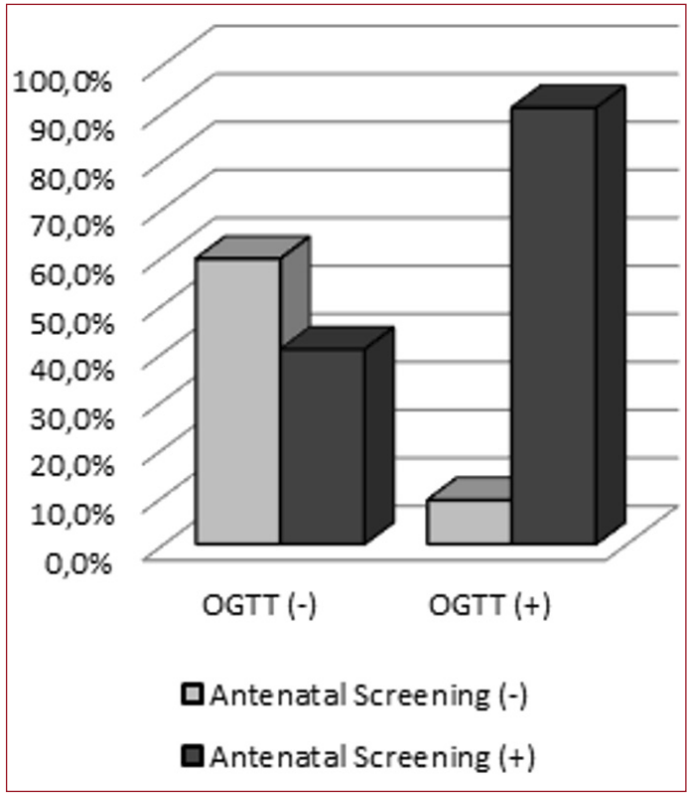

Figure 1. Approach to OGTT of those who had antenatal test

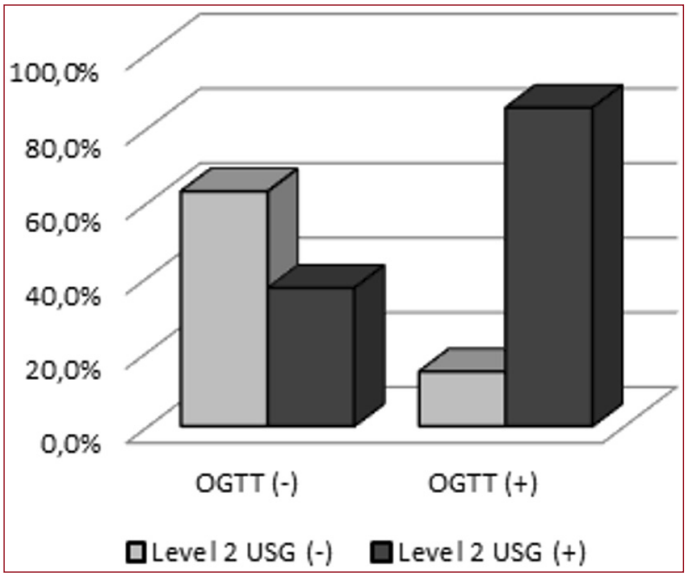

Figure 2. Approach to OGTT of those who had Level 2 Obstetrcis USG

Although there is a lot of confusing and misleading information on social media, there is no reliable study in the literature showing that the GDM screening tests are harmful to the mother and the fetus. During the OGTT, some pregnant women may experience non-serious side effects such as nausea, dizziness and sweating. None of these side effects cause harmful effects to the mother or the baby. Although there is no known harm, we see that the most common reason for not having OGTT in our study was the belief that the test could be harmful to the baby. Other reasons suggested for not having an OGTT are having a negative screening test in the previous pregnancy and the thought that the screening test is unnecessary. Many studies showed that the main reason for not performing the OGTT is the concern of the test that will harm the fetus and the mother.[13-15,23-25] In the source of the misinformation about the GDM screening test, there are posts with false content from social media and visual media.[12-15,26,27] In order to correct this negative perception, pregnant women should be given detailed information about the harms of gestational diabetes and pregnant women should be directed to a screening test. It should be explained with scientific arguments that there are no reported complications of the screening test in the literature so far. We think that the information to be made especially from social media and visual media will correct this misconception.

The limitations of our study are that it was a single-centered study and it was conducted with a small number of people. In addition, as it is made with a sample consisting of only those who applied to the hospital, it does not reflect society.

CONCLUSION

Age, parity, planned pregnancy, regular follow-up, educational status, physical activity, anomaly screening test and level 2 USG decision of the pregnant women were observed to affect the GDM screening decision ($p < 0.05$). In the multivariate reduced model, antenatal screening test and level 2 USG were found to have significant -independent efficacy in predicting patients who would have OGTT ($p < 0.05$). Based on these parameters, we can increase the screening rate by informing the pregnant women who may have a tendency not to have the OGTT test.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Maltepe University Medical Ethics Committee (Decision No: 2019/900/47).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Sacks DA, Hadden DR, Maresh M, et al. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria:the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Diabetes Care 2012;35(3):526-8.
2. Alfadhli EM. Gestational diabetes mellitus. Saudi Med J 2015;36(4):399-406.
3. Moyer VA;U.S. Preventive Services Task Force. Screening for gestational diabetes mellitus:U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014;160(6):414-20.
4. ACOG Practice Bulletin No 190:Gestational Diabetes Mellitus. Obstet Gynecol 2018;131(2):49-64.
5. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nat Rev Dis Primers 2019;5(1):47.
6. Johns EC, Denison FC, Norman JE, Reynolds RM. Gestational Diabetes Mellitus:Mechanisms, Treatment, and Complications. Trends Endocrinol Metab 2018;29(11):743-54.
7. Tieu J, McPhee AJ, Crowther CA, Middleton P, Shepherd E. Screening for gestational diabetes mellitus based on different risk profiles and settings for improving maternal and infant health. Cochrane Database Syst Rev 2017;8(8):CD007222.
8. Moore TR. A comparison of amniotic fluid fetal pulmonary phospholipids in normal and diabetic pregnancy. Am J Obstet Gynecol 2002;186(4):641-50.
9. Rosenstein MG, Cheng YW, Snowden JM, Nicholson JM, Doss AE, Caughey AB. The risk of stillbirth and infant death stratified by gestational age in women with gestational diabetes. Am J Obstet Gynecol 2012;206(4):309.e1-309.e3097.
10. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358(19):1991-2002.
11. Chiefari E, Arcidiacono B, Foti D, Brunetti A. Gestational diabetes mellitus:an updated overview. J Endocrinol Invest 2017;40(9):899-909.
12. Turan Z. , Toker E. Gebelerin oral glukoz tolerans testi yaptırmalarını etkileyen faktörlerin incelenmesi. ADYÜ Sağlık Bilimleri Derg 2020;6(2):174-81.

13. Başbuğ A, Sönmez Cİ, Ellibeş Kaya A, Yıldırım E. Gestasyonel Diyabet Taramasında Karşılaşılan Önemli Bir Problem:Gebeler Neden Oral Glukoz Tolerans Testi Yaptırmak İstemiyor?. Konuralp Med J 2018;10(2):144-8.
14. Yaprak M. , Gümüştakım R. Ş. , Tok A. , Doğaner A. Gebelerde Oral Glukoz Tolerans Testi Farkındalığının Tespiti. Ankara Med J 2019;19(3):635-47.
15. Turkyilmaz E, Kelestemur E, Karatas Eray İ, Ocal FD, Yavuz AF. Knowledge Level, Attitude and Behaviours About Glucose Challenge Test Among Turkish Pregnant Women. Ankara Med J 2016;16(2).
16. Hussain Z, Yusoff ZM, Sulaiman SA. Evaluation of knowledge regarding gestational diabetes mellitus and its association with glycaemic level:A Malaysian study. Prim Care Diabetes 2015;9(3):184-90.
17. Shriraam V, Rani MA, Sathiyasekaran BW, Mahadevan S. Awareness of gestational diabetes mellitus among antenatal women in a primary health center in South India. Indian J Endocrinol Metab 2013;17(1):146-8.
18. Champion ML, Harper LM. Gestational Weight Gain:Update on Outcomes and Interventions. Curr Diab Rep 2020;20(3):11.
19. Gregg VH, Ferguson JE 2nd. Exercise in Pregnancy.Clin Sports Med 2017;36(4):741-52.
20. Wang C, Wei Y, Zhang X, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. Am J Obstet Gynecol 2017;216(4):340-51.
21. WHO. Guideline:Daily iron and folic acid supplementation in pregnant women. Geneva, World Health Organization, 2012.
22. ACOG Committee on Practice Bulletins. ACOG Practice Bulletin No. 77:screening for fetal chromosomal abnormalities. Obstet Gynecol 2007;109(1):217-27.
23. Kusaslan Avci D, Oner E. Examination of the Knowledge, Attitude and Behaviours of Pregnant Women on Screening Tests made during Pregnancy. Eastern J Med 2018;23(2):84-9
24. Hocaoglu M, Turgut A, Guzin K, et al. Why some pregnant women refuse glucose challenge test? Turkish pregnant women's perspectives for gestational diabetes mellitus screening. North Clin Istanb 2019;6(1):7-12.
25. Destegül E, Gençdal S. Oral glucose tolerance test in pregnant women and factors affecting their decisions. Cumhuriyet Med J 2020;42(2):224-9.
26. Desdicioğlu R, Yıldırım M, Süleymanova İ, Atalay İ, Özcan M, Yavuz AF. Factors Affecting the Approach of Pregnant Women to Prenatal Tests. Ankara Med J 2017;17(1).
27. Koyucu RG. Gestasyonel Diyabet Risk Faktörleri Çerçevesinde Gebelerin Glukoz Tolerans Testine İlişkin Tutumları. Sağlık ve Toplum 2018;28(2):65-76.

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Original Article / Orijinal Araştırma

The Antibacterial Effect of Boron Compounds and Evaluation of the Effects on Biofilm Formation in the Infection Model of *Klebsiella pneumoniae* on the HepG2 Cell Line

Klebsiella pneumoniae Enfeksiyon Modelinde HepG2 Hücre Hattında Bor Bileşiklerinin Antibakteriyel Etkisi ve Biyofilm Oluşumuna Etkilerinin Değerlendirilmesi

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Abstract

Aim: *Klebsiella pneumoniae* causes pneumonia, urinary tract infection and bacteremia in immunocompromised patients. *Klebsiella pneumoniae*, which has become more common recently, causes antibiotic resistance as well as pyogenic liver abscesses and hematogenous metastatic spread in humans. Developing antibiotic resistance complicates the treatment of liver infections. In our study, we aimed to evaluate the effect of boron compounds in an infection model created by *Klebsiella pneumoniae* 700603.

Material and Method: The minimum inhibitory concentration, fractional inhibitory concentration and biofilm optical density levels of boron compounds against *Klebsiella pneumoniae* were determined. In these determined dose ranges, a non-toxic dose range for the HepG2 cell line was selected and evaluated by showing with immunofluorescence staining.

Results: We determined the low and high minimum inhibitory concentration values of boron components, sodium perborate monohydrate and etidote, respectively. In addition, sodium perborate monohydrate is also effective on biofilm formation and resistance genes. Our findings have shown that boron compounds are more effective when used in a combination. In the toxicity model created in the cellular study, the boron compounds cytotoxic effect decreased due to their antibacterial effects.

Conclusion: İt seems that boron compounds are effective, and the positive effect increases when used together.

Keywords: HEPG2, *Klebsiella pneumoniae*, minimum inhibitory concentration, boron components

Öz

Amaç: *Klebsiella pneumoniae* bağışıklığı baskılanmış hastalarda pnömoni, idrar yolu enfeksiyonu ve bakteriyemiye neden olur. Son zamanlarda daha sık görülen *Klebsiella pneumoniae*, insanlarda piyojenik karaciğer apselerine ve hematojen metastatik yayılımın yanı sıra antibiyotik direncine de neden olmaktadır. Gelişen antibiyotik direnci karaciğer enfeksiyonlarının tedavisini zorlaştırmaktadır. Çalışmamızda HepG2 hücre hattında *Klebsiella pneumoniae* 700603 tarafından oluşturulan enfeksiyon modelinde bor bileşiklerinin etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: *Klebsiella pneumoniae*'ye karşı bor bileşiklerinin minimum inhibitör konsantrasyonu, fraksiyonel inhibitör konsantrasyonu ve biyofilm optik dansite düzeyleri belirlendi. Belirlenen bu doz aralıkların da HepG2 hücre hattı için toksik olmayan doz aralığı seçildi ve immünofloresan boyama ile gösterilerek değerlendirildi.

Bulgular: Bor bileşenleri sodyum perborat monohidrat ve etidot için sırasıyla düşük ve yüksek minimum inhibitör konsantrasyonu değerleri tespit edildi. Ayrıca biyofilm oluşumu ve direnç genleri üzerine sodyum perborat monohidrat etkili olduğu belirlendi. Bulgularımız, bor bileşiklerinin kombine halinde kullanıldığında daha etkili olduğunu göstermiştir. HepG2 hücre hatında oluşturulan toksisite modelinde, bor bileşiklerinin sitotoksik etkisi antibakteriyel etkilerinden dolayı azalmıştır.

Sonuç: HepG2 hücre hattında oluşturulan *Klebsiella pneumoniae* enfeksiyona karşı bor bileşiklerinin etkili olduğu ve birlikte kullanıldıklarında sinerjistik etkisinin arttığı görüldü.

Anahtar Kelimeler: Bor bileşenleri, HepG2, *Klebsiella pneumoniae*, minimum inhibitör konsantrasyon

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INTRODUCTION

Klebsiella pneumoniae is a well-known opportunistic nosocomial pathogen. Most community-acquired *Klebsiella pneumoniae* infections cause pneumonia and urinary tract infections. However, over the past two decades, a distinctly invasive syndrome causing liver abscesses has been increasingly reported and is emerging as a global disease.[1] Studies have shown that *Klebsiella pneumoniae* strains infect the liver due to the gastrointestinal system. They stated that *Klebsiella pneumoniae* strains isolated from patients with liver abscesses and healthy *Klebsiella pneumoniae* carriers were identical with the same virulence-related genes and median lethal dose values.[2,3] These findings suggest that healthy adults carry virulent strains in their gut. When bacteria migrate through the intestinal epithelium, they can cross the intestinal barrier and form a liver abscess. Fecal-oral transmission, gastrointestinal colonization, and environmental exposure are possible routes of acquisition. A liver abscess develops after *Klebsiella pneumoniae* infiltrates the liver from a patient's intestine via portal circulation.[4] In addition, virulence factors in *Klebsiella pneumoniae*, capsular serotype, mucoviscosity-associated gene A (magA), rmpA and aerobactin are important in the formation of liver abscesses.[4,5]

Klebsiella pneumoniae strains expressing the capsular type K1 or K2 antigen are virulent. These serotypes have a high prevalence of resistance to phagocytosis and intracellular killing by neutrophils and bactericidal complements in a patient's serum. Although *Klebsiella pneumoniae* serotypes K1 and K2 isolated from patients with liver abscesses usually show hypermucoviscosity, they are known to be an indicator of capsular polysaccharide expression, which is related to resistance to phagocytosis.[5] magA has been identified as the gene that causes *Klebsiella pneumoniae* liver abscess and septic metastatic complications.[6] RmpA aids in capsule synthesis in addition to magA and capsular serotype K1/K2.[7] All strains of *Klebsiella pneumoniae* that cause liver abscesses and abscesses at other sites regulate rmpA capsular polysaccharide synthesis.[8] Aerobactin, a type of siderophore, is an iron chelator that increases the virulence of *Klebsiella pneumoniae* 100-fold and is an important factor for pathogenicity in *Klebsiella pneumoniae*. Aerobactin genes play an important role in the virulence of *Klebsiella pneumoniae* in combination with rmpA.[9]

These virulence factors have an important place in the formation of resistance against antibiotics. The World Health Organization has published a list of antibiotic-resistant bacteria that seriously threaten society. There is an urgent need for new classes of antibiotics with new mechanisms of action against *Klebsiella pneumoniae* on this list.[10-12] Boron compounds are single-active site-directed serine-type β-lactamase inhibitors that are not based on a β-lactam structure. The inhibitory activity of these modules has been extensively studied against various potent β-lactamases. Studies have shown that different boron compounds reversibly and rapidly inhibit C class AmpC enzymes, various A class β-lactamases, such as Bacillus cereus chromosomal penicillinase, and some CTX-M-type enzymes. Since the glycyl-boronic acid compound does not show inhibition of AmpCs alone, compounds with good activity in the β-lactamase classes are scarce. They are important inhibitors for treating infections caused by β-lactamase-producing bacteria.[13-15] In light of this information, we aimed to evaluate the synergistic effect of boron compounds and the presence of biofilms in infections caused by *Klebsiella pneumoniae*.

MATERIAL AND METHOD

Reagents

Etidote (disodium octaborate tetrahydrate), Sodium perborate monohydrate (SPM), Zinc borate (ZB), Mueller-Hinton broth, tryptic soy broth, Dulbecco's modified Eagle's medium (DMEM), phosphate buffer solution (PBS), fetal calf serum (FCS), antibiotic antimitotic solution (100×), L glutamine, trypsin–EDTA, paraformaldehyde and ethanol were obtained from Sigma Aldrich (St. Louis, MO, USA).

Bacterial Strain

Klebsiella pneumoniae 700603 was used in our study. The isolate was identified by conventional methods and an automated system (Phoenix, Becton Dickinson, USA). Suspensions equivalent to strain 0.5 McFarland turbidity were prepared.

Experimental design

The experiment was designed in two different parts.

The first part evaluated the minimal inhibitory concentration (MIC) of Etidote (39, 78, 156, 312, 625, 1250, 5000, and 10000 µg/mL), sodium perborate monohydrate (39, 78, 156, 312, 625, 1250, 5000, and 10000 µg/mL), and zinc borate (9.38, 18.75, 37.50, 75, 150, 300, 600, 1200, and 2400 µg/mL). The antibacterial effects of etidote, sodium perborate monohydrate, and zinc borate were analyzed according to the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS). *Klebsiella pneumoniae* 700603 strains were used for the test. The minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial that inhibits the visible growth of a microorganism after overnight incubation. MICs were defined as the lowest concentration of etidote, sodium perborate monohydrate, and zinc borate, inhibiting the visible growth of the bacteria. The MICs of etidote, sodium perborate monohydrate, and zinc borate were conventionally determined in triplicate for each strain by the microdilution broth method as described by the NCCLS. Serial dilutions of etidote, sodium perborate monohydrate and zinc borate were prepared in microdilution with concentrations ranging between 1000 µg/mL (40 mM) and 0.97 µg/mL (40 mM). A total of 125 µg/mL etidote, 62.5 µg/mL sodium perborate monohydrate, and 31.25 µg/mL zinc borate showed minimal inhibition of *Klebsiella pneumoniae* 700603.

In the second step, a *Klebsiella pneumoniae* 700603 model was induced using the HepG2 cell line; SPM 62,5 µg/mL + Etidote 125 µg/mL, SPM 62,5 µg/mL + ZB 31,25 µg/mL and ZB 31,25 µg/mL + Etidote 125 µg/mL were applied for 24 h treatments. It was preferred because it did not show toxicity in these dose ranges. After the end of the experiment, MTT, TAC, TOS, Gr, LDH and immunohistochemistry analyses were performed.

Cell cultures

HepG2 cell (HB-8065 ATCC) cultures were obtained from the Department of Medical Pharmacology of Ataturk University (Erzurum, Turkey). Briefly, the cells were resuspended in fresh medium (Dulbecco's modified Eagle's medium, DMEM), 10% fetal bovine serum (FBS) and 1% antibiotic (penicillin, streptomycin, and amphotericin B). Then, the cells were seeded in 24-well plates (Corning, USA) and stored in an incubator (5% CO_2; 37°C).[16] After gaining an 85% confluence ratio, the model was performed using a 100 µL yellow pipet tip; the McFarland 0.5 scale bacterial suspension was added to the cell culture. After 30 min of treatment with the HepG2 cell line, SPM 62,5 µg/mL + Etidote 125 µg/mL, SPM 62,5 µg/mL + ZB 31,25 µg/mL and ZB 31,25 µg/mL + Etidote 125 µg/mL were applied for 24 h.

MTT Assay

At the end of the two-part experiment (after 24 h of treatment with boric acid and potassium metaborate), 10 µL of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) solution was added to each well plate, and the samples were incubated for 4 h; 100 µL of DMSO solution was incorporated into all wells to dissolve formazan crystals. The optical density of the solutions was read at 570 nm using a Multiskan™ GO Microplate Spectrophotometer reader.[17,18]

Immunofluorescence

Cells cultivated in cell culture were incubated for 30 min in paraformaldehyde solution. The cells were then incubated in 3% H_2O_2 for 5 min. A 0.1% Triton-X solution was dripped onto the cells, washed with PBS and left for 15 min. After incubation, protein blocks were dripped onto the cells and kept in the dark for 5 minutes. Then, the primary antibody (8-OHdG cat no: sc-66036, dilution ratio: 1/100 US) was added dropwise and incubated following the instructions for use. Immunofluorescence secondary antibody was used as a secondary marker (FITC Cat No: ab6785, dilution ratio: 1/500, UK) and incubated in the dark for 45 minu. Then, the second primary antibody (H2A. X Cat No: I 0856-1, dilution ratio: 1/100, US) was dripped onto the tissues and incubated per the instructions. Immunofluorescence secondary antibody was used as a secondary marker (Texas Red Cat No: ab6787, dilution ratio: 1/1000 UK) and kept in the dark for 45 min. Then, DAPI with mounting medium (Cat no: D1306, dilution ratio: 1/200 UK) was dripped onto the sections and kept in the dark for 5 min, and the sections were closed with a coverslip. The stained sections were examined under a fluorescence microscope (Zeiss AXIO GERMANY).

Bacterial Production

The bacterial stock of *Klebsiella pneumoniae* 700603 was added to 100 µL of tryptic soy broth (TSB) medium, and after 24 h of incubation at 37°C and 150 rpm, its production was carried out. Then, 200 µL of the growth medium was taken and inoculated into fresh TSB, and the stock medium was made ready for the study.

Minimum Inhibitory Concentration

The MIC values of sodium perborate monohydrate (SPM), zinc borate (ZB), and etidote compounds against *Klebsiella pneumoniae* 700603 were determined using the microdilution method. Dose ranges were determined as 1000-0.97 µg/mL. Müeller-Hinton broth (MHB) medium was inoculated into 96-well plates to which 180 µL of each dilution was added. Then, 20 µL of *Klebsiella pneumoniae* 700603 (10^6CFU/mL) was added to each well and incubated at 37°C.

Biofilm Analysis

A total of 180 µl of the compounds whose MIC value was determined, prepared with TSB medium, was inoculated into a flat-bottomed 96-well plate. Glucose-enriched TSB medium was used as a negative control, and the *Klebsiella pneumoniae* 700603 strain was used as a positive control. Then, 20 µL (10^6 CFU/mL) of the *Klebsiella pneumoniae* 700603 strain was inoculated into each well except the negative well. It was incubated at 37°C for 48 h. Biofilm analysis was performed in 3 repetitions.

The effects of SPM, ZB, and Etidote on *Klebsiella pneumoniae* 700603

The most effective MIC concentrations of SPM, ZB, and Etidote compounds were prepared in combination. In the analysis performed, similar to the biofilm evaluation test principle, the *Klebsiella pneumoniae* 700603 strain was inoculated into MHB medium enriched with glucose and incubated at 37°C for 48 h. Bacterial growth was expected. In addition, the medium was made fresh by adding TSB medium to the plates at 24-36 h intervals. After 48 h, the liquid in the plates was evacuated. A 200 µL aliquot of glucose-enriched culture medium containing TTC (5 mg/mL) was added to each well and incubated at 37°C for 3-4 h. The intensity of the red color at the end of the resulting test was considered an indicator of viable cell number and was measured at 490 nm. The results were compared with controls. The test was repeated in triplicate.

Microdilution panels

The solutions were prepared by calculating the final concentrations of SPM, ZB, and Etidote compounds on the prepared panels. Intermediate dilutions with a concentration of four times the final concentration desired in the well were prepared. Then, 100 µL of TSB medium was dispensed into all wells. First, 100 µL of SPM was diluted in half and dispersed, and then 100 µL was added to the wells diluted sequentially with ZB and Etidote 1000 µg/mL. The medium was prepared

as a negative control, and bacterial wells were prepared as a positive control. Except for the negative control well, antimicrobial agents (5 µl) were dispensed into the plates. This process was repeated for the other ZB and Etidote, and 3 repetitions were applied.

Fractional Inhibitor Concentration Index-Combination (FIC)

The FIC for each drug is determined by dividing the MIC of each drug when used in combination by the MIC of each drug used alone. The FIC index quantifies drug interactions and the value is used to determine interactions between tested drugs. It was applied according to the FIC index formula used to determine the effectiveness of the combinations. The results were determined according to the formula.

A: Antimicrobial 1 used in combination
B: Antimicrobial 2 used in combination
Calculation of the FIC index:
FIC A: MIC numerical value of An in the presence of B/MIC numerical value of A alone
FIC B: MIC numerical value of B in the presence of A/MIC numerical value of B alone
Σ FIC index FIC A + FIC B
Σ FIC index ≤ 0.5: Synergism
Σ FIC index >0.5 and <1: additive
Σ FIC index ≥1 and 4 ≤: ineffective (indifference)
Σ FIC index >4: antagonism

RESULTS

Microbiology Analysis

Minimal inhibitory concentrations (MICs) were determined at concentrations of SPM +Etidote 31.25 µg/ml+125 µg/ml, SPM +ZB 31.25 µg/ml+62.5 µg/ml and ZB+Etidote 62.5 µg/ml+125 µg/ml. The dose ranges in which boron compounds are synergistic, ineffective, additive and antagonism against *Klebsiella pneumoniae* are shown in **Figures 1A**, **1B** and **1C**, respectively.

The optical density (570/OD) results of the combinations made with the microdilution plate method are summarized in **Figure 2**. **Figure 2A**. Etidote 1024 µg/ml+SPM 64 µg/ml concentrations were found to have the highest effect on biofilms. **Figure 2B** shows that the highest effect on biofilm formation was detected at Etidote 1024 µg/mL+ZB 512 µg/mL. In **Figure 2C**, the highest effect on biofilm formation was detected at the ZB 512 µg/ml+SPM 64 µg/ml concentration.

MTT Assay

We evaluated the toxicological effects of ZB, SPM, and etidote on the HepG2 cell line. Our results revealed that cell viability did not decrease significantly for SPM + Etidote or SPM + ZB (**Figure 3**).

Immunohistochemical Evaluation

In mitochondrial and nuclear DNA, 8-hydroxy-2'-deoxyguanosine is the predominant form of free radical-induced oxidative lesions, and thus, it serves as a marker of oxidative stress. In line with previous findings, a significant dose-dependent increase in the 8-OHdG fluorescent signal was observed in the bacterial control group (**Table 1**).

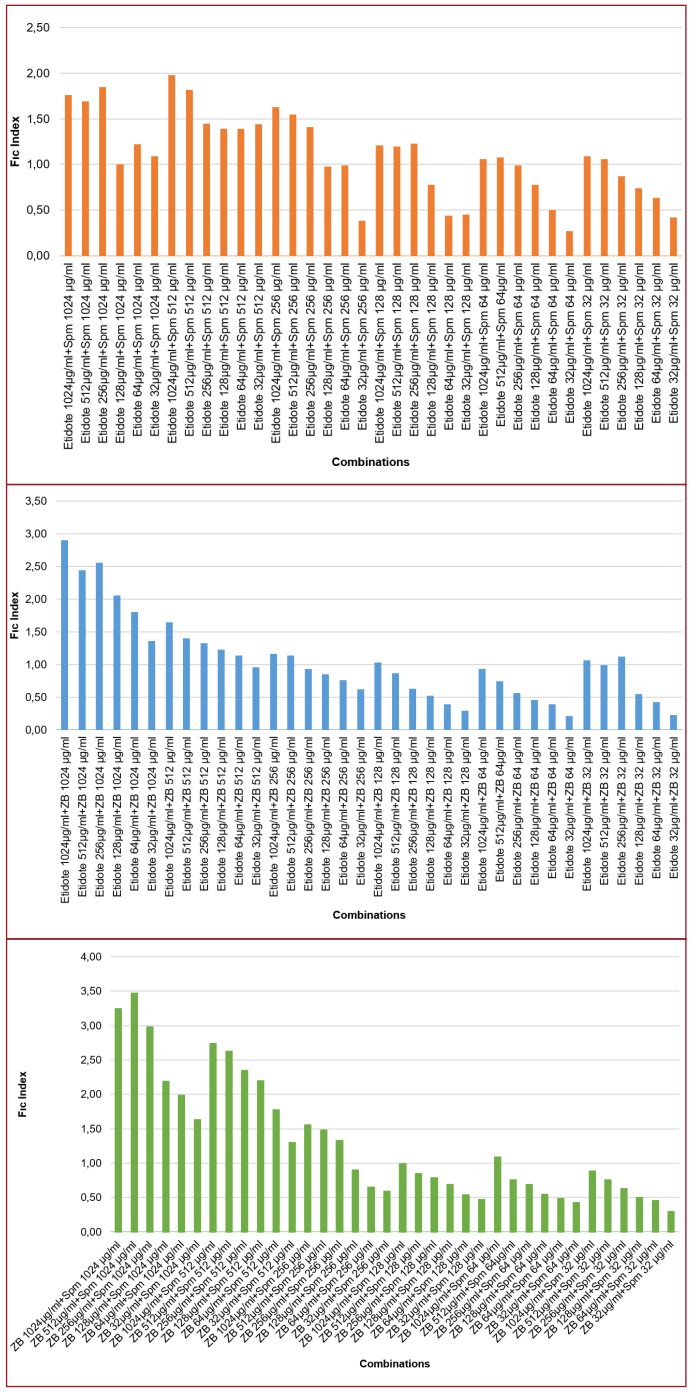

Figure 1. Boron compound FIC index results. A) Etidote+SPM combination FIC index, B) Etidote+ZB combination fix index, C) ZB+SPM combination fix index. Value ranges of boron combinations corresponding to Σ FIC index ≤ 0.5: synergy, >0.5 and <1: additive and ≥1 and 4 ≤: ineffective (indifference).

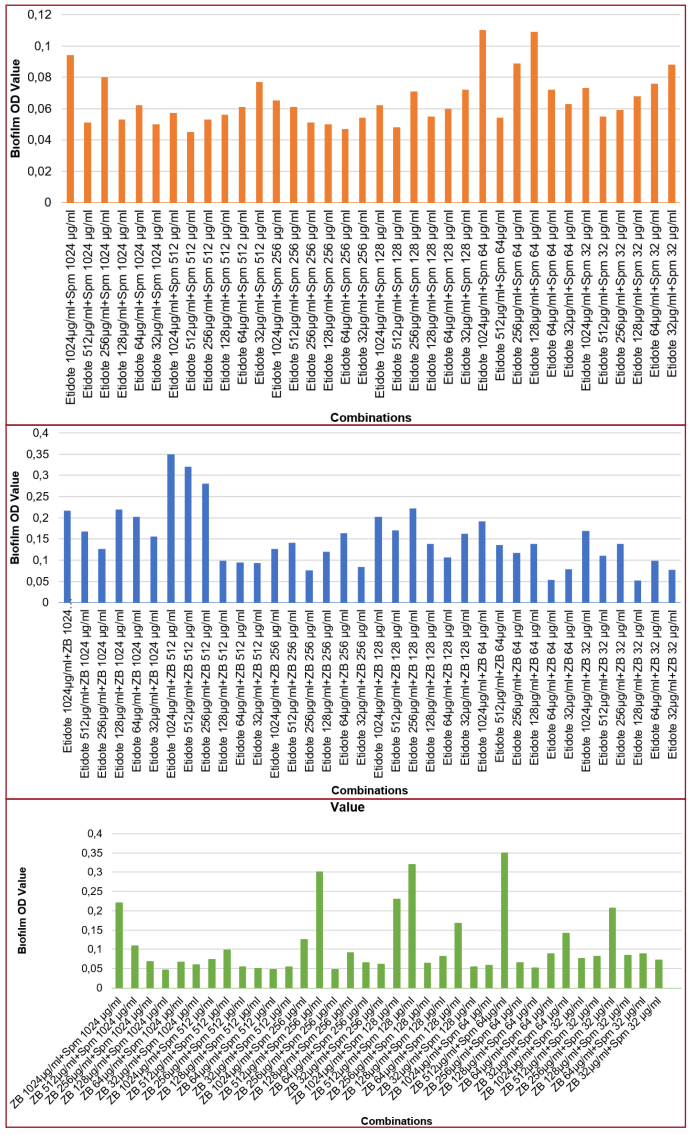

Figure 2. Biofilm OD Results. A) Etidote+SPM, B) Etidote+ZB, C) ZB+SPM biofilm OD values. The minimum and maximum OD values of Etidote+SPM, Etidote+ZB, and ZB+SPM biofilms ranged at 570 OD.

Table 1. Statistical analysis of immunofluorescent staining results.

	8-OHdG	H2A.X
Control	23.38±5.34[a]	19.26±4.58[a]
SPM+Etidote	30.44±5.86[a]	27.39±5.08[a]
SPM+ZB	29.88±6.24[a]	25.15±4.38[a]
ZB+Etidote	44.16±3.89[b]	38.26±4.74[b]

These results further support the data related to the oxidant abilities of *Klebsiella pneumoniae* bacteria already observed in MTT assays demonstrating how SPM 62,5 µg/ml + Etidote 125 µg/ml, SPM 62,5 µg/ml + ZB 31,25 µg/ml, able to reduce 8-OHdG, is one of the major products of DNA oxidation and consequently of DNA damage accumulation and HepG2 cell death. In particular, mild fluorescent signal intensity was observed at SPM 62,5 µg/ml + Etidote 125 µg/ml, SPM 62,5 µg/ml + ZB 31,25 µg/ml and mild-moderate ZB 31,25 µg/ml + Etidote 125 µg/ml compared to the control group (**Figure 4**).

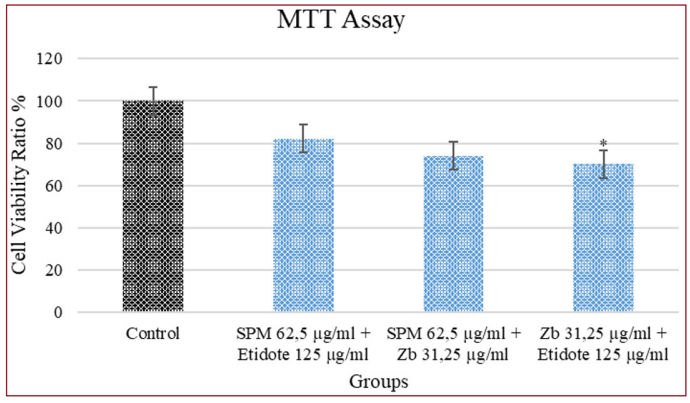

Figure 3. MTT assay results for the HepG2 cell line, Control group (received only medium), *Klebsiella pneumoniae* bacteria coculture for 24 h SPM 62,5 µg/ml + Etidote 125 µg/ml, and SPM 62,5 µg/ml + ZB 31.

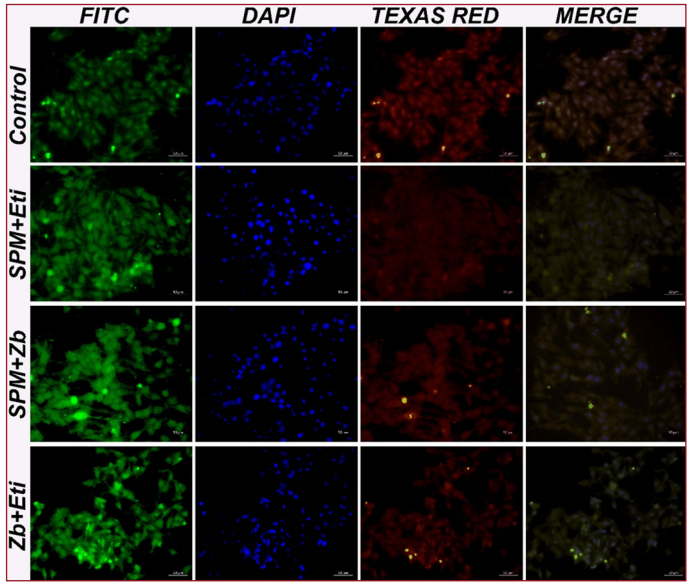

Figure 4. Cell lines, 8-OHdG expression (FITC) and H2A. X expression (Texas Red), IF, Bar: 50 µm.

Statistical Analysis

The results were calculated as the mean ± standard error. Statistical comparisons between groups were calculated using one-way ANOVA and Tukey's LSD method. All calculations were performed using SPSS 20 software for statistical analysis, and $P<0.05$ was considered a significant difference in all tests.

DISCUSSION

Klebsiella pneumoniae is a common opportunistic pathogen that frequently causes nosocomial infections, including pneumonia, meningitis, and bloodstream and urinary tract infections. In addition, *Klebsiella pneumoniae* can potentially cause community-associated infections, such as liver abscesses, endophthalmitis, and meningitis, in healthy individuals.

In this study, we aimed to evaluate the synergistic effect of boron compounds and their effect on biofilms in an infection model induced by *Klebsiella pneumoniae* 700603

on the HepG2 liver cell line. In addition to potential use as β-lactamase inhibitors in studies evaluating the synergistic activity of boron compounds and antibiotics, boron compounds have been used for the phenotypic detection of plasmid-mediated AmpC enzymes. Tests using cefoxitin discs and boronic acid compounds, mainly 3′-aminophenylboronic acid (APBA), successfully detect AmpC enzymes in organisms that do not classically produce these enzymes.[19,20]

These tests using extended-spectrum cephalosporins combined with clavulanic acid have helped detect isolates harboring both ESBLs and AmpCs.[21] A tentative observation of the inhibitory effect of boric acid on *Klebsiella pneumoniae* carbapenemase (KPC) was made by Pasteran et al. During the evaluation of a chromogenic assay that detects s), two KPC-2-producing isolates showed synergy between APBA and cefotaxime, ceftazidime, or carbapenems.[22]

After the first observations of the inhibitory activity of boric acid on KPC, specific phenotypic tests were developed to detect KPCs. This investigation initially revealed that KPC production in isolates that did not produce AmpC-type enzymes was associated with positive combined boronic acid disc tests using cefamycins and cefotaxime as substrates, specifically cefepime and carbapenems. The synergy of phenylboronic acid (PBA) with these antibiotics has been applied to the phenotypic identification of the first KPC-producing isolate in Greece.[23]

Further evaluation with an extensive collection of KPC-producing isolates showed an apparent synergistic effect between PBA and carbapenems, revealing an enhanced interaction of the PBA fragment with the active site serine residue of class A KPC β-lactamase.[24]

Combined disc tests were considered positive when the addition of PBA to a β-lactam disc resulted in an enlargement of ≥5 mm in diameter of the growth inhibition zone compared to the zone of inhibition around the β-lactam disc alone. In these studies, combined disc tests using 400 µg PBA with and without cefepime, imipenem, or meropenem demonstrated the highest sensitivity and specificity for detecting KPC enzymes.[23,24]

Our study examined the synergistic effects of boron compounds since resistance to antimicrobials applied in pathogen-oriented treatments leads to alternative searches. Boron compounds have been reported to inhibit this enzyme, especially by binding to the serine residue, especially with the overexpression of β-lactamase classes. In studies conducted to discover new compounds that can be applied with β-lactam antibiotics, boron compounds have also taken their place in the literature.[25]

In the checkerboard study, we examined the interaction of these inhibitors with each other, and a synergistic effect of 32 µg/ml Etidote + 32 µg/ml SPM was detected. SPM: Due to the use of SPM: sodium perborate monohydrate, especially in wound cleaning, in our study, nontoxic appropriate dose ranges were determined, and its combination with etidote was made. Etidote is especially important for using plants in the soil to yield nitrogen and phosphorus sources. In addition, in a study, etidote used together with gelatin was shown to inhibit the growth of *P. aeruginosa*, *S. aureus* and *C. albicans* pathogens.[26]

CONCLUSİONS

In microbiological analyses of boron compounds, FIC and MIC concentrations were high. Statistical significance was determined in the combination of ZB+Etidote against *Klebsiella pneumoniae* in cell culture compared to other groups. Although the results are promising for us, we think that after a more comprehensive examination of the mechanisms of action of these compounds, we should consider whether they will be antimicrobial candidates after in vivo studies on the pathogen and the host.

ETHICAL DECLARATIONS

Ethics Committee Approval: The standard strain was used in this study. No ethical approval is required.

Informed Consent: Since this study was not conducted on patients, a consent form is not required.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Zhu Z, Zhang B, Wang Y, et al. A wide clinical spectrum of pulmonary affection in subjects with community-acquired *Klebsiella pneumoniae* liver abscess (CA-KPLA). J Infect Chemother 2023;29(1):48-54.
2. Choby JE, Howard-Anderson J, Weiss DS. Hypervirulent *Klebsiella pneumoniae* - clinical and molecular perspectives. J Intern Med 2020;287(3):283-300.
3. Pandak N, Mahdi AS, Al Majrafi A, et al. Characteristics of Pyogenic Liver Abscess:Experience of a single centre in Oman. Sultan Qaboos Univ Med J 2022;22(2):257-61.
4. Sun Y, Wu H, Shen D. Clinical and Molecular Analysis of *Klebsiella pneumoniae* Causing Liver Abscess in China. J Mol Microbiol Biotechnol 2016;26(4):245-51.
5. Sohrabi M, Alizade Naini M, Rasekhi A, et al. Emergence of K1 ST23 and K2 ST65 hypervirulent *Klebsiella pneumoniae* as true pathogens with specific virulence genes in cryptogenic pyogenic liver abscesses Shiraz Iran. Front Cell Infect Microbiol 2022;12:964290.
6. Kuş H, Arslan U, Türk Dağı H, Fındık D. Hastane enfeksiyonu etkeni *Klebsiella pneumoniae* izolatlarında çeşitli virülans faktörlerinin araştırılması.[Investigation of various virulence factors of *Klebsiella pneumoniae* strains isolated from nosocomial infections] Mikrobiyol Bul 2017;51(4):329-39.
7. Yu WL, Ko WC, Cheng KC. et al. Association between rmpA and magA genes and clinical syndromes caused by *Klebsiella pneumoniae* in Taiwan. Clin Infect Dis 2006;42:1351-8.

8. Zhang Y, Zhao C, Wang Q, et al. High Prevalence of Hypervirulent *Klebsiella pneumoniae* Infection in China:Geographic Distribution, Clinical Characteristics, and Antimicrobial Resistance. Antimicrob Agents Chemother 2016;60(10):6115-20.
9. Shankar C, Basu S, Lal B, et al. Aerobactin Seems To Be a Promising Marker Compared With Unstable RmpA2 for the Identification of Hypervirulent Carbapenem-Resistant *Klebsiella pneumoniae*:In Silico and In Vitro Evidence. Front Cell Infect Microbiol 2021;11:709681.
10. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 2018;18:318–27.
11. Wencewicz TA. New antibiotics from Nature's chemical inventory. Bioorg Med Chem 2016;24:6227–52.
12. Butler MS, Paterson DL. Antibiotics in the clinical pipeline in October 2019. J Antibiot (Tokyo) 2020;73:329–364.
13. Crompton IE, Cuthbert BK, Lowe G, et al. β-Lactamase inhibitors. The inhibition of serine β-lactamases. Biochem J. 1988;251:453-9.
14. Kiener PA, Waley SG. Reversible inhibitors of penicillinases, Biochem J, 1978;169:197-204.
15. Chen Y, Shoichet B, Bonnet R. Structure, function, and inhibition along the reaction coordinate of CTX-M β-lactamases. J Am Chem Soc 2005;127:5423-34.
16. Demirci S, Dogan A, Karakus E, et al. Boron and Poloxamer (F68 and F127) Containing Hydrogel Formulation for Burn Wound Healing. Biol Trace Elem Res 2015;168(1):169-80.
17. Nzietchueng RM, Dousset B, Franck P, Benderdour M, Nabet P, Hess K. Mechanisms implicated in the effects of boron on wound healing. J Trace Elem Med Biol 2002;16(4):239-44.
18. Celebi D, Taghizadehghalehjoughi A, Baser S, et al. Effects of boric acid and potassium metaborate on cytokine levels and redox stress parameters in a wound model infected with methicillin-resistant Staphylococcus aureus. Mol Med Rep 2022;26(3):294.
19. Coudron PE. Inhibitor-based methods for detection of plasmid-mediated AmpC β-lactamases in Klebsiella spp., Esche-richia coli, and Proteus mirabilis.J Clin Microbiol.2005;43:4163-7.
20. Doi Y, Paterson DL. Detection of plasmid-mediated class C β-lactamases, Int J Infect Dis, 2007;11:191-7.
21. Livermore DM, Warner M, Mushtaq S. Evaluation of the chromogenic Cica-β-Test for detecting extended-spectrum, AmpC and metallo-β-lactamases. J Antimicrob Chemother 2007;60:1375-9.
22. Pasteran FG, Otaegui L, Guerriero L, et al. *Klebsiella pneumoniae* carbapenemase-2, Buenos Aires, Argentina, Emerg In-fect Dis, 2008;14:1178-80.
23. Tsakris A, Kristo I, Poulou A. et al. First occurrence of KPC-2-possessing *Klebsiella pneumoniae* in a Greek hospital and recommendation for detection with boronic acid disc tests. J Antimicrob Chemother.2008;62:1257-60.
24. Tsakris A, Kristo I, Poulou A, et al. Evaluation of boronic acid disc tests for differentiating KPC-possessing *Klebsiella pneumoniae* isolates in the clinical laboratory, J Clin Microbiol, 2009;47:362-7.
25. Eidam O, Romagnoli C, Dalmasso G, et al. Fragment-Guided Design of Subnanomolar β-Lactamase Inhibitors Active in Vivo. Proc. Natl. Acad. Sci. USA 2012;109:17448–53
26. Argın S, Gülerim M, Şahin F. Development of antimicrobial gelatin films with boron derivatives. Turk J Biol 2019;43:47-57.

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Original Article / Orijinal Araştırma

Clinical Significance of Gastrointestinal Symptoms in Hospitalized Patients with COVID-19 Infection

Hastanede Yatan COVID-19 Enfeksiyonlu Hastalarda Gastrointestinal Semptomların Klinik Önemi

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Abstract

Aim: To determine the clinical significance of gastrointestinal (GI) symptoms in mild hospitalized patients with COVID-19 infection.

Material and Method: This study included adult patients who were hospitalized with a confirmed diagnosis of COVID-19 infection. The demographical features, symptoms, clinical presentations, medical history, medications and clinical progress and outcomes were noted using data collection form by the clinicians. The effect of GI symptoms on clinical outcomes in patients with mild COVID-19 infection was statistically evaluated.

Results: 307 patients were included to the study. 159 of patients (51.7%) had an at least one GI symptoms, 18.2% of those presented only GI symptoms while 21.2% only non-GI symptoms. 27% were asymptomatic at admission. The most common GI symptom was loss of appetite that presenting 16.9% patients. The second and third most common GI symptoms were diarrhea in 15% patients, nausea and loss of taste in 14% patients, respectively. There was no significant difference in laboratory parameters between GI and non-GI symptoms groups. When age, gender, smoking status, and comorbidities of patients with GI and non-GI symptoms groups were compared, there was no difference in mean age, gender, smokers, and comorbidities. In addition, the length of hospital stay (p=0.377), complete healing (p=0.372) and mortality (p=0.351) was similar in patients with GI and non-GI symptoms groups respectively.

Conclusion: Early diagnosis of COVID-19 infection presenting with GI symptoms can help prevent infection spread. The majority of these symptoms were mild, and their presence was not associated with worse clinical outcomes.

Keywords: COVID-19, gastrointestinal symptoms, loss of appetite, nausea, diarrhea

Öz

Amaç: Bu çalışmamızda hastanede yatan hafif COVID-19 enfeksiyonu olan hastalarda gastrointestinal (GI) semptomların klinik önemini belirlemeyi amaçladık.

Gereç ve Yöntem: Bu çalışma, doğrulanmış bir COVID-19 enfeksiyonu teşhisi ile hastaneye yatırılan yetişkin hastaları içermektedir. Demografik özellikler, semptomlar, klinik tablolar, tıbbi öykü, ilaçlar ve klinik ilerleme ve sonuçlar klinisyenler tarafından veri toplama formu kullanılarak not edildi. Hafif COVID-19 enfeksiyonu olan hastalarda GI semptomlarının klinik sonuçlara etkisi istatistiksel olarak değerlendirildi.

Bulgular: 307 hasta çalışmaya dahil edildi. Hastaların 159'unda (%51,7) en az bir GI semptomu vardı. Hastaların %18.2'si sadece GI semptomları, %21,2'si ise sadece GI dışı semptomlar gösterdi. Hastaların %27'si başvuru sırasında asemptomatikti. En sık görülen GI semptom hastaların %16.9'unda görülen iştahsızlıktı. En sık görülen ikinci ve üçüncü GI semptomları sırasıyla %15 hastada ishal, %14 hastada bulantı ve tat kaybıydı. GI ve GI olmayan semptom grupları arasında laboratuvar parametrelerinde anlamlı bir fark yoktu. GI ve GI olmayan semptom grupları olan hastaların yaş, cinsiyet, sigara içme durumu ve komorbiditeleri karşılaştırıldığında, ortalama yaş, cinsiyet, sigara içenler ve komorbiditeler açısından fark yoktu. Ayrıca hastanede kalış süresi (p=0,377), tam iyileşme (p=0,372) ve mortalite (p=0,351) GI ve GI olmayan semptom gruplarında sırasıyla benzerdi.

Sonuç: GI semptomlarıyla kendini gösteren COVID-19 enfeksiyonunun erken teşhisi, enfeksiyonun yayılmasını önlemeye yardımcı olabilir. Hastalarda saptanan GI semptomların çoğu hafif olup bunların varlığı daha kötü klinik sonuçlarla ilişkili saptanmamıştır.

Anahtar Kelimeler: COVID-19, gastrointestinal semptomlar, iştahsızlık, bulantı, diyare

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INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was firstly reported in Wuhan, China.[1] It swiftly spread over the world and was designated as a pandemic. According to the World Health Organization, there have been over 211 million confirmed cases of COVID-19 and more than 4.4 million deaths worldwide as of August 23, 2021.[2] Fever, cough, and shortness of breath are the most common symptoms, while one-third of patients are asymptomatic.[3] Besides these symptoms nausea, vomiting, diarrhea, lack of appetite, abdominal pain, swelling, loss of taste, and loss of smell are some of the gastrointestinal (GI) symptoms that might occur.[4] Intestinal injury and increased intestinal permeability cause GI symptoms, which trigger immune system activation. In addition, the angiotensin converting enzyme-2 receptor, which is found in the gastrointestinal tract at higher levels than in the respiratory system, was the anchor point for COVID-19 virus. However, its unclear if enteric infection progresses or leads to more serious respiratory and systemic disease.[5,6]

It is estimated in one of five COVID-19 patients have GI symptoms.[7] However, according to other research, GI symptoms occur in 50% of the patients who are impacted. Moreover, some cases have only GI symptoms as presenting symptoms.[4] There was no approved effective treatment of COVID-19 infection in the last 17 months. As a result, it is critical to take steps to avoid the spread of illnesses, such as maintaining a safe social distance, wearing gloves, and being vaccinated. Early detection of COVID-19 infection presenting with GI symptoms can also help to prevent the infection from spreading. Early stages of the disease, also known as the viral phase, are also connected with gastrointestinal illness, whereas the late stages of the illness develop more serious symptoms, such as respiratory issues.[8-11]

Because the studies involved patients with varied degrees of clinical severity (mild, moderate, and severe), it's unclear whether GI symptoms associated with COVID-19 infection are symptoms of the disease or symptoms related to a significant inflammatory response. In our study, only mild individuals with COVID-19 infection were assessed for the incidence of GI symptoms and the prognosis of these patients with GI symptoms.

MATERIAL AND METHOD

Study design

This study was conducted in patients referred to a pandemic hospital in Turkey for follow up and treatment of COVID-19 cases over a 3-month period (between March 23, 2020, and June 30, 2020).

Patients

Adult patients who were hospitalized with a confirmed diagnosis of COVID-19 according to local real-time PCR testing were considered eligible. Throat and nasal swab were taken from all the patients before hospitalization. SARS-CoV-2 PCR test negative patients were excluded, even though they have typical symptoms. Informed consent was obtained from all patients who participated in our study.

Management

All patients have been examined in terms of typical symptoms (fever, chilling, cough, shortness of breath etc.) and GI symptoms (nausea-vomiting, diarrhea, appetite, abdominal pain, swelling, loss of taste and smell) at admission by three gastroenterologists. Fever, blood pressure, pulse, and fingertip oxygen saturation were measured four times a day, or more if necessary. Blood sample was taken for complete blood count (CBC), biochemistry (included kidney functional tests, transaminases, bilirubin, LDH, C-reactive protein), ferritin, d-dimer, coagulation tests as soon as they were hospitalized. Chest X-ray and/or thoracic computerized tomography (CT) was taken. All patients were evaluated with their test results by an infectious diseases specialist, and medical therapy was started based on the recommendations of the COVID-19 Scientific Study Committee of the Turkish Republic Health Ministry. The scientific committee's guideline was first published in march 2020 and then revised in April 2020 and in June 2020. Hydroxychloroquine and azithromycin were given for five days if there were no contraindications (prolonged QRS and QTc). During the patients stay in the hospital, they were also given enoxaparin sodium. When bacterial superinfection was suspected, ceftriaxone, levofloxacin, or piperacillin-tazobactam were added after consulting with an infectious diseases specialist. Every day, all patients were visited and their symptoms, general well-being, and hemodynamic state were assessed. In two weeks, patients who were making good clinical progress were discharged. Before being released, all blood samples and X-ray chest graphy were repeated. Patients whose clinics deteriorated were sent to a higher level of care.

Definitions

Clinic deterioration was considered by the following criteria: Respiratory rate per minute >30/min, $SatO_2$<90% in room air and Lymphocyte count <800/ microliter or C-reactive protein >40 mg/L or ferritin >500 ng/ml or D-dimer >1000 ng/ml in the peripheral blood samples. Diffuse and bilateral pneumatic infiltration on chest X-ray and/or CT.

Mild disease was defined by the following criteria: Respiratory rate per minute < 12/min, $SatO_2$ >93% in room air and non diffuse or bilateral pneumatic infiltration on chest X-ray and/or CT.

For males, the upper limit of normal ALT (alanine aminotransferase) was set at 33 units/L, and for females, it was set at 25 units/L.[12] Loss of appetite was formerly thought to be a GI symptom, although it is a non-specific symptom of viral infection.

Data collection

The demographical features, clinical presentations, symptoms, medical history, medications and clinical progress and outcomes were noted using data collection form (supplement). Laboratory tests and radiologic imaging were collected using electronic medical records. All records were analyzed by the clinicians. Data collection form was manually filled to make certain of high accuracy by only three gastroenterologists.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.23 (SPSS, IBM, Chicago, IL, USA). Normality of distribution of the continuous variables was tested using Kolmogorov-Smirnov test. For regularly distributed variables, the results are provided as mean standard deviation, and for abnormally distributed variables, the median (interquartile range 25-75). For parametric continuous variables, the Student t test was employed, and for nonparametric continuous variables, the Mann-Whitney U test was utilized. Categorical variables were compared using the Chi-square test, the results of which are presented as percentages. A two tailed p value<0.05 was considered statistically significant.

Ethics

This study was complied with the ethical guidelines of the 1975 Helsinki Declaration that was then modified in 2008. The study protocol was approved by ethics committee.

RESULTS

307 patients were included in the study, 190 (61.8%) were men, mean age of whole study group was 42.3± 15.9. 124 (40%) patients were active smokers and 68 (22%) had at least one comorbidity. Three percent of patients had a preexisting gastrointestinal luminal disease. The most prevalent non-GI symptom was dry cough, which was reported by 92 (30%) patients. The second and third most common symptoms were fever in 83 (27%) patients and fatigue in 67 (21.8%) patients, respectively. 159 of patients (51.7%) had an at least one GI symptoms, 111 of those (36.1%) at admission and 48 (15.6%) of those during hospitalization. 56 (18.2%) presented only GI symptoms while 65 (21.2%) only non-GI symptoms. 83 (27%) were asymptomatic at admission. The most common GI symptom was loss of appetite that presenting 52 (16.9%) patients. The second and third most common GI symptoms were diarrhea in 46 (15%) patients, nausea and loss of taste in 43 (14%) patients, respectively. The median day between symptom onset to admission was 2.3 day±1.2-day. GI symptoms improved during hospitalization in 119 (74.8%) patients and persisted at discharge in 40 (25.2%) patients. 89 (29%) patients had elevated liver enzymes at admission. Mean length of hospital stay was 12.6±4.2 day. 20 (6.5%) patients were referred to a tertiary center or intensive care unit during hospitalization. 64 of those (%20.8) had a travel abroad history. Patients' demographics, symptoms, comorbidities and clinical outcomes were listed in **Table 1**.

Table 1. Demographic characteristics, comorbidities and clinical outcomes of patients with COVID-19 disease.

	n: 307 (%)
Mean Age (mean year±SD)	42.3 ±15.9
Gender (male)	190 (61.8%)
Smokers	124 (40%)
Comorbidities (at least one)	68 (22%)
Hypertension	24 (8%)
Diabetes	17 (6%)
Coronary artery disease	11 (4%)
Gastrointestinal luminal disease	10 (3%)
Chronic pulmonary disease	4 (1%)
Cerebrovascular disease	1 (0.3%)
Chronic kidney disease	1 (0.3%)
Symptoms (Non GI)	
Cough	92 (30%)
Fever	83 (27%)
Fatigue	67 (21.8%)
Myalgia	41 (13.4%)
Pharyngalgia	34 (11.1%)
Headache	33 (10.7%)
Dizziness	21 (6.8%)
Dyspnea	11 (3.6%)
Symptoms (GI)	
Anorexia(loss of appetite)	52 (16.9%)
Diarrhea	46 (15%)
Nausea	43 (14%)
Loss of taste	43 (14%)
Loss of smell	26 (8.5%)
Abdominal pain	13 (4.2%)
swelling	10 (3.3%)
Vomiting	9 (2.9%)
Heartburn/regurgitation	2 (0.7%)
Asymptomatics	83 (27%)
Patients with only GI symptoms	56 (18.2%)
Patients both GI and non-GI symptoms	103 (33.6%)
Patients with only non-GI symptoms	65 (21.2%)
Patients with GI symptoms	159 (51.7%)
At admission	111 (36.1%)
During hospitalisation	48 (15.6%)
Symptom onset to admission (median days ±SD)	2.3±1.2
Course of GI symptoms	
Improved during hospitalisation	119 (74.8%)
Persisted at discharged	40 (25.2%)
Liver Enzyme Abnormalities at admission	89 (29%)
Length of stay (mean day)	12.6±4.2
Referral to tertier center or ICU	20 (%6.5)

The physical examination, laboratory data, and CT results of individuals with GI and non-GI symptoms were compared. Patients presenting with non- GI symptoms had higher fever values at admission (36.7±0.4 vs. 37.0±0.7, p=0.002) than GI symptoms. While the fingertip oxygen saturations of both groups were similar at admission, there was no significant difference in laboratory parameters (white blood cell, lymphocyte, hemoglobin, platelet, urea, creatinine, AST, ALT, LDH, CRP, ferritin, d-dimer, procalcitonin) between GI and non-

GI symptoms groups (for all parameters p>0.05). Pulmonary involvement on computed tomography was similar between two groups (23 versus 36, p=0.286) (**Table 2**).

Table 2. Physical examination, Laboratory parameters and CT findings based on patients with GI symptoms or Gon-GI syptoms.

	GI Sympytoms n: 56	Non-GI Symptoms n: 65	P value
Fever (°C)	36.7±0.4	37.0±0.7	0.002
Fingertip oxygen saturation, SO_2, (%)	96.8±1.2	96.5±1.5	0.149
Wbc, count x103/mm³	6.6±2.0	6.2±2.4	0.342
Lymphocyte, count x103/mm³	1.9±0.6	1.7±0.6	0.101
Hemoglobin, gr/dl	14.2±1.6	14.2±1.8	0.807
Platelet count, x103/mm³	234.0±49.8	235.0±79.0	0.930
Urea, mg/dL	26.2±7.5	26.9±9.7	0.672
Creatinin, mg/dL	0.8±0.2	0.8±0.2	0.932
ALT, IU/L	20.0 (14.2-34.7)	25.0 (17.5-40.0)	0.051
AST, IU/L	22.0 (18.2-27.7)	23.0 (19.5-33.0)	0.099
LDH, IU	217.3±64.6	223.7±60.4	0.592
CRP, mg/dL	0.5 (0.1-1.1)	0.8 (0.3-1.8)	0.089
Ferritin, ng/ml	152.0 (94.7-259.7)	152.0 (79.0-219.0)	0.257
D-dimer, ng/ml	0.3 (0.1-0.6)	0.3 (0.1-0.5)	0.849
Procalcitonin, ng/ml	0.03 (0.02-0.07)	0.04 (0.02-0.06)	0.659
Lung involvement in CT (pneumonia), n (%)	23 (41)	36 (54)	0.286

Results are expressed as mean±SD or median (IQR) or frequency (%). GIS: Gastrointestinal system, WBC: White blood cell , AST: Aspartate aminotransferase, ALT: Alanin aminotransferase, LDH: , CRP: C-reactive protein., CT: computed tomography

When age, gender, smoking status, and comorbidities of patients with GI and non-GI symptoms groups were compared, there was no difference in mean age (38.3 15.3 vs. 41.0 16.3, p=0.540), gender (39 vs. 45, p=0.961), smokers (24 vs. 22, p=0.309), and comorbidities (9 vs. 11, p=0.900). In addition, the length of hospital stays (12.0 vs. 13.0, p=0.377), complete healing (55 vs. 61, p=0.372) and mortality (0 versus 1, p=0.351) was similar in patients with GI and non-GI symptoms groups respectively (**Table 3**).

Table 3. Clinical findings and outcomes of SARS-CoV-2 infection with GI and without GI symptoms.

	GI symptoms n: 56	Non GI symptoms n: 65	P value
Age, years	38.3 ± 15.3	41.0 ± 16.3	0.540
Gender (Male), n (%)	39 (70)	45 (69)	0.961
Smoking, n (%)	24 (43)	22 (34)	0.309
Comorbidity, n (%)	9 (16)	11 (17)	0.900
Outcomes			
Length of stay, days	12.0 (11.0-14.0)	13.0 (12.0-14.0)	0.377
Complete healing	55 (98)	61 (94)	0.372
Referral to tertier center or ICU	1 (2)	4 (6)	0.372
Mortality, n (%)	0 (0)	1 (2)	0.351

Results are expressed as mean ± SD or median (IQR) or frequency (%). SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, GI: Gastrointestinal.

DISCUSSION

In this prospective study, 44.6% of patients with COVID-19 had at least one gastrointestinal symptom. While this rate was as low as 15% in the first studies on COVID-19, however, our results were consisted with more recent studies.[13,14] 30.3% of patients had GI symptoms at admission and 14.3% of patients developed GI symptoms during hospitalization. GI symptoms developing during hospitalization may be associated with GI side effects of medications such as hydroxychloroquine and azithromycin.[15] The majority of gastrointestinal symptoms were mild level.

In this study, most common GI symptom was loss of appetite (16.9%) and was similar to recent studies (16). Also, diarrhea (15%), nausea (14%), and loss of taste (14%), respectively, were the most prevalent second and third GI symptoms, with a higher incidence than some previous research.[14-17] While 27.4% of the patients were asymptomatic in our study, it was found as high as 51% in some studies.[18] GI symptoms are frequently underreported, and patients are mistakenly labeled as asymptomatic. According to certain studies, the prevalence of GI symptoms is reduced in this scenario.[19] At the beginning of the COVID-19 pandemic in our country, all patients with COVID-19 were hospitalized and followed up. In this study, consideration of GI symptoms (by using collecting data form) and prospective study design may have provided more consistent estimation rates of GI symptoms. Additionally, the symptoms of the patients were observed daily and thus the presence of symptoms was revealed with high accuracy.

GI symptoms may occur in the course of infectious diseases. This is more prominent in severe disease. One of the advantages of our study is that we detected the presence of GI symptoms in patients with non-severe COVID-19. The presence of GI symptoms in mild disease may increase the likelihood of being a characteristic symptom of COVID-19 infection rather than symptoms secondary to a severe inflammatory response.

The presence of GI symptoms at admission or during hospitalization was not associated with disease progression or transfer to the internal care unit, similar to previous studies.[13,14]

The limitations of our study are that we cannot distinguish whether patients with elevated transaminase levels are associated with underlying liver disease or, medication, or COVID-19 disease. Another limitation of the study was the low mortality rate since the majority of the patients had a mild course, and we could not evaluate the relationship between GI symptoms and mortality.

CONCLUSION

Gastrointestinal symptoms and liver test abnormalities are common among patients with COVID-19 disease, and early diagnosis of SARS-CoV-2 infection presenting with GI symptoms can help prevent infection spread. However, the majority of these symptoms were mild, and their presence was not associated with worse clinical outcomes.

Main Points

- Gastrointestinal symptoms and liver test abnormalities are common among patients with COVID-19 disease.
- Early diagnosis of SARS-CoV-2 infection presenting with GI symptoms can help prevent infection spread.
- The presence of GI symptoms at admission or during hospitalization was not associated with disease progression or transfer to the internal care unit.
- The presence of GI symptoms in mild disease may increase the likelihood of being a characteristic symptom of COVID-19 infection rather than symptoms secondary to a severe inflammatory response.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by Ankara City Hospital ethics committee (Approval No: E1/785/2020).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: The author declare that he has all participated in the design, execution, and analysis of the paper, and that he has approved the final version.

REFERENCES

1. Cao Y, Cai K, Xiong L. Coronavirus disease 2019: A new severe acute respiratory syndrome from Wuhan in China. Acta Virol. 2020;64(2):245-50.
2. who.int. Weekly operational update on COVID-19 - 23 August 2021 who.int2021 [updated 23 August 2021. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
3. Liu J, Huang J, Xiang D. Large SARS-CoV-2 Outbreak Caused by Asymptomatic Traveler, China. Emerg Infect Dis. 2020;26(9).
4. Lin L, Jiang X, Zhang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020;69(6):997-1001.
5. Ziegler CGK, Allon SJ, Nyquist SK, et al. SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. Cell. 2020;181(5):1016-35 e19.
6. Xiao F, Tang M, Zheng X, et al. Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology. 2020;158(6):1831-3 e3.
7. Lee IC, Huo TI, Huang YH. Gastrointestinal and liver manifestations in patients with COVID-19. J Chin Med Assoc. 2020;83(6):521-3.
8. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020;26(5):672-5.
9. Liu Y, Yan LM, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis. 2020;20(6):656-7.
10. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy. 2020;75(7):1564-81.
11. Sokolowska M, Lukasik ZM, Agache I, et al. Immunology of COVID-19: Mechanisms, clinical outcome, diagnostics, and perspectives-A report of the European Academy of Allergy and Clinical Immunology (EAACI). Allergy. 2020;75(10):2445-76.
12. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. Am J Gastroenterol. 2017;112(1):18-35.
13. Elmunzer BJ, Spitzer RL, Foster LD, et al. Digestive Manifestations in Patients Hospitalized With Coronavirus Disease 2019. Clin Gastroenterol Hepatol. 2021;19(7):1355-65 e4.
14. Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5(7):667-78.
15. Bilbul M, Paparone P, Kim AM, et al. Psychopharmacology of COVID-19. Psychosomatics. 2020;61(5):411-27.
16. Tariq R, Saha S, Furqan F, et al. Prevalence and Mortality of COVID-19 Patients With Gastrointestinal Symptoms: A Systematic Review and Meta-analysis. Mayo Clin Proc. 2020;95(8):1632-48.
17. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
18. Mizumoto K, Kagaya K, Zarebski A, et al. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro Surveill. 2020;25(10).
19. Kim GU, Kim MJ, Ra SH, et al. Clinical characteristics of asymptomatic and symptomatic patients with mild COVID-19. Clin Microbiol Infect. 2020;26(7):948 e1- e3.

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Original Article / Orijinal Araştırma

Evaluation of the Effectiveness of Trans Obturator Tape Operation in the Treatment of Stress Incontinence

Stres İnkontinans Tedavisinde Trans Obturator Bant Operasyonunun Etkisinin Değerlendirilmesi

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Abstract

Objective: In this study, In this study, we aimed to assess the effectiveness of transobturator tape operation in the treatment of stress incontinence

Material and Method: We retrospectively evaluated 454 patients who had TOT operations due to stress urinary incontinence between January 01.01. 2017, and December 31.12.2020, at the Traning and Research Hospital. The basic clinical characteristics of the participants were recorded. The number of daily peds, values of Q-type test and urinary retention, and scores of urogenital disorder inventory-6 and impact of incontinence inquiry form at the clinical evaluation perioperatively and 6 months after the operation. Data analysis of the study was done with the SPSS version 24.0 package program. Kolmogorov-Smirnov test was used for normality analysis. Wilcoxon test was used for the comparisons of preop and postop data. It was considered statistically significant when the P value was below 0.05

Results: The study was conducted on 454 patients aged 26-83 years with a mean age of 50.3±10 years. The overall complication rate was 15.9. The rate of those who recovered six months after the operation was 89.6%. The number of daily peds, values of Q-tip test and urinary retention, and scores of questionnaires were significantly reduced after surgery (p=0.001).

Conclusion: The TOT operation can be preferred in treating stress incontinence with acceptable success and outcome. The scales of questionnaires successfully determine patient satisfaction with surgical efficacy for SUI.

Keywords: Stress urinary incontinence, transobturator tape operation, urogenital disorder inventory-6, the impact of incontinence inquiry

Öz

Amaç: Bu çalışmada, stres inkontinans tedavisinde transobturator bant operasyonunun etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yötem: 1 Ocak 2017-31 Aralık 2020 tarihleri arasında bir il Eğitim ve Araştırma Hastanesi'nde stres üriner inkontinans nedeniyle TOT ameliyatı olan 454 hasta retrospektif olarak değerlendirildi. Katılımcıların temel klinik özellikleri kaydedildi. Operasyonun klinik değerlendirmesi perioperatif ve 6 ay sonra günlük ped sayısı, Q-tipi test ve idrar retansiyonu değerleri, ürogenital bozukluk envanteri-6 puanları ve inkontinans sorgulama formu ile yapıldı. Çalışmanın veri analizi SPSS versiyon 24.0 paket programı ile yapılmıştır. Normallik analizi için Kolmogorov-Smirnov testi kullanıldı. Ameliyat öncesi ve sonrası verilerin karşılaştırılmasında Wilcoxon testi kullanıldı. P değeri 0.05'in altında olduğunda istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışma yaş ortalaması 50.3±10 yıl olan 26-83 yaş arası 454 hasta üzerinde yapıldı. Genel komplikasyon oranı 15.9 idi. Ameliyattan altı ay sonra iyileşenlerin oranı %89,6 idi. Ameliyattan sonra günlük ped sayısı, Q-tip testi ve idrar retansiyonu değerleri ve anket puanları önemli ölçüde azaldı (p=0,001).

Sonuçlar: Stres inkontinans tedavisinde TOT operasyonu kabul edilebilir başarı ve sonuçlarla tercih edilebilir. Anket ölçekleri, SUI için cerrahi etkinlik ile hasta memnuniyetini başarılı bir şekilde belirler.

Anahtar Kelimeler: Stres üriner inkontinans, transobturator bant operasyonu, ürogenital bozukluk envanteri-6, inkontinans sorgulamasının etkisi

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INTRODUCTION

Urinary incontinence is an objectively demonstrable involuntary event that causes a social or hygienic problem, according to the definition of the International Continence Association. [1] Although the prevalence of urinary incontinence increases with age, it should not be accepted as the natural course of old age. The most common types of urinary incontinence are stress incontinence 45%, urgency incontinence 25%, and mixed types 28%.[2] Stress and mixed urinary incontinence, the most frequent causes in women, have become significant public health problems affecting the quality of life. Urodynamically, it develops due to intravesical pressure exceeding the urethral closure pressure without detrusor contraction.[3,4] The main mechanism in the emergence of stress urinary incontinence is the loss of bladder neck and urethral support. In 1995, Ulmsten and Petros described tension-free vaginal tape (TVT) surgery, which provides hammock-like support to the ureterovesical junction.[5] Non-tight support of the mid-urethra has yielded more than 80% success.[6] The TVT procedure had been shown to have the same efficacy as Burch colposuspension.[7] In tension-free vaginal tape surgery, the needle or trocar passes blindly through the retropubic space. To avoid life-threatening complications and develop different techniques, the trans obturator tape (TOT) technique was proposed in 2001.[8] In the transobturator band technique, the trocar or needle does not pass through the retropubic area. The tape is placed between the two obturator foramen. (trans obturator tape method (TOT)). Studies have reported that the success of TOT and TVT in providing continence is similar, and the complication rate of the TOT technique is lower.[9] The TOT operation has been widely used because of its safe, effective, easy to apply, high treatment success rate of 84%-95%, and low complication rates.[10] In this study, we aimed to assess the effectiveness of Transobturator Tape Operation in the treatment of Stress İncontinence.

MATERIAL AND METHOD

We retrospectively evaluated the patients who had TOT operations due to stress urinary incontinence between January 1, 2017, and December 31, 2020, at the Traning and Research Hospital. The study was conducted on 454 patients, 398 (87.7%) with pure stress urinary incontinence and 56 (12.3%) with mixed urinary incontinence. This study was conducted by the 2013 revision of the Declaration of Helsinki. The study was carried out with the permission of Istanbul Kanuni Sultan Süleyman Training and Research Hospital (KAEK/2021.05.168). The requirement for patient consent to participation and publication was waived due to the retrospective nature of the study. Written informed permission for treatment was obtained from all patients.

Demographic characteristics of the patients were recorded. Urogenital distress inventory-6 and incontinence impact questionnaire-7 were used to determine incontinence severity preoperatively and postoperatively in all patients.[11] Urodynamic testing was only used to confirm the absolute diagnosis of mixed-type urinary incontinence. All patients were subjected to detailed physical, urogynecological, and neurological examinations, and pelvic organs were evaluated with pre-and post-operative urinalysis, urine culture, post-void residual urine measurement, and ultrasound. To detect urethral hypermobility, a Q-tip test was performed with 200 mL of urine in the bladder in the lithotomy position. Bladder neck mobility was evaluated as positive when the amount of angle change in the straining and resting states of the cotton swab, the tip of which was placed in the internal urethral meatus, was above 30 degrees. When the bladder was full of saline, the patient coughed in the examination position or outpatient. It was checked whether there was urinary incontinence. The stress test was considered positive in cases with urinary incontinence. Urinary tract infections were treated with appropriate antibiotics.

Postoperative cases were called for controls in the 1st, 3rd, and 6th months, and urogynecological examinations were performed, Urogenital distress inventory-6 and incontinence impact questionnaire-7, stress test, examination findings, neurological evaluation, residual urine, and Q-tip test. The patients were re-evaluated with the number of daily pads, and the operational success and perioperative complications were evaluated and recorded

After the operation, those who had a post-operative stress test (-), whose residual urine amount was below 100 mL, and who had complete continence were as 'full recovery'; Those who had a post-operative stress test (+) but did not incontinent were considered as partial recovery. Patients evaluated as having 'full recovery,' and 'partial recovery' were accepted as successful, and patients with a post-operative stress test (+) and incontinence continued were considered 'TOT failure.[12] The women included in the study such as diagnosed with stress incontinence, who did not plan to give birth in the next life, who did not have urinary system infection, who did not show a bleeding tendency, who had no anti-incontinence surgery before, who had involuntary urine leakage with coughing, sneezing, had urethral hypermobility more than 30 degrees with Q-type test, had preoperative residual urine volume of less than 100 mL and had no neurological disease

The women were excluded from the study such as those diagnosed with no stress incontinence, who planned to give birth in the next life, who had urinary system infections, who showed a bleeding tendency, who had anti-incontinence surgery before, who had no involuntary urine leakage with coughing, sneezing, had urethral hypermobility less than 30 degrees with Q-type test, had preoperative residual urine volume of more than 100 mL and had a neurological disease

An informed consent form was obtained from all patients before the operation. For prophylactic treatment, a total of 2 g of cefazolin sodium was administered IV approximately one hour before and 6 hours after the operation. All procedures were performed with an outside-in Obtryx™ (Boston Scientific, Natick, MA, USA) brand kit.

Surgical technique

Spinal anesthesia was used in surgical procedures, and a vertical incision of approximately 1.5-2 cm was made about 1 cm distal to the external urethral meatus. With Metzenbaum scissors, sharp and blunt dissections were made, and the periurethral fascia was dissected approximately 1 cm laterally. The ischiopubic ramus was palpated with the index finger, and two 0.5 cm skin incisions were made in both genito-inguinal folds at a distance of approximately 2 cm at the clitoris level. A hook-shaped needle was inserted through the incision. Simultaneously, the index finger was inserted through the paraurethral area to guide the hand, and the needle was removed from the paraurethral site by passing it through the obturator foramen. Here, a polypropylene sling material was applied with its attachment to the needle tip, and then it was pulled back, and the same procedure was applied on the opposite side of the urethra. While removing the sling material, a clamp was placed between the urethra and mesh to ensure that the mesh was not tight, and the ends were cut at the subcutaneous level above. The incision in the urethral region was sutured with soluble 2/0 Vicryl.[13] Complications that occurred during the operation were recorded. The bladder was filled with 400 mL of physiological saline to measure the amount of residual urine. After the patient urinated, the catheter was inserted again, and the amount of urine remaining in the bladder was measured. Catheterization was continued for an additional 6-8 h in patients with more than 100 mL of residual urine. Patients with less than 100 mL residual urine volume were discharged with oral antibiotics. All patients were recommended sexual abstinence for 45 days.

Statistical analysis

Data analysis of the study was done with IBM SPSS for Windows 24.0 package program (IBM SPSS Inc, Chicago, Illinois, USA). Kolmogorov-Smirnov test were used for normality analysis. Descriptive statistics are numbers and percentages for categorical variables, mean with standard deviation as normally distributed numeric variables, or median with minimum and maximum as appropriate. Wilcoxon test was used for the comparisons of preop and postop data. It was considered statistically significant when the P value was below 0.05

RESULTS

During the study period, 481 patients with stress incontinence were included. Of the study population, 27 were excluded because of postoperative loss to follow-up. **Table 1** shows the selected clinical characteristics of the study population undergoing surgical management of stress incontinence.

Approximately 48% of study participants whose clinical and incontinence data were analyzed were in menopause. However, the age of surgery ranged from 26 to 83 years. Chronic disease history rates such as diabetes mellitus, hypertension, and heart and thyroid diseases were between 5.3% and 23.8%.

Table 1. Selected clinical characteristics of participants with stress incontinence (n=454).

		min-max
Age (year)	50.3 (9.8)	26-83
Parity	3.5 (1.7)	0-11
History of		
Diabetes mellitus	74 (16.3%)	
Hypertension	108 (23.8%)	
Heart disease	24 (5.3%)	
Thyroid disease	39 (8.6%)	
Number of vaginal delivery	3.4 (1.8)	0-11
History of macrosomia	123 (27.1%)	
Menopause	220 (48.5%)	
Smoking	58 (12.8%)	
BMI (kg/m²)	27.0 (3.0)	20.5-40.6
Duration of incontinence (year)	4.0 (2.6)	1-20
Type of incontinance		
Stress	399 (87.9%)	
Mixed	55 (12.1%)	
Surgery procedure		
only TOT	364 (80.17%)	
TOT with colporraphy anterior	44 (9.69%)	
TOT with colporraphy posterior	14 (3.1%)	
TOT with vaginal hysterectomy	32 (7.04%)	
Operation time (min)	45.2 (22.0)	25-115
Hospital stay (day)	2.4 (1.3)	2-6
Complications (total)	72 (15.9%)	
Hemorrhagia (more than 200 m)	6 (1.3%)	
Mesh erosion	12 (2.6%)	
Urinary retantion	7 (1.5%)	
Bladder perforation	4 (0.9%)	
Perineal pain	12 (2.6%)	
De novo urge incontinence	14 (3.1%)	
Vaginal perforation	5 (1.1%)	
Dyspareunia	12 (2.6%)	
Success of surgery		
Complet recovery	382 (84.1%)	
Partial recovery	25 (5.5%)	
No recovery	47 (10.4%)	

Data are expressed as mean (standard deviation) or count (%).

Our data supported the impact of many vaginal deliveries, history of macrosomic deliveries, menopausal status, smoking, and being overweight and obese. Duration of incontinence before surgical treatment changed from 1 to 20 years with a mean value of 4 years. This highlighted the importance of time incontinence as a determiner of surgical success. Of the study participants, about 88% had only stress incontinence and the rest had mixed incontinence; for this condition, the physicians paid attention while giving information about the surgical treatment of patients and relatives. The complication rate was about 16%, and the complete success of the surgery was about 84%. Considering the clinical characteristics of study participants, stress incontinence and its surgery have many complex aspects encountered during urogynecological management.

Table 2 shows the Preoperative and postoperative 6-month follow-up results of the patients

Table 2: Preoperative and postoperative 6-month follow-up results of the patients

	Preoperative	Postoperative	P value
(UDI-6)	10,9±0.7	2,1±1.6	0.001
(IIQ-7	15.6±2,2	1,56±1,2	0.001
Average number of pads/d	2.5±2,2	0.3±0,6	0.001
Amount of residue urine /ml	66.30±11,5	28.4.2±8,4	0.001
Q type test	62,9±1.4	27.5±8,1	0.001
Stresstest(+)	%100	72(%15.9)	0.001

Mean ,SD, standard deviation,d,days,ml milliliter,(+) positive.

Compared to the pre-operative period, the number of pads used daily decreased, and the Q-type test results improved significantly. There was a significant decrease in residual urine volume.

Of the study population, the variables measured preoperatively and postoperatively were shown in **Figures 1** and **2**. The scores of urogenital disorder inventory-6, and incontinence impact inquiry forms preoperatively were significantly reduced after surgery (p=0.001).

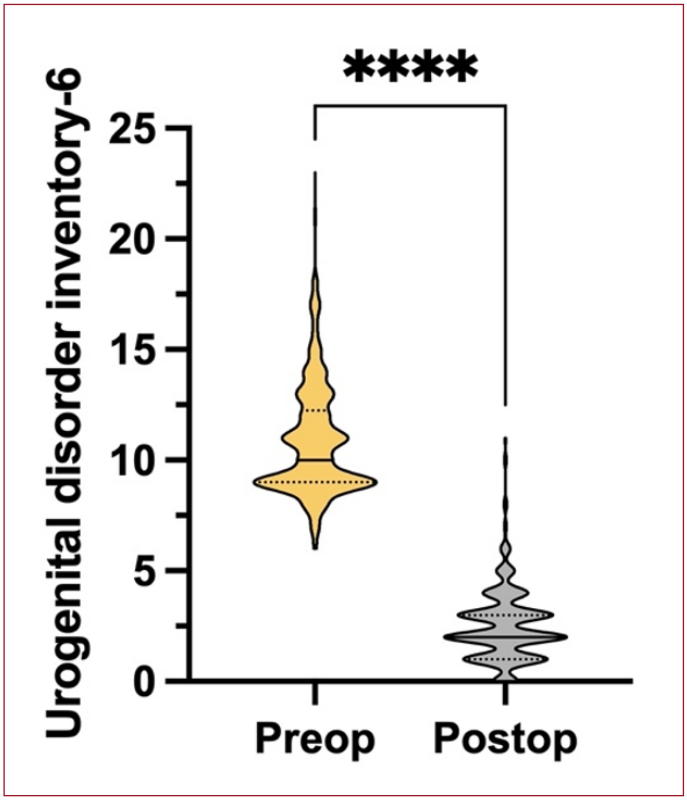

Figure 1. Scores of urogenital disorder inventory-6 measured in the study participants with stress incontinence. Data are expressed as median with a 25-75 interquartile range. The score of urogenital disorder inventory-6 preoperatively was significantly reduced after surgery (p=0.001).

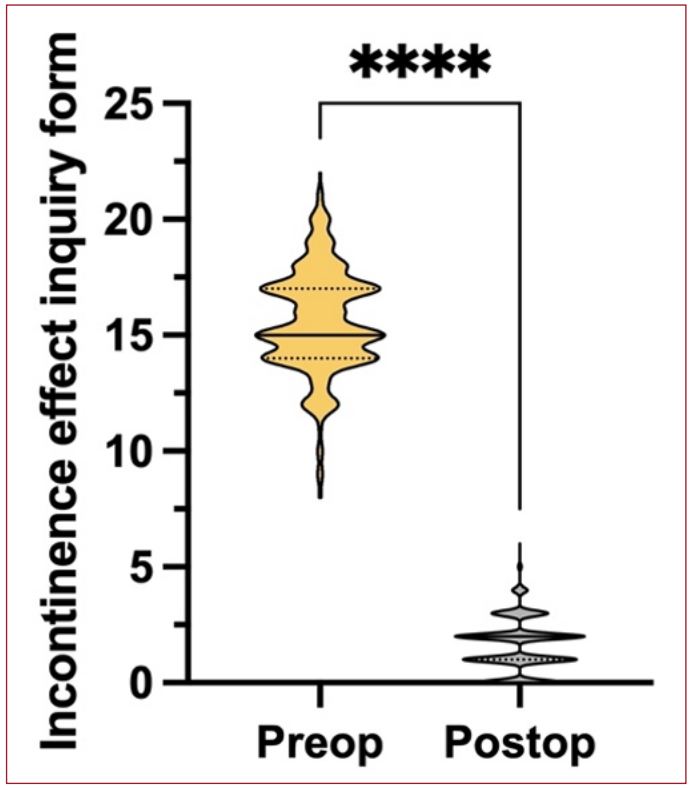

Figure 2. Scores of the impact of incontinence inquiry form measured in the study participants with stress incontinence. Data are expressed as median with a 25-75 interquartile range. The score of the impact of incontinence inquiry form preoperatively was significantly reduced after surgery (p=0.001).

DISCUSSION

TOT operation is effective in treating stress urinary incontinence, 89.6% at six months postoperatively.

After the TOT operation, The clinical severity of urinary incontinence improved meaningfully when considering a reduced number of daily peds, improved Q-tip test results, and decreased urinary residue volume. The scores of urogenital disorder inventory-6 and incontinence impact inquiry forms were also significantly reduced after surgery .

The most critical factors for stress urinary incontinence are genetic differences, previous gynecological operation, advanced age, hypoestrogenic, birth trauma, obesity, and smoking.[14] With the decrease of estrogen hormone in menopause, stress urinary incontinence increases. Today, colposuspension and mid-urethral sling operations are most frequently performed to elevate and support the urethra-vesical junction. Mid-urethral sling methods are the most commonly used in the treatment of stress urinary incontinence because they are easy to apply, have a shorter learning curve, have common complications, and have successful long-term results.[15] The necessity of performing urodynamic studies before stress urinary incontinence surgery is controversial.[16] In our research, urodynamic testing was performed only on mixed-type urinary incontinence to confirm the diagnosis.

Since the surgical success rates in mid-urethral sling surgeries are based on the definition of success, follow-up time, and subjective data, success evaluation is in a wide range in the literature. But generally, it varies between 64% and 100%(17). In the literature, the cure rate in the TOT procedure varies between 51-95%.[18] Treatment is unsuccessful if there is persistence and recurrence after stress incontinence surgery. Persistence is defined as the persistence of urinary incontinence after surgery. On the other hand, recurrence can be defined as the patient who has benefited after surgery becomes incontinent again.[19] To differentiate recurrence and persistence, the time between surgery and the onset of symptoms was expressed as six weeks.[20] In our study, the scores of urogenital disorder inventory -6 and the impact of incontinence inquiry form-7 were used as quality of life measures to report patients' urinary incontinence symptoms and to obtain concrete evidence of its effects on their lives. Urinary symptoms with daily activities such as physical activity, travel, social relationships, and mental health status moderated these scores.[21] Significant decreases were detected in these scores before and six months after the operation compared to the preoperative period. Recovery of urethral mobility is unnecessary in mid-urethral sling operations, and postoperative continuation of mobility allows the urethra to bend dynamically during stress.[22] Our study in the post-operative period did not show a significant improvement in bladder neck mobility compared to the pre-operative Q-type test.The average operation time for the TOT operation is 20-25 minutes which is by the durations stated in the literature.[23] The average operation time in our study is about 45 min. The reason for our longer operation time is that 90 (19.82%) patients underwent simultaneous prolapse surgery in addition to the TOT operation.

Complication rates reported after TOT operation ranged from 10.5% to 31.3%[20], with 72 patients (15.9%) in our study. Mesh vaginal erosion is one of the critical complications that can be observed after TOT. The mesh quality used in the development of mesh erosion, the surgical technique applied, early sexual activity, individual hygiene, and postoperative follow-up period. Features such as foreign body reactions to mesh, infections and careless surgery, diabetes mellitus, corticosteroid use, and menopause are compelling. Erosion is less common in monofilament and macroporous meshes.[24] As a result of 27 months follow-up of 233 cases after TOT operation, mesh erosion was detected in 17 patients (7.1%).[25] Mesh erosion rate has been reported between 1% and 10.9% in the literature.[26] Our study observed Mesh erosion in 12 (2.6%) patients. In cases with mesh erosion, the mesh was partially removed. In our study, six months post-operative patient follow-up and the use of macroporous mesh may be the reason for the low mesh erosion rate in Obtryx™ (Boston Scientific, Natick, MA, USA). Mesh erosion can occur years after TOT operation. Bladder perforation can be seen in TOT operations (0-2.8%).[27] In our study, urinary retention occurred in 7 1.5% of patients. After two more days of bladder catheterization, the patients improved. There was no situation requiring band loosening or cutting. Dyspareunia, seen between 4.5% and 24% after TOT.[18] In our study, urinary retention occurred in 7 1.5% of patients. After two more days of bladder catheterization, the patients improved. There was no situation requiring band loosening or cutting. Dyspareunia, seen between 4.5% and 24% after TOT.[28] was found to be 2.6% in our study.In previous studies, the incidence of de novo urge incontinence has varied from 2% to 15%.[29,30] The most important reason is that it causes urethral obstruction because the mesh is tighter than usual. Anticholinergic drugs are effective in their treatment. In our study, de novo urge incontinence occurred in 14 (3.1%) patients. They were improved with anticholinergic medications.

The rate of bleeding more than 200 ml due to injury of the venous flexus during urethro-vaginal dissection in TOT operations has been reported as 0-2.8% in the literature.[31] In our study, more than 200 ml of bleeding was seen in 6 (1.3%) patients and stopped with compression and hemostasis. One of the complications observed in the early period after TOT operation is a pain in the inguinal region. Studies have reported that this rate varies between 5% and 26%.[32] Pain in most patients is usually temporary and resolves spontaneously within a few months. The causes of pain are foreign body reactions against the mesh passing near the branches of the obturator nerve and trauma to the obturator membrane and muscles.[33]

CONCLUSION

The TOT operation can be preferred in treating stress incontinence with acceptable success and outcome. The scales of questionnaires successfully determine patient satisfaction with surgical efficacy for SUI.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Istanbul Kanuni Sultan Süleyman Training and Research Hospital (KAEK/2021.05.168).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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REFERENCES

1. Abrams P, Cardozo L, Fall M et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol. Urodyn. 2002;21(2):167–178.
2. Hunskaar S, Lose G, Sykes D, Voss S. The prevalence of urinary incontinence in women in four European countries. BJU Int. 2004;93(3):324–330.
3. Trowbridge ER, Hoover EF. Evaluation and Treatment of Urinary Incontinence in Women. Gastroenterol. Clin. North Am. 2022;51(1):157–175.
4. Nambiar AK, Arlandis S, Bø K et al. European Association of Urology Guidelines on the Diagnosis and Management of Female Non-neurogenic Lower Urinary Tract Symptoms. Part 1: Diagnostics, Overactive Bladder, Stress Urinary Incontinence, and Mixed Urinary Incontinence. Eur. Urol. 2022.
5. Ulmsten U, Petros P. Intravaginal slingplasty (IVS): an ambulatory surgical procedure for treatment of female urinary incontinence. Scand. J. Urol. Nephrol. 1995;29(1):75–82.
6. Ulmsten U, Falconer C, Johnson P et al. A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence. Int. Urogynecology J. 1998;9(4):210–213.
7. Ward KL, Hilton P. A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: two-year follow-up. Am. J. Obstet. Gynecol. 2004;190(2):324–331.
8. Delorme E, Droupy S, de TAYRAC R, Delmas V. La bandelette trans-obturatrice (Uratape®). Un nouveau procédé mini-invasif de traitement de l'incontinence urinaire de la femme. Prog. En Urol. Paris 2003;13(4):656–659.
9. Costa P, Grise P, Droupy S et al. Surgical treatment of female stress urinary incontinence with a trans-obturator-tape (TOT®) Uratape®: Short term results of a prospective multicentric study. Eur. Urol. 2004;46(1):102–107.
10. Leone Roberti Maggiore U, Finazzi Agrò E, Soligo M et al. Long-term outcomes of TOT and TVT procedures for the treatment of female stress urinary incontinence: a systematic review and meta-analysis. Int. Urogynecology J. 2017;28(8):1119–1130.
11. Skorupska K, Grzybowska ME, Kubik-Komar A, Rechberger T, Miotla P. Identification of the Urogenital Distress Inventory-6 and the Incontinence Impact Questionnaire-7 cutoff scores in urinary incontinent women. Health Qual. Life Outcomes 2021;19(1):1–6.
12. Latthe PM, Foon R, Toozs-Hobson P. Transobturator and retropubic tape procedures in stress urinary incontinence: a systematic review and meta-analysis of effectiveness and complications. BJOG Int. J. Obstet. Gynaecol. 2007;114(5):522–531.
13. Mangano E, Campagne-Loiseau S, Curinier S et al. Transobturator vaginal tape in 10 Steps. J. Minim. Invasive Gynecol. 2020;27(1):27–28.
14. Hägglund D, Olsson H, Leppert J. Urinary incontinence: an unexpected large problem among young females. Results from a population-based study. Fam. Pract. 1999;16(5):506–509.
15. Ford AA, Taylor V, Ogah J et al. Midurethral slings for treatment of stress urinary incontinence review. Neurourol. Urodyn. 2019;38:S70–S75.
16. CHAIKIN DC, Rosenthal J, Blaivas JG. Pubovaginal fascial sling for all types of stress urinary incontinence: long-term analysis. J. Urol. 1998;160(4):1312–1316.
17. Cubuk A, Yanaral F, Savun M et al. Modified autologous transobturator tape surgery—evaluation of short term results. Ginekol. Pol. 2020;91(2):51–56.
18. Deval B, Ferchaux J, Berry R et al. Objective and subjective cure rates after trans-obturator tape (OBTAPE®) treatment of female urinary incontinence. Eur. Urol. 2006;49(2):373–377.
19. Verbrugghe A, De Ridder D, Van der Aa F. A repeat mid-urethral sling as valuable treatment for persistent or recurrent stress urinary incontinence. Int. Urogynecology J. 2013;24(6):999–1004.
20. Bakali E, Buckley BS, Hilton P, Tincello DG. Treatment of recurrent stress urinary incontinence after failed minimally invasive synthetic suburethral tape surgery in women. Cochrane Database Syst. Rev. 2013;(2).
21. FitzGerald MP, Kenton K, Shott S, Brubaker L. Responsiveness of quality of life measurements to change after reconstructive pelvic surgery. Am. J. Obstet. Gynecol. 2001;185(1):20–24.
22. Lo T-S, Wang AC, Horng S-G, Liang C-C, Soong Y-K. Ultrasonographic and urodynamic evaluation after tension free vagina tape procedure (TVT). Acta Obstet. Gynecol. Scand. 2001;80(1):65–65.
23. Zengin K, Kara M, Tanik S, Sertcelik MN, Eraslan A. Comparison of Transobturator Tape and Mini-Sling Tissue Fixation in Female Patients Who Had Stress Urinary Incontinence. Adv. Clin. Exp. Med. Off. Organ Wroclaw Med. Univ. 2015;24(5):851–855.
24. But I. Vaginal wall erosion after transobturator tape procedure. Int. Urogynecology J. 2005;16(6):506–508.
25. Kaelin-Gambirasio I, Jacob S, Boulvain M, Dubuisson J-B, Dällenbach P. Complications associated with transobturator sling procedures: analysis of 233 consecutive cases with a 27 months follow-up. BMC Womens Health 2009;9(1):1–7.
26. Dalpiaz O, Knopf HJ, Orth S et al. Mid-term complications after placement of the male adjustable suburethral sling: a single center experience. J. Urol. 2011;186(2):604–609.
27. Abdel-Fattah M, Ramsay I, Pringle S. Lower urinary tract injuries associated with transobturator tension free vaginal tape procedure: a large retrospective study. BJOG 2006;113(12):1377–1382.
28. Cholhan HJ, Hutchings TB, Rooney KE. Dyspareunia associated with paraurethral banding in the transobturator sling. Am. J. Obstet. Gynecol. 2010;202(5):481-e1.
29. Grise P, Droupy S, Saussine C et al. Transobturator tape sling for female stress incontinence with polypropylene tape and outside-in procedure: prospective study with 1 year of minimal follow-up and review of transobturator tape sling. Urology 2006;68(4):759–763.
30. Juma S, Brito CG. Transobturator tape (TOT): two years follow-up. Neurourol. Urodyn. Off. J. Int. Cont. Soc. 2007;26(1):37–41.
31. Barber MD, Gustilo-Ashby AM, Chen CCG et al. Perioperative complications and adverse events of the MONARC transobturator tape, compared with the tension-free vaginal tape. Am. J. Obstet. Gynecol. 2006;195(6):1820–1825.
32. Dobson A, Robert M, Swaby C, Murphy M, Birch C, Mainprize T, Ross S. Trans-obturator surgery for stress urinary incontinence: 1-year follow-up of a cohort of 52 women. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Jan;18(1):27-32. DOI: 10.1007/s00192-006-0115-9.
33. Mellier G, Moore R, Jacquetin B. A meta-analysis of the intra-operative safety and effectiveness of the transobturator hammock seen in results of two prospective studies in 9 countries with 204 patients. ICS/IUGA Joint meeting. Paris 2004.

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Original Article / Orijinal Araştırma

The Effect of Pulmonary Rehabilitation on Pain, Respiratory Functions and Activities of Daily Living in COVID-19 Patients

Pulmoner rehabilitasyonun COVID-19 Hastalarında Ağrı, Solunum Fonksiyonları ve Günlük Yaşam Aktivitelerine Etkisi

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Abstract

Aim: Coronavirus disease 2019 (COVID-19) requires a multidisciplinary approach owing to its multisystem involvement. Pulmonary rehabilitation may be required in patients with COVID-19. In our study, we aimed to examine the effect of the pulmonary rehabilitation program applied after the acute period of back pain in patients with severe pulmonary involvement, dyspnea and health profiles of the patients.

Material and Method: In our retrospectively planned study, 50 patients with advanced pulmonary involvement who were treated for COVID-19 and discharged from the hospital and who were diagnosed with shortness of breath, back pain and difficulties in daily living activities in the 1st month chest diseases polyclinic controls and who were given a pulmonary rehabilitation program for a period of 1 month were included in our study. Before and 1 month after the pulmonary rehabilitation program, back pain was evaluated with the Visual Analog Scale (VAS), respiratory functions were evaluated with the Modified Medical Research Council (mMRC) Scale, and activities of daily living were evaluated with the Notthingham scale.

Results: A statistically significant difference was found between the beginning and the end of the pulmonary rehabilitation program in the mMRC Scale scores ($p<0.001$) and back pain VAS scores ($p<0.001$) was detected. Moreover, it was obtained significant improvement at baseline scores of "The Nottingham Health Profile" scores after the pulmonary rehabilitation program in all subgroups (NHP "pain": $p<0.001$, NHP "emotional reactions": $p<0.001$, NHP "sleep": $p<0.001$, NHP "social isolation": $p<0.001$, NHP "physical activity": $p<0.001$, NHP "energy level": $p<0.001$).

Conclusion: Post-COVID syndrome treatment and follow-up are important for early prevention. The pulmonary rehabilitation program applied after the acute period of with severe lung involvement COVID-19 has been seen to improve back pain, dyspnea symptoms and health profile. Need for new randomized controlled studies on this subject.

Keywords: COVID-19, Health Profile, Pulmonary Rehabilitation

Öz

Amaç: Koronavirüs hastalığı 2019 (COVID-19), çoklu sistem tutulumu nedeniyle multidisipliner bir yaklaşım gerektirir. COVID-19 hastalarında pulmoner rehabilitasyon gerekebilir. Çalışmamızda şiddetli akciğer tutulumu, nefes darlığı olan hastalarda sırt ağrısı sonrası uygulanan pulmoner rehabilitasyon programının etkisini ve hastaların sağlık profillerini incelemeyi amaçladık.

Gereç ve Yöntem: Retrospektif olarak planlanan çalışmamıza, ileri akciğer tutulumu tanısı ile COVID-19 tedavisi gören, hastaneden taburcu edilen ve göğüs hastalıkları polikliniği 1.ay kontrollerinde nefes darlığı, sırt ağrısı ve günlük yaşam aktivitelerinde güçlük saptanması sonrası 1 ay süre ile pulmoner rehabilitasyon programına alınan 50 hasta dahil edildi. Pulmoner rehabilitasyon programı öncesi ve 1 ay sonrasında sırt ağrısı Vizüel Analog Skala (VAS) ile, dispne düzeyi Modifiye Tıbbi Araştırma Konseyi Skalası (mMRC) ile ve sağlık profili Nothingam Sağlık Profili (NHP) skalası ile değerlendirilmişti.

Bulgular: Pulmoner rehabilitasyon programının başlangıcı ile bitişi arasında mMRC Skalası puanları ($p<0.001$) ve sırt ağrısı VAS puanları ($p<0.001$) arasında istatistiksel olarak anlamlı fark bulundu ($p<0.001$). Ayrıca pulmoner rehabilitasyon programı sonrası "Nottingham Sağlık Profili" puanlarında tüm alt gruplarda (NHP "ağrı": $p<0,001$, NHP "duygusal reaksiyonlar": $p<0,001$, NHP "uyku": $p<0.001$, NHP "sosyal izolasyon": $p<0.001$, NHP "fiziksel aktivite": $p<0.001$, NHP "enerji düzeyi": $p<0.001$) başlangıç puanlarına göre anlamlı iyileşme tespit edildi.

Sonuç: Post COVİD sendrom erken tanı takip açısından önemlidir. Bu çalışmada şiddetli akciğer tutulumu olan COVID-19'un akut döneminden sonra uygulanan pulmoner rehabilitasyon programının sırt ağrısı, nefes darlığı semptomlarını ve sağlık profilini iyileştirdiği görülmüştür. Bu konuda yapılmış randomize kontrollü yeni çalışmalara ihtiyaç olduğunu düşünmekteyiz.

Anahtar Kelimeler: COVID-19, Pulmoner rehabilitasyon, Sağlık Profili

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), which was emerged in December 2019. In addition to causing a severe acute respiratory tract infection, COVID-19 has been observed to cause a multisystem disease which requires a multidisciplinary approach during follow-up and treatment. The most common disease-related symptoms were fever (82%), cough (61%), muscle pain (36%), dyspnea (26%).[1,2]

We do not yet have sufficient scientific reports on the physiotherapy of COVID-19. Based on the data on the long-term follow-up results of COVID-19 patients, the importance of pulmonary rehabilitation in the follow-up of COVID-19 patients was determined. Pulmonary rehabilitation is an important part of multidisciplinary treatment and plays a very important role in the treatment, improvement and care of patients with respiratory dysfunctions. However, international indications for the application of pulmonary rehabilitation in patients have been specified by physical therapy and rehabilitation associations of many countries. In this direction, pulmonary rehabilitation guidelines have been published by the physical therapy and rehabilitation associations of many countries. It is necessary to implement an appropriate personal rehabilitation program for patients at all stages of COVID-19. This program will support the development of respiratory functions and physical strength, reduce complications related to physical inactivity, enable patients to adapt to family, work and community life as soon as possible, and increase their quality of life by reducing the risk of anxiety and depression.[3,4]

Our aim in this study was to determine the effect of the pulmonary rehabilitation program on respiratory complaints, back pain and activities of daily living in patients who applied to the pulmonary diseases outpatient clinic after with severe pulmonary involvement COVID-19 and continued to have respiratory distress, back pain, and problems in daily living activities.

MATERIAL AND METHOD

This study was carried out in Adana City Training and Research Hospital between January and March 2021. Hospitalized after COVID-19 RT-PCR (Real time- polymerase chain reaction) test (nasopharyngeal/oropharyngeal swab sample) and positive lung computed tomography findings consistent with severe COVID-19 pneumonia, and one month after discharge, pulmonary rehabilitation program for 1 month as a result of physical therapy and rehabilitation consultation with complaints of respiratory distress, back pain and deterioration in daily living activities in chest diseases polyclinic controls the patients who were treated were included in the study. Data for the study were obtained by retrospectively scanning the files of patients who completed a one-month pulmonary rehabilitation program by March 10, 2021.

In our study, the number of patients to be reached was calculated using the G Power 3.1 program. The sample size analysis performed by accepting the type 1 error level as .05, the power as 95%, and the effect size as 0.5, revealed a minimum sample size of 45 participants. A total of 50 patient were reached at the end of the study. Pregnant women, children under 18 years of age, patients with history of lung disease and cancer, who did not meet the criteria for severe COVID-19 pneumonia, and patients with missing data were not included in the study.

As a pulmonary rehabilitation program, upper and lower extremity range of motion exercises (2x10 times/day), pursed lip breathing, diaphragm breathing and deep breathing exercises (2x4/day) were started in the patients included in the study, accompanied by a physiotherapist. As a home program, COVID-19 exercise brochures prepared by the Turkish Physical Therapy and Rehabilitation Association[5] were given. Compliance of the patients to the program was followed up with outpatient clinic controls and weekly video phone calls.

The study was carried out with the permission of Adana City Training and Research Hospital, Clinic Ethics Committee (Date:10.03.2021, Decision No:1324). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Outcome Measures

The participants were assessed before the pulmonary rehabilitation program which was continued one month and after the end of the one-month. The Medical Research Council Scale (mMRC) was applied to assess the severity of dyspnea. The mMRC is a five-item scale based on various physical activities that cause shortness of breath. Patients are asked to mark the activity level that causes shortness of breath. Patients are asked to mark the activity level that causes shortness of breath. 0 indicates mild, 4 indicates severe shortness of breath.[6,7] Back pain severity was assessed with a 10 cm Visual Analog Scale (VAS) (0 no pain and 10 most severe pain).[8] The quality of life was evaluated by the Nottingham Health Profile (NHP). It is a patient-reported questionnaire that assesses quality of life according to six subscales: pain, sleep, physical mobility, energy level, emotional reaction, and social isolation. The scores range between 0 and 100, and lower scores suggest higher quality of life. The second part consists of 7 questions about whether the patient has problems in 7 different situations due to health problems and is between 0-7 points. High scores indicate an excess of health problems.[9,10]

Statistical Analysis

SPSS version 25 (SPSS, Chicago, IL, United States of America) software were used. Mean±SD, median (IQR), number and percentage (%) values were given for descriptive statistics. The normality was tested by the Shapiro-Wilk test. Parametric tests (Paired Samples T Test) were used for data fitting the normal distribution, non-parametric tests (Wilcoxon Signed-Rank Test) were used for data not fitting the normal

distribution. p< 0.05 value was accepted statistical signifcant. The effect size was calculated using the G Power 3.1 Program in the analyzes performed with the Paired Samples T Test.[11] Cohen's d values:[12]

Effect Size (d)= 0.20 ≤ small<0.50, 0.50 ≤ medium<0.80 and 0.80 ≤ large effect

Effect size formula in the analyses using Wilcoxon Signed Ranks Test

$$r = Z/\sqrt{N_{pairs}}$$

and Pearson's r values:[12]

Effect Size (r)= 0.10 ≤ small<0.30, 0.30 ≤ medium<0.50 and 0.50 ≤ large effect

RESULTS

A total of 50 patients were reached in our study. Patients were aged between 20 and 70 years.

Demographic and other characteristics of the patients are shown in **Table 1**.

Table 1. Demographic and Disease Characteristics of Patients

		$\bar{x}$ ±S.D	Median (IQR)
Age		45.30±10.73	44 (11)
Size		167.72±9.71	165 (14)
Weight		74.02±14.84	74.50 (16.50)
BMI[a]		26.24±4.27	26.13 (4.09)
		N	**%**
Sex	Female	31	62
	Male	19	38
Total		50	100

[a]BMI: Body Mass Index

NHP 'Pain', 'Emotional Reaction', 'Sleep', 'Social Isolation', 'Physical Mobility' and 'Energy' sub-dimension scores decreased significantly after one month of pulmonary rehabilitation, compared to the before. (p<0.001). The total scores of NHP Parts 1 and 2 also decreased significantly compared to before (p<0.001).

The effect size of the intervention was found to be 'Medium' for the 'Social Isolation' sub-dimension of the NHP 1st section and 'Large' for the other sub-dimensions. The effect size of the intervention was found to be 'Very Large' for the total scores of the NHP 1st section. The effect size of the intervention for the NHP 2nd section scores was found to be 'Medium'.

VAS scores decreased significantly after one month of pulmonary rehabilitation compared to before (p<0.001). The effect size of the intervention for VAS score was 'Large'.

mMRC scores decreased significantly after one month of pulmonary rehabilitation compared to before (p<0.001). The effect size of the intervention for mMRC score was 'Large'. Comparisons of scale scores at before and after pulmonary rehabilitation are shown in **Table 2**.

DISCUSSION

COVID-19 is a respiratory infectious disease that can cause long-term respiratory, physical and psychological dysfunction. It can progress with symptoms such as myalgia, arthralgia, anxiety and shortness of breath. After the acute phase, patients may experience ongoing symptoms. In many studies, it has been shown that symptoms such as shortness of breath and pain persist and progress with causing restriction in patients' daily activities.[2,13,14]

Table 2. Comparison of Scale Scores of Patients Before and After Pulmonary Rehabilitation

			$\bar{x}$ ±S.D	Median (IQR)	Z score	E.S	P value
NHP[e]	Pain	Before	58.76±33.59	59.40 (66.87)	5.970	0.597[c]	<0.001[a]
		After	20.70±16.16	24.13 (33.25)			
	Emotional Reaction	Before	43.79±31.0	44.78 (40.09)	5.512	0.551[c]	<0.001[a]
		After	21.71±24.63	13.95 (22.24)			
	Sleep	Before	48.56±31.58	60.49 (61.53)	5.454	0.545[c]	<0.001[a]
		After	22.83±21.66	16.10 (43.36)			
	Social İsolation	Before	17.66±28.94	0 (26.39)	3.633	0.363[c]	<0.001[a]
		After	6.22±14.81	0 (0)			
	Physical Mobility	Before	52.39±23.37	54.47 (31.75)	6.032	0.603[c]	<0.001[a]
		After	17.92±12.74	22 (17.75)			
	Energy	Before	96.96±10.41	100 (0)	6.015	0.601[c]	<0.001[a]
		After	41.23±25.84	39.20 (20.60)			
	NHP-Total Score	Before	318.15±97.23	322.48 (144.37)	6.154	3.44[d]	<0.001[b]
		After	130.63±76.27	126.34 (93.34)			
	NHP-Seven Spheres of Life Total Score	Before	3.86±1.48	4 (2)	3.262	0.326[c]	<0.001[a]
		After	3.28±1.84	3 (3)			
VAS[f]		Before	7.34±1.82	7 (3)	6.216	0.621[c]	<0.001[a]
		After	2.36±1.60	2 (2)			
mMRC[g]		Before		3 (2)	6.652	0.665[c]	<0.001[a]
		After		1 (2)			

[a]Wilcoxon Signed-Rank Test, [b]Paired Samples T Test, [c]E.S:Effect size (E.S) (r), [d]E.S: Effect Size (E.S) (d), [e]NHP: Notthingham Health Profile, [f]VAS: Visuel Analog Scala, [g]mMRC: Modified Medical Research Council

COVID-19 has caused distress in all health services, including rehabilitation. Studies investigating the rehabilitation need of COVID-19 patients and whether they benefit or not have recently emerged. In the post-COVID period, patients experience severe respiratory failure requiring respiratory rehabilitation in conditions such as presence of sequelae of pneumonia and lung fibrosis.Suggestions have emerged that a pulmonary rehabilitation program can be shaped according to the individual needs of each patient. Yang et al.[15] recommended general pulmonary rehabilitation based on 4S (simple, safe, satisfy, save) to patients with pneumonia caused by SARS-CoV2. Liu et al.[16] found that a 6-week rehabilitation program significantly improved respiratory functions, quality of life, and anxiety in elderly patients with COVID-19. While there are suggestions that early rehabilitation may be beneficial, Italy and the Chinese Association of Rehabilitation Medicine did not recommend early pulmonary rehabilitation due to lack of well tolerance and potential of rapid desaturation.[17,18] Considering the prevalence of physical impairment after such a critical illness, it has been reported that patients can benefit from physiotherapy during the COVID-19 recovery period after discharge from the hospital.[19]

Through a rehabilitation program in COVID-19; a comprehensive assessment and individualized progressive treatment plan focusing on return to function, disability and community participation can help each patient to maximize their function and quality of life.[20]

In a study evaluating symptoms and health-related quality of life after hospitalization and discharge from hospital with COVID-19, the most common ongoing symptoms were fatigue (55%), and dyspnea (42%). Researchers underlined the importance of long-term follow-up and rehabilitation program in COVID-19 patients.[21] Demeco et al. reviewed the studies on the effect of rehabilitation in COVID-19 patients, and reported that patients who are in recovery of the post-COVID period are subjected to respiratory rehabilitation according to their clinical status.[22] In our study, rehabilitation was applied to patients with dyspnea, pain and low health profile, and the pulmonary rehabilitation program was determined individually for the patient.

After discharge, COVID-19 patients may experience conditions that require rehabilitation, such as difficulty in breathing, post-traumatic stress disorder, and muscle weakness. A rehabilitation program is recommended for patients with mild pulmonary dysfunction to restore vitality and reduce anxiety and depression.[23] Pulmonary rehabilitation has been recommended for patients who have passed the critical phase of lung infection, had severe COVID-19, and were discharged, but whose symptoms of pulmonary dysfunction persist.[17,23] In our study, the patients were those who passed the critical phase of lung infection, were discharged, but still had pulmonary symptoms, as recommended.

In a study investigating the benefit of applying pulmonary rehabilitation after discharge from COVID-19 infection, improvements in respiratory functions, quality of life, and anxiety were observed. In the same study by Liu et al. patients were recommended with respiratory muscle training, coughing exercises, diaphragm training, stretching exercises, and home exercises consisting of two sessions in a week for 10 minutes once a day during 6 weeks.[16] Although the specific indications for COVID-19 of pulmonary rehabilitation, which is a part of the rehabilitation program, are not fully clarified, the Turkish Physical Therapy and Rehabilitation Association has published a guideline containing recommendations for pulmonary rehabilitation in patients with COVID-19, particularly considering the damage to the respiratory system.[24]

In patients with severe COVID-19 pneumonia, it is recommended to establish an individualized pulmonary rehabilitation program for a patient who meets the criteria. General physical assessment of the patient, findings such as fever and dyspnea, blood values, radiological findings, SpO_2, range of motion (ROM), muscle strength, respiratory muscle strength, in-bed activities, functional capacity, exercise capacity and other comorbid conditions were evaluated according to the findings obtained in each patient. Accordingly, a rehabilitation program is planned. Although it is thought that pulmonary rehabilitation to be applied in this period will help the patients' problems such as dyspnea, cough and sputum, muscle weakness that may occur in respiratory and other body muscles, immobilization, anxiety and depression, there is no data in the context of evidence-based medicine. Current evidence from studies evaluating the effectiveness of pulmonary rehabilitation is largely based on studies conducted in individuals with chronic lung disease. In suitable post COVID-19 patients; mobilization, diaphragm breathing, air turning technique, pursed lip breathing may be recommended.[25-28]

Pulmonary rehabilitation should include inspiratory muscle exercises if the inspiratory muscles are weakened in the postacute phase. Deep and slow breathing, thoracic expansion by raising the shoulders, diaphragmatic breathing, movement of respiratory muscles, and airway clearance techniques can be performed, if necessary.[29] In our study, similar exercises were applied to the required patients.

A randomized controlled trial showed improvement in respiratory function, quality of life, and depression with 10 minutes of respiratory rehabilitation twice a week for 6 weeks after discharge.[24]

In the WHO clinical severity of classification COVID-19; the respiratory system is severely affected between the second and fourth stage of the disease.[30] Whether or not COVID-19 will cause a sequelae in the future is still not clear, therefore, rehabilitation programs that are applied as early as possible in the appropriate patient are crucial.

In our study, after the medical treatment for COVID-19 was completed, a one month personalized pulmonary rehabilitation program was applied to the patients during the COVID-19 recovery period.

As a result of the studies carried out during the COVID-19 pandemic, the importance of rehabilitation programs has been revealed, and physical therapy and rehabilitation clinics have started to play an active role in this regard. When necessary, patients should be directed to physical therapy and rehabilitation clinics, and patients should be provided with rehabilitation. It is stated that accelerating the recovery process with the effective and personalized rehabilitation practices of these clinics can reduce the financial losses of this disease, which brings a heavy financial burden to the our country and the world.[31] In the current study, a significant improvement was observed in the pain and dyspnea indexes health profiles including pain, emotional reactions, sleep, social isolation, physical activity and energy status of post-COVID-19 patients with 1-month pulmonary rehabilitation program.

The limitations of our study include the differences in the psychological status of the participants, which could affect the perception of the severity of pain and dyspnea. In order to minimize the differences, patients who had completed their COVID-19 treatment, who could apply to the outpatient clinic, and who could describe their pain and dyspnea were included in the study. Another limitation was the small sample size and lack of a control group. Since the aim of the study was to compare the conditions before and after rehabilitation, the control group was not included. In our study, patients who were evaluated at the first control after having COVID-19 were included in the study. These patients were those who applied within the first month, mostly after the 2nd week of the disease. Future studies may evaluate the benefit of rehabilitation in patients with longer-term symptoms, such as 1 month or 3 months, in which the time elapsed after COVID-19 is also evaluated.

CONCLUCION

This study demonstrated that the rehabilitation program implemented due to the ongoing symptoms after the acute period of COVID-19 improved the back pain and dyspnea symptoms and health profiles of post-COVID-19 patients. Patients who have had COVID-19 and have completed their treatment may have ongoing symptoms in the early period. These patients should be evaluated as potential candidates of rehabilitation programs. Need for new randomized controlled studies on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Adana Health Sciences University Faculty of Medicine Ethics Committee (Date: 10.03.2021, Number: 1324).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Borges do Nascimento IJ, Cacic N, Abdulazeem HM, et al. Novel Coronavirus Infection (COVID-19) in Humans. J Clin Med 2020;9(4):941.
2. Zhu Y, Wang Z, Zhou Y, et al. Summary of respiratory rehabilitation and physical therapy guidelines for patients with COVID-19 based on recommendations of World Confederation for Physical Therapy and National Association of Physical Therapy. J Phys Ther Sci 2020;32(8):545-9.
3. Cieloszczyk A, Lewko A, Śliwka A, Włoch T, Pyszora A. (2020) Recommendations for physiotherapy of adult patients with COVID-19. (https://www.wcpt.org/sites/wcpt.org/files/files/wcptnews/images/Recommendations%20for%20physiotherapy%20of%20adult%20patients%20with%20COVID-19_POLISH.pdf)
4. Gosselink R, Bott J, Johnson M, et al. Physiotherapy for adult patients with critical illness:recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. Intensive Care Med 2008 Jul;34(7):1188-99.
5. Turkey Association of Physical Medicine and Rehabilitation. Pulmonary Rehabilitation After SARS-COV-2 (COVID-19) Guide. Access:(https://www.tftr.org.tr/covid19/files/doc01.pdf Access Date:15.11.2022
6. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988 Mar;93(3):580-6.
7. Bestall J.C, Paul E.A, Garrod R. Usefulness Of The Medical Research Council (MRC) Dyspnea Scale As A Measure Of Disability İn Patients With Chronic Obstructive Pulmonary Disease. Thorax 1999;54:581-6. Gümüşhane Üniversitesi Sağlık Bilimleri Derg / Gümüşhane Uni J Health Sci 2013;2(1):149
8. Amelot A, Jacquot A, Terrier LM, et al. Chronic low back pain during COVID-19 lockdown:is there a paradox effect? Eur Spine J 2022 Jan;31(1):167-75.
9. Kücükdeveci AA, McKenna SP, Kutlay S, et al. The Development and Psychometric Assessment of the Turkish Version of The Nottingham Health Profile. International Journal of Rehabilitation Research 2000;23(1):31-8.
10. Kind P, Hill CR. The Nottingham Health Profile:A Useful Tool For Epidemiologist, Soc. Sci Med 1987;25(8):905-10.
11. Faul F, Erdfelder E, Lang A.-G, Buchner A. G*Power 3:A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods 2007;39:175-91.
12. Fritz C. Effect Size Estimates:Current Use, Calculations, and Interpretation. J Exp Psychol Gen 2012;141(1):2-18.
13. Tuzun S, Keles A, Okutan D, et al. Assessment of musculoskeletal pain, fatigue and grip strength in hospitalized patients with COVID-19. Eur J Phys Rehabil Med 2021;57(4):653-62.
14. Yaşa Öztürk G, Berik Safçi S. "Effects of Eucalyptus Essential Oil in Post-COVID Syndrome:A Pilot Study". Journal of Immunology and Clinical Microbiology 2022;7:74-9
15. Yang F, Liu N, Hu JY, et al. [Pulmonary rehabilitation guidelines in the principle of 4S for patients infected with 2019 novel coronavirus (2019-nCoV)]. Zhonghua Jie He He Hu Xi Za Zhi 2020;43(3):180-2. Chinese.
16. Liu K, Zhang W, Yang Y, et al. Respiratory rehabilitation in elderly patients with COVID-19:A randomized controlled study. Complement Ther Clin Pract 2020;39:101166.
17. Chinese Association of Rehabilitation Medicine, Respiratory rehabilitation committee of Chinese Association of Rehabilitation Medicine, Cardiopulmonary Rehabilitation Group of Chinese Society of Physical Medicine and Rehabilitation. [Recommendations for respiratory rehabili tation of COVID-19 in adults]. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:E029.

18. Kiekens C, Boldrini P, Andreoli A, et al. Rehabilitation and respiratory management in the acute and early post-acute phase. "Instant paper from the field" on rehabilitation answers to the COVID-19 emergency. Eur J Phys Rehabil Med 2020;56(3):323-6.
19. Smith JM, Lee AC, Zeleznik H, et al. Home and Community-Based Physical Therapist Management of Adults With Post-Intensive Care Syndrome. Phys Ther 2020;100:1062–73.
20. Sheehy LM. Considerations for Postacute Rehabilitation for Survivors of COVID-19. JMIR Public Health Surveill 2020;6(2):e19462.
21. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect 2020;81(6):e4-e6.
22. Demeco A, Marotta N, Barletta M, et al. Rehabilitation of patients post-COVID-19 infection:a literature review. J Int Med Res 2020;48(8):300060520948382.
23. Stam HJ, Stucki G, Bickenbach J. Covid-19 and Post Intensive Care Syndrome:A Call for Action. J Rehab Med 2020;52:jrm00044
24. Turkey Association of Physical Medicine and Rehabilitation. Pulmonary Rehabilitation Principles After SARS-COV-2 (COVID-19):A Guide For The Management Of The Acute and Subacute Process Group 13 April 2020 Version 1.0.
25. Spruit MA, Singh SJ, Garvey C, et al. ATS/ERS Task Force on Pulmonary Rehabilitation. An official American Thoracic Society/European Respiratory Society statement:key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013;188(8):13-64.
26. Bolton CE, Bevan-Smith EF, Blakey JD, et al. British Thoracic Society Pulmonary Rehabilitation Guideline Development Group;British Thoracic Society Standards of Care Committee. British Thoracic Society guideline on pulmonary rehabilitation in adults. Thorax 2013;68:1-30.
27. Chinese Association of Rehabilitation M, Respiratory rehabilitation committee of Chinese Association of Rehabilitation M, Cardiopulmonary rehabilitation Group of Chinese Society of Physicai M, Rehabilitation:[Recommendations for respiratory rehabilitation of COVID-19 in adult]. Zhonghua Jie He He Hu Xi Za Zhi 2020;43(0):E029.
28. Ambrosino N. Clini EM:Response to pulmonary rehabilitation:toward personalised programmes? Eur Respir J 2015;46(6):1538-40.
29. Zhao H, Xie Y, Wang C. Recommendations for respiratory rehabilitation in adults with COVID-19. Chin Med J (Engl) 2020;133(13):1595-602.
30. Clinical management of severe acute respiratory infection when COVID-19 is suspected Interimguidance. Access:(https://www.who.int/publications/i/item/10665-332299). Access Date:15.11.2022
31. Duarte A, Bojke C, Cayton W, et al. Impact of specialist rehabilitation services on hospital length of stay and associated costs. Eur J Health Econ 2018;19(7):1027-34.

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Original Article / Orijinal Araştırma

Ergonomics-Related and Work-Related Musculoskeletal Disorders in A High-Hazard Factory in Hatay Region

Hatay'da Çok Tehlikeli Sınıfta Bir Fabrikada Ergonomi ve İş ile İlişkili Kas İskelet Sistemi Yakınmaları

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Abstract

Aim: The most common work-related diseases are musculoskeletal system disease. This study aims to determine the prevalence of work-related musculoskeletal disorders (WMSDs) in a high-hazard factory and to determine sociodemographic, occupational, and ergonomic risks.

Material and Method: The research is cross-sectional and was conducted in a high-hazard factory, in Hatay, in 2017. The research population was all factory employees (N=190), and it was aimed to reach the whole population. Of the (97.3%), 185 employees participated in the study. Anthropometric measurements, the Cornell Musculoskeletal Discomfort Scale, the observation-based Rapid Upper Limb Assessment (RULA) Ergonomic Risk Analysis Scale, and a questionnaire developed by the researchers are used for data collection. In the statistical analyses p<0,05was accepted as significant.

Results According to the Cornell Scale, the frequency of WMSDs was 58.9%. The most common WMSDs were in the lumbar region (34.1%). According to the RULA Scale, 31.9% of the employees had 3rd and 4th-degree ergonomic risk. There were linear relationships between the Cornell Waist Score and each of the three RULA scores (p<0.001). The risk factors for WMSDs in the lumbar region were the presence of chronic disease (OR=5.35), hand tool use (OR=2.63), not having had a work accident (OR=0.04) and RULA scores (OR=1.61),

Conclusion: Approximately one-third of the high-hazard factory employees had a high ergonomic risk. WMSDs existed in more than half of the employees. As the ergonomic risk increases, WMSDs increase.

Keywords: Ergonomy, work related musculo-skeletal system disorders, RULA

Öz

Amaç: İşle ilgili en sık görülen hastalıklar kas-iskelet sistemi hastalıklarıdır. Bu çalışmanın amacı, çok tehlikeli sınıfta yer alan bir fabrikada işe bağlı kas-iskelet sistemi rahatsızlıklarının İKİSR sıklığını ve sosyodemografik, iş ve ergonomik riskleri belirlemektir.

Gereç ve Yöntem: Araştırma kesitsel tipte olup 2017 yılında yapılmıştır. Araştırmanın evrenini fabrika çalışanlarının tamamı (N=190) oluşturmaktadır. Araştırmaya 185 fabrika çalışanı (%97,3) katılmış olup, verilerin toplanmasında antropometrik ölçümler, Cornell Kas İskelet Sistemi Rahatsızlık Anketi ve Hızlı Üst Ekstremite Değerlendirmesi (RULA) ergonomik risk analizi ölçeğine dayalı gözlem kullanılmıştır. İstatistiksel analizlerde p<0,05 anlamlı olarak kabul edildi.

Bulgular: Cornell Anketine göre İKİSR sıklığı %58,9 idi. En sık İKİSR bel bölgesindeydi (%34,1). RULA Ölçeğine göre çalışanların %31,9'u 3. ve 4. Derece ergonomik risk altındadır. Cornell Bel Skoru ile üç RULA skorunun her biri arasında doğrusal ilişkiler vardı. Bel bölgesinde İKİSR için risk faktörleri; kronik hastalık varlığı (OR=5,35), el aletleri kullanımı (OR=2,63), RULA puanı (OR=1,61) ve iş kazası geçirmemiş olmaktır. (OR=0,04).

Sonuç: Çalışanların yaklaşık üçte birinde yüksek ergonomik risk, yarısından fazlasında ise İKİSR bulunmaktadır. Ergonomik risk arttıkça İKİSR de artar.

Anahtar Kelimeler: Ergonomi, iş ile ilişkili kas iskelet sistemi yakınmaları, RULA

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INTRODUCTION

The most common work-related diseases are musculoskeletal. Work-related musculoskeletal disorders (WMSDs) account for 50% of new cases.[1] This stand generally upper extremity diseases (neck, shoulder, elbow, hand, and wrist) and lower back diseases.[2] These diseases, which are also defined as Cumulative Trauma Disorders, negatively affect the work-life quality of the employees, work efficiency, and cost.[3]

WMSDs caused by work-related activities are a vital health problem in industrialized countries and are one of the leading causes of disability. Millions working in various sectors in European countries experience issues due to work-related musculoskeletal diseases every year.[4,5] The significant increase in the frequency of WMSDs and the costs related in industrialized countries has drawn the attention of employees, employers, governments, healthcare providers, and insurance companies. Studies on risk factors in the workplace and ergonomics programs on ergonomic initiatives, training, and rehabilitation are gaining momentum.[6]

In Europe, 22.8% of employees report having general muscular pain, while 24.7% report having lower back pain.[6] In the Years Lost due to Disability (YLD) ranking, musculoskeletal diseases are in the third place with 9.9% and are accepted as occupational diseases by law in Turkey. Despite this fact, this situation is not recognized sufficiently by employees, employers, and professionals dealing with occupational health and safety.[7]

Although it is prevalent, WMSDs are not easily detected because their etiologies are multifactorial. Cause and effect relations affiliated with WMSDs might not be easily demonstrated, work-related effects might be ignored, and WMSDs may occur due to non-work-related reasons (hobbies, sports activities, etc.).[8] The WMSDs data are mainly obtained from the records of insurance and health institutions. These hardships cause WMSDs that do not require labor loss or compensation to be ignored and make it difficult to determine the incidence and prevalence accurately and thus, make comparisons.[9]

The risk factors of work-related musculoskeletal diseases are divided into two: Work-related and personal. The primary risk factors are repetitive movements, strength, inappropriate body postures, and prolonged performance.[10] Ergonomic factors in the work environment are also crucial risk factors. The suitability of the height and use of the seat, desk, keyboard, and screen for those who work in a seated position, and of the tables, manipulators, and fixtures for those who work in industry, play an important role. Additionally, inadequate lighting and temperature are noteworthy ergonomic risk factors, as well.[11]

This study aims to determine the prevalence of work-related musculoskeletal disorders (WMSDs) in employees in a high-hazard factory and to determine related sociodemographic, occupational, and ergonomic risk factors.

MATERİAL AND METHOD

This cross-sectional study was carried out in a hazardous factory in Kırıkhan, Hatay, in 2017. The population of the research was all employees of the factory (N=190). No sampling method was accustomed, since reaching the entire population was aimed. Of 97.3% (n=185) people participated in the study.

Instruments

In the study, three different methods are used for data collection. While anthropometric measurements were carried out with the direct method, the questionnaire and the Cornell Musculoskeletal Discomfort Scale were applied by the face-to-face interview method. The Rapid Upper Limb Assessment (RULA) form was applied by direct observation to evaluate the ergonomic risk.

Anthropometric Measurement: The body mass index was calculated by measuring the height and weight of the employees from the anthropometric measurements.

Questionnaire Form: The researchers developed a form consisting of 50 questions regarding the sociodemographic and work-related characteristics of the employees. Three of the questions were graphical, in which the employees were asked to mark their body postures in lifting, pushing, and pulling while working in the factory.

Cornell Musculoskeletal Discomfort Questionnaire: The form evaluates the musculoskeletal disorders experienced by the person in 20 body regions during the previous week under the headings of frequency, severity and resulting in not being able to work. There are male and female types of the scale, and a minimum of 0 and a maximum of 16 points can be obtained from the scale for each body region. The Turkish validity and reliability study was conducted by Erdinç, Hot, and Özkaya in 2008.[12]

Rapid Upper Limb Assessment Tool: RULA was developed by Atamney and Corlett in 1992 to identify upper extremity movements that cause musculoskeletal disorders and is a method designed to quickly analyze an employee's ergonomic risks related to the upper extremity.[13] The form is based on direct observation and is applied by the researcher. Ergonomic risk is evaluated in 3 stages. The employee's arm/wrist score is measured in the first stage. The second stage calculates the neck/body/legs score. In the third stage, the scores in the first two stages are compared and the total score is calculated.

The RULA scores that can be obtained for each region and general body are 0 for the minimum and 8 for the largest. Ergonomic risk is evaluated in terms of position, muscle use, and power overload by grading the total score between 1 and 4. Accordingly, the ergonomic risk of the employee is evaluated as follows:

- Grade 1 (1-2 points): Acceptable ergonomic situation.
- Grade 2 (3-4 points): The individual needs to be evaluated further.

- 3rd Degree (5-6 points): The individual should be evaluated further and measures should be taken in a short time regarding the individual or working conditions.
- Grade 4 (7 ≤ points): The individual should be evaluated further and measures should be taken urgently for the individual or working conditions.

Statistical Analysis

Kolmogorov Smirnow, Chi-square, Mann Whitney-U, Kruskal Wallis, Spearman Correlation, Linear Regression, and Logistic Regression analyzes were used for statistical analysis. Furthermore, sociodemographic, work-related, and ergonomic variables affecting the presence of lower back pain (household monthly income, regular exercise, chronic disease, unit working at, blue/white collar working type, pushing-pulling action, lifting weights, weight lifted, using hand tools, RULA arm-hand-wrist, RULA neck-trunk-leg, and RULA total scores) in the last week were evaluated according to the Cornell scale with the binary logistic regression (Backward LR) model. $p<0.05$ was considered significant.

Ethics committee and factory institution permissions were obtained for the study. (Ethics Committee Decision Nr: 07/11/2016-216). The financial support for the study was provided by the Scientific Research Projects Coordination Unit of the Rectorate of Mustafa Kemal University (Project No: 16445).

RESULTS

The mean age of the employees participating in the study was 35.6±6.3 (18-57), of which 93.8% were male, and 85.7% were married. The results pointed out that 31.4% of the participants were high school graduates and 90.8% were blue-collar workers. The average monthly income was 2243.2±1281.2 Turkish Lira (TRY) per month. According to the survey responses, 12.4% had a previous work accident, 17.8% had a chronic disease diagnosed by a doctor, 14.2% used alcohol and 50.8% smoked. Smokers were an average of 13.8±8.0 package/year smokers. 36.8% of the employees were doing regular physical activity and the average daily sleep time was 7.2±1.2 hours.

The result of anthropometric measurements showed that the mean body mass index (BMI) was 27.3±3.9 kg/m² (17-44), 48.1% were overweight and 22.3% were obese. The BMI of women was 25.7±5.1 kg/m² and that of men was 27.4±3.8 kg/m² ($p>0.05$).

Most participants (55.1%) worked in the main production facility and 73.5% worked in shifts, whereas the average working year was 6.89±2.70 years, and the average weekly working time was 44.27±3.27 hours. Employees took an average of 2.18±1.03 breaks (times) during the day, 13.5% of them were doing additional work outside the factory.

Sixty-one percent of the participants had at least one night shift in the last 1 month, 44.2% were absent from work in the last year, and 42.2% found the physical burden of their work heavy. The mean age of those who found the physical burden of their job to be light, medium, and heavy were similar ($p>0.05$).

The most common actions while working were sitting (38.4%) and standing (33.0%), respectively. In the working environment, 17.8% of them were lifting weights frequently and 10.3% of them were lifting weights constantly. The weight lifted was 20.08±8.73 kgs on average and the distance carried was 2.22±2.30 meters on average. In addition, near twelve percent of the employees frequently, 13.0% constantly push and pull, 17.8% frequently and 19.5% constantly stay in the same position while working. 34.6% of the research group used hand tools at work. According to the answers given to the question with the graphic, 65.9% of employees while lifting weights, 59.8% while pushing action, and 68.6% while pulling action were acting with wrong ergonomic posture.

According to the Cornell Scale, 58.9% of the employees who participated in the study had WMSDs in any part of their body. The scores of all body regions and 95% confidence intervals of those with WMSDs according to the Cornell Scale are shown in (**Figure 1**). According to the Cornell Scale, the body regions where they felt the most complaints were the waist (34.1%) and the neck (13.5%), respectively (**Figure 2**).

Relationships between WMSDs and sociodemographic characteristics, anthropometric measurements, habits, work environment, and factors related to work practice were analyzed according to the Cornell Scale. WMSDs were found more frequently in women, those with low income, with chronic diseases, who perceive the physical burden of work as heavy, who lift more weights, who did not work night shifts in the last month, and those who use hand tools ($p<0.05$) (**Tables 1, 2,** and **3**).

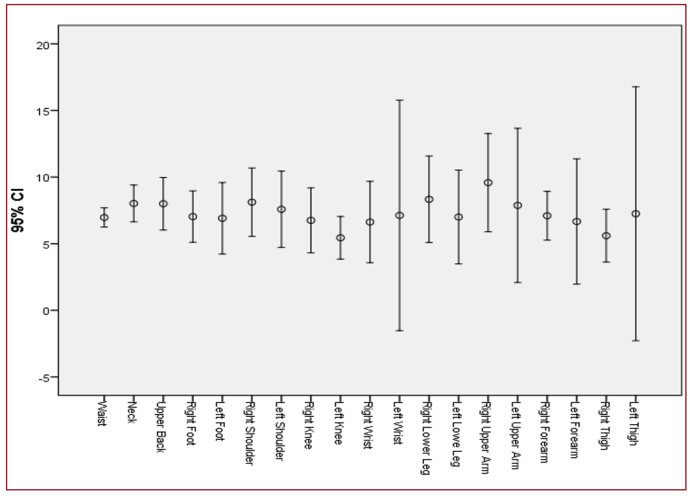

Figure 1. Scores Based on Body Regions from the Cornell Scale and 95% Confidence Intervals

Table 1. Gender, Marital Status, Education Status, BMI, Place of Residence, Smoking, Alcohol Use, Physical Activity, Chronic Disease Status According WMSDs

		WRMSC Yes		WRMSC No		p*
		n	%	n	%	
Gender	Male	84	48.8	88	51.2	0.025[a]
	Female	11	84.6	2	15.4	
Marital status	Married	84	51.5	79	48.5	0.739
	Single	11	50.0	11	50.0	
Education Status	Primary School	17	45.9	20	54.1	0.661
	Middle School	19	61.3	12	38.7	
	High School	30	51.7	28	48.3	
	Vocational high School	13	52.0	12	48.0	
	University	16	47.1	18	52.9	
BMI	Normal	28	50.9	27	49.1	0.347
	Overweight	56	62.9	33	37.1	
	Obese	25	61.0	16	39.0	
Place	Rural	18	51.4	17	48.6	0.197
	District	77	51.3	73	48.7	
Cigarette	Smoker	67	56.8	51	43.2	0.371
	Not smoker	28	41.8	39	58.2	
Alcohol	Drinker	16	59.3	11	40.7	1.000
	Not Drinker	93	58.9	65	41.1	
Physical Activity	Yes	37	54.4	31	45.6	0.342
	No	72	61.5	45	38.5	
Chronic Disease	Yes	27	81.8	6	18.2	0.006[a]
	No	82	53.9	70	46.1	

*ChiSquare Test a Yates Correction

Table 2. WMSDs According to Some Work-Related Features of Employees

		WRMSC Yes		WRMSC No		p*
		n	%	n	%	
Department	Main	61	59.8	41	40.2	0.786
	Product	48	57.8	35	42.2	
Group	Blue Collar	98	58.3	70	41.7	0.802[a]
	White Collar	11	64.7	6	35.3	
Working Schedule	Shift Procedure	74	54.4	62	45.6	0.057[a]
	Daytime Shift	35	71.4	14	28.6	
Last Month Night Work	Yes	61	2.6	55	47.4	0.034[a]
	No	48	69.6	21	30.4	
Last Week Night Work	Yes	50	52.1	46	47.9	0.050
	No	59	66.3	30	33.7	
Extra Job	Yes	8	32.0	17	68.0	0.006[a]
	No	101	63.1	59	36.9	
Physical Burden of Work	Soft	16	42.1	22	57.9	0.001[b]
	Middle	56	56.6	43	43.4	
	Heavy	37	77.1	11	22.9	
Weight Lifting Work	Yes	78	61.9	48	38.1	0.228
	No	31	52.5	28	47.5	
Push Pull Job	Yes	64	63.4	37	36.6	0.178
	No	45	53.6	39	46.4	
Hand Tools	Yes	49	76.6	15	23.4	0.001[a]
	No	60	49.6	61	50.4	
Discontinuity for the last 1 year	Yes	57	67.9	27	32.1	0.024
	No	52	51.5	49	48.5	
Work accident	Yes	12	54.5	10	45.5	0.831[a]
	No	97	59.5	66	40.5	

**ChiSquare Test a Yates Correction b Chi Square on Slope

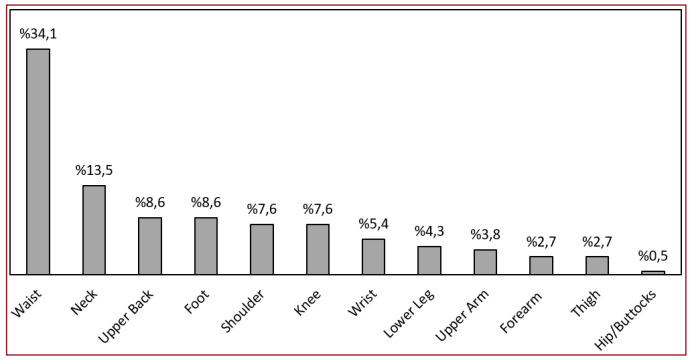

Figure 2. Body Regions During the Last 1 Week According to Cornell Questionnaire Feeling Pain (N=185)

Table 3. WMSDs According to Some of the Employees' Quantitative Demographic and Work Related Situations

	WRMSC Yes	WRMSC No	P*
	Mean±Sd	Mean±Sd	
Age	35.85±6.57	35.39±5.92	0.396
BMI	27.53±4.24	27.02±3.49	0.461
Household Monthly Income (TL)	2145.27±1303.44	2383.6±1243.85	0.043
Cigarettes (Pack / Year) (n=109)	14.57±8.91	12.62±6.31	0.478
Weekly Working Time (Hours)	44.43±3.87	44.05±2.14	0.100
1 year discontinuity (days) (n=93)	9.64±10.83	8.18±11.20	0.346
Number of Nights Worked in the Last Month (n=117)	8.98±4.60	9.17±3.85	0.799
Number of Nights Worked in the Last Week (n=95)	9.74±4.52	9.60±3.67	0.852
Daily Break Number	2.11±0.94	2.15±1.16	0.372
Daily Break Time (minutes)	43.39±19.95	46.57±21.91	0.339
Lifted Weight (kg) (n=125)	21.20±9.73	18.22±6.34	0.041
Number of Work Accidents (n=22)	1.46±0.66	1.00±0.00	0.031

*Mann Whitney-U Test

According to the RULA ergonomic risk assessment, the mean overall body RULA score of all employees was 3.61±1.86 (min.1-max.7). When the RULA score is graded; 31.9% had first-degree, 36.2% second-degree, 24.9% third-degree and 7.0% fourth-degree ergonomic risk

The arm-hand-wrist, the neck-trunk-leg, and whole body RULA scores of the employees were compared according to gender, unit worked in, being blue/white collar, lifting weights, pushing and pulling, and using hand tools.The mean RULA scores of men, blue-collar workers, weight lifters, and push-pullers were found higher ($p<0.05$) . In addition, the arm-hand wrist, neck-trunk-leg, and whole-body region RULA score averages of those with WMSDs were found to be higher than those who do not have ($p<0.01$, $p<0.05$, $p<0.01$).

Since the most common WMSDs were in the lumbar region (34.1%), the risk factors associated with WMSDs in the lumbar region were evaluated by logistic regression analysis. The risk factors for WMSDs in the lumbar region are found to be the presence of chronic disease (OR=5.35), hand tool use

(OR=2.63), the RULA score (OR=1.61), and previous work accident (OR=0.04). In this established model, low back pain risks were predicted correctly with an effect size of 65.9%.

Since the most common WMSDs were in the lumbar region (34.1%), the risk factors associated with WMSDs in the lumbar region were evaluated by logistic regression analysis. The risk factors for WMSDs in the lumbar region are found to be the presence of chronic disease (OR=5.35), hand tool use (OR=2.63), the RULA score (OR=1.61), and not have previous work accident (OR=0.04). In this established model, low back pain risks were predicted correctly with an effect size of 65.9%.

The causal relationship between the employees' total Cornell score and the RULA total score was evaluated by linear regression for genders, separately. Contrary to participating women (p=0.476), a causal relationship was discovered in men (Cornell Total score=1.603 X RULA Total score; p=0.001).

Positive moderate correlations were detected between the employees' Cornell Scale waistline scores and RULA Scale arm/hand/wrist scores (r=0.339; p=0.001), between RULA scale neck/trunk/leg scores (r=0.304; p=0.001) and RULA Scale total scores (r=0.344; p=0.001). When linear regression analysis was separately performed to reveal the causal relationship between the Cornell Scale waistline score and all three RULA Scale scores, the models established were as follows:

- Cornell Scale Waist Score= 0.674 x RULA Scale arm/hand/wrist score (p<0.001)
- Cornell Scale Waist Score= 0.634 x RULA Scale neck/trunk/leg score (p<0.001)
- Cornell Scale Waist Score= 0.670 x RULA Scale total score (p<0.001)

DISCUSSION

This study aimed to determine the prevalence of work-related musculoskeletal disorders (WMSDs) in a high-hazard factory and to determine sociodemographic, occupational, and ergonomic risks. WMSDs were evaluated with the Cornell Scale, and ergonomic risk was evaluated with the RULA Scale in this study. Most studies performed with the Cornell Scale were conducted with office workers, computer workers, and healthcare workers.[14-18] Though, the sample size was limited in which the studies combined Cornell and RULA Scales. While a sample size of 92 people was used in the study conducted on dentists in Iran and 7 in the study in the metal industry in Malaysia.[19,20] The sample size of our study was 185. Besides, each employee was evaluated separately under observation in the factory environment in this study.

In our study, the WMSDs frequency was 58.9% according to the Cornell Scale, and most WMSDs were found in the lumbar region. Likewise, the frequency was 58.6% in the research conducted by Choobineh et al. in a sugar factory in İran, and 55.9% in the study conducted in the industry sector by Yıldırım et al. In İzmir/Turkey.[21-23] By contrast, the frequency of WMSDs was 73.5% in the study conducted by Jansen et al. at the production site in Estonia .

Many studies have shown that WMSDs are higher in women than in men.[24] Likewise, in our study, the frequency of WMSDs in women was found significantly higher than in men. However, in the Binary logistic regression analysis performed to reveal the risk factors for WMSDs in the lower back region, no difference was found in terms of gender. Again, in our study, no significant difference was found between women and men in terms of BMI, and no relationship was found between WMSDs and BMI.

Studies are showing that WMSDs increase with age in the literature, as well as studies showing that there is no relationship with age. In a cohort study conducted in France in 2008, it was shown that lower back pain is more common in older employees.[25] In a study conducted on women working in the carpet weaving business in Iran, no relationship was found between age and WMSDs.[26] Similarly, no relationship was found between age and WMSDs in the study.

A significant relationship was found between the perception of the difficulty of the work and WMSDs in our study. In parallel, in a prospective study conducted in 2004 by Nahit et al. aimed at investigating the relationship between musculoskeletal complaints and psycho-social factors, with 1081 participants from 12 different professions were followed for one year, it is found that high physical and mental load of the work increased participants' musculoskeletal pain.[27]

In the study, a relationship was found between WMSDs in the lower back region and weight lifting and the amount of weight lifted. In addition, the frequency of lower back pain in those who use hand tools is higher than in those who do not. According to the model we obtained in the logistic regression analysis, using a hand tool while working increases the risk of low back pain on the Cornell Scale by 2.63 points. This situation shows that employees using hand tools not only use hand tools but also have difficulty while using hand tools, lifting weights, displaying the wrong posture, and making movements that force the anatomical structure of the waist. Again, the logistic regression analysis showed that the risk of lumbar region complaints increased by 1.61 points with each increase in the RULA Scale total score. Both studies from the literature found a correlation between RULA scores and Cornell scores.[20,21] Another risk factor for WMSDs in the lumbar region was a previous work accident. The risk of low back pain in those who not have had a past work accident is 0.04 points higher than in those who have .

CONCLUSION

More than half of the very hazardous factory employees have WMSDs, and about a third have a high ergonomic risk. The most common complaint is in the lumbar region. Women employees with chronic diseases, who lift weights while working, who use hand tools, and with high ergonomic

risk are at risk of WMSDs. However, while there was a causal relationship between WMSDs and ergonomic risk in the workplace in men, it did not apply to women. Managers should assign proper jobs to employees, use technology appropriately, and regulate the ergonomics. Employee/employer training is needed to eradicate WMSDs risk factors. In addition, women's non-job-related musculoskeletal complaints and related risk factors should be taken into consideration.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Mustafa Kemal University Faculty of Medicine Local Ethics Committee (Date: 09/02/2017, Decision No: 06, Protocol Code: 07/11/2016/216).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Cabeças JM. Occupational musculoskeletal disorders in Europe: impact, risk factors and preventive regulations 2006. 2006:2;95-104
2. Aptel M, Aublet-Cuvelier A, Cnockaert JC. Work-related musculoskeletal disorders of the upper limb. Joint Bone Spine 2002;69(6):546-55.
3. Kilbom s, Armstrong T, Buckle P, Fine L, Hagberg M, Haring-Sweeney M et al. Musculoskeletal Disorders: Work-related Risk Factors and Prevention. Int J Occup Environ Health. 1996;2(3):239-46.
4. Melhorn JM, Gardner P. How we prevent prevention of musculoskeletal disorders in the workplace. Clin Orthop Relat Res 2004;(419):285-96.
5. Buckle P. Ergonomics and musculoskeletal disorders:overview. Occup Med (Lond) 2005;55(3):164-7.
6. Nazmi B. Mesleksel kas iskelet sistemi hastalıkları. İş Sağlığı ve Güvenliği Derg 2007;34:10-3.
7. Stellman JM. Encyclopaedia of occupational health and safety: ILO;1998.
8. Punnett L, Wegman DH. Work-related musculoskeletal disorders:the epidemiologic evidence and the debate. J Electromyogr Kinesiol 2004;14(1):13-23.
9. Yildirim Y, Gunay S, Karadibak D. Identifying factors associated with low back pain among employees working at a package producing industry. J Back Musculoskelet Rehabil 2014;27(1):25-32.
10. Devereux JJ, Vlachonikolis IG, Buckle PW. Epidemiological study to investigate potential interaction between physical and psychosocial factors at work that may increase the risk of symptoms of musculoskeletal disorder of the neck and upper limb. Occup Environ Med 2002;59(4):269-77.
11. Rodríguez Y, Viña S, Montero R. A method for non-experts in assessing exposure to risk factors for work-related musculoskeletal disorders--ERIN. Ind Health 2013;51(6):622-6.
12. Erdinc O, Hot K, Ozkaya M. Turkish version of the Cornell Musculoskeletal Discomfort Questionnaire:cross-cultural adaptation and validation. Work 2011;39(3):251-60.
13. McAtamney L, Nigel Corlett E. RULA:a survey method for the investigation of work-related upper limb disorders. Appl Ergon. 1993;24(2):91-9.
14. Roman-Liu D. Comparison of concepts in easy-to-use methods for MSD risk assessment. Appl Ergon 2014;45(3):420-7.
15. Telles S, Dash M, Naveen KV. Effect of yoga on musculoskeletal discomfort and motor functions in professional computer users. Work 2009;33(3):297-306.
16. Fagarasanu M, Kumar S. Musculoskeletal symptoms in support staff in a large telecommunication company. Work 2006;27(2):137-42.
17. Rudakewych M, Valent-Weitz L, Hedge A, editors. Effects of an ergonomic intervention on musculoskeletal discomfort among office workers. Proceedings of the Human Factors and Ergonomics Society Annual Meeting;2001:SAGE Publications Sage CA:Los Angeles, CA.
18. Menzel NN, Brooks SM, Bernard TE, Nelson A. The physical workload of nursing personnel:association with musculoskeletal discomfort. Int J Nurs Stud 2004 Nov;41(8):859-67.
19. Tamrooiy, Farzane Rahnamaye, et al. "A survey on prevalence of musculoskeletal disorders in dentists of Tehran and their posture assessment by RULA method." Int Res J Appl Basic Sci 9.5 (2015):666-671.
20. Mean, Vathna, et al. "Investigation on musculoskeletal symptoms and ergonomic risk factors at metal stamping industry." Advanced Engineering Forum. Vol. 10. Trans Tech Publications Ltd, 2013.
21. Jansen K, Luik M, Reinvee M, et al. Musculoskeletal discomfort in production assembly workers. Acta Kinesiologiae Universitatis Tartuensis 2012:18;102-10.
22. Choobineh A, Tabatabaee SH, Behzadi M. Musculoskeletal problems among workers of an Iranian sugar-producing factory. Int J Occup Saf Ergon 2009;15(4):419-24.
23. Yildirim Y, Gunay S, Karadibak D. Identifying factors associated with low back pain among employees working at a package producing industry. J Back Musculoskelet Rehabil 2014;27(1):25-32.
24. Wijnhoven HA, de Vet HC, Picavet HS. Explaining sex differences in chronic musculoskeletal pain in a general population. Pain 2006;124(1-2):158-66.
25. Leclerc A, Gourmelen J, Chastang JF, Plouvier S, Niedhammer I, Lanoë JL. Level of education and back pain in France:the role of demographic, lifestyle and physical work factors. Int Arch Occup Environ Health 2009;82(5):643-52.
26. Karimi N, Moghimbeigi A, Motamedzade M, Roshanaei G. Evaluation of Related Risk Factors in Number of Musculoskeletal Disorders Among Carpet Weavers in Iran. Saf Health Work 2016;7(4):322-25.
27. Nahit ES, Hunt IM, Lunt M, Dunn G, Silman AJ, Macfarlane GJ. Effects of psychosocial and individual psychological factors on the onset of musculoskeletal pain:common and site-specific effects. Ann Rheum Dis 2003;62(8):755-60.

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Original Article / Orijinal Araştırma

Toward to Explain of Working Principles of Blood-Brain Barriers Like X-Ray Devices: A Neurophysical Hypothesis

X-Ray Cihazına Benzeyen Kan-Beyin Bariyerlerinin Çalışma Prensiplerini Açıklamaya Doğru: Bir Nörofizik Hipotez

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Abstract

Aim: The blood-brain barrier is an electromagnetic mechanism on a neurophysical basis. In this study, we compared the X-Ray device, which shows similarity to the blood-brain barrier.

Material and Method: We collected brain samples from deep temporal cortex sections of ten rats, stained them via the glial fibrillary acidic protein (GFAP) technique, visualized the architectural structures of the blood-brain barriers, and compared them with X-ray devices.

Results: With the arterioles forming the tube blood-brain barrier in the X-ray device, the anode-cathode that provides the electric current and determines the direction of the current flow corresponds to the astrocytes surrounding the anode-cathode vessel, the cooling system to the cerebrospinal fluid circulating the vessel, and the electrons emitted from the cathode to the particles flowing in the vessel.

Conclusion: With the architecture presented by the blood-brain barrier, we envision it functioning as an X-Ray and optical reader that display objects in passenger baggage and direct them according to barcode numbers.

Keywords: Astrocyte, blood-brain barrier, glial fibrillary acidic protein technique, rat, X-ray devices

Öz

Amaç: Kan-beyin bariyeri, nörofiziksel temelde elektromanyetik bir mekanizmadır. Bu çalışmada kan-beyin bariyerini, ona birçok yönden benzeyen X-Ray cihazı ile karşılaştırdık.

Gereç ve Yöntem: On sıçanın derin temporal korteks bölümlerinden beyin örnekleri topladık. Daha sonra glial fibriler asidik protein (GFAP) tekniği ile boyadık. Akabinde kan-beyin bariyerlerinin mimari yapılarını görselleştirdik ve X-ray cihazlarıyla karşılaştırdık.

Bulgular: X-ray cihazında tüp kan-beyin bariyerini oluşturan arterioller ile elektrik akımını sağlayan ve akımın yönünü belirleyen anot-katot; damarları çevreleyen astrositlere, damarlar için soğutma sistemi örevi gören beyin omurilik sıvısına ve katottan damarda akan parçacıklara yayılan elektronlara karşılık gelir.

Sonuç: Kan-beyin bariyerinin sunduğu mimari yapısı sayesinde yolcu bagajındaki nesneleri görüntüleyen ve barkod numaralarına göre yönlendiren bir X-Ray ve optik okuyucu olarak işlev gördüğünü düşünüyoruz.

Anahtar Kelimeler: Astrosit, kan-beyin bariyeri, glial fibriler asidik protein tekniği, sıçan, X-ray cihazı

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INTRODUCTION

X-rays have electromagnetic wave identity and polarization features. Electrons of the scattering medium emit electromagnetic waves at the same frequency by vibrating with the effect of the electric field vector of the X-rays on it. Anode and cathode electrodes are placed in a glass vacuum tube. The heated cathode takes the system in the old fluorescent lamp. Electrons are scattered when the cathode, passed through a high electric current, heats up. Electron jump has appeared, and photons belonging to energy have a high energy capacity. These are what we call X-ray photons. [1] X-rays are formed due to the interaction of rapidly moving electron current with atoms of the target material.[2] They are thrown from a fixed source to the photodiodes opposite. The images projected on the screen may be of different colors depending on the model of X-ray baggage scanning devices.

The blood-brain barrier separates the circulating blood from the extracellular fluid in the central nervous system. [3] This structure is formed by endothelial cells connected by tight junctions.[4] The blood-brain barrier does not allow the passage of many microorganisms and neurotoxins. Astrocytes are essential for the formation and proper functioning of the blood-brain barrier.[5] There are plenty of capillaries above the blood-brain barrier. Tight connections around them are not seen in average blood circulation. Endothelial cells prevent the diffusion of even tiny creatures such as bacteria.[6] Many proteins are used during active transport.[3]

In our opinion, the neural network surrounding the blood-brain barrier resembles the electrical setup of X-Ray devices. Just as X-ray scanners and barcode readers used in international transportation detect harmful substances and the direction of passenger connections, the blood-brain barrier may similarly regulate the course of atoms and molecules inside the brain arteries.

MATERIAL AND METHOD

Animal Selection and Study Groups

The data studied brains in the study were obtained from ten healthy male rats 18 months old age, and 350±20 gr (n=10). Hippocampus samples were examined by stereological methods to determine histological architectures of blood-brain barriers. The study protocol and permissions were reviewed and approved by the Ethics Committee for Animal Experiments, Medical Faculty, Ataturk University of Turkey. The management of the animals and the experiments themselves were done according to the guidelines set forth by the same ethics committee. A balanced, injectable anesthetics was preferred to reduce the pain and mortality. Anesthesia was triggered with isoflurane applied by a face mask, 0.2 mL/kg of the anesthetic combination (Ketamine HCL, 150 mg/1.5 mL; Xylazine HCL, 30 mg/1.5 mL; and distilled water, 1 mL) was subcutaneously injected before surgery. Following the experimental procedures, the animals were decapitated humanely under general anesthesia.

Histopathological Procedures

Brain tissue samples were stored in 10% formalin solutions for seven days after required cleaning procedures for retrograde histologic evaluation. The brain samples were subjected to a graded alcohol series embedded in liquid paraffin. Deep temporal sections were analyzed stereologically to evaluate similarities between X-ray devices and rat blood-brain barriers. The brain sections at the deep levels of temporal sections were stained with the glial fibrillary acidic protein (GFAP) method for examination. Twenty consecutive sections were taken at 5-micron intervals, and the BBB morphologies were examined.

Histopathological Findings

The blood-brain barrier is found in sensitive areas of the brain. It consists of a multi-functional endothelium, a dense innervated smooth muscle layer, and a neurovascular structure surrounded by a dense network of astrocytes surrounding the adventitia. Glial cells determine and direct the flow direction of the particles flowing in the vessel by producing negative and positive currents, just like the X-Ray device.

Mechanical and Anatomical Similarities Are as Follows:

The main components of the blood-brain barrier consist of arterioles like an X-ray tube, basal lamina, endothelium, astrocytes, end-feet of astrocytes, and pericytes, all of them like as anode (A)-cathode (K) (**Figure 1**). An X-ray tube is a high voltage cathode ray tube (B). The tube consists of a glass sheath that has been evacuated at a high vacuum. It has an anode (positive electrode, A) on one end and a cathode (negative electrode, C) on the other, tightly sealed with solder. The electrical energy of the X-Ray Tube is supplied from two poles (Uh-Ua). The cathode is a streamer made of tungsten material that releases electrons when heated. The anode consists of a thick rod and a metal target at the end of this rod. Electrons are emitted in the cathode filament when high voltage is applied between the anode and cathode. These electrons are accelerated towards the anode under high voltage and reach high speeds before hitting the target. A photon is emitted when high-speed electrons hit the metal target, transferring their energy. An X-ray beam consisting of glass passes through the narrow glass window inside the envelope. Some tubes use a filter to obtain single wavelength X-rays. X-Ray Tube: As the X-ray tube generates high heat, a coolant flows into the tube to make it enter (Win) and exit (Wout) to cool it. In our blood-brain barrier pictures, the astrocyte marked as K on the left shows the cathode, which is the mainstream generator, and the collector anode on the opposite astrocyte is marked as A. Electromagnetic waves originating from the anode to the particles signaled by the K astrocyte may be performing identity control (**Figure 2**).

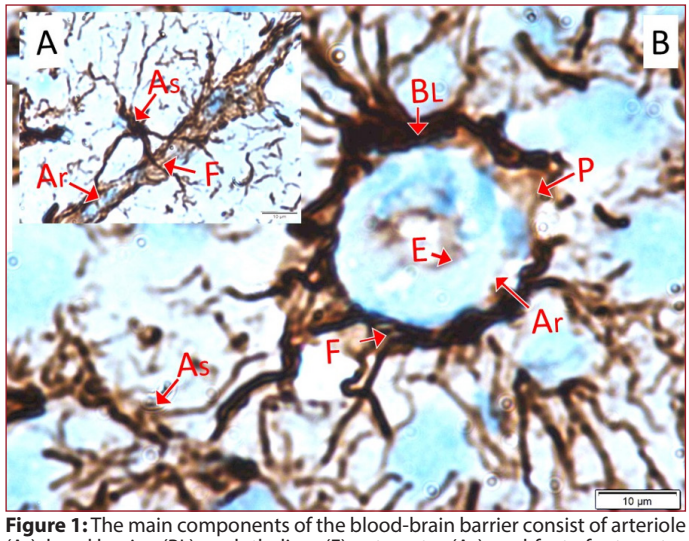

Figure 1: The main components of the blood-brain barrier consist of arteriole (Ar), basal lamina (BL), endothelium (E), astrocytes (As), end-feet of astrocytes (F) and pericytes (P) are seen (LM, GFAP, x10/A-Longitudinal section; x100/B-Transverse section).

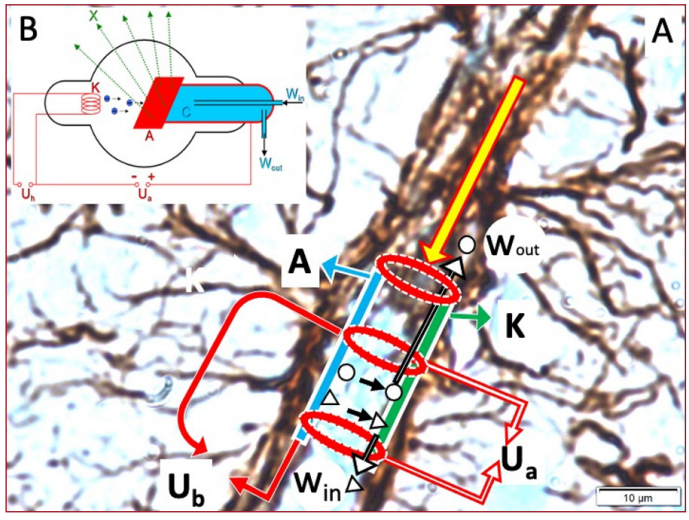

Figure 2: X-Ray Tube: X-ray tube is a high voltage cathode ray tube. The tube consists of a glass sheath that has been evacuated at high vacuum. It has an anode (positive electrode, A) on one end and a cathode (negative electrode, C) on the other, both of which are tightly sealed with solder. The electrical energy of the X-Ray Tube is supplied from two different poles (Uh-Ua). The cathode is a streamer made of tungsten material that releases electrons when heated. The anode consists of a thick rod and a metal target at the end of this rod. When high voltage is applied between the anode and cathode, electrons are emitted in the cathode filament. These electrons are accelerated towards the anode under high voltage and reach high speeds before hitting the target. When high-speed electrons hit the metal target, a photon is emitted, transferring their energy. X-ray beam consisting of glass it passes through the thin glass window inside the envelope. Some tubes use a filter to obtain single wavelength X-rays. X-Ray Tube: As the X-ray tube generates high heat, a coolant flows into the tube to make it enter (Win) and exit (Wout) to cool it. In our blood brain barrier pictures, the astrocyte marked as K on the left shows the cathode, which is the mainstream generator, and the collector anode on the opposite astrocyte marked as A. Electromagnetic waves originating from the anode to the particles signaled by the K astrocyte may be performing identity control.

The blood-brain barrier is found in sensitive areas of the brain. It consists of a multi-functional endothelium, a dense innervated smooth muscle layer, and a neurovascular structure surrounded by a dense network of astrocytes surrounding the adventitia. Glial cells determine and direct the flow direction of the particles flowing in the vessel by producing negative and positive currents, just like the X-Ray device.

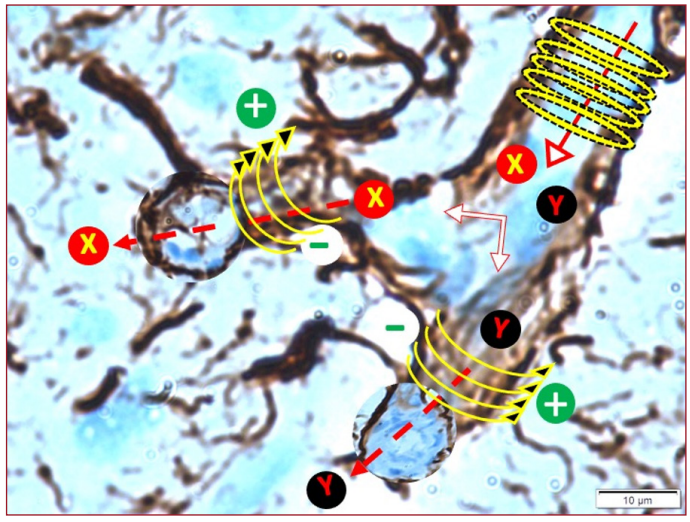

Figure 3: The blood brain barrier is found in sensitive areas of the brain. It consists of a multi-functional endothelium, a dense innervated smooth muscle layer, and a neurovascular structure surrounded by a dense network of astrocytes surrounding the adventitia. Glial cells determine and direct the flow direction of the particles flowing in the vessel by producing negative and positive currents just like the X-Ray device. In the figure, while XY particles flow distally, positive, and negative charges direct the X and Y particles to separate channels. Some of the astrocytes surrounding the artery may be acting as anode, and the opposite astrocyte cluster may also act as a cathode. This mechanism, which is viewed individually in two dimensions in the cross-section, exhibits a spiral structure. This neuroelectromagnetic mechanism may direct the particles in the vasculature to the neural, humoral, endocrine, and immune components of the brain according to their load and electromagnetic properties.

DISCUSSION

Working Principles of Blood-Brain Barrier

The blood-brain barrier separates the circulating blood from the extracellular fluid in the central nervous system.[3] This barrier is a highly permeable structure. Endothelial cells connected by tight junctions form this structure.[4] The blood-brain barrier allows the passive diffusion of water, some gases, and fat-soluble molecules. The transport of glucose and amino acids is done by active transport. The blood-brain barrier does not allow the passage of many microorganisms and neurotoxins. Astrocytes are essential for the formation and proper functioning of the blood-brain barrier. This structure encompasses the entire brain but is absent in a small brain section called circumventricular organs. This area immediately becomes an alarm if various toxic substances are detected in the blood. Various behaviors are seen to expel the poison, such as vomiting.

There are plenty of capillaries above the blood-brain barrier. Tight connections around them are not seen in average blood circulation. Endothelial cells prevent the diffusion of even tiny creatures such as bacteria. In addition, the passage of hydrophilic or structurally massive molecules into the cerebrospinal fluid is also prevented. Only diffusion of hydrophobic substances, including oxygen, carbon dioxide, and hormones, is allowed. Cells in the blood-brain barrier take metabolic products such as glucose by active transport. Many proteins are used during active transport. In our opinion, the neural network surrounding the blood-brain

barrier resembles the electrical setup of X-Ray devices. Just as X-ray scanners and barcode readers used in international transportation detect harmful substances and the direction of passenger connections, the blood-brain barrier may similarly regulate the course of atoms and molecules inside the brain arteries.

Tight junctions among the endothelial cells that make up the brain capillaries have a so-called tight connection, and a continuous they have a basement membrane. These connections are the blood-brain barrier endothelium. They create a high electrical resistance between their cells and 3.33 W / cm² in other tissues and 1500.2000 in K-BB W / cm².[7] As a result, paracellular permeability falls. The molecular weight of molecules below 10,000 absences of pores and fenestrations that allow passage differ from peripheral capillaries.[8]

The blood-brain barrier is found in sensitive areas of the brain. It consists of a multi-functional endothelium, a dense innervated smooth muscle layer, and a neurovascular structure surrounded by a dense network of astrocytes surrounding the adventitia. Glial cells determine and direct the flow direction of the particles flowing in the vessel by producing negative and positive currents, just like the X-Ray device.

Lymphatic System

CSF secretion, circulation, and absorption are dynamic processes modulated by different autonomic networks.[9] CSF can cool the brain like water in X-Ray devices. The brain is protected by barriers such as the blood-brain barrier that prevents foreign materials from accessing the brain. CSF flow into the pericapillary Virchow-Robin space (VRS) through the astrocytic aquaporin-4 (AQP-4) system is essential in cooling, nourishing, and detoxifying the brain. This structure also provides CSF dynamics in the subarachnoid space and ventricles.[10] Cerebral microglia also carry out essential activities in the synthesis and function of molecules variably modulated by astrocytes and choroid plexus epithelial cells and play essential roles in neuroinflammatory processes.[11] Therefore, the glymphatic fluid circulation can be considered the brain's lymphatic system. AQPs play crucial roles in the system.[12]

Similarities Between BBB and Barcode Reading X-Ray Devices

When current information is analyzed, it is evident that there is a close similarity between BBB and baggage reader systems. The working principles of current baggage scanners are based on measuring the energy loss between X-rays sent from a source and returned by hitting that source. When particles with different X-ray absorption properties are exposed to different X-ray spectra, unique images appear on the X-ray screen.[13] According to our theory, the BBB might work like baggage scanners and barcode readers used at airports or customs gates. The endothelium and blood vessels are surrounded by the dendrites of astrocytes, which produce and conduct electric current, forming a coiled tube.[6] Many astrocyte foot processes radiating along the vessel wall[7] produce an electric current. They may act as an anode-cathode, reading the particles passing through the vessel like barcode readers, ensuring the passage of beneficial particles to the brain, and eliminating harmful ones.

CONCLUSION

Suppose we comment on the summary X-Ray device in the literature and the pictures of the blood-brain barrier we have obtained. In that case, some of the astrocytes surrounding the artery may act as an anode, and the opposite astrocyte cluster may act as a cathode. This neuroelectromagnetic mechanism may direct the vessels' particles to the brain's neural, humoral, endocrine, and immune components according to their load and electromagnetic properties. This mechanism, viewed individually in two dimensions in the cross-section, has a spiral structure.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol and permissions were reviewed and approved by the Ethics Committee for Animal Experiments, Medical Faculty, Ataturk University of Turkey. The management of the animals and the experiments themselves were done according to the guidelines set forth by the same ethics committee.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. W.C. Rontgen. On a new kind of rays. Radiography. 1970;36(428):185-8.
2. Attwood DT. Soft x-rays and extreme ultraviolet radiation: principles and applications. In: Attwood DT, editor. New York Cambridge Univ Press; 2000.
3. Mahringer A, Puris E, Fricker G. Crossing the blood-brain barrier: A review on drug delivery strategies using colloidal carrier systems. Neurochem Int. 2021;147:105017.
4. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015;7(1):a020412.
5. Cheslow L, Alvarez JI. Glial-endothelial crosstalk regulates blood-brain barrier function. Curr Opin Pharmacol. 2016;26:39-46.
6. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. Neurobiol Dis. 2010;37(1):13-25.
7. Butt AM, Jones HC, Abbott NJ. Electrical resistance across the blood-brain barrier in anaesthetized rats: a developmental study. J Physiol. 1990;429:47-62.
8. MB DHaS. The blood brain-barrier. In: Physiology of the CSF and of the Blood-Brain Barrier. New York CRC. 1995:49-91.

9. Shapey J, Toma A, Saeed SR. Physiology of cerebrospinal fluid circulation. Curr Opin Otolaryngol Head Neck Surg. 2019;27(5):326-33.
10. Nakada T, Kwee IL. Fluid Dynamics Inside the Brain Barrier: Current Concept of Interstitial Flow, Glymphatic Flow, and Cerebrospinal Fluid Circulation in the Brain. Neuroscientist. 2019;25(2):155-66.
11. Kazakos EI, Kountouras J, Polyzos SA, Deretzi G. Novel aspects of defensins' involvement in virus-induced autoimmunity in the central nervous system. Med Hypotheses. 2017;102:33-6.
12. de Laurentis C, Cristaldi P, Arighi A, Cavandoli C, Trezza A, Sganzerla EP, et al. Role of aquaporins in hydrocephalus: what do we know and where do we stand? A systematic review. J Neurol. 2020.
13. Ignatyev K, Munro PRT, Chana D, Speller RD, Olivo A. A New Generation of X-ray Baggage Scanners Based on a Different Physical Principle. Materials (Basel). 2011;4(10):1846-60.

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Original Article / Orijinal Araştırma

Assessment of Mothers' Mood and Cognition Functions in Perinatal Period and Their Influences on Breastfeeding Success

Perinatal Dönemde Annelerin Duygu Durumlarının ve Kognitif Fonksiyonlarının Değerlendirilmesi ve Emzirme Başarısına Etkileri

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Abstract

Aim: In this study, we aimed to examine the effects of peripartum mother's cognitive functioning, anxiety, and postpartum depression of mothers on the practice of exclusive breastfeeding.

Material and Method: The pregnant women in the last trimester who were attended in the outpatient department of obstetrics and gynecology were included in the study as the study group. A total of three follow-ups were conducted in the study group. In our study Mini-Mental State Examination (MMSE) was used to assess cognitive functioning, State-Trait Anxiety Inventory (STAI) 1,2 to assess anxiety, Edinburgh Postnatal Depression Scale (EPDS) to assess postpartum depression, Breastfeeding Self-Efficacy Scale (BSES) to assess mother's self- efficacy in breastfeeding, LATCH Breastfeeding Assessment Tool to assess mother's and baby's breastfeeding technique.

Results: All of 158 pregnant and 96 non-pregnant women were enrolled in the study. After delivery, there was a significant decrease in STAI 2 scores compared to the prenatal period (p=0.001) and a significant increase in MMSE scores (p=0.001). There was no difference in STAI 1,2, and MMSE scores between the groups with and without successful breastfeeding (p >0.05). LATCH scores were statistically significantly higher in the group that successfully breastfed (p =0.001). LATCH (r=-0.427, p<0.001) and postpartum MMSE (r=-0.16, p=0.45) scores correlated negatively with EPDS scores.

Conclusion: The maintenance of exclusive breastfeeding should be considered from a biopsychosocial perspective as a whole, including the mother's cognitive level during the peripartum period, and support should be provided to achieve the desired success rates in initiating and maintaining breastfeeding.

Keywords: exclusive breast feeding, postpartum period, depression, anxiety

Öz

Amaç: Biz bu çalışmada sadece anne sütü ile emzirme pratiği üzerine peripartum dönemdeki annenin kognitif fonksiyonlarının (bilişsel işlev, öğrenme, bellek), anksiyete ve postpartum depresyonun etkilerini incelemeyi amaçladık

Gereç ve Yöntem: Kadın Hastalıkları ve Doğum polikliniğinde takip edilen son trimesterdeki gebeler çalışma grubu olarak çalışmaya alındı. Çalışma grubuna toplamda üç izlem yapıldı. Çalışmamızda kognitif fonksiyonların değerlendirilmesinde Mini Mental Durum Değerlendirme Ölçeği (MMSE), anksiyete değerlendirmesinde Durumluk-Sürekli Duygudurum Envanteri (STAI) 1, 2, postpartum depresyonun değerlendirilmesinde Edinburgh Postpartum Depresyon Ölçeği (EPDS), annenin emzirme öz yeterliliğinin değerlendirilmesinde Emzirme Özyeterlilik ölçeği (BSES), anne ve bebeğin emzirme tekniğinin değerlendirilmesinde Latch Emzirme Tanılama Ölçeği uygulandı.

Bulgular: Çalışmaya 158 gebe ve 96 gebe olmayan kadın alındı. Doğum sonrası doğum öncesine göre STAI 2 skorlarında anlamlı derecede azalma (p=0,001), MMSE skorlarında anlamlı derede yükselme tespit edildi (p= 0,001). Emzirmede başarılı ve başarısız olan gruplar arasında STAI 1,2 ve MMSE skorları açısından fark saptanmadı (p>0,05). Emzirmede başarılı olan grupta LATCH skorları istatistiksel anlamlı derecede daha yüksekti (p=0.001). EPDS skorları ile LATCH (r=-0,427, p<0,001) ve postpartum MMSE(r=-0,16, p=0,45) skorları arasında negatif bir korelasyon saptandı.

Sonuç: Sadece anne sütü ile beslenme uyumu, emzirmenin başlatılması ve sürdürülmesinde istenilen başarı oranlarını yakalamak için peripartum dönemde anne, kognitif düzeyini de içirecek şekilde biyopsikososyal açıdan bir bütün olarak ele alınıp destek sağlanmalıdır.

Anahtar Kelimeler: özel emzirme, postpartum dönem, depresyon, anksiyete

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INTRODUCTION

Breast milk, with its unique microbiome, bioactive compounds, and macro-and micronutrient composition, is the most ideal natural food for the growth and functional development of the baby during the first six months of life. According to the World Health Organization (WHO), the American Academy of Pediatrics (AAP), and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), exclusive breastfeeding (EBF) during the first six months of life is important for the optimal development of the baby. It is recommended that breastfeeding continue for at least two years by introducing appropriate complementary foods during this time.[1]

Despite all international studies supporting breastfeeding worldwide, the Global Breastfeeding Scale reports 40% exclusive breastfeeding in infants younger than six months.[2] While the rate of exclusive breastfeeding among 0–1-month-old infants in Turkey is 59%, this rate drops to 14% among 4–5-month-old infants.[3]

The failure to achieve the desired rates of exclusive breastfeeding (EBF) makes it necessary to investigate the factors that may influence this situation. Although there are many studies in the literature on the possible causes that influence the initiation and maintenance of breastfeeding, there are not enough studies that assess the cognitive abilities (cognitive abilities such as concentration ability and forgetfulness) of the mother in the peripartum period.[4-9] The main objective of our study is to show the relationship between the level of maternal cognitive functions in the peripartum period and the exclusive breastfeeding of the infant. Specifically, we hypothesize that mothers' cognitive complaints decrease due to increased levels of anxiety and depression in the postpartum period, which negatively affects exclusive breastfeeding of the infant.

MATERIAL AND METHOD

This study was conducted as a prospective cohort study in a large college hospital's obstetrics and gynecology outpatient clinic and maternal secondary care unit.

Participants

Pregnant women aged 18 and 45 years who had no psychiatric illness, were proficient in Turkish, and stated that they wanted to breastfeed their baby after delivery were invited to the study. This age group has been chosen because it is a fertile population. Between February and August 2018, 210 women in their third trimester of pregnancy were enrolled in the study. When evaluated in the first 24 hours after birth, 25 infants (5 infants with infections, 3 infants with hypoglycemia, 1 infant with meconium aspiration, 2 infants with jaundice, 6 infants with respiratory problems, 8 infants with dehydration) and their mothers were excluded from the study. 12 women who did not voluntarily participate in the study on the 10th day after delivery, 15 women whose babies had medical complications (8 babies were dehydrated, 7 babies were infected) were excluded from the study. The study was completed on postnatal day 10 with 158 women and babies (**Figure 1**).

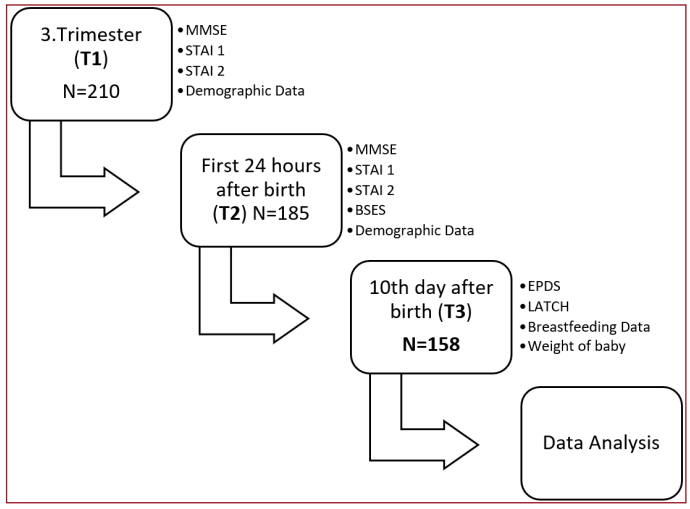

Figure 1. Number of participants and scales applied

STAI: State-Trait Anxiety Inventory, MMSE: Mini-Mental State Examination, BSES: Breastfeeding Self-Efficacy Scale, LATCH: Breastfeeding Assessment Tool, EPDS: Edinburgh Postnatal Depression Scale

Since we did not have data on the pre-pregnancy anxiety and cognitive abilities of the participants, non-pregnant women with similar sociodemographic characteristics were included in the study as a reference group.

Our study included 96 individuals aged between 18and 45 years who did not have children or whose last pregnancy was at least 2 years ago, who were not breastfeeding, had no known psychiatric or cognitive disorders, and were proficient in Turkish.

Sample Size

In order to determine the number of samples used in the study, a power analysis was performed using the G*Power v. 3.1.6 program. In the analysis conducted using the correlation test between EPDS and STAI, it was found that the Type 1 error: 0.05 Power: 80% and 84 subjects should be included in the study if the mean effect level is assumed. The sample size was calculated as 100 subjects, with 20% of the subjects added as a reserve.

Instruments

The Mini Mental State Assessment (MMSE) test is the most widely used screening test for assessing cognitive functioning. It has the advantage that it can be easily administered to patients by trained health care professionals.[10] Scores above the cut-off score (23/24) indicate a possible decline in cognitive function, and scores below normal cognitive function levels indicate that a comprehensive neuropsychological and clinical examination should be performed

While the State Anxiety Inventory (STAI-1) assesses anxiety resulting from current developments, the Trait Anxiety Inventory (STAI-2) assesses the degree of anxiety that has

become a personality trait. High scores indicate high levels of anxiety, and low scores indicate low levels of anxiety. Both are self-report scales.[11]

Breastfeeding Self-Efficacy Scale: BSES is a self-report scale where the possible scores range from 14 to 70. An increase in score indicates an increase in breastfeeding self-efficacy, mother's confidence (breastfeeding confidence).[12]

Edinburgh Postpartum Depression Scale (EPDS) is a 4-point Likert-type self-rating scale consisting of 10 questions. Scores above the cut-off point (12/13) are considered to be at increased risk for Postpartum Depression (PPD).[13,14]

Health professionals use LATCH Breastfeeding Diagnostic Scale (LATCH) to assess maternal and infant breastfeeding techniques. The total score ranges from 0 to 10, and a score of >8 is considered successful.[15]

Data Collection Procedure

The data of this study were collected by the researchers by face-to-face interview technique.

The study was conducted in a total of 3 sessions, namely in the last stage of pregnancy (the period between the 27th and 40th week of pregnancy) (T1), in the first 24 hours after birth (T2) and on the 10th day of pregnancy (T2). T1 was conducted on average 28 weeks before delivery. On test days T1 and T2, participants were first administered MMSE, STAI 1, and STAI 2. In addition, participants were administered the BSES at T2. At T3, participants were administered the EPDS and the LATCH Breastfeeding Diagnostic Scale. At T3, the babies' weight and nutritional status (exclusive breastfeeding or non-exclusive breastfeeding) were recorded (**Figure 1**). Mothers of infants who reached birth weight through exclusive breastfeeding were classified as "successfully breastfed." Data from participants in the "successfully breastfed" group were compared with other variables.

MMSE, STAI 1, STAI 2 tests and scales were applied to the participants in the reference group of our study. Questionnaires with socio-demographic and obstetric data prepared by reviewing the literature were used with the reference and study groups. Feeding habits (exclusive breastfeeding, non-exclusive breastfeeding, pacifier, and bottle use) were followed until the day of birth.

All participants with high anxiety and depression scores were referred to the appropriate clinics for diagnosis and treatment. The study was carried out with the permission of Ankara Yıldırım Beyazıt University (Yenimahalle Training and Research Hospital Ethic Committee, Date: 10.04.2018, Decision Number: 2018/4). All participants were enrolled in the study by obtaining informed consent.

Statistical Analysis

The SPSS Version 16.0 (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.) program was used to analyze the data in our study. The conformity of the variables to the normal distribution was examined by Kolmogorov–Smirnov/Shapiro–Wilk tests. Descriptive analyzes were given as mean and standard deviation for normally distributed data, median, and minimum-maximum for non-normally distributed data. The Chi-square test was used for categorical data. Group comparisons were performed using the paired-samples test and the Mann-Whitney -U test, as appropriate. When examining the relationships between test scores, correlation coefficients and significance were calculated using the Spearman test. A p value less than 0.05 was considered statistically significant.

RESULTS

The mean age of the 158 participants in the study was 31 years (20–44), and the mean age of the 96 participants in the reference group was 33 years (18–44). The median gravidity of participants in the study group was 2 (1-6) and the median parity was 1 (0-4). 43.0% of mothers (n=68) breastfed their baby in the first half-hour after birth, and 36.1% (n=57) reported that they thought their milk was sufficient for their baby.

At the 10th postpartum day evaluation, 20.3% of babies (n=32) were not able to reach their birth weight, and 6.3% (n=10) of mothers had an EPDS score of ≥13. When the tests performed on the mothers before and after delivery were compared, the STAI 2 was statistically significantly higher before delivery than after (p=0.001), and the prenatal MMSE was significantly lower than the postnatal one (p=0.001) (**Table 1**).

Table 1. The mean score of the tests in the study group

		Mean±SD	p
STAI 1	Prenatal	42.19±5.27	0.753
	Postnatal	41.93±3.56	
STAI 2	Prenatal	47.30±5.78	0.001
	Postnatal	45.43±5.65	
MMSE	Prenatal	24.15±3.31	0.001
	Postnatal	26.16±2.51	

STAI: State-Trait Anxiety Inventory, MMSE: Mini-Mental State Examination, SD: Standard Deviation

When the tests performed on the mothers prenatally and postnatal were compared with the control group, it was found that the mothers' prenatal STAI-2 score was significantly higher than that of the reference group, and the mothers' postnatal MMSE scores were significantly higher than that of the reference group (p=0.005, p=0.003, respectively) (**Table 2**). On postnatal day 10, mothers of babies who achieved birth weight by breastfeeding alone were classified as "successful" and mothers who fed their babies with formula were classified as "unsuccessful." For the assessment by success, the LATCH scale score was statistically significantly higher in the successful group (p=0.001), but no significant difference was found for other tests. However, although not statistically significant, BSES scores were higher and EPDS scores were lower in the successful group. (**Table 3**).

Table 2. Comparison of prenatal and postnatal test results with the reference group

Group Type		n	Mean ± SD	Median	Min-Max	p
STAI 1	Working Group (Prenatal)	158	42.19±5.27	42	29–60	0.25
	Reference Group	96	41.36±4.67	41	32–52	
STAI 1	Working Group (Postnatal)	158	41.93±3.56	41	35–54	0.31
	Reference Group	96	41.36±4.67	41	32–52	
STAI 2	Working Group (Prenatal)	158	47.30±5.78	47	35–64	0.005*
	Reference Group	96	45.19±5.01	45	36–58	
STAI 2	Working Group (Postnatal)	158	45.43±5.65	45	10_30	0.98
	Reference Group	96	45.19±5.01	45	36–58	
MMSE	Working Group (Prenatal)	158	24.15±3.31	24	10–30	0.11
	Reference Group	96	24.93±3.54	25	16–30	
MMSE	Working Group (Postnatal)	158	26.16±2.51	26	20–30	0.003*
	Reference Group	96	24.93±3.54	25	16–30	

*Mann-Whitney U test, STAI: State-Trait Anxiety Inventory, MMSE: Mini-Mental State Examination, Min: Minimum, Max: Maximum, SD: Standard Deviation

Table 3. Test results of the prenatal and postnatal study group (n=158) in relation to breastfeeding success.

	Success Status	n	Mean ± SD	Median	Min-Max	p
STAI 1 Prenatal	Successful	120	42.31±5.52	42	29–60	0.58
	Unsuccessful	38	41.82±4.41	41.5	35–53	
STAI 1 Postnatal	Successful	120	41.77±3.66	41	35–54	0.16
	Unsuccessful	38	42.45±3.17	42	37–51	
STAI 2 Prenatal	Successful	120	47.18±5.79	47	35–64	0.68
	Unsuccessful	38	47.68±5.76	47.5	38–64	
STAI 2 Postnatal	Successful	120	45.17±4.93	44.50	35–60	0.56
	Unsuccessful	38	46.26±7.49	45.5	35–70	
MMSE Prenatal	Successful	120	24.03±3.40	24	10–30	0.36
	Unsuccessful	38	24.52±3.02	24.5	17–30	
MMSE Postnatal	Successful	120	26.07±2.58	25	20–30	0.399
	Unsuccessful	38	26.47±2.31	26	23–30	
BSES	Successful	120	56.72±7.22	57	25–70	0.066
	Unsuccessful	38	54.21±7.47	56	34–70	
LATCH	Successful	120	9.64±0.80	10	5–10	0.001*
	Unsuccessful	38	9.11±1.15	10	6–10	

*Mann–Whitney U test, STAI: State-Trait Anxiety Inventory, MMSE: Mini-Mental State Examination, BSES: Breastfeeding Self-Efficacy Scale, LATCH: Breastfeeding Assessment Tool , Min: Minimum, Max: Maximum, SD: Standard Deviation

Making the first breastfeeding time after 30 minutes, using a pacifier (p=0.001), bottle use (p=0.001), and cesarean delivery was statistically significantly higher in the unsuccessful group than in the successful group (**Table 4**).

Table 4. Comparison of variables according to breastfeeding success in the study group

Variables		Successful n (120)		Unsuccessful n (38)		p
		n	%	n	%	
Smoking	Yes	13	10.8	4	10.5	0.950
	No	107	89.2	34	89.5	
Sex of the infant	Female	54	45.0	17	44.7	0.970
	Male	66	55.0	21	55.3	
First breastfeeding time	<30 minutes	60	50.0	8	21.1	0.002*
	≥30 minutes	60	50.0	30	78.9	
Mother's breastfeeding satisfaction	Yes	65	54.2	11	28.9	0.007*
	No	55	45.8	27	71.1	
Sufficiency thought of mother's milk	Yes	51	42.5	6	15.8	0.001*
	No	32	26.7	23	60.5	
	Undecided	37	30.8	9	23.7	
EPDS	≥13	4	3.3	6	15.8	0.006*
	< 13	116	96.7	32	84.2	
Pacifier use	Yes	19	15.8	21	55.3	0.001*
	No	101	84.2	17	44.7	
Feeding bottle use	Yes	2	1.7	33	86.8	0.001*
	No	118	98.3	5	13.2	
Type of delivery	NVY	62	51.7	9	23.7	0.003*
	C/S	58	48.3	29	76.3	

*Mann-Whitney U test, NVY: Normal Vaginal Delivery, C/S: Cesarean Birth, EPDS: Edinburgh Postnatal Depression Scale

The relations between the applied tests were examined using Spearman's Correlation coefficient, and accordingly, a weak and statistically significant correlation (r=-0.351**, p<0.001) was found between the MMSE prenatal test score and the STAI 2 prenatal test score. A moderate (r=0.632**) and statistically significant correlation was found between the MMSE prenatal test score and MMSE postnatal test score in the same direction (p=0.000). (Values marked with * are considered significant at the 0.05 level, and values marked with ** are considered significant at the 0.001 level)

An inverse, very weak, and statistically significant correlation was found between the Prenatal STAI 1 test score and the MMSE Prenatal test score (r=-0.162* p=0.042). A weak and statistically significant correlation was found between the STAI 1 Prenatal test score and the STAI 2 Prenatal test score in the same direction (r=0.380**, p=0.000). A very weak and statistically significant correlation was found between the STAI 1 Prenatal test scores and the STAI 1 Postnatal test scores in the same direction (r=0.209**, p=0.008).

A very weak and statistically significant correlation was found between the EPDS test score and the STAI 2 Prenatal test score in the same direction (r=0.171*, p=0.032).

A very weak and statistically significant correlation was found between the postnatal MMSE test score and the BSES test score in the same direction (r=0.163*, p=0.041). There is an inverse, very weak, and statistically significant relationship between the postnatal MMSE test score and the EPDS test score (r=-0.160*, p=0.045).

There is an inverse, weak grade, and statistically significant relationship between LATCH test score and EPDS test score (r=-0.427, p<0.001).

DISCUSSION

Many observational studies have shown that maternal psychological problems in the perinatal period negatively impact EBF and, consequently, on infant growth and development. However, the impact of maternal cognitive level on EBF has been overlooked. In this study, the effects of women's cognitive functioning, anxiety level, and presence of postpartum depression symptoms on exclusive breastfeeding in the peripartum period were investigated. Our study contributes to a deeper understanding of the complex relationship between breastfeeding and maternal biopsychosocial well-being by incorporating maternal cognitive levels in the peripartum period.

Cognitive Condition

There was no significant difference between the mothers' prenatal MMSE scores and the reference group scores in our study. Still, the mean of the postpartum MMSE scores was statistically significantly higher than the reference group. Contrary to our hypothesis, this suggests a cognitive improvement in mothers in the early postpartum periods. The limited number of studies in the literature on this topic contains conflicting information. The study by Ciafaloni et al. claimed that pregnant women have short-term memory loss compared to non-pregnant women and mentioned a terminology called "placenta brain" "baby brain.".[16] On the other hand, Christensen et al., in their study examining the changes in cognitive functions during pregnancy and maternity, found no significant changes between maternal cognitive functions during pregnancy and the postpartum period, similar to our study.[17] A meta-analysis by Davies et al. involving 709 pregnant women and 521 non-pregnant women also found that cognitive memory and executive functions decline from the first trimester to the second trimester. Still, there was no such difference between the second and third trimesters.[18] This study found that the differences occurred mainly in the first trimester and that overall cognitive functions decreased significantly in the last trimester of pregnancy compared to the control group. Fiterman et al. studied pregnant women and non-pregnant women in the last trimester with regard to cognitive functions. This study found that the response to the test Stop-Signal Task, which assesses response inhibition, considered an important part of executive cognitive functions, was better in the pregnant group than in the control group. This was interpreted to mean that the pregnant group was more successful in using cognitive functions in decision-making by inhibiting impulsivity.[19-21] Our study shows that prenatal MMSE scores did not differ from the reference group, which suggests that cognitive functions do not deteriorate during pregnancy. However, the fact that the scores in the postpartum period were better than those of the reference group and the possibility of remembering the questions due to the short MMSE application interval (3rd trimester and postnatal first 24 hours) were ignored, suggesting that there was some improvement in this regard and the birth was good for the mother. This situation can be interpreted to mean that the mother's desire to take good care of her baby and her responsibility for her baby may have strengthened her potential for cognitive functioning.

We think that the discrepancy in the information about the changes in maternal cognitive functions during pregnancy and postpartum period in the few studies in the literature is due to the small number of samples, the short follow-up periods, the unknown baseline cognitive status of the mothers before pregnancy, and the differences in the methods used in the evaluation, and we think that more studies should be conducted on this topic.

We also found that there is a very weak and statistically significant relationship between postnatal MMSE test score and BSES test score in the same direction. This suggests that as mothers' cognitive functioning increases, so does their perception of motherhood and hence their confidence in breastfeeding.

Anxiety- Postpartum Depression (PPD) Level of The Participants

Anxiety is a type of restlessness, fear, and worry that has cognitive, somatic, behavioral, and emotional components that evoke feelings of fear. It can include two types of behavioral symptoms, namely state anxiety and trait anxiety.[22,23] In our study, we found a weak and statistically significant relationship in the same direction between prenatal STAI 1 and STAI 2 test scores. This is consistent with the literature confirming that individuals with anxious personality traits respond to immediate situations with strong anxiety.[11] We found that the level of anxiety (STAI 2) was higher in the pregnant women who participated in our study than in the reference group participants and that the level of anxiety decreased with delivery. Similarly, in a study by Zaman et al. (2018), it was found that the anxiety level of pregnant women was significantly higher compared to the non- pregnant control group.[19] These findings suggest that not only pregnant women but all women preparing for pregnancy should be assessed for anxiety and receive support as needed to positively support the process of preparing for motherhood.

The risk of PPD was increased in 6.3% of mothers who participated in our study. There are many studies in the literature that examine the negative effects of PPD on the well-being of the mother and baby.[24-26] In a study conducted by Fonsace et al. with 441 postpartum women, they showed that women at high risk for PPD had more dysfunctional beliefs about motherhood than women at low risk for dysfunctional beliefs (bad experiences, perfectionism, ideal-perfect mother role).[27] Pregnancy and childbirth are important events in a woman's life cycle, and good identification of risk factors and taking preventive measures PPD during this time will help reduce the devastating effects of PPD.

Our study found that the risk of PPD increased in individuals with a high level of anxiety (STAI 2) during the prenatal and postnatal period (in individuals with an anxious personality). This result points to the possibility of comorbidity between PPD and anxiety, although they are two different conditions. In the literature, some studies mention that the EPRS is a scale used to determine the risk of postnatal and prenatal PPD in women and also includes components for anxiety symptoms.

Factors Affecting Exclusive Breastfeeding Success

In our study, we found no difference between the successful and unsuccessful groups in terms of mean anxiety scores for exclusive breastfeeding. However, there are studies in the literature that show the negative impact of maternal anxiety on exclusive breastfeeding.[4,8,9,28] In our study, we found that the risk of PPD was significantly lower in the successful group than in the unsuccessful group, consistent with the literature.[4,9,29]

In our study, we did not find any significant difference between the successful and unsuccessful groups in terms of mean MMSE scores. No study in the literature clearly demonstrates the relationship between cognitive functioning and breastfeeding success. In the limited number of studies available, the relationship between PPD and cognitive variables was investigated. The 2018 study by Denis et al. of 124 mothers examined the cognitive response to depression by showing the effects of rumination and maternal self-esteem on the intensity of depression and found that cognitive variables should also be considered a neglected factor among PPD risk factors.[30]

It was found that LATCH scores, a breastfeeding assessment tool, were statistically significantly higher in the successful group than in the unsuccessful group. Moreover, in our study, it was observed that the scores of LATCH decreased as the risk of PPD increased, and we thought that this was due to the negative effects of PPD on mother-infant attachment and interaction.[26]

Looking at the other results of our study, the rates of breastfeeding initiation in the first 30 minutes, maternal breastfeeding satisfaction, perception of milk sufficiency, pacifier use, and cesarean section rates were lower in the group that breastfed successfully. These results were consistent with the literature.[4,31-34]

Limitations

Our study had some limitations. In our study, there are no data on laboratory parameters that could be potential factors for changes in cognitive functions. The lack of data on participants' cognitive scores before pregnancy, in the early stages of pregnancy (1st and 2nd trimesters), and in the late postpartum period limited our inferences about changes in cognitive levels. The partial cognitive improvement observed in postnatal participants might be due to the lack of time interval between the application times of the same test. The same test must be repeated in the late postnatal period. In our study, the reference group was assessed only once, and changes in cognitive ability and anxiety were ignored in repeated observations. The difference in sample size between the reference group and the study group is also one of the limitations of our study.

CONCLUSION

Although the data of our study do not support our hypothesis that mothers' cognitive functions decline after childbirth, the partial improvement in mothers' cognitive levels after childbirth led us to believe that labor is perceived by mothers as a stressor, although it is a physiological process. Indeed, in our study, the mothers' anxiety level was high in the prenatal period and decreased after birth, supporting this assumption. Our results showed that the LATCH scores indicating the success of breastfeeding technique were high in the successful breastfeeding group. At the same time, there was no difference between the successful and unsuccessful groups in the tests assessing anxiety and cognitive functions. This situation led us to believe that breastfeeding skills can be improved by helping mothers improve breastfeeding techniques. There is a weak linear relationship between STAI 2 scores and EPD scores during pregnancy and postpartum. We believe that the association between maternal anxiety levels in the peripartum period and the presence of PPD is important to ensure the well-being of the mother and baby and that this issue should be further investigated with specific screening tests for the peripartum period.

Our findings draw attention to the importance of considering EBF adherence, initiation, and maintenance of breastfeeding from a biopsychosocial perspective, including the mother's cognitive level during the peripartum period. Well-designed longitudinal studies on this topic are needed to provide more meaningful results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Yıldırım Beyazıt University (Yenimahalle Training and Research Hospital Ethic Committee, Date: 10.04.2018, Decision Number: 2018/4).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Verduci E, Giannì ML, Vizzari G, Vizzuso S, Cerasani J, Mosca F, Zuccotti GV. The Triad Mother-Breast Milk-Infant as Predictor of Future Health: A Narrative Review. Nutrients 2021; 13(2): 486.
2. World Health Organization. Babies and mothers worldwide failed by lack of investment in breastfeeding. Saudi Med J 2017;38(9):974-5.
3. Hacettepe University Institute of Population Studies. 2018 Turkey Demographic and Health Survey (TNSA). Ankara, Turkey: Hacettepe University Institute of Population Studies, TC Presidency Strategy and Budget Directorate and TUBITAK;2019.
4. Cato K, Sylvén SM, Georgakis MK, et al. Antenatal depressive symptoms and early initiation of breastfeeding in association with exclusive breastfeeding six weeks postpartum: a longitudinal population-based study. BMC Pregnancy and Childbirth 2019;19:49.
5. Chowdhury R, Sinha B, Sankar MJ, et al. Breastfeeding and maternal health outcomes: a systematic review and meta-analysis. Acta Paediatr Suppl 2015;104:96-113.
6. Lou Z, Zeng G, Huang L, et al. Maternal indicators reported and causes of insufficient milk supply. J Hum Lact 2014;30(4):466-73.
7. Galipeau R, Dumas L, Lepage M. Perception of Not Having Enough Milk and Actual Milk Production of First-Time Breastfeeding Mothers: Is There a Difference? Breastfeed Med 2017;210-7.
8. Dimitraki M, Tsikouras P, Manav B, et al. Evaluation of the effect of the natural and emotional stress of labor on lactation and breastfeeding. Arch Gynecol Obstet 2016;293(2):317-28.
9. Coo S, García MI, Mira A, Valdés V. The Role of Perinatal Anxiety and Depression in Breastfeeding Practices. Breastfeed Med 2020;15(8):495-500.
10. Güngen C, Ertan T, Eker E, et al. Reliability and Validity of the Standardized Mini- Mental State Examination in The Diagnosis of Mild Dementia in Turkish Population. Turk Psikiyatri Derg 2002;13(4):273-81.
11. Oner N, Le Compte AW. Discontinuous State; Trait Anxiety Inventory Handbook, 1st edition. Istanbul, Turkey: Boğaziçi University Publications;1983.
12. Küçükoğlu S, Çelebioğlu A. Hasta yenidoğanların annelerinin emzirme özyeterlilik düzeyi ve emzirme başarılarının incelenmesi. ERÜ Sağlık Bilimleri Fakültesi Dergisi. 2014;2(1):1-11.
13. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987;150:782–6.
14. Aydin N, Inandi T, Yigit A, et al. Validation of the Turkish version of the Edinburgh Postnatal Depression Scale among women within their first postpartum year. Soc Psychiatry Psychiatr Epidemiol 2004;39:483–6.
15. Jensen D, Wallace S, Kelsay P. LATCH: a breastfeeding charting system and documentation tool. J Obstet Gynecol Neonatal Nurs 1994;23(1):27-32.
16. Ciafaloni E, Thornburg LL, Bushnell CD(Eds.); Neurological Diseases and Pregnancy: A Coordinated Care Model for Best Management; Oxford University Press;2018.
17. Christensen H, Leach LS, Mackinnon A. Cognition in pregnancy and motherhood: prospective cohort study. Br J Psychiatry 2010;196(2):126-32.
18. Davies SJ, Lum JA, Skouteris H, et al., Cognitive impairment during pregnancy: a meta-analysis. MJA 2018;208(1):35-40.
19. Zaman FK, Özkan N, Toprak D. Depression and Anxiety in Pregnancy. Konuralp Med J 2018;10(1):20-5.
20. Sinesi A, Maxwell M, O'Carroll R, Cheyne H. Anxiety scales used in pregnancy: systematic review. BJPsych Open 2019;5(1):e5.
21. Fiterman O, Raz S. Cognitive, neural and endocrine functioning during late pregnancy: An Event-Related Potentials study. Horm Behav 2019;116:104575.
22. Spielberger CD Emotional reactions to surgery. J Consult Clin Psychol 1973;40(1):33- 8.
23. Moser JS, Moran TP, Leber AB. Manipulating attention to nonemotional distractors influences state anxiety: a proof-of-concept study in low-and high anxious college students. Behav Ther 2015; 46(6):834-43.
24. Ayhan B. The Evaluation of the Relationship Between Postpartum Depression and Breastfeeding. Ankara Med J 2018;(3):276-85.
25. Dönmez H. Effect of Postpartum Depression on Breast-Feeding Duration of Infants And Infant Growth. Selcuk Med J 2015;31(4):158-62.
26. Field T. Postpartum Anxiety Prevalence, Predictors and Effects on Child Development: A Review. J Psychiatry Psychiatric Disord 2017;1(2):86-102.
27. Fonseca A, Canavarro MC. Cognitive correlates of women's postpartum depression risk and symptoms: the contribution of dysfunctional beliefs and negative thoughts. J. Ment. Health 2019;29(6):1-9.
28. Klenzman R, Spence M, Colby S, Springer C, Kavanagh K. Postpartum Anxiety, Breastfeeding Self-Efficacy & Breastfeeding Outcomes. Curr Dev Nutr 2020;4(Supplement_2):1020.
29. Gila-Díaz A, Carrillo GH, López de Pablo Á.L, Arribas SM, Ramiro-Cortijo D. Association between maternal postpartum depression, stress, optimism, and breastfeeding pattern in the first six months. Int. J. Environ. Res. Public Health 2020;17(19):7153.
30. Denis A, Luminet O. Cognitive factors and post-partum depression: What is the influence of general personality traits, rumination, maternal self-esteem, and alexithymia?. Clin Psychol Psychother 2018;25(2):359-67.
31. Walsh SM, Cordes L, McCreary L, Norr KF. Effects of early initiation of breastfeeding on exclusive breastfeeding practices of mothers in Rural Haiti. J Pediatr Health Care 2019;33(5):561-7.
32. Fan HSL, Wong JYH, Fong DYT, et al. Association Between Intrapartum Factors and the Time to Breastfeeding Initiation. Breastfeed Med 2020;15(6):394-400.
33. Gebremeskel SG, Gebru TT, Gebrehiwot BG, et al. Early initiation of breastfeeding and associated factors among mothers of aged less than 12 months children in rural eastern zone, Tigray, Ethiopia: cross-sectional study. BMC Res Notes 2019;12:671.
34. Wu X, Gao X, Sha T, et al. Modifiable Individual Factors Associated with Breastfeeding: A Cohort Study in China. Int. J. Environ. Res. Public Health 2019;16;820.

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Original Article / Orijinal Araştırma

Cystic Echinococcosis in Children: Ten Years of Experience and Which Laboratory Results are Significant in the Evaluation of Ruptured Cases?

Çocuklarda Kistik Ekinokokkoz: On Yıllık Tecrübe ve Rüptüre Olguları Değerlendirmede Hangi Laboratuar Sonuçları Önemlidir?

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Abstract

Aim: Hydatid disease (Echinococcosis) is a common zoonosis in countries that are involved in livestock such as our country. Our study aims to evaluate pediatric cases with hydatid disease over the last decade in our region and to determine the significance of initial clinical and laboratory findings in distinguishing ruptured hydatid cyst cases.

Material and Method: A retrospective analysis was made on demographic characteristics, presenting symptoms, physical examination, laboratory and radiological findings, and treatments of children with hydatid disease who were treated in our hospital and followed up regularly between January 2011 and December 2020.

Results: Of the 42 cases included in the study, 19 were female (45.2%) and the median age of cases was 125.5 (34-209) months. The most common symptom was abdominal pain (50%), and the most common physical examination finding was decreased breath sounds (23.8%). Thirty-five (83.3%) patients had single organ involvement and 7 (16.7%) patients had multiple organ involvement. Cysts were detected in the right lobe of the liver in 24 (75%) of hepatic hydatid cysts and the left lobe in 7 (58.3%) of pulmonary hydatid cysts. The median size of the cysts was 57.5 (12-140) mm. The initial IHA titer, eosinophil count, eosinophil percentage, and sedimentation value were statistically significantly higher in patients with ruptured cysts than in those without rupture (p=0.002, p=0.003, p=0.003, p=0.02, respectively).

Conclusion: Initial pathological examination findings and at initial laboratory findings such as high IHA titer, eosinophil count, eosinophil percentage, sedimentation value can be used to distinguish rupture cases.

Keywords: Cyst, echinococcus, liver, lung, pediatrics

Öz

Amaç: Kist hidatik hastalığı (Echinococcosis) Türkiye gibi hayvancılıkla uğraşan ülkelerde yaygın olan bir zoonozdur. Çalışmanın amacı bölgemizde son 10 yılda görülen çocuk kist hidatik olgularını değerlendirip, rüptüre kist hidatik olgularını ayırt etmede başlangıç klinik ve laboratuvar bulgularının önemini belirlemektir.

Gereç ve Yöntem: Ocak 2011-Aralık 2020 tarihleri arasında hastanemizde tedavi edilen ve düzenli olarak takiplere gelen kist hidatikli çocukların demografik özellikleri, başvuru şikayeti, fizik muayene, laboratuvar, radyolojik bulguları ve tedavileri geriye dönük incelendi.

Bulgular: Çalışmaya dahil edilen 42 olgunun 19'u kız (%45,2), ortanca yaşları 125,5 (34-209) aydı. En yaygın belirti %50 ile karın ağrısı, en yaygın fizik muayene bulgusu ise %23,8 ile solunum seslerinde azalmaydı. Hastaların 35'inde de (%83,3) tek organ, 7'sinde (%16,7) çoklu organ tutulumu vardı. Karaciğer kist hidatiklerinin 24'ünde (%75) kist karaciğerin sağ lobunda, akciğer kist hidatiklerinin ise 7'si (%58,3) sol lobunda tespit edildi. Kistlerin ortanca boyu 57,5 mm (12-140 mm) idi. Rüptüre kisti olan hastalarda başlangıç İHA titresi, eozinofil sayısı, eozinofil yüzdesi ve sedimantasyon değeri rüptür olmayan hastalara göre istatistiksel olarak anlamlı yüksekti (sırasıyla p=0,002, p=0,003, p=0,003, p=0,02).

Sonuç: İlk başvuruda patolojik muayene bulgusu ve yüksek İHA titresi, eozinofil sayısı, eozinofil yüzdesi ve sedimantasyon değeri rüptür olgularını ayırt etmek için kullanılabilir.

Anahtar Kelimeler: Akciğer, ekinokok, karaciğer, kist, pediatri,

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INTRODUCTION

Hydatid disease is a zoonosis caused by the larvae of Echinococcus, a ~2–7 mm long tapeworm, which is common in countries engaged in agriculture and livestock.[1] Dogs are the definitive host of the disease, while goats, sheep, camels, and cattle are intermediate hosts and humans are accidental hosts.[2] Humans become infected by ingesting the eggs in contaminated food, water, and soil, or via contact with dogs. While it can occur in all age groups, it is often acquired in childhood in endemic regions.[3] It is common in countries with poor preventive medicine. The endemic regions include the Middle East, South America, New Zealand, South Africa, Asia, China, and the Mediterranean countries such as Turkey. In endemic areas, the incidence of cystic echinococcosis are 50 per 100,000 person-years. Prevalence are 5-10% in Argentina, Peru, East Africa, Central Asia, and parts of China. Worldwide, there may be in excess of 1 million people living with these diseases at any one time. The 2015 WHO Foodborne Disease Burden Epidemiology Reference Group estimated echinococcosis to be the cause of 19 300 deaths and around 871 000 disability-adjusted life-years (DALYs) globally each year. The annual cost associated with echinococcosis in the livestock industry is estimated at US$ 3 billion.[4]

Clinical signs vary with the organ involved, the size of the cyst, and the interaction between the enlarged cyst and adjacent organs. Most of the cysts are asymptomatic and may regress spontaneously. The most commonly involved organ is the liver in adults and the lungs in children. Rarely, it can also affect such organs as the spleen, pancreas, heart, brain, kidney, muscles, and bones.[5] The diagnosis is established by clinical signs, radiological imaging techniques, and serological tests. Treatment may be medical, surgical, or puncture-aspiration-injection-reaspiration (PAIR).[6]

Our study aimed to evaluate the demographic characteristics, clinical symptoms, radiological images, laboratory findings, and treatment methods of children diagnosed with hydatid disease in our region. We aimed to determine the significance of initial clinical and laboratory findings in distinguishing ruptured hydatid cyst cases and to contribute to the literature.

MATERIAL AND METHOD

The medical records of patients with hydatid disease who were treated and followed up regularly at the Departments of Pediatrics and Pediatric Surgery of Suleyman Demirel University Faculty of Medicine between January 2011 and December 2020 were retrospectively reviewed. The study was carried out in the province of Isparta with a population of 445,678 located in the central Mediterranean region of Turkey.

Diagnosis

Hydatid disease was diagnosed by clinical, radiological, and serological tests. Demographic characteristics of the patients, presenting symptoms, initial physical examination and radiological findings, initial laboratory values (echinococcal indirect hemagglutination (IHA), complete blood count, transaminase levels, sedimentation, C-reactive protein (CRP), and total Ig E), the localization, number and size (largest diameter) of the cyst, duration of treatment, duration of follow-up, medical treatment, PAIR and surgical method, complications, and post-treatment echinococcal IHA results were evaluated. Before the treatment, patients underwent chest radiography, abdominal ultrasonography (US), thoracic or cranial computerized tomography (CT), cranial magnetic resonance imaging, and echocardiography according to indications. In asymptomatic patients, hydatid disease was diagnosed incidentally after US or other radiological examinations for other reasons. Echinococcus IHA titers of ≥1/320 were considered positive.

Treatment

All patients were administered albendazole 15 mg/kg/day (in two divided doses, maximum 800 mg/day) as medical treatment in cycles of 28 days with a drug-free interval of 14 days between the cycles. Medical treatment was administered by monitoring complete blood count and transaminase levels. Eligible patients with hepatic hydatid cysts were treated with the PAIR technique. This technique was performed under US guidance; the cystic content was aspirated first and then 20% hypertonic saline was injected into the cyst, followed by reaspiration. Patients ineligible for PAIR and with indications for surgery underwent surgical techniques (cystectomy, cystotomy and capitonnage). Patients scheduled for surgery were initiated on andazole treatment 1-4 weeks before the operation according to the World Health Organization's recommendations, and the treatment was continued for at least one more month after the operation.[7]

Assessment

Response to treatment was evaluated together with clinical, radiological, and serological tests. Along with the improvement of clinical signs, complete disappearance of the cyst or reduction in size, the collapse of the cyst, calcification of the cyst, and progressive increase in the echogenicity and density of the cystic fluid were considered an improvement. The formation of new cysts in the same or another organ, recurrence of the cyst, and increase or no change in the size of the cyst were considered non-response to treatment.

Approval for the study was granted by the Local Ethics Committee for Research (decision no: 83, date: 10/03/2022). Written consent was obtained from the families for publication. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (SPSS) version 26.0 (SPSS Inc. Chicago, IL, USA). Continuous variables were expressed as median (range) and categorical variables

as frequency (percentage). The normality of continuous data was analyzed by the Kolmogorov-Smirnov test. The significance value was considered <0.05. For non-parametric data, continuous variables were compared using the Chi-square and Mann-Whitney U tests. A p-value of <0.05 was considered statistically significant for all tests.

RESULTS

Epidemiological profiles

The study included 42 patients, who were treated for hydatid disease in our clinics, followed up regularly, and had accessible information. The patients consisted of 19 (45.2%) girls and 23 (54.8%) boys. The median age was 125.5 (min-max: 34-209) months. Of the patients, 61.9% presented between 2013 and 2016. Thirteen (33.3%) patients had a history of contact with dogs and 28 (66.7%) were living in rural areas.

Clinical features

At the time of first admission, 34 (81%) of the patients had complaints related to hydatid cyst and 22 (52.4%) had pathological findings on physical examination. Eight (19%) patients were asymptomatic and diagnosed incidentally during investigations for other reasons. Three of the eight patients had a history of trauma and were diagnosed by imaging requested for this purpose. The most common symptoms were abdominal pain in 21 (50%), fever in 9 (21.4%), and cough in 8 (19%). The most common presenting symptom was abdominal pain (63.8%) in patients with hepatic involvement and cough (58.3%) in those with pulmonary involvement. The most common physical examination findings were decreased breath sounds in 10 (23.8%), abdominal distention in 6 (14.3%), and hepatomegaly in 5 (11.9%). The presenting symptoms and physical examination findings of the patients are presented in **Tables 1** and **2**.

Table 1. Patients' complaints at presentation

Symptoms	n	%
Stomach ache	21	50
High fever	9	21.4
Cough	8	19
Vomiting	7	16.7
Shortness of breath	6	14.3
Anorexia	5	11.8
Weakness	4	9.5
Skin rash and pruritus	3	7.1
Chest pain	2	4.8
Jaundice	2	4.8
Spitting up salty liquid	1	2.4

Table 2. Physical examination findings of the patients

Results	n	%
Decreased breath sounds	10	23.8
Abdominal distention	6	14.3
Hepatomegaly	5	11.9
Urticaria	2	4.8
Icterus	2	4.8

Thirty-five (83.3%) patients had single organ involvement and 7 (16.7%) patients had multiple organ involvement. Of 35 cases with single organ involvement, the liver was involved in 26 (74.2%), the lungs in 7 (20%), and the spleen in 2 (5.7%) patients. Of 7 cases with multiple organ involvement, both the liver and lungs were involved in 4 (57.1%), both the liver and spleen in 2 (28.6%), and both the lungs and pancreas in 1. Concerning the localization of the cysts, 32 (76.2%) were in the liver, 12 (28.6%) were in the lung, 4 (9.5%) were in the spleen, and 1 (2.4%) was in the pancreas. Radiological imaging of a patient with pulmonary hydatid cysts is presented in **Figure 1**. Cysts were detected in the right lobe of the liver in 24 (75%), in the left lobe in 6 (18.8%), in both lobes in 2 (6.2%) of hepatic hydatid cysts, while the cysts were in the right lobe in 5 (41.7%) and the left lobe in 7 (58.3%) of pulmonary hydatid cysts.

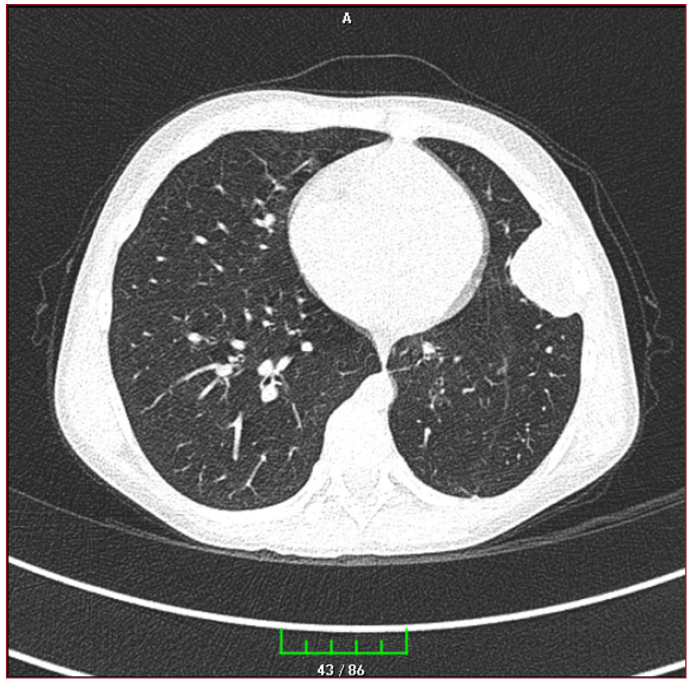

Figure 1. Radiological image of one patient. Tomography image of the cyst in the left lung periphery

The median size of overall cysts was 57.5 (min-max=12-140) mm. The cysts were small (≤50 mm) in 17 (40.5%) patients, 50-100 mm in 17 (40.5%) patients, and giant (>100 mm) in 8 (19%) patients. The mean cysts diameter was 57.09±29.28 mm (12-120) in the liver and 72.16±32.68 mm (23-140) in the lungs. Thirteen patients had multiple cysts in the same organ.

Laboratory findings

The echinococcus IHA was positive in 18 (42.9%) patients. The IHA was positive in 36.4% of hepatic hydatid cysts and 75% of pulmonary hydatid cysts. When the patients were classified according to the IHA results, the titer was 1/10240 in 4 (9.5%) patients, 1/5120 in 1 (2.4%) patient, 1/2560 in 2 (4.8%) patients, 1/1280 in 5 (11.9%) patients, 1/640 in 2 (4.8%) patients, and 1/320 in 5 (11.9%) patients. After the treatment,

echinococcus IHA titers were decreased in 9 (21.4%) patients and the results became negative in 4 (9.5%) patients. The median eosinophil count at diagnosis was 0.2 10^9/L (0-3 10^9) and the median percentage was 3.15% (0-19.7). Ten (23.8%) patients had eosinophilia (>0.5 10^9/L). The median leukocyte count was 7.9 10^9/L (4.1-32.9 10^9), the median neutrophil count was 4.3 10^9/L (1.5-31.6 10^9), and the median lymphocyte count was 2.25 10^9/L (0.3-5.3 10^9).

Complications

When the patients were evaluated for hydatid cyst complications, there were 10 (23.8%) patients with complications and 8 (19%) with cyst rupture. The cysts were ruptured into the bronchus in five cases and into the biliary system in three cases. These three cases were followed up and treated with clinical signs of cholangitis. Pleural effusion was detected in 4 (9.5%) of the cases. The initial IHA titer, eosinophil count, eosinophil percentage, and sedimentation value were statistically significantly higher in patients with ruptured cysts than in those without rupture (p=0.002, p=0.003, p=0.003, p=0.02, respectively). Moreover, the initial physical examination findings were pathological at a statistically significantly higher rate in the rupture group than in the non-rupture group (p= 0.003). There was no difference in age, gender, symptoms such as abdominal pain, cough, fever, and respiratory distress at diagnosis between the two groups. The comparison of patient characteristics is provided in **Table 3**.

Table 3. Comparison of children with and without rupture

	With rupture, n=8	Without rupture, n=34	p
Age (month)	148.62	117.64	0.091
Cyst size (mm)	83.12	59.67	0.069
IHA titer	4280	771.76	0.002
Leukocytes /L	11.87 109	9.28 109	0.251
Eosinophil/L	1.18 109	0.36 109	0.003
Eosinophil percent	10.67	4.09	0.003
ALT (IU/L)	38.74	23.23	0.339
AST (IU/L)	39.87	33.47	0.575
Neutrophil/L	7.46 109	5.72 109	0.432
Lymphocyte/L	2 109	2.48 10	0.356
CRP (nmol/L)	330.28	203.90	0.386
Sedimentation (mm/h)	45.42	20.1	0.020

Treatments

All patients received albendazole as medical treatment, 17 (40.5%) underwent surgical treatment, and 11 (26.2%) underwent PAIR. Sixteen (38.1%) patients received only albendazole treatment, nine (21.4%) patients both albendazole and PAIR, 15 patients both albendazole and surgery, and two (4.8%) patients received triple treatment with albendazole, PAIR, and surgery. Considering the treatment methods according to organ involvement, all patients with pulmonary hydatid cysts received both albendazole and surgical treatments. Of the patients with hepatic hydatid cysts, albendazole treatment alone was administered to 15 (46.9%), PAIR and albendazole treatment to 8 (25%), surgery and albendazole treatment to 7 (21.9%), and triple treatment to 2 (6.2%). One patient had elevated transaminase levels during the albendazole treatment, the transaminase elevation persisted at follow-up and the patient was diagnosed with autoimmune hepatitis based on tests and liver biopsy. In addition, one patient had transient transaminase elevation, which spontaneously regressed when albendazole treatment was discontinued. There were no other side effects related to albendazole treatment. After the treatment, the patients were evaluated by clinical and radiological examinations. There was no mortality. Recurrence of cysts occurred in 9 (21.4%) patients. The mean number of treatment cycles was 5.78±2.03 (1-12) and the mean follow-up was 39.11±21.55 (9-91) months.

DISCUSSION

Hydatid disease remains a serious health problem in Turkey, where livestock and agriculture are common sources of income. New echinococcal infections continue to occur throughout life. The prevalence of hepatic and pulmonary hydatid cysts increases with age. Despite the lack of definite data, the reported prevalence in Turkey is around 50 per 100000 and the incidence is around 2-6 per 100000.[8] In our country, hydatid disease most frequently occurs in the Central Anatolia, Eastern Anatolia, and Southeastern Anatolia. A study from Uruguay reported the overall prevalence as 5.6%. The prevalence was shown to increase from 1% in patients aged 4-6 years to 11% in patients over 60 years of age.[9] Living in rural areas (p=0.003), especially residing in rural areas for the first 5 years of life (p=0.000), always drinking water from natural sources (p=0.007), and living in the current address for more than 20 years were indicated as risk factors for the development of cystic echinococcosis.[10]

According to the reports in the literature, hydatid cysts are more common in men (53.6–54.2%). This can be attributed to the behavioral characteristics of men, such as spending more time outdoors, and more contact with animals. In addition, the median age of children with hydatid disease was reported to range from 123 to 134 months.[11-13] In a study, it was stated that children aged 7-11 years were most affected. Also, of the 94.4% children had single organ involvement and 5.6% had multiple organ involvement.[14] In our study, male predominance was evident, which was consistent with the literature, and the median age was 125.5 months.

Since most cysts progress slowly, they can remain asymptomatic for years, usually until they reach 50 mm. Some cysts can also regress spontaneously. Abdominal pain was reported 28.6-55.4%, vomiting 15.3-25%, jaundice 2-5.3%, cough 39.3-50%, fever 35.7-42.9%, shortness of breath 14.2-17.9%, chest pain 10.7-28.6%, fatigue 15-17.9%, rock water vomiting 2-3.6%, and hemoptysis 7.1-14.3%. Due to the high elasticity of the lung parenchyma and weak immune response, children are asymptomatic and may be diagnosed late. Physical examination was reported to reveal decreased

breath sounds in 37.5%-39.3%, hepatomegaly in 7.1-8.9%, hepatosplenomegaly in 2-3.6%, and urticaria 2-3.6% of cases.[12-15] In our study, the most common symptoms were abdominal pain in 50%, fever in 21.4%, and cough in 19%. The most common physical examination findings were decreased breath sounds in 23.8%, abdominal distention in 14.3%, and hepatomegaly in 11.9%.

Hydatid disease can affect any part of the body, more often the lungs and liver. Single organ involvement was reported in 67.8-90% of cases in previous studies.[16,17] In our study, the rate of single organ involvement was 83.3%. Two studies from Greece and Turkey reported the rate of pulmonary involvement to be 51.3-54%,[18,19] while another studies from Bulgaria and Turkey reported a rate of 51.4-71.5%.[13,20] In our study, the rate of hepatic involvement was 76.2%. The most affected areas reported in children are the right lobe of the liver and the right lung.[13,21] In a study evaluating the cases with multiple organ involvement, it was reported that the liver, lung and spleen (38.5%) were affected most frequently.[22] In our study, the most involved areas were the right lobe of the liver (75%) and the left lung (58.3%). Cysts <50 mm in size are called small cysts and >100 mm are "giant cysts".[23] In our study, 19% of the patients had giant cysts.

The IHA, a serological test, has low reliability because it cross-reacts with other parasitic infections, a negative serology test result does not rule out the diagnosis of hydatid disease, its positivity does not give a definitive diagnosis, but only supports it, and can remain positive even if many years pass since treatment.[24] IHA test positivity in combination with abdominal ultrasonography is useful in diagnosing liver hydatid cyst, but thoracic CT is usually required to diagnose hydatid cyst of the lung.[25] In our study, echinococcus IHA was positive in 42.9% of the children.

Eosinophilia was reported in 20-34% of hydatid cyst cases.[13] Leukocyte and eosinophil counts were shown to be higher in cases with ruptured cysts.[26] The study by Özyurtkan et al. found statistically significantly elevated sedimentation in rupture cases, while the elevation in leukocytes and eosinophils was insignificant.[27] In our study, the initial IHA titer, eosinophil count, eosinophil percentage, and sedimentation value were statistically significantly higher in patients with ruptured cysts than in those without rupture. These findings suggest that the initial IHA titer, eosinophil count, eosinophil percentage, and sedimentation value are significant in evaluating ruptured cysts. Skin rashes, biliary peritonitis, and severe anaphylactic reaction may develop after hydatid cyst rupture. Since rupture of hydatid cysts has vital consequences, early diagnosis of rupture is important.

There is no standard choice of treatment for echinococcosis and treatment is planned on a patient basis. Treatment may vary with the patient's age, the localization, number, and structure of the cyst, and the presence of complications. Surgery is the main treatment for pulmonary hydatid cysts. In children, parenchyma-preserving surgery, such as cystotomy and capitonnage, is more often preferred. In a study, it was concluded that cystotomy and capitonnage method reduced the occurrence of emphysema, pneumothorax, and the long-term retention of residual cavity statistically significantly compared to cystotomy method alone.[28] Lobectomy and pneumonectomy cause loss of parenchyma and thus are recommended especially in endemic regions with a high risk of recurrence.[29] It has been reported that benzimidazoles used in medical treatment are also effective in hydatid cysts with pulmonary involvement by softening the cysts, reducing the intracystic pressure, and allowing the removal of the cyst. These agents are not recommended in large cysts because they have a role in weakening the cyst wall and therefore increase the risk of cyst rupture.[30,31]

The US-guided PAIR technique allows the treatment of simple and accessible cysts, especially in the liver. This technique is contraindicated for superficial, calcified cysts with biliary communication.[32] In our study, all patients received albendazole as medical treatment, 40.5% underwent surgical treatment, and 26.2% underwent PAIR. Hydatid disease usually has a good prognosis in children. Depending on the location of the cyst and the treatment of choice, the recurrence rate varies between 8,8% and 25%.[33,34] In our study, the rate of hydatid cyst recurrence was 21.4%. In a study, the frequency of cyst rupture was higher in the male sex (p=0.023), in those who complained of dyspnea (p=0.001) and in cases with rock water vomitting (p=0.005).[34] In our study, 23.8% of the cases had complications and 19% had cyst rupture.

The limitations of our study are the single-center and retrospective design, and the lack of laboratory comparison because other serological methods used in the diagnosis were not examined.

CONCLUSION

Our study suggest that the presence of pathological examination findings, high initial IHA titer, high eosinophil count and eosinophil percentage, and high sedimentation value in children with hydatid disease are likely to indicate a ruptured cyst. We believe that it is important to pay attention to the abovementioned signs and to manage the patient. Periodic deworming of dogs with praziquantel (at least 4 times per year), improved hygiene in the slaughtering of livestock and public education campaigns are necessary for prevention of cyst hidatid.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Süleyman Demirel University Local Ethics Committee (Date: 10/03/2002, Decision No: 83)

Informed Consent: Written consent was obtained from the families for publication.

Referee Evaluation Process: Externally peer-reviewed.

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

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REFERENCES

1. Eckert J, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clin Microbiol Rev 2004;17:107
2. Petropoulos AS, Chatzoulis GA. Echinococcus granulosus in childhood:a retrospective study of 187 cases and newer data. Clin Pediatr (Phila) 2019;58:864-88
3. Bhutani N, Kajal P. Hepatic echinococcosis:a review. Ann Med Surg (Lond) 2018;36:99-105
4. World Health Organization. Echinococcosis. 17 May 2021 http://www.who.int/echinococcosis/en/ (Accessed on April 1, 2022)
5. Shams M, Khazaei S, Naserifar R, Shariatzadeh SA, Anvari D, Montazeri F, et al. Global distribution of Echinococcus granulosus genotypes in domestic and wild canids:a systematic review and meta-analysis. Parasitology. 2022;149(9):1147-59.
6. Ben Brahim M, Nouri A, Ksia A et al. Management of multiple echinococcosis in childhood with albendazole and surgery. J Pediatr Surg 2008;43:2024-30
7. Brunetti E, Kern P, Vuitton DA. Writing panel for the WHO-IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop 2010;114:1-16
8. Uysal A, Gürüz Y, Köktürk O et al. Türk Toraks Derneği Paraziter Akciğer Hastalıkları Tanı ve Tedavi Uzlaşı Raporu. Turkish Thoracic Journal 2009,10;Suppl B (in Turkish)
9. Cohen H, Paolillo E, Bonifacino R et al. Human cystic echinococcosis in a Uruguayan community:a sonographic, serologic, and epidemiologic study. Am J Trop Med Hyg 1998;59(4):620-7.
10. Uchiumi L, Mujica G, Araya D, et al. Prevalence of human cystic echinococcosis in the towns of Ñorquinco and Ramos Mexia in Rio Negro Province, Argentina, and direct risk factors for infection. Parasit Vectors 2021;14(1):262.
11. Aslanabadi S, Zarrintan S, Abdoli-Oskouei S et al. Hydatid cyst in children:a 10-year experience from Iran. Afr J Paediatr Surg 2013;10:140-4
12. Aygün D, Yıldırım T, Başoğlu Öner Ö, Kuzdan Ö. Hydatid Disease in Childhood:A Single Center Experience. J Pediatr Inf 2020;14(2):80-86
13. Tural-Kara T, Özdemir H, Karbuz A, Kocabaş BA. Clinical characteristics of childhood hydatid disease:a single tertiary centre experience from Turkey. HK J Paediatr (new series) 2018;23:162-8
14. Amahmid O, El Guamri Y, Zenjari K, et al. The pattern of cystic echinococcosis in children in an endemic area in Morocco. J Parasit Dis. 2019;43(2):209-214.
15. Dopchiz MC, Elissondo MC, Andresiuk MV et al. Pediatric hydatidosis in the south-east of the Buenos Aires province, Argentina. Rev Argent Microbiol 2009;41:105-1
16. Bhutani N, Kajal P. Hepatic echinococcosis: a review. Ann Med Surg (Lond) 2018;36:99-105
17. Escola-Verge L, Salvador F, Sanchez-Montalva A et al. Retrospective study of cystic echinococcosis in a recent cohort of a referral center for liver surgery. J Gastrointest Surg 2019;23:1148-56
18. Petropoulos AS, Chatzoulis GA. Echinococcus granulosus in childhood:a retrospective study of 187 cases and newer data. Clin Pediatr (Phila) 2019;58:864-88
19. Çakır D, Çelebi S, Gürpınar A, Agın M, Bozdemir E. Evaluation of cases with hydatid diseases. J Pediatr Inf 2009;3:104-8
20. Jordanova DP, Harizanov RN, Kaftandjiev IT, Rainova IG, Kantardjiev TV. Cystic echinococcosis in Bulgaria 1996-2013, with emphasis on childhood infections. Eur J Clin Microbiol Infect Dis 2015;34:1423-8
21. Morar R, Feldman C. Pulmonary echinococcosis. Eur Respir J 2003;21:1069-77
22. Çay Ü, Alabaz D, Gündeşlioglu Ö, Tutuş K, Çil M, Pehlivan UA. Multi-organ/disseminated echinococcosis in children:Case series and review of the literature. J Paediatr Child Health 2022;58(7):1193-200.
23. Djuricic SM, Grebeldinger S, Kafka DI, Djan I, Vukadin M, Vasiljevic ZV. Cystic echinococcosis in children–the seventeen-year experience of two large medical centers in Serbia. Parasitol Int 2010;59:257-61
24. Tamarozzi F, Silva R, Fittipaldo VA, Buonfrate D, Gottstein B, Siles-Lucas M. Serology for the diagnosis of human hepatic cystic echinococcosis and its relation with cyst staging:A systematic review of the literature with meta-analysis. PLoS Negl Trop Dis. 2021;15(4):e0009370.
25. Kaman A, Tanır G, Çakmakçı E, Demir P, Öz FN, Teke TA, et al. Characteristics, diagnosis, and treatment modality of pediatric patients with cystic echinococcosis:a single centre experience. Turk J Pediatr. 2019;61(5):704-13.
26. Sarkar M, Pathania R, Jhobda A, Thakur B, Chopra R. Cytic pulmonary hydatidosis. Lung India 2016;33:179-91
27. Ozyurtkan MO, Balci AE. Surgical treatment of intrathoracic hydatid disease:a 5-year experience in an endemic region. Surg Today 2010;40(1):31-7.
28. Ksia A, Fredj MB, Zouaoui A, Kechiche N, Belhassen S, Mosbahi S, et al. Capitonnage seems better in childhood pulmonary hydatid cyst surgery. J Pediatr Surg 2020;55(4):752-5.
29. Onal O, Demir OF. Is anatomic lung resection necessary in surgical treatment of giant lung hydatid cysts in childhood? Ann Thorac Cardiovasc Surg 2017;23:286-90
30. Oral A, Yigiter M, Yildiz A, Yalcin O et al. Diagnosis and management of hydatid liver disease in children:a report of 156 patients with hydatid disease. Journal of Pediatric Surgery 2012;47:528-34
31. Doğru D, Kiper N, Ozçelik U, Yalçin E, Göçmen A. Medical treatment of pulmonary hydatid disease:for which child? Parasitol Int 2005;54:135-8
32. Brunetti E, Junghanss T. Update on cystic hydatid disease. Curr Opin Infect Dis 2009;22:497-502
33. Bozkurt B, Soran A, Karabeyoğlu M, Unal B, Coşkun F, Cengiz O. Follow-up problems and changes in obliteration of the residual cystic cavity after treatment for hepatic hydatidosis. J Hepatobiliary Pancreat Surg 2003;10:441-5
34. Tüz AE, Ekemen Keleş Y, Şahin A, et al. Hydatid Disease in Children from Diagnosis to Treatment:A 10-year Single Center Experience. Turkiye Parazitol Derg 2022;46(3):189-94.

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Original Article / Orijinal Araştırma

Investigation of the Relationship Between Prognostic Nutrition Index and Mortality in Patients with Femur Fracture

Femur Kırığı Olan Hastalarda Prognostik Nutrisyon İndeksi ile Mortalite Arasındaki İlişkinin Araştırılması

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Abstract

Aim: The incidence of adverse postoperative outcomes in surgeries for femur fractures is high and is associated with malnutrition. In this study, it was aimed to determine the independent factors for 6-month survival in patients with femur fracture and to evaluate the predictive value of the prognostic nutrition index (PNI).

Material and Method: One hundred and sixteen patients operated on only for femoral fracture were divided into survival and non-survival groups according to mortality.Demographic characteristics of the patients, operation data, fracture sites, need for intensive care unit and length of stay, postoperative hospital stay, and preoperative laboratory values, prognostic nutrition indices and mortality were evaluated.

Results: Twenty-six (22.4%) of 116 patients who were operated for femoral fracture resulted in 6-month mortality. CRP, albumin, prealbumin, crp/albumin ratio and PNI values at admission were independent risk factors for postoperative mortality (p=0.014, p<0.001, p=0.041, p=0.003, p<0.001). The optimal cut-off value for PNI was determined as 29.0. In the group with PNI>29.0, survival rates were found to be higher at the end of the 1st, 3rd and 6th months (94.2%, 89.5%, 89.5%).

Conclusion: Nutritional indices should be evaluated when patients with femoral fractures are admitted to the hospital. A low prognostic nutritional index may a predict mortality in patients with femoral fractures.

Keywords: Prognostic nutrition index, mortality, femur fracture

Öz

Amaç: Femur kırıkları için yapılan ameliyatlarda postoperatif olumsuz sonuçların insidansı yüksektir ve yetersiz beslenme ile ilişkilidir. Bu çalışmada femur kırığı olan hastalarda 6 aylık sağkalım için bağımsız faktörlerin belirlenmesi ve prognostik beslenme indeksinin (PNI) prediktif değerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Sadece femur kırığı nedeniyle opere edilen 116 hasta mortaliteye göre hayatta kalan ve hayatta kalmayan gruplara ayrıldı. Hastaların demografik özellikleri, operasyon verileri, kırık bölgeleri, yoğun bakım ihtiyacı ve kalış süresi, postoperatif hastanede kalış süresi, preoperatif laboratuvar değerleri, prognostik beslenme indeksleri ve mortalite değerlendirildi.

Bulgular: Femur kırığı nedeniyle opere edilen 116 hastanın 26'sı (%22.4) 6 aylık mortalite ile sonuçlandı. CRP, albumin, prealbumin, crp/albumin oranı ve PNI değerleri postoperatif mortalite için bağımsız risk faktörleriydi (p=0.014, p<0.001, p=0.041, p=0.003, p<0.001). PNI için optimal cut-off değeri 29,0 olarak belirlendi. PNI>29.0 olan grupta 1., 3. ve 6. ay sonunda sağkalım oranları daha yüksek bulundu (%94.2, %89.5, %89.5).

Sonuç: Femur kırığı olan hastalar hastaneye kabul edildiğinde beslenme indeksleri değerlendirilmelidir. Düşük bir prognostik beslenme indeksi, femur kırığı olan hastalarda mortaliteyi öngörebilir.

Anahtar Kelimeler: Prognostik beslenme indeksi, mortalite, femur kırığı

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INTRODUCTION

The number of patients with fractures is increasing worldwide, especially with the increase in the elderly population.[1,2] Femoral fractures are one of the most clinically encountered fracture types. It may cause a high complication rate, a severe decrease in the quality of life, morbidity, mortality, and serious economic costs.[2,3] Femoral fractures are generally classified according to the fracture site; proximal, shaft, and distal. The most common type is proximal femur fracture. With the rapid aging of the world population, the increase in osteoporosis will probably continue to increase this incidence.[4,5] Femoral shaft fractures are more common in young patients due to trauma. Distal femur fractures are rare and may be due to traumas and sports injuries.[5]

Surgery is the best treatment for patients with femoral fractures. It is applied frequently. However, it can cause many adverse postoperative outcomes, including deep vein thrombosis, pulmonary embolism, pneumonia, wound infection, chronic disease activation, intensive care unit admission, and death. Age, additional diseases, surgery, stress, trauma, hemorrhage, infection, pain, and immobilization are considered the causes of these results. Such patients may be at risk of protein catabolism and malnutrition. In addition, nutrition has a impact on fracture healing, and impaired fracture healing has been observed among significant malnourished individuals.[6] Meesters et al. In their study stated that protein deficiency causes higher complications and longer hospitalizations in patients with femoral fractures.[6] However, a study showing the negative effects of nutrition on femur fracture has not been found in the literature.

Perioperative malnutrition was found to be an independent risk factor for postoperative complications in orthopedic surgery patients.[7] There is evidence that adequate nutritional support can prevent postoperative complications. Therefore, the patient's nutritional status should be closely monitored and evaluated in terms of nutritional risk.[8] Although serological tests, anthropometric measurements, and screening tools are used for this, there has yet to be a method that has been reported as the gold standard.[9] Studies have shown that the Prognostic Nutrition Index (PNI) is also a comprehensive marker for evaluating the nutritional status of patients undergoing surgery.[10] PNI can be used to assess the nutritional and immunological situation of patients who have had surgery. (PNI: 10 x serum albumin (ALB, g/dl) + 0.005 total lymphocyte count (LYM, per mm^3)) Studies have reported that PNI is an essential predictor of poor postoperative outcomes and increased mortality in various malignancies.[11] However, PNI studies focusing on postoperative survival outcomes of patients operated on for femoral fractures are scarce. Therefore, we aimed to identify independent factors for adverse postoperative effects in patients with femoral fractures and to evaluate the association of PNI with 6-month survival in these patients.

MATERIAL AND METHOD

The study was carried out with the permission of Kastamonu University Clinical Researches Ethics Committee (Date: 19.10.2022, Decision No: 2022-KAEK-105). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data Source

The data of this retrospective observational study were obtained from the Hospital Electronic Medical Record Information System (sisoft) and operating room patient records.

Patients

A retrospective evaluation was made using the hospitalization data obtained from the database of 210 patients who were operated only for femur fracture in Kastamonu Training and Research Hospital between January 2021 and November 2022. It was determined that the patients were not given any nutrition education during their hospitalization. Albumin (ALB) replacement therapy was used as conventional treatments only when the ALB concentration was < 30 g/l. The exclusion criteria were as follows:

- Missing data (n=7)
- Systemic slimming diseases (malignancy, tbc, hyperthyroidism) (n=11)
- Those who had major surgery in the last 6 months (n=4)
- Those who use drugs that can cause bone marrow depression (n=2)
- Patients under 65 years of age (n=47)
- Patients with chronic renal failure and severe liver dysfunction (n=23)

After applying all exclusion criteria, a total of 116 patients were identified; of these, 105 (90.5%) had proximal, 5 (4.3%) trunk fractures, and 6 (5.2%) had distal fractures.

Variables

Various potential factors that may affect mortality were investigated: age, gender, comorbidities, fracture sites, American Society of Anesthesiologists (ASA), type of anesthesia used in operation, duration of operation, need and amount of blood transfusion in operation, need for intensive care unit and length of stay, postoperative hospital stay, and preoperative laboratory values such as leukocyte, hemoglobin, platelet, neutrophil, lymphocyte, neutrophil-lymphocyte ratio, C-reactive protein (CRP), albumin, CRP/albumin ratio, prealbumin and PNI.

Statistical Analysis

The normality assumption was evaluated using the Kolmogorov-Smirnov test. Continuous data are presented as standard deviation according to statistical distribution, Categorical parameters, frequencies, and associated percentages. Student's t-test was used to analyze normally distributed continuous variables, and the Mann-Whitney U test was used to examine non-normally distributed continuous variables and ordinal variables. Chi-square or

Fisher's exact test was used to analyze categorical variables. The optimal cut-off value for PNI was determined using ROC curve analysis. In the analyzes, variables with an unadjusted p-value < 0.50 were identified as confounding factors and included in multivariate regression analyzes to identify independent predictors of adverse postoperative outcomes. Results were expressed as OR and 95% CI. Then, Kaplan Meier analysis was applied for survival processes according to the determined parameters. Log Rank (Mantel-Cox) statistics were used in the Kaplan-Meier survival analysis. All statistical analyzes were performed using the Statistical Package for Social Sciences version 26.0 (SPSS Statistics for Windows, Chicago, USA), and p<0.05 was considered significant.

RESULTS

Twenty-six (22.4%) of 116 patients who were operated for femoral fracture resulted in 6-month mortality. Demographic characteristics and laboratory values of the patients are given in **Table 1**.

Table 1. Demographic, clinical and laboratory characteristics.

N=157(ortalama±SS or percent)		
Age		80.73±8.06
Gender	Female	82(70.6%)
	Male	34(29.4%)
Additional Desease	No	71(61.2%)
	Diabetes Mellitus	8(6.8%)
	Hypertension	11(9.4%)
	Cardiac Disease	13(11.2%)
	Respiratory Disease	14(12.0%)
	Neurological Disease	7(6.0%)
Femur fracture	Proximal	105(90.5%)
	Saft	5(4.3%)
	Distal	6(5.2%)
Anesthesia Type	General Anesthesia	6(5.1%)
	Spinal Anesthesia	110(94.9%)
ASA	II	8(6.8%)
	III	61(52.5%)
	IV	47(40.5%)
Operation Time (min)		58.34±23.914
Blood Trasfusion Need	No	52(44.8%)
	Yes	64(55.2%)
Intensive Care Need	No	38 (32.7%)
	Yes	78 (67.3%)
Blood Transfusion Amount (Unit)		0.95±1.12
Hospitalization Time		6.83±4.88
Leukocyte		10.45±3.86
Hemoglobin		11.19±1.58
Platelet		222.02±73.24
Neutrophil		8.16±3.25
Lymphocyte		1.37±0.99
Neutrophil/Lymphocyte		8.07±6.65
Preoperative C Reactive Protein		30.26±44.96
Albumin		3.21±0.51
Prealbumin		13.32±4.85
C Reactive Protein / Albumin		10.39±16.52
Prognostic Nutrition İndex		32.17±5.16
Mortality	No	90 (77.6%)
	Yes	26 (22.4%)

ASA; American Society of Anesthesiologists

There was no difference in the demographic characteristics of the patients when they were compared according to their 6-month mortality status. Preoperative c-reactive protein (CRP), albumin, prealbumin, crp/albumin ratio and PNI values were found to be statistically significant among the groups according to mortality (p<0.05, **Table 2**).

Table 2. Demographic, clinical and laboratory characteristics of patients with and without mortality

		non-survived patients N=26 (22.4%) (mean±SD or percent)	Surviving patients N=90 (77.6%) (mean±SD or percent)	p
Age		83.19±7.07	80.02±8.22	0.071
Gender	Female	16 (61.5%)	66 (73.3 %)	.358
	Male	10 (38.5%)	24 (26.7 %)	
Additional Desease	No	15 (57.6%)	56 (62.2%)	0.426
	Diabetes mellitus	2 (7.6 %)	2 (2.2%)	
	Hypertension	2 (7.6%)	6 (6.6%)	
	Cardiac disease	3 (11.5%)	9 (10.0 %)	
	Respiratory disease	3 (11.5 %)	11 (12.2 %)	
	Neurological disease	1 (3.8 %)	6 (6.6%)	
Femur fracture	Proximal	24 (92.4 %)	80 (89.0%)	0.926
	Saft	1 (3.8%)	4 (4.4%)	
	Distal	1 (3.8%)	6 (%6.6%)	
Anesthesia Type	General anesthesia	3 (11.6 %)	3 (3.4%)	0.125
	Spinal anesthesia	23 (88.4%)	87 (96.6 %)	
ASA	II	1 (3.8%)	7 (7.7%)	0.127
	III	10 (38.4%)	52 (57.7%)	
	IV	15 (57.8 %)	31 (34.6%)	
Operation Time (min)		58.50±29.93	58.30±22.07	0.759
Blood Trasfusion Need	No	10 (38.4%)	42 (46.6%)	0.605
	Yes	16 (61.6%)	48 (53.4%)	
Intensive Care Need	No	4 (15.3%)	34 (37.7%)	0.057
	Yes	22 (84.7%)	56 (62.3%)	
Blood Transfusion Amount (Unit)		1.08±1.16	0.91±1.11	0.446
Hospitalization Time		7.77±7.21	6.56±3.98	0.965
Leukocyte		11.98±5.65	10.00±3.07	0.211
Hemoglobin		10.92±1.53	11.27±1.59	0.308
Platelet		218.04±69.35	223.17±74.66	0.650
Neutrophil		9.21±4.19	7.86±2.88	0.226
Lymphocyte		1.75±1.69	1.26±0.63	0.731
Neutrophil/Lymphocyte		9.30±11.16	7.71±4.65	0.837
Preoperative C Reactive Protein		42.71±47.81	26.67±43.72	0.014
Albumin		2.76±0.50	3.34±0.44	<0.001
Prealbumin		11.52±4.20	13.84±4.92	0.041
C Reactive Protein / Albumin		16.29±19.34	8.69±15.31	0.003
Prognostic Nutrition İndex		27.67±5.07	33.47±4.42	<0.001

ASA; American Society of Anesthesiologists

The female population was higher in both groups. Respiratory tract diseases were the most common chronic disease in both groups. Proximal femoral fracture was the most common type of fracture in both groups.

The optimal cut-off value for PNI was determined as 29.0 using ROC curve analysis. When the patients were evaluated according to the PNI cut-off value, there was a statistically significant difference between the two groups in terms of age, preoperative crp, albumin, prealbumin, crp/alb and mortality. (**Table 3**).

Table 3. PNI ≤29.0 and >29.0 patient characteristics

		PNI≤29.0	PNI>29.0	P
Age		84,47±6,80	79,43±8,09	0.003
Gender	Female	22 (73.3 %)	60 (69.7%)	0.891
	Male	8 (26.7%)	26 (30.3%)	
Additional Desease	No	17 (56.7%)	54 (62.7%)	0.369
	Diabetes mellitus	2 (6.7%)	2 (2.3%)	
	Hypertension	2 (6.7%)	6 (7.0%)	
	Cardiac disease	1 (3.3%)	11 (12.8%)	
	Respiratory disease	4 (13.3%)	10 (11.6%)	
	Neurological disease	4 (13.3%)	3 (3.6%)	
Femur fracture	Proximal	28 (93.4%)	77 (89.5%)	0.846
	Saft	1 (3.3%)	4 (4.6%)	
	Distal	1 (3.3%)	5 (5.9%)	
Anesthesia Type	General anesthesia	3 (10.0%)	3 (3.5%)	0.178
	Spinal anesthesia	27 (90.0%)	83 (96.5%)	
ASA	II	1 (3.3%)	7 (8.1%)	0.218
	III	13 (43.3%)	48 (55.8%)	
	IV	16 (53.4%)	31 (36.1%)	
Operation Time (min)		59,00±28,51	58,12±22,27	0.947
Blood Trasfusion Need	No	13 (43.3%)	39 (45.3%)	0.849
	Yes	17 (56.7%)	47 (54.7%)	
Intensive Care Need	No	3 (10.0%)	35 (40.6%)	0.004
	Yes	27 (90%)	51 (59.4%)	
Blood Transfusion Amount (Unit)		1,00±1,17	0,93±1,15	0.814
Hospitalization Time		7,63±6,71	6,55±4,06	0.701
Leukocyte		11,47±5,41	10,09±3,11	0.420
Hemoglobin		10,86±1,68	11,30±1,53	0.075
Platelet		229,13±74,77	219,53±72,98	0.607
Neutrophil		8,57±4,02	8,02±2,95	0.781
Lymphocyte		1,66±1,60	1,26±0,64	1,000
Neutrophil/Lymphocyte		7,63±4,63	8,22±7,24	0.975
Preoperative C Reactive Protein		51,78±58,80	22,76±36,53	0.012
Albumin		2,53±0,24	3,45±0,34	<0.001
Prealbumin		11,01±4,19	14,13±4,82	0.001
C Reactive Protein / Albumin		20,47±23,30	6,87±11,64	0.001
Mortality	No	13 (43.3%)	77 (89.5%)	<0.001
	Yes	17 (56.7%)	9 (10.5%)	

ASA; American Society of Anesthesiologists

All confounding factors other than ALB concentrations (which correlated with PNI) were included in the multivariate regression analyzes to identify independent factors associated with adverse postoperative outcomes (**Table 4**). For postoperative 6-month mortality, a PNI value >29.0 at admission (odds ratio [OR]: 7.610, 95% confidence interval [CI]: 2.131–27,171, P = 0.002) was defined as an independent factor.

Table 4. Multivariate regression analyzes of confounding factors

Confounding factors	OR (95% CI)	P values
Admission CRP	0.967 (0.900-1.059)	0.567
Prealbumin	0.948 (0.838-1.073)	0.401
CRP/Albumin ratio	1.066 (0.858-1.324)	0.563
Age	1.017 (0.949-1.090)	0.640
PNI <29.0	7.610 (2.131-27.171)	0.002

CRP; C-reactive protein

Kaplan Meier survival analysis (Log Rank) statistic was used to investigate the relationship between PNI and survival. In the group with PNI>29.0, the survival rates at the end of the 1st, 3rd and 6th months were 94.2%, 89.5%, and 89.5%, respectively, while the survival rates at the end of the 1st, 3rd and 6th months were %, respectively, in the group with PNI ≤29.0. 73.3%, 56.7% and 43.3% (**Figure 1**).

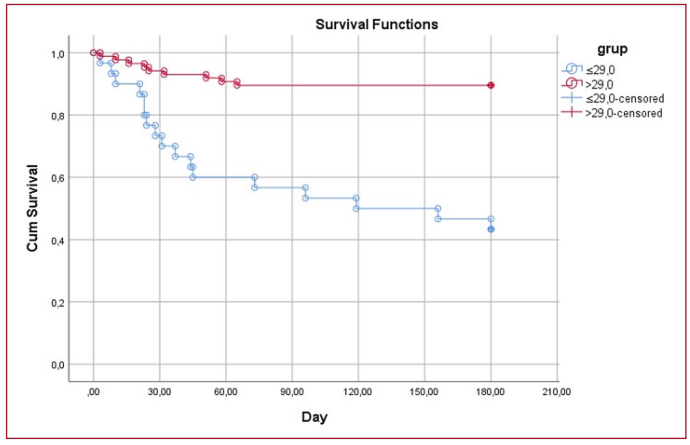

Figure 1. Kaplan Meier survival analysis

DICUSSION

In this study, we found that PNI, CRP, Albumin, CRP/Albumin ratio and Prealbumin at admission were independent factors for postoperative mortality in patients operated for femoral fracture, and PNI at admission was a good independent predictor. Our findings showed that in patients who will be operated for femoral fracture, nutritional evaluation is required at the time of admission and appropriate nutritional intervention should be considered for these patients.

In a study conducted by Li et al., they stated that albumin values decreased acutely, deeply and for a long time in the postoperative period in approximately 20-40% of patients who underwent surgical procedures.[12] In our study, mean albumin value was found to be low as 2.76±0.50 in patients with mortality in the postoperative 6-month period (p<0.001). This shows that there may be a risk of malnutrition that cannot be neglected in patients presenting with a femoral fracture. These patients received parenteral nutrition interventions as routine care when ALB concentration was < 3 g/dl.

Multivariate regression analysis showed that the nutritional status at admission of patients with femoral fracture was negatively associated with adverse outcomes in the

postoperative period. Albumin, prealbumin and PNI values at the time of admission were found to be statistically significantly lower in non-survival patients. The negative effects of malnutrition on the organism are quite high. Malnutrition significantly increases the risk of morbidity, mortality and hospitalization in surgical patients due to these adverse effects on the respiratory system, cardiovascular system, kidney functions, gastrointestinal system, immune system and wound healing.[13,14] Serological tests, anthropometric measurements and many nutritional scoring are used for malnutrition. The most commonly used definition for methods to identify malnutrition is ALB level <3.5 g/dL or LYM number <1500 cells (per mm^3).[15] The PNI value, which is calculated using albumin and lymphocyte values, may represent the general physiological functions and status of patients undergoing surgery, such as nutrition, immunity, and inflammation.[12,16] Therefore, PNI, which is used as a pre-treatment nutritional risk assessment tool, may be effective in predicting postoperative mortality. In a study including patients who underwent aortic valve replacement, it was reported that mortality was significantly higher in the patient group with a low PNI score.[17] Similarly, in our study, PNI was significantly lower in the mortality group ($p<0.001$). The 6-month survival rate was more than twice as high in the group with a high PNI score than in the group with a low score. Hypoalbuneemia is considered an indicator of global protein depletion.[18]

It has been reported that decreased albumin levels are associated with increased length of hospital stay, impaired wound healing, increased rates of wound infection, pneumonia and sepsis, increased incidence of postoperative complications, delayed physical rehabilitation, and decreased survival probability.[18-20] Koval et al. reported that albumin level was predictive for the length of hospital stay, in-hospital mortality and recovery of daily living activities after hip fracture.[19] Similarly, Pioli et al. showed that serum albumin level was a strong independent predictor of in-hospital and late mortality.[20] In our study, albumin levels were significantly lower in the mortal group. Based on the high correlation between nutrition and postoperative outcomes, this study suggested that patients with femur fracture should undergo nutritional assessment and nutritional intervention at presentation. Among the nutritional assessment parameters, there is also serum prealbumin, which is more sensitive to malnutrition that may occur due to its short serum half-life. According to Gianotti et al. showed a significant decrease in serum prealbumin values in the early postoperative period in the study conducted by him in which preoperative and early postoperative immunonutrition was applied.[21] In our research, prealbumin values were similarly lower than those with a mortal course ($p=0.041$).

Serum C-reactive protein (CRP), synthesized by the liver, is a positive acute phase reactant.[22] CRP is a non-specific systemic marker of inflammation.[23] Reports on the relationship between hip fracture and CRP levels are controversial in the literature. Belosesky et al. found no association between preoperative and postoperative CRP levels and 6-month mortality in geriatric patients undergoing hip fracture surgery.[24] Kim et al. showed that a high preoperative CRP level (>10.0 mg/dL) is associated with 1-year mortality after hip fracture surgery in the elderly. In our study, CRP values were approximately 1.5 times higher in patients who died within six months postoperatively ($p=0.014$). The CRP/ALB ratio (CAR), a new prognostic marker associated with inflammation, can be easily calculated by dividing the serum CRP level by the serum albumin level. CAR is mainly a marker of infection and malignancy.[25,26] However, few studies have focused on elderly patients undergoing orthopedic surgery.[27] On the other hand, Sercan et al. stated in their study that CAR is an essential marker in predicting 1-year mortality in the elderly after hip fracture.[28] Similarly, CAR was a predictor of mortality in our study ($p=0.003$).

This study has several limitations. First, this was a single-center study. Second, this study did not evaluate body mass index (BMI). BMI is an indicator for assessing nutritional status and is a good predictor of morbidity and mortality. Height values were not documented in this study, mainly because patients with femur fractures could not stand up to provide an accurate height measurement. Finally, we did not observe long-term complications and mortality.

CONCLUSION

This study showed that CRP, albumin, prealbumin, CRP/Albumin ratio and PNI values at presentation are independent risk factors for adverse postoperative outcomes in patients with femoral fractures. Our findings showed that all patients with femur fractures require nutritional assessment and appropriate nutritional intervention at presentation. PNI at admission can be a good indicator of nutritional assessment. A low prognostic nutritional index may predict mortality in patients with femoral fractures.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Clinical Researches Ethics Committee (Date: 19.10.2022, Decision No: 2022-KAEK-105).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Melton LJ 3rd. Hip fractures: a worldwide problem today and tomorrow. Bone 1993;14 Suppl 1:1-8.
2. Hughes MS, Kazmier P, Burd TA, et al. Enhanced fracture and soft-tissue healing by means of anabolic dietary supplementation. J Bone Joint Surg Am 2006;88(11):2386-94.
3. Amarilla-Donoso FJ, López-Espuela F, Roncero-Martín R, et al. Quality of life in elderly people after a hip fracture:a prospective study. Health Qual Life Outcomes 2020;18(1):71.
4. Giancola R, Marchesi LP, Lettera MG, Antonini G. A complex proximal femoral fracture. Injury 2016;47 Suppl 4:121-3.
5. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet 2002;359(9319):1761-7.
6. Meesters DM, Wijnands KAP, Brink PRG, Poeze M. Malnutrition and Fracture Healing: Are Specific Deficiencies in Amino Acids Important in Nonunion Development? Nutrients 2018;10(11):1597.
7. Phan K, Ranson W, White SJ, et al. ThirtyDay Perioperative Complications, Prolonged Length of Stay, and Readmission Following Elective Posterior Lumbar Fusion Associated With Poor Nutritional Status. Global Spine J 2019;9(4):417-23.
8. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003;22(4):415-21.
9. Williams DG, Wischmeyer PE. Perioperative Nutrition Care of Orthopedic Surgery Patient. Tech Orthop 2020;35(1):15-8.
10. Caputo F, Dadduzio V, Tovoli F, et al. The role of PNI to predict survival in advanced hepatocellular carcinoma treated with Sorafenib. PLoS Bir 2020;15(5):e0232449.
11. Cadwell JB, Afonso AM, Shahrokni A. Prognostic nutritional index (PNI), independent of frailty is associated with six-month postoperative mortality. J Geriatr Oncol 2020;11(5):880-4.
12. Li X, Chen J. Is the prognostic nutritional index (PNI) a useful predictive marker for postoperative complications after lung surgery? J Thorac Dis 2019;11(Suppl 3):334-6.
13. Hill GL, Witney GB, Christie PM, Church JM. Protein status and metabolic expenditur determine the response to intravenous nutrition-a new classification of surgical malnutrition. Br J Surg 1991;78:109-13.
14. Meakins JL, Christou NV, Shizgal HM, MacLean LD. Therapeutic approaches to anergy in surgical patients. Surgery and levamisole. Ann Surg 1979;190:286-96.
15. Morey VM, Song YD, Whang JS, Kang YG, Kim TK. Can serum albumin level and total lymphocyte count be surrogates for malnutrition to predict wound complications after total knee arthroplasty? J. Arthroplasty 2016;31(6):1317–21.
16. Buzby GP, Mullen JL, Matthews DC, Hobbs CL, Rosato EF. Prognostic nutritional index in gastrointestinal surgery. Am J Surg 1980;139(1):160–7.
17. Özbek M, Acun B, Arık B, Demir M, Oylumlu M, Toprak N. "Prognostic value of nutritional and inflammatory scores in Transcatheter aortic valve replacement patients." Dicle Med J 2022;49 3):422-9.
18. Bistrian BR, Blackburn GL, Hallowell E, Heddle R. Protein status of general surgical patients. JAMA 1974;230:858-60
19. Koval KJ, Maurer SG, Su ET, Aharonoff GB, Zuckerman JD. The effects of nutritional status on outcome after hip fracture. J Orthop Trauma 1999;13:164-9.
20. Pioli G, Barone A, Giusti A, et al. Predictors of mortality after hip fracture:results from 1-year follow-up. Aging Clin Exp Res 2006;18:381-7
21. Gianotti L, Braga M, Fortis C, et al. A prospective, randomized clinical trial on perioperative feeding with an arginine-, omega-3 fatty acid-, and RNAenriched enteral diet: effect on host response and nutritional status. J Parenter Enteral Nutr 1999;23:314-20.
22. Ansar W, Ghosh S. Inflammation and inflammatory diseases, markers, and media-tors: Role of CRP in some inflammatory diseases. In:Biology of C Reactive Pro-tein in Health and Disease. Berlin, Germany:Springer;2016. p. 67–107
23. Li JJ, Fang CH. C-reactive protein is not only an inflammatory marker but also a direct cause of cardiovascular diseases. Med Hypotheses 2004;62:499–506.
24. Beloosesky Y, Hendel D, Weiss A, et al. Cytokines and C-reactive protein production in hip-fracture-operated elderly pa-tients. J Gerontol Ser Biol Sci Med Sci 2007;62:420–6.
25. Ranzani OT, Zampieri FG, Forte DN, Azevedo LC, Park M. Creactive protein/albumin ratio predicts 90-day mortality of septic patients. PLoS One 2013;8(3):e59321.
26. Wu M, Guo J, Guo L, Zuo Q. The C-reactive protein/albumin ratio predicts overall survival of patients with advanced pancreatic cancer. Tumor Biol 2016;37(9):12525–33.
27. Peng J, Wu G, Chen J, Chen H. Preoperative C-reactive protein/albumin ratio, a rrisk factor for postoperative delirium in elderly patients after total joint arthroplasty. J Arthroplasty 2019;34(11):2601–5.
28. Capkin, Sercan, Serkan Guler, and Ramadan Ozmanevra. "C-reactive protein to albumin ratio may predict mortality for elderly population who undergo hemiarthroplasty due to hip fracture." J Investigative Surgery 2021;34.11:1272-7.

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Original Article / Orijinal Araştırma

Evaluation of The Relationship Between Level of Nutrition Knowledge and Sustainable Food Literacy

Beslenme Bilgi Düzeyi ve Sürdürülebilir Gıda Okuryazarlığı Arasındaki İlişkinin Değerlendirilmesi

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Abstract

Aim: The purpose of this study is to evaluate the relationship between level of nutrition knowledge and sustainable food literacy.

Material and Method: It was carried out in 280 people aged 19 to 75 years. Data were collected through face-to-face interviews. The Sustainable Food Literacy Scale and Nutrition Knowledge Questionnaire were applied.

Results: Participants in the low nutrition knowledge group had lower sustainable food knowledge scores than those of the medium and high nutrition knowledge groups ($p<0.05$). There were positive relationships in the total general nutrition knowledge score and the sustainable food knowledge, food skills and action intent and action strategies subscale scores (r: 0.356, $p<0.001$; r:0.347 $p<0.001$; r:0.226 p:0.035, respectively).

Conclusion: Nutrition knowledge should be considered as part of efforts to increase sustainable food literacy and relationship has the potential to be critical in ensuring that future generations inherit a more habitable world.

Keywords: Sustainable food literacy, nutrition knowledge, sustainable diet

Öz

Amaç: Bu çalışmanın amacı, beslenme bilgi düzeyi ile sürdürülebilir gıda okuryazarlığı arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Bu çalışmaya 19-75 yaş arası 280 birey katılmıştır. Katılımcılara ait bilgiler yüz yüze görüşmeler yoluyla toplanmıştır. Gıda okuryazarlığının sürdürülebilirlik düzeyini ölçmek için Sürdürülebilir Gıda Okuryazarlığı Ölçeği ve beslenme bilgisini ölçmek için Beslenme Bilgisi Anketi kullanılmıştır.

Bulgular: Beslenme bilgi düzeyi düşük bireylerin sürdürülebilir gıda bilgisi ortalama puanının beslenme bilgi düzeyi orta ve yüksek olan bireylere göre daha düşük olduğu saptanmıştır ($p<0,05$). Genel beslenme bilgisi toplam puanı ile sürdürülebilir gıda okuryazarlığı alt ölçeklerinden sürdürülebilir besin bilgisi, besin becerileri ve eyleme geçme niyet ve eylem stratejileri puanları arasında pozitif yönde anlamlı ilişki saptanmıştır (sırasıyla; r:0,356, $p<0,001$; r:0,347 $p<0,001$; r:0,226 p:0,035).

Sonuç: Gelecek nesillere daha yaşanabilir bir dünya bırakabilmek için beslenme bilgisi, sürdürülebilir gıda okuryazarlığını geliştirmeye yönelik girişimlerin önemli bir parçası olarak değerlendirilmelidir.

Anahtar Kelimeler: Sürdürülebilir gıda okuryazarlığı, beslenme bilgi düzeyi, sürdürülebilir diyet

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INTRODUCTION

Nutrition is the basis of a healthy lifestyle, and its significance is becoming increasingly recognised.[1] Nutrition knowledge involves healthy nutrition recommendations, nutrition resources and nutrition requirements, as well as the relationship between diet and disease.[2-4] A complex and changing combination of nutrition knowledge and food attitudes enhances people's ability to choose healthy foods from the food system.[5]

Nowadays, it is emphasized that nutrition should not only focus on its effects on human health, but also on its effects on the environment.[6] The type and quantity of food consumed has an effect on the environment, and it is believed that healthy eating can promote public health by encouraging more environmentally friendly eating behaviour. In this context, the concept of sustainable diets is offered to characterise diets that avoid excessive damage, contribute to food and nutrition security, have low environmental impacts, and promote a healthy life for current and future generations.[7, 8] Sustainable food literacy not only supports dietary changes but also enables individuals to understand the impact of food choices on the environment, society, and the preservation of food systems through sustainable dietary behaviours.[9]

To our knowledge, to date there has been no research on the association between nutrition knowledge and sustainable food literacy in the literature. The purpose of this study is to evaluate the relationship between nutrition knowledge and sustainable food literacy.

MATERIAL AND METHOD

Participants

In this study, 280 individuals, aged 19 to 75, living in the districts in the center of Gaziantep were selected using a simple random sampling method. People with chronic diseases, those who follow special diets or those who declined to participate were excluded from the investigation. Participants who agreed to contribute voluntarily to this study were asked to sign a written consent form in accordance with the Declaration of Helsinki. This study was approved by the Local Ethics Board (No:2022-157).

Data Collection

For data collection, face-to-face interviews were used. The questionnaire consists of four parts. The first section consists of questions regarding demographic factors such as gender, age, level of education, income, and anthropometric measures (weight and height). The second section includes questions regarding dietary habits, including the frequency of food purchases, the individuals responsible for food purchases, the frequency of eating outside, and the individuals responsible for cooking. The third part includes the general nutrition knowledge questionnaire, and the last part includes the sustainable food literacy scale. Body mass index was also calculated using self-reported weight and height.

General Nutrition Knowledge Questionnaire

The Turkish version of the General Nutrition Knowledge Questionnaire was validated by Alsaffar in 2012.[2] and updated in 2014.[10] The final version, Cronbach's alpha coefficient was 0.92. The questionnaire consisted of four dimensions: dietary recommendations (11 items), nutrition knowledge (70 items), everyday food choices (11 items), and diet-disease relationships (35 items). The correct answers to each question were valued at 1 point, while incorrect or unsure responses were valued at 0 points. The sum of the points for each item was used to calculate sub-dimension scores. The total general nutrition knowledge score is the sum of all sub-dimension scores. A higher score shows a higher level of knowledge.[2, 10]

Sustainable Food Literacy Scale

The Sustainable Food Literacy Scale.[11] was used to evaluate the level of sustainable food literacy in adults. The scale is comprised of a total of 26 items and four subscales (sustainable food knowledge (9 items), food skills (6 items), attitudes (4 items), action intent and action strategies (7 items). All measurement items were measured using a 7-point Likert scale with scores ranging from 1 (strongly disagree) to 7 (strongly agree). The mean score for each subscale was calculated. Regarding the sustainable food literacy scale, Cronbach's Alpha (α) coefficient was found to be 0.89 for the sustainable food knowledge subscale, 0.86 for the sustainable food skills subscale, 0.72 for the attitude subscale and 0.78 for the action intent and action strategies subscale in this study.

Statistical analysis

Data were analysed using Statistical Package for the Social Sciences software (version 23.0, Chicago, United States). Visual and analytical methods were used to analyse the normality of the data. For continuous and categorical variables, the characteristics of the participants were expressed as mean with standard deviation or frequency with proportions, respectively. For a more detailed interpretation of nutrition knowledge with respect to sustainable food literacy, the total score of general nutrition knowledge of the participants was categorised into three groups. The total general nutrition knowledge score less than or equal to the 33rd percentile (29–75 scores) was evaluated as 'low', the score between the 33rd and 66th percentiles (76–88 scores) was evaluated as 'medium', and the score equal to or greater than the 66th percentile (89–117 scores) was evaluated as 'high'. To compare mean scores, independent sample t test and one-way analysis of variance (ANOVA) with Bonferonni post-hoc tests were considered for two groups and more than two groups, respectively. The relationship age, BMI, general nutrition knowledge, and sustainable food literacy scores were determined with the Pearson correlation test. The value of $p< 0.05$ was established as statistically significant.

RESULTS

The descriptive statistics and scale scores of the participants are presented in **Table 1**. A total of 280 135 (48.2%) men and 148 (51.8%) women volunteered to participate in the study. 41.1% of those who participated were given the responsibility of being the main food purchasers in the family, and 38.5% of those who participated were given the responsibility of being the main cooks in the family.

The sustainable food knowledge score of primary school graduates was significantly lower than high school and university graduates. Furthermore, the sustainable food knowledge score of people who cooked the food themselves was significantly higher than the participants whose mothers, father, spouses or other cooked the food. (**Table 2**).

Based on levels of nutrition knowledge, the mean score of sustainable food literacy scores is shown in **Table 3**. Participants in the low nutrition knowledge group (5.03±1.03) had lower sustainable food knowledge scores than those of the medium (5.42±0.72) and high (5.45±0.88) nutrition knowledge groups ($p<0.05$). However, there were no significant differences between food skills, attitudes, action intent and action strategies scores based on classification of nutrition knowledge ($p>0.05$).

Table 3. Sustainable Food Literacy Scale scores according to nutrition knowledge classification

	Nutrition Knowledge Classification			p
	Low (n=96)	Medium (n=93)	High (n=91)	
Sustainable food literacy scale				
Sustainable food knowledge	5.03±1.03[a]	5.42±0.72[b]	5.45±0.88[b]	0.002
Food skills	5.75±0.92	5.88±0.66	5.96±0.62	0.157
Attitudes	2.68±1.00	2.78±0.86	2.80±0.99	0.183
Action intent and action strategies	3.28±0.90	3.32±1.01	3.54±1.11	0.161

One-way ANOVA with Bonferroni post-hoc test, different lower letters in the same row indicate a statistically significant difference among groups.

The relationship between age, BMI, general nutrition knowledge, and food literacy scores is presented in **Table 4**. The sustainable food knowledge score was positively correlated with the dietary recommendations (r: 0.305, $p<0.001$), nutrition knowledge (r:0.411, $p<0.001$), everyday food choices (0.318, p: 0.049) and diet-disease relationships (r:0.436, $p<0.001$) scores and the total general nutrition knowledge score (r:0.356, $p<0.001$). In addition, positive correlations were found between food skills and dietary recommendation, nutrition knowledge, diet-disease relationship, total general nutrition knowledge scores (r: 0.272, p: 0.004; r:0.338, $p<0.001$; r:0.294, p:0.001; r:0.347, $p<0.001$, respectively). In addition, there were positive associations between action intent and action strategies and nutrition knowledge score (r:0.334, p:0.025), total general nutrition knowledge score (r:0.226, p:0.035). There was no correlation between the attitude score and the total score or any subscale of general nutrition knowledge (all $p>0.05$) (**Table 4**).

Table 1. General characteristics and scale scores of participants

Variables	
Age (years) *M*±SD	38.71±12.71
Gender n (%)	
Men	135 (48.2)
Women	145 (51.8)
Marital Status n (%)	
Single	104 (37.1)
Married	176 (62.9)
Education Level n (%)	
Literate	
Primary school	22 (7.9)
Secondary school	17 (6.1)
High school	92 (32.9)
University	149 (53.2)
Income n (%)	
Low	53(18.9)
Medium	137(48.9)
High	90(32.1)
Nutritional Habits	
Frequency of food purchase n (%)	
Twice or more per week	56 (20.0)
Once per week	114 (40.7)
Once per two weeks	64 (22.9
Once per three weeks or less	46 (16.4)
People who are responsible for purchasing food n (%)	
Mother	46 (16.4)
Father	26 (9.2)
Spouse	76 (27.1)
Self	115 (41.1)
Others	17 (6.1)
Frequency of eating out n (%)	
Everyday	41 (15.6)
5-6 times per week	40 (14.3)
3-4 times per week	29 (10.4)
1-2 times per week	67 (23.9)
Hardly ever	11 (3.9)
People who are responsible for cooking n (%)	
Mother	56 (20.0)
Father	6 (2.1)
Spouse	62 (29.3)
Self	108(38.5)
Others	48 (17.1)
Anthropometric measurements *M*±SD	
Body weight (kg)	75.13±14.31
BMI(kg/m²)	26.31±4.67
General Nutrition Knowledge *M*±SD	
Dietary Recommendations	6.25±1.50
Nutrition Knowledge	45.42±8.55
Everyday Food Choices	4.43±2.08
Diet-Disease Relationships	24.71±5.13
Total General Nutrition Knowledge	80.80±14.01
Sustainable Food Literacy Scale *M*±SD	
Sustainable Food Knowledge	5.29±0.90
Food Skills	5.86±0.75
Attitudes	2.77±0.95
Action Intent And Action Strategies	3.38±1.01

M: mean, SD: standard deviation, BMI: Body mass index, Income was estimated in three categories: Low (<6000Turkish Liras), Average (6000---12000 Turkish Liras) and High (>12000 Turkish Liras).

Table 2. Sustainable Food Literacy Scale scores according to the general characteristics of participants.

	Sustainable Food Literacy Scale			
	Sustainable Food Knowledge	Food Skills	Attitudes	Action Intent And Action Strategies
Gender				
Men	5.19±0.82	5.88±0.78	2.81±0.96	3.37±1.03
Women	5.40±0.97	5.84±0.73	2.73±0.95	3.39±1.00
p*	0.054	0.675	0.474	0.896
Marital Status				
Single	5.20±0.86	5.90±0.73	2.85±1.02	3.43±0.98
Married	5.35±0.93	5.84±0.77	2.72±0.91	3.35±1.03
p*	0.197	0.508	0.279	0.489
Education Level n (%)				
Primary school	5.37±1.56[a]	5.39±1.06	2.78±0.72	3.34±0.96
Secondary school	5.77±0.83[ab]	4.97±1.30	2.84±1.07	2.89±0.76
High school	5.93±0.61[b]	5.25±0.90	2.64±0.90	3.33±0.91
University	5.89±0.67[b]	5.35±0.82	2.84±1.00	3.47±1.09
p**	0.040	0.365	0.462	0.142
Income				
Low	5.22±0.91	5.89±0.85	2.78±0.90	3.39±1.04
Medium	5.39±0.91	5.88±0.69	2.67±0.97	3.26±0.97
High	5.20±0.89	5.82±0.79	2.92±0.96	3.55±1.03
p**	0.354	0.823	0.109	0.084
Nutritional Habits				
Frequency of food purchase				
Twice or more per week	5.04±0.76	5.85±0.71	2.83±0.95	3.28±0.92
Once per week	5.33±0.97	5.79±0.83	2.81±0.92	3.50±1.08
Once per two weeks	5.38±0.74	5.97±0.47	2.71±1.11	3.24±1.02
Once per three weeks or less	5.41±1.07	5.91±0.91	2.67±0.81	3.39±0.92
p**	0.106	0.473	0.761	0.345
People who are responsible for purchasing food				
Mother	5.03±0.73[a]	5.61±0.86	2.83±0.96	3.16±1.02
Father	5.04±0.97[a]	5.87±0.82	2.78±1.06	3.44±0.95
Spouse	5.27±0.89[a]	5.79±0.86	2.72±0.91	3.33±1.03
Self	5.67±0.85[b]	5.90±0.66	2.79±1.02	3.36±0.94
Others	5.01±0.93[a]	6.00±0.57	2.79±0.79	3.50±1.17
p**	0.042	0.376	0.991	0.779
Frequency of eating out				
Everyday	5.19±0.85	5.90±0.93	2.93±1.03	3.48±1.00
5-6 times per week	5.37±0.95	5.80±0.96	2.92±1.19	3.34±0.93
3-4 times per week	5.20±1.08	6.09±0.35	2.92±1.08	3.43±0.71
1-2 times per week	5.19±0.83	5.81±0.68	2.63±0.90	3.38±1.21
Hardly ever	5.40±0.90	5.84±0.70	2.70±0.80	3.34±0.99
p**	0.474	0.467	0.293	0.949

*Independent sample t-test, * * One-way ANOVA with Bonferroni post-hoc test. Different lower letters in the same column indicate a statistical difference among the groups.

Table 4. Correlation of age, BMI, General Nutrition Knowledge and Food Literacy Scale scores

		Sustainable Food Knowledge	Food Skills	Attitudes	Action Intent and Action Strategies
Age	r	0.083	-0.077	0.033	-0.084
	p	0.165	0.199	0.585	0.162
BMI	r	0.053	-0.034	0.103	-0.028
	p	0.379	0.574	0.084	0.643
Dietary Recommendations	r	0.305**	0.272**	-0.066	0.112
	p	<0.001	0.004	0.273	0.062
Nutrition Knowledge	r	0.411**	0.338**	0.007	0.334*
	p	<0.001	<0.001	0.911	0.025
Everyday Food Choices	r	0.318*	0.087	-0.068	0.075
	p	0.049	0.146	0.258	0.211
Diet-Disease Relationships	r	0.436**	0.294**	-0.092	0.058
	p	<0.001	0.001	0.126	0.333
Total General Nutrition Knowledge	r	0.356**	0.347**	-0.046	0.226*
	p	<0.001	<0.001	0.439	0.035

BMI: Body mass index, *p< 0.05, **p< 0.01

DISCUSSION

The purpose of this study was to assess the associations between level of nutrition knowledge and sustainable food literacy. Past research has focused on factors affecting food literacy, nutrition literacy, or food and nutrition literacy or the impact of these literacy levels on food intake and diet quality; or the relationship between nutrition education and sustainable and healthy eating behaviours.[12-19] To our knowledge, this is the first study to investigate the relationship between level of nutrition knowledge and sustainable food literacy. The results of this study indicated that participants with low nutrition knowledge had lower sustainable food knowledge scores than those in the medium and high nutrition knowledge groups. In addition, it was found that nutrition knowledge had a positive correlation with sustainable food knowledge, food skills and action intent and action strategies, all of which are subscales of sustainable food literacy.

In the study conducted in Taiwan on sustainable food literacy[9], the subscale scores ranged from 5.043 to 5.687. According to the results of that study, gender was not associated with sustainable food literacy. Furthermore, in the same study conducted by Chen et al.[9] it was found that level of education and food skills, attitudes and action intent and action strategies were not related, but sustainable food knowledge was significantly related to education, but the correlation was very weak. In addition, in that study it was found that frequency of cooking and food purchase connected with sustainable food literacy. In the current research, sustainable food knowledge and food skills score is between the means reported in a previous study.[9] However, the scores for the attitudes (2.77±0.95) and action intent and action strategies (3.38±1.01) subscales are lower than the scores found in the Taiwan study. Furthermore, our findings indicated that, there were no significant differences between sustainable food literacy scores according to gender, marital status, income level, frequency of food purchase and eating out. There were significant differences in sustainable food knowledge scores based on education level or the person responsible for preparing the food ($p<0.05$). Those with a high school degree or university degree, or who prepare their own meals, have better scores of sustainable food knowledge. The results of this study regarding gender and education level are consistent with the previous study.[9] Additional research is required to investigate the specific characteristics of individuals that would have an impact on their attitudes regarding sustainable food literacy.

Using the general nutrition knowledge questionnaire to assess nutrition knowledge, the mean general nutrition knowledge score was found to be 37.86±0.25 in the study with Syrian students[20], 61.9±16.68 in the study with people residing in Cyprus[21], and 98.8±8.1 in dietetic students in England.[22] When the results of this study were compared with those of other studies, it was found that the mean general nutrition knowledge score of this study was higher than that of Syrian students[20], Cyprus adults[21] and lower than the mean scores obtained with English students.[22] Differences in scores among countries may be related to the countries' plans and policies to promote the nutrition knowledge of the population.

The focus of earlier research has been the relationship between nutrition knowledge and food intake or diet quality. According to a study by Almasi et al. on university students[23], those with higher nutrition knowledge scores consumed less energy, carbohydrates, and sugar. The nutrition knowledge and total general nutrition knowledge scores of women with poor food quality were found to be lower in an adult study.[21] According to the findings of another study[24] carried out in Australia, a higher total general nutrition knowledge score is associated with a higher quality. A similar study.[25] indicated that improved attitudes toward healthy eating are a direct result of increased nutrition knowledge, which in turn is associated to higher diet quality.

Furthermore, some research has found that nutrition knowledge influences sustainable and healthy eating behaviours. In a study conducted with university students in Turkey, it was determined that students educated in the department of nutrition and dietetics had a higher mean score for the factor 'healthy and balanced nutrition' on the scale of sustainable and healthy eating behaviours than students educated in other departments.[18] In another study with Australian nutrition and dietetics students, it was found that the students understood the value of sustainability and applied their knowledge to their advocacy and interest behaviour.[19] The current study's results showed that high levels of nutrition knowledge were associated with higher scores on all subscales of the sustainable food literacy scale, but the difference was statistically significant only for the sustainable food knowledge subscale. In addition, positive associations were demonstrated between nutrition knowledge and sustainable food literacy subscales, except the attitude subscale. The results of this study indicated that increasing nutrition knowledge among individuals can improve sustainable food literacy.

This study has some limitations. First limitation of this study is that there is a wide age range. Future research should target certain age groups. The second limitation of this study is that it was only carried out in a single city and it was a cross-sectional investigation. Multi-central large sample studies would be beneficial for establishing a stronger relationship between nutrition knowledge and sustainable food literacy.

CONCLUSION

The results of this study showed that individuals with high levels of nutrition knowledge had higher scores on the sustainable food knowledge subscale. Another impressive finding was that nutrition knowledge is positively associated with sustainable food knowledge, food skills and action intent

and action strategies, which are subscales of sustainable food literacy. Our findings suggest that increasing the level of nutrition knowledge among individuals can increase sustainable food literacy. Therefore, nutrition knowledge should be considered as part of efforts to increase sustainable food literacy. This relationship has the potential to play a crucial role in ensuring that future generations inherit a more habitable world.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Ethics Board of Gaziantep Islam Science and Technology University (Date: 03.11.2022 and No:2022-157).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Barzegari A, Ebrahimi M, Azizi M, Ranjbar K. A study of nutrition knowledge, attitudes and food habits of college students. World Appl Sci J 2011;15:1012-7.
2. Alsaffar AA. Validation of a general nutrition knowledge questionnaire in a Turkish student sample. Public Health Nutr 2012;15:2074-85.
3. Okoro CS, Musonda I, Agumba J: Evaluating the influence of nutrition determinants on construction workers' food choices. Am J Mens Health 2017;11:1713-27.
4. Worsley A. Nutrition knowledge and food consumption: can nutrition knowledge change food behaviour? Asia Pac J Clin Nutr 2002;11:579-85.
5. Palumbo R. Sustainability of well-being through literacy. The effects of food literacy on sustainability of well-being. Agric Agric Sci Procedia 2016;8:99-106.
6. Friel S, Barosh LJ, Lawrence M. Towards healthy and sustainable food consumption: an Australian case study. Public Health Nutr 2014;17:1156-66.
7. Alsaffar AA. Sustainable diets: The interaction between food industry, nutrition, health and the environment. Food Sci Technol Int 2016;22:102-11.
8. Jones AD, Hoey L, Blesh J, Miller L, Green A, Shapiro LF: A systematic review of the measurement of sustainable diets. Adv Nutr 2016;7:641-64.
9. Teng CC, Chih C. Sustainable food literacy: A measure to promote sustainable diet practices. Sustain Prod Consum 2022;30:776-786.
10. Alsaffar AA. Exploring the level of nutrition knowledge and influencing factors in a Turkish community sample. International Peer-reviewed Journal Of Nutrition Research 2014; 2:45–57
11. Ellis JM, Galloway AT, Webb RM, Martz DM: Measuring adult picky eating. The development of a multidimensional self-report instrument. Psychol Assess 2017;29:955-66.
12. Kimura AH. Food education as food literacy: privatized and gendered food knowledge in contemporary Japan. Agric. Human Values 2011;28:465-82.
13. Colatruglio S, Slater J. Food literacy: bridging the gap between food, nutrition and well-being. Deer F, Falkenberg T, McMillan B, Sims L ,editors. Sustainable well-being: Concepts, issues, and educational practices. Winnipeg, MB: ESWB Press; 2014. p.37.
14. Chung L. Food literacy of adolescents as a predictor of their healthy eating and dietary quality. J Child Adolesc Behav 2017;5:10.4172.
15. Kalkan I. The impact of nutrition literacy on the food habits among young adults in Turkey. Nutr Res Pract 2019;13:352-7.
16. Ashoori M, Omidvar N, Eini-Zinab H, Shakibazadeh E, Doustmohamadian A, Abdar-Esfahani B, Mazandaranian M. Food and nutrition literacy status and its correlates in Iranian senior high-school students. BMC Nutr 2021;7:19.
17. Mohsen H, Sacre Y, Hanna-Wakim L, Hoteit M. Nutrition and Food Literacy in the MENA Region: A Review to Inform Nutrition Research and Policy Makers. Int J Environ Res Public Health 2022;19:10190.
18. Yolcuoğlu İZ, Kızıltan G. Effect of Nutrition Education on Diet Quality, Sustainable Nutrition and Eating Behaviors among University Students. J Am Nutr Assoc 2022;41:713-9.
19. Burkhart S, Verdonck M, Ashford T, Maher J. Sustainability: Nutrition and dietetic students' perceptions. Sustainability 2020;12:1072.
20. Labban L. Nutritional knowledge assessment of Syrian university students. Journal of the scientific society 2015;42:71-7.
21. Akkartal Ş, Gezer C. Is Nutrition Knowledge Related to Diet Quality and Obesity? Ecol Food Nutr 2020;59:119-29.
22. Parmenter K, Wardle J. Development of a general nutrition knowledge questionnaire for adults. Eur J Clin Nutr 1999;53:298-308.
23. Almasi N, Rakicioğlu N. Assessing the level of nutrition knowledge and its association with dietary intake in university students. BAUN Sağ Bil Derg 2021;10:274-80.
24. Kullen CJ, Farrugia JL, Prvan T, O'Connor HT. Relationship between general nutrition knowledge and diet quality in Australian military personnel. Br J Nutr 2016;115:1489-97.
25. Tabbakh T, Freeland-Graves JH. The home environment: a mediator of nutrition knowledge and diet quality in adolescents. Appetite 2016;105:46-52.

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Original Article / Orijinal Araştırma

Analysis of The Complaints of The Patients and Their Relatives to Healthcare Professionals

Sağlık Çalışanlarına Yönelik Hasta ve Yakınlarının Şikâyetlerinin Analizi

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Abstract

Aim: The aim of this study is to determine the complaints of patients and their relatives, to provide necessary measures and to find solutions.

Material and Method: It was retrospectively analyzed and conducted as a single-center study. The complaints of patients and their relatives who applied to the Patient Rights Unit, Ministry of Health Communication Center, Prime Ministry Communication Center, Presidential Communication Center from the hospital medical records between 2018 and 2019 were examined. Data were analyzed on IBM SPSS Statistics 22.0 package program.

Results: 1385 applications were examined. The number of male genders of the complainant was 66.1%. The most frequent complainants were between the ages of 20-40 (56.3%), high-school graduates (56.3%), in the self- employed/artisan group (24.2%). The most of the complaints were made application to the Patient Rights Unit (58.7%). Complaints were most common for physicians who in charge of primary care of the patient (49.5%) and least common for consultant physician (0.2%). The most common complaints were about poor attitude (26.9%) and long waiting time (21.7%). Most of the complaints were made in 2019 (n:835), July (n:239) and on Friday (n:326), and also most of the complaints were made against the Department of Pediatrics (n:190 (13.7%)) and Emergency Medicine (n:129 (9.3%). When the complaint-patient ratio was examined, it was perceived that the most complaints were from the laboratory and pathology departments.

Conclusions: It is concluded that patient rights units are very crucial and they have an important role in evaluating the quality of institutions and determining the existing deficiencies as well as increasing patient satisfaction.

Keywords: Patient rights, analysis of complaints, patient right unit, hospital complaints

Öz

Amaç: Bu çalışmanın amacı hasta ve hasta yakınlarının şikâyetlerini araştırmak ve buna yönelik olarak gerekli önlemleri almak ve çözüm bulmaktır.

Gereç ve Yöntem: Araştırma tek merkezli ve geriye yönelik olarak yapıldı. 2018-2019 yılları arasındaki hastane kayıtlarından Hasta Hakları Birimi, Sağlık Bakanlığı İletişim Merkezi, Başbakanlık İletişim Merkezi, Cumhurbaşkanlığı İletişim Merkezi'ne başvuran hasta ve hasta yakınlarının şikâyetleri incelendi. Veriler IBM SPSS Statistics 22.0 paket programında analiz edildi.

Bulgular: 1385 şikâyet başvurusu incelenmiştir. Şikâyetçilerin çoğu erkek (%66.1), 20-40 yaş arası (%56.3), lise mezunu (%56.3) ve serbest meslek/esnaf grubundadır (%24.2). Şikâyetlerin çoğu Hasta Hakları Birimi'ne (%58.7) yapılmıştır. Şikâyetler en çok hastanın birincil bakımı ile ilgilenen hekimlerine (%49.5), en az da konsültan hekimlere (%0.2) yapılmıştır. En sık şikâyetler kötü tutum (%26.9) ve uzun bekleme süresidir (%21.7). En çok şikâyet 2019 yılında (n:835), Temmuz ayında (n:239) ve Cuma günü (n:326) yapılmış olup en çok Çocuk Sağlığı ve Hastalıkları Anabilim Dalı (n:190 (%13.7)) ve Acil Tıp Anabilim Dalına (n:129 (%9.3)) şikâyet yapılmıştır. Şikâyet-hasta oranı incelendiğinde ise en çok şikâyet oranının laboratuvar ve patoloji bölümleri olduğu görülmüştür.

Sonuç: Hasta hakları birimlerinin çok önemli birimler olduğu; kurumların kalitesinin değerlendirilmesinde, mevcut eksikliklerin tespit edilmesinde ve hasta memnuniyetinin artırılmasında önemli bir role sahip olduğu sonucuna varılmıştır.

Anahtar Kelimeler: Hasta hakları, şikâyetlerin analizi, hasta hakları birimi, hastane şikâyetleri

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INTRODUCTION

In recent years, the concept of patient rights has gained importance in many countries, especially in European nations. With the adoption of the Universal Declaration of Human Rights in 1948, patient rights, like many other rights, have made quite an important progress.[1]

Patient rights refer to the rights of individuals who need to benefit from health services just because they are human and are guaranteed by the Constitution of the Republic of Turkey, international treaties, laws, and other legislation.[2]

Patient rights are defined as a sub-branch of human rights. The first international document on patients' rights was the Lisbon Declaration published in 1981. In 1989, the World Health Organization published a limited declaration of patients' rights. Thereby, in the following years, efforts for patients' rights intensified. Thereafter, the "Amsterdam Declaration" was published on March 28-30, 1994.[3,4]

The World Medical Association published the Bali Statement in 1995 to resolve the problems concerned with patients' rights.[5] In regard to patient rights, the Ljubljana Health Care Reform Charter was published in 1996,[6] the European Patient Rights Charter in 2003,[7] and the Santiago Declaration in 2005.[8]

In parallel with the developments in the world, it can be said that the development of patient rights in Turkey has a similar history. The right to health was included in the 1961 Constitution for the very first time. In 1998, the Patient Rights Regulation was published. Later on, in the year 2005, the Patient Rights Implementation Directive got published and it has been an explanatory and guiding regulation on patient rights since then. Following the regulation, the state and public institutions started to put the necessary practices into action.[9]

After all these regulations were issued on patient rights in Turkey, an official organizational structure got established. “Patient Rights Units and Institutions” and “Patient Rights Communication Units” were recognized under the “General Directorate of Treatment Services” affiliated with the Ministry of Health 2. Patient rights units are generally located in polyclinics in hospitals and are located in easily accessible places. Applications of the patient or their relatives are received and evaluated, if they can find a solution on the spot, they are applied, but if not, applications are further submitted to the Patient Rights Board.

Within the scope of the Health Transformation Project, which started in Turkey in 2003, the Ministry of Health Communication Center (SABIM) was established in 2004.[10] Then in 2006, another interactive service, known as the Prime Ministry Communication Center (BIMER), was established.[11] Due to the transition to the Presidency management system in Turkey in 2018, the activities of the Office of the Prime Minister were terminated, BIMER was closed, and the operations related to this service were transferred to Presidency Communication Center (CIMER).[12,13]

Nowadays, the use and delivery of health services are among the most important indicators that determine the socio-economic development level of countries. In modern nations, the quality of medical care plays an essential role in the improvement of patient satisfaction and the development of their positive perception. In order to provide good health care, it is necessary to measure the quality of the service received; This can be possible by performing satisfaction surveys and evaluating the patient complaints received.

The aim of this study is to define patient complaints, then examine the resources of the objections made and assess the demographic characteristics of patients and their relatives. With the evaluations made, the inadequacies that are the subject of complaints in health services will be determined and thus, it will be possible to take distinct measures to repair the origin of these defects.

MATERIAL AND METHOD

Study Design

Patients formally conveyed their complaints to four different units in the Turkish Health System as presented below:

Patient Rights Unit of the Hospital: These are the entities formed by the Patient Rights Units and Institutions in hospitals containing 100 beds or more under the General Directorate of Treatment Services of the Ministry of Health.

Ministry of Health Communication Center (SABIM): It is the unit that is operated under the Ministry of Health as a facility that aims to put people at the center of service by providing multi-interactive participation of those benefiting from health services.

Prime Ministry Communication Center (BIMER): It is an important communication center where patient complaints are made, collected and the necessary actions are initiated. It was closed in 2018 and this task was transferred to the Presidential Communication Center (CIMER).

Presidency Communication Center (CIMER): Due to the transition to the Presidential management system in 2018, CIMER is the center that was formed to collect all the transactions previously made by BIMER after it got terminated.

The study is based on the patient complaint application records made to **XXXXXXXXXXXX** University **XXXX** Research and Application Hospital Patient Rights Unit, Ministry of Health Communication Center (SABIM), Prime Ministry Communication Center (BIMER), and Presidency Communication Center (CIMER) between January 1, 2018,

and December 31, 2019. It was retrospectively analyzed and conducted as a single-center study.

Gaziantep University Faculty of Medicine Ethics Committee's approval was obtained for the following study (Ethics committee decision no: 2019/430, date: 13.11.2019). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Progress:

1987 complaint applications made to the four patient rights units mentioned above were examined, and 1385 of these applications were evaluated. The applications obtained were examined under the following headings:

- Demographic characteristics of complainants;
  - Gender
  - Age
  - Educational status
  - Profession
  - The degree of closeness with the patient
- Occupation of the complained personnel
- Complained section
- Subject of complaint
- The day and month of the complaint were examined.

Statistical Analysis

- Data were analyzed on IBM SPSS Statistics 22.0 package program.

Inclusion Criteria of the Study

- All official complaints made by patients and their relatives to the hospital patient rights unit, SABIM, and CIMER (all pediatric and adult patients)

Exclusion Criteria of the Study

- Complaints that were not officially submitted
- Complaints that included an incomplete complaints application form

RESULTS

Between January 1, 2018, and December 31, 2019, 2,268,042 patients applied to XXX University XXX Research and Application Hospital, and complaints against healthcare professionals were detected by 1987 patients and/or their relatives. Due to the lack of data on some of these complaints, which were applied to the patient rights unit, only 1385 were included in the study. The male and female gender numbers of the complainants were 916 (66.1%) and 469 (33.9%), respectively, and it was determined that the most common age group was between 20-40 years (n:448 (56.3%)) (**Table 1**). When the complaints were examined, it was revealed that most of them were high-school graduates (n:448 (56.3%)) and in the self- employed/artisan group (n:192 (24.2%)) (**Table 1**). Furthermore, it was shown that most of the complaints were made to the Patient Rights Unit (n:813 (58.7%)) (**Table 2**). Also, it was reported that the submitted objections about health personnel were physicians (n:686 (49.5%)) and secretaries (n:229 (16.5%)) (**Table 3**). It was observed that the most common complaints were caused by poor attitude (n:371 26.9%) and long waiting time (n:300 (21.7%)) (**Table 3**). Most of the complaints were made in 2019 (n:835), July (n:239) and Friday (n:326) (**Table 4**), and most of the complaints were made against Pediatrics (n:190 (13.7%)) and Emergency Medicine departments (n:129 (9.3%) (**Table 5**). When the complaint-patient ratio was examined, it was perceived that the most complaints were from the laboratory (0.011) and pathology departments (0.01) (**Table 5**).

Table 1. Demographic characteristics of complainants

	n (%)
Gender	
Male	916 (66.1)
Female	469 (33.9)
Age	
20-40	448 (56.3)
41-60	289 (36.3)
>60	38 (4.8)
<20	21 (2.6)
Educational status	
High school	398 (50.3)
University	237 (30.0)
Primary school	108 (13.7)
Secondary school	48 (6.1)
Profession	
Self-employment / Artisan	192 (24.2)
House wife	176 (22.2)
Officer	109 (13.7)
Unemployed	78 (9.8)
Student	77 (9.7)
Teacher	55 (6.9)
Retired	48 (6.0)
Military Personal	29 (3.7)
Worker	28 (3.5)
Other	2 (0.3)
Kinship	
Self	983 (71.0)
Parent	229 (16.5)
Child	86 (6.2)
Spouse	59 (4.3)
Sibling	20 (1.4)
Friend	2 (0.1)
Other	6 (0.4)

Table 2. Distribution of Complaints by Unit and Years

Years	Number of Applications to the Patient Rights Unit	Number of Applications to SABIM*	Number of Applications to CIMER**	Total
2018	324	130	96	550
2019	489	205	141	835
Total	813	335	237	1385

*SABIM: Ministry of Health Communication Center, **CIMER: Presidency Communication Center

Table 3. Health Worker Complained and Subject of Complaint

	n (%)
Health Worker Complained	
Physician	686 (49.5)
Cashier (secretary)	229 (16.5)
Hospital administration	139 (10.0)
Technician	121 (8.7)
Personnel	82 (5.9)
Nurse	62 (4.5)
Cleaning staff	52 (3.8)
Security staff	5 (0.4)
Consultant physician	3 (0.2)
Other	6 (0.4)
Subject of Complaint	
Poor attitude	371 (26.9)
Long waiting time	300 (21.7)
Nonappointment	125 (9.0)
Physical conditions	125 (9.0)
Dissatisfaction with treatment	120 (8.7)
Poor communication	111 (8.0)
Dissatisfaction with examination	94 (6.8)
Financial affair	69 (5.0)
Misdiagnosis	61 (4.4)
Other	8 (0.6)

Table 4. The relationship between examination days, months and complaints

	n (%)
Days	
Friday	326 (23.5)
Wednesday	322 (23.2)
Monday	253 (18.3)
Thursday	245 (17.7)
Tuesday	236 (17.0)
Sunday	2 (0.14)
Saturday	1 (0.07)
Months	
July	239 (17.2)
August	178 (12.9)
September	178 (12.9)
October	150 (10.8)
June	121 (8.7)
November	116 (8.4)
December	98 (7.1)
April	92 (6.6)
May	89 (6.4)
March	58 (4.2)
January	40 (2.9)
February	26 (1.9)

Table 5. Distribution of Complained Units

Complained Unit	n (%)	Number of Patients Applying to the Unit	Complaint/ Number of patients
Pediatric	190 (13.7)	376014	0.0005053
Emergency Medicine	129 (9.3)	465902	0.0002768
Obstetrics and Gynecology	81 (5.8)	77255	0.0010484
Otorhinolaryngology	80 (5.8)	68918	0.0011608
Radiology	69 (5)	20486	0.0033681
Orthopedics	64 (4.6)	77442	0.0008264
Ophthalmology	58 (4.2)	125465	0.0004622
Neurology	54 (3.9)	56760	0.0009513
Cardiology	54 (3.9)	51472	0.0010491
Oncology	47 (3.4)	38174	0.0012312
Laboratory	42 (3)	3733	0.0112510
Gastroenterology and Hepatology	41 (3)	71114	0.0005765
Urology	36 (2.6)	57449	0.0006266
Endocrinology and Metabolism	29 (2.1)	82271	0.0003524
Anesthesia and Reanimation	28 (2)	27866	0.0010048
Respiratory Medicine	27 (1.9)	28829	0.0009365
Hematology	26 (1.9)	53456	0.0004863
Psychiatry	24 (1.7)	50946	0.0004710
Dermatology	23 (1.7)	97287	0.0002364
Physical Therapy and Rehabilitation	22 (1.6)	82874	0.0002654
Nephrology	22 (1.6)	37285	0.0005900
General Surgery	19 (1.4)	50962	0.0003728
Vascular Surgery	17 (1.2)	13628	0.0012474
Neurosurgery	15 (1.1)	30525	0.0004914
Pathology	14 (1)	1386	0.0101010
Infectious Diseases	11 (0.8)	41212	0.0002669
Geriatric Medicine	10 (0.7)	13520	0.0007396
Plastic and Reconstructive Surgery	8 (0.6)	11366	0.0007038
Pediatric Surgery	7 (0.5)	13280	0.0005271
Child and Adolescent Psychiatry	5 (0.4)	28554	0.0001751
Forensic Medicine	4 (0.3)	10567	0.0003785
Nuclear Medicine	4 (0.3)	7021	0.0005697
Thoracic Surgery	3 (0.2)	12075	0.0002484
Other	122 (8.8)	82948	0.0014708
Total	1385 (100)	2268042	

DISCUSSION

In our study, it was determined that the majority of complaints were made by patients and/or their relatives who were male gender, most frequently between the ages of 20-40, and 50.3% (n=398) are high school graduates. When we look at the occupational group of the applicants, it is reported that most of them are self-employed/tradesmen (n=192 (24.2%)) and housewives (n:176 (22.2%)) in comparison to other occupational groups. There are differences in the literature in terms of gender, age range, educational status, and occupation of the complainant.[10,14-22] We attribute this to the type of health institutions, sample size, time zone, data source, and socio-cultural structure of the society.

When we examined which unit the patients applied to, it was determined that 58.7% (n=813) had applied to the patient rights unit. In the study conducted by İşeri,[15] the number of applications made for patients' rights was 96.5% (n=782). In the study of Yazıcıoğlu,[16] 58.3% (n=3043) of all applications were made to SABIM, while 57.4% (n=2998) were made to the patient rights unit. The number of applications received through SABIM and CIMER has increased gradually compared to previous years since it is the shortest, most accessible, and most effective way for patients and/or their

relatives to submit their objections. We suppose that most of the complaint applications are made to the patient rights unit due to reasons such as filling out the application form by directly speaking to the unit manager.

In our study, in correspondence to the health workers, doctors (n:686 (49.5%)), and secretaries (n:229 (16.5%)) were the most frequently complained about by patients and/or their relatives. In the study by Manouchehri et al.[23] nurses (n:218 (38.8%)) and doctors (n:110 (19.6%)) were complained about the most. Moreover, in the research conducted by İşeri,[15] doctors were the most complained about with a percentage of 34.5% (n:287). Whereas in the study of Yazıcıoğlu,[16] secretaries, security guards, and cleaning personnel occupied a higher proportion of 61.3%(n:1838) when compared to other laborers. Although the health workers who are complained about usually vary depending on various factors, when we look at the other research,[15,16,23] it is stated that the most complained personnel are usually doctors.

We think that this result is due to the fact that patients and/or patients' relatives expect immediate solutions from doctors. Since they mostly deal with doctors during the diagnosis and treatment process, they think that all improvements and solutions are the responsibility of doctors only. In addition, due to the high number of patients per doctor in our country, doctors may be the center of their complaints.[24] This problem can be overcome by reducing the patient density and workload of doctors, or it can be decreased by providing doctors training in communication skills.

In our study, it was seen that the most common complaint by patients and/or their relatives were due to poor attitude with 26.9% (n:372) and long waiting time with 21.7% (n:300). While in the study conducted by İşeri,[15] the most common complaint was on account of the inappropriate style and behavior of the staff with a ratio of 16.5% (n=150). When we examine the statistics on the distribution of the subject matter of the applications published by the Ministry of Health in 2013 regarding patient rights, it is seen that 46% of the applications are due to the inability to benefit from the service in general, while 21% are the applications made about the lack of dignity and comfort. In the research performed by Uludağ[19] in 2011, 40.6% (n=236) of them applied because of not being able to benefit from the service. When we look at the distribution of the subject according to the content, 40.4% (n=233) applied due to communication problems. Unlike the studies mentioned, in the research conducted by Gürlek, Kanber and Çiçek,[14] in 2011, more applications were made with 45.0% due to lack of respect and comfort. In the literature, it has been observed that patients and/or their relatives mostly complain about communication, long waiting time and behavior (poor attitude).[14,15,19,20,22,23,25-27] Although the results of our study seem to be similar to the literature, it is assumed that the complaints of the patients and/or their relatives will decrease by getting the patient's examination results more quickly, providing communication training to health workers, reducing the problems caused by the hospital system and reducing the problems experienced due to the lack of medical equipment.

In our study, Pediatrics (n=190 (13.7%)) and Emergency Medicine Department (n:129 (9.3%) were determined as the most frequently complained departments. In the different studies conducted by İşeri,[15] and Yazıcıoğlu,[16] the most frequently complained units were polyclinics with 82.7% (n=670) and 52.6% (n=1576), respectively. When we examine the statistics published by the Ministry of Health on patient rights in 2013, Policlinics comes first with 44% while Emergency Services follows with 16% among the units applied.[28] The Department of Pediatrics and Emergency Medicine is the two units with the highest number of complaints. In this study, when compared to other units, it is clearly seen that the ratio of the number of complaints to the number of patients coming to these units is very low. When we look at the ratio of the number of complaints made to the unit to the total number of patients coming to the unit, the laboratory comes with the highest rate of 0.011, followed by pathology with a rate of 0.01. The fact that the number of patients applying to the units and the complaints are not proportional may give the hospital management units the idea that the problem is not only related to the congestion. It is striking that these units are the units that examine the medical examinations made. It is possible that the complaint rate is high due to the problems related to the receipt, transmission and storage of the examination reports and the results being concluded after a long time. We think that there will be a decrease in the complaints by solving these problems.

Limitation

A single-centered study: The data of the complaints belonging to SABIM and CIMER were obtained from the hospital patient rights unit, and not directly from the center. This ensued in the failure to evaluate the cases that were only applied to SABIM and CIMER but were not reported to the patient rights unit.

The study was planned to examine all complaints made between 2015-2019, but the data before 2018 could not be accessed because the hospital patient rights unit started saving their data after the year 2018.

CONCLUSION

According to the results of our research, it is a fact that there are various difficulties in providing the right to benefit from health services, which is one of the most basic rights of patients. In this context, in addition to serving the patient, various disruptions have occurred in paying sufficient attention to human values. It is observed that there are problems in the services provided to the patients as a result of the high number of patients, the inadequacy of the personnel and the inadequate physical conditions. As a result of these disruptions, it is thought that there are communication

problems between the patients and healthcare professionals. As a result of these problems, the behavior of the patients and their relatives towards healthcare professionals also changes and causes them to be inappropriate.

The importance given to patient rights is increasing in Turkey as well as in the rest of the world. With each passing day, patients and their relatives become more conscious about patient rights, and as a result, their expectations from health services are increasing day by day. The most effective unit in determining the demands and needs of patients and their relatives, and in identifying the problems they experience is the patient rights unit. We think that the institutions that want to evaluate the quality of the service provided and increase the satisfaction of the patients, consider the applications received by the patient rights unit, will increase the quality of their services.

ETHICAL DECLARATIONS

Ethics Committee Approval: Gaziantep University Faculty of Medicine Ethics Committee's approval was obtained for the following study (Ethics committee decision no: 2019/430, date: 13.11.2019).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Hatun Ş. Hasta Hakları. 1st ed. Istanbul. İletişim Yayınları; 1999.
2. Mevzuat Bilgi Sistemi. Hasta Hakları Yönetmeliği. Vol 23420.; 1998. Accessed 15 th September 2020. https://www.mevzuat.gov.tr/File/GeneratePdf?mevzuatNo=4847&mevzuatTur=KurumVeKurulusYonetmeligi&mevzuatTertip=5
3. Fidaner C, Fidaner H. Dünya Hekimler Birliği Bildirgeleri. Ankara. Ankara Tabip Odası; 1987.
4. Kaur SR, Herxheimer A. Recognising Patients Right Pachy Progress. The Lancet. 1994;343(8890):132.
5. Demirhan Erdemir A, Şaylıgil Elçioğlu Ö. Tıp Etiği Işığında Hasta ve Hekim Hakları. 1st ed. Istanbul. Türkiye Klinikleri; 2000.
6. Madenoğlu Kıvanç M. Sağlık Bildirgeleri ve Türkiye'de Sağlık Reformları. Sağlık ve Hemşirelik Yönetimi Derg 2015;2(3):162-166.
7. Karaca Dedeoğlu A. Uluslararası Sağlık Turizminde Hastanın Özel Hayatının Gizliliği ve Mahremiyetinin Korunması Hakkı. Uluslararası Toplum Araştırmaları Derg 2019;10(17):1875-1910.
8. Öztürk Türkmen H. Hekim-Hasta İlişkisinde Haklar ve Sorumluluklar. Toraks Cerrahisi Bülteni 2014;5(1):1-13.
9. Sert G. Hasta Hakları - Uluslararası Bildirgeler ve Tıp Etiği Çerçevesinde. 1st ed. Istanbul. Babil Yayınları; 2004.
10. Bostan S, Kılıç T, Çiftçi F. Sağlık Bakanlığı 184 SABİM Hattına Yapılan Şikayetlerin Karşılaştırmalı Analizi. Global Journal of Economics and Business Studies 2014;3(5):35-40.
11. Yeşiltaş A, Erdem R. Defansif Tıp Uygulamalarına Yönelik Bir Derleme. Süleyman Demirel Üniversitesi Vizyoner Derg 2019;10(22):137-50.
12. Mert YL. Kamu Yönetiminde Kurumsal İletişim: Web Siteleri Üzerine Bir Analiz. Uluslararası Sosyal Araştırmalar Derg 2019;12(62):1513-22.
13. Turan E, Aydilek E, Şen AT. Bimer Uygulaması ve Türk Kamu Yönetimi Sistemine Etkileri. Kastamonu Üniversitesi İktisadi ve İdari Bilimler Fakültesi Derg 2015;8(2):215-25.
14. Gürlek Ö, Aytuğ Kanber N, Çiçek H. Bir Devlet Hastanesinde Hasta Hakları Birimine Yapılan Başvuruların Değerlendirilmesi. TC Sağlık Bakanlığı Tedavi Hizmetleri Genel Müdürlüğü III Uluslararası Sağlıkta Performans ve Kalite Kongresi 2011;3(1):476-83.
15. İşeri S. Bir Eğitim Araştırma Hastanesinde Hasta Hakları Birimine Yapılan Başvuruların Değerlendirilmesi. Thesis. Türk Hava Kurumu Üniversitesi Sosyal Bilimler Enstitüsü; 2014. Accessed September 10 2020.
16. Yazıcıoğlu B. İl Kamu Hastanesi Hasta Hakları Birimine Yapılan Başvuruların Değerlendirilmesi. Thesis. Ondokuz Mayıs Üniversitesi Sağlık Bilimleri Enstitüsü Sağlık Yönetimi Anabilim Dalı; 2019. Accessed July 24 2020.
17. Şeremet F. Kamu Hastanelerinde Hasta Hakları Birim Çalışanlarının Sorunları, Birime Gelen Şikayetler ve Hasta Memnuniyeti. Thesis. Marmara Üniversitesi Sağlık Bilimleri Enstitüsü; 2013. Accessed June 23 2020.
18. Kırgın Toprak D. Sağlık Bakanlığı Hastanelerine Yapılan Hasta Şikayetlerinin Değerlendirilmesi. Sağlıkta Performans ve Kalite Derg 2012;3(1):1-28.
19. Uludağ A. View of the Patient Rights Committees of the Hospitals on Applications Including Communication Problems: Sample of Konya Hospitals. Turkiye Klinikleri J Med Sci 2011;31(3):653-63.
20. McSweeney W, Leaning M, Dastouri D, Parkinson D, Hendahewa R. It's not you, it's me: a descriptive study of patient complaints and surgeon understanding. ANZ Journal of Surgery 2021;91(10):1991-5.
21. Eriksson EM, Raharjo H, Gustavsson S. Exploring complaints by female and male patients at Swedish hospitals using a probabilistic graphical model. Scand J Caring Sci 2018;32(3):1148-56.
22. Friele RD, Sluijs EM, Legemaate J. Complaints handling in hospitals: an empirical study of discrepancies between patients' expectations and their experiences. BMC Health Serv Res 2008;8(1):199.
23. Manouchehri Moghadam J, Ibrahimipour H, Sari Akbari A, Farahbakhsh M, Khoshgoftar Z. Study of patient complaints reported over 30 months at a large heart centre in Tehran. BMJ Quality & Safety 2010;19(5):e28-e28.
24. Oecd Data. Doctors. Accessed 25th July 2020. https://data.oecd.org/healthres/doctors.htm
25. Claydon O, Keeler B, Khanna A. Understanding complaints made about surgical departments in a UK district general hospital. International Journal for Quality in Health Care 2021;33(3).
26. Veneau L, Chariot P. How do hospitals handle patients complaints? An overview from the Paris area. Journal of Forensic and Legal Medicine 2013;20(4):242-7.
27. Hsieh SY. The use of patient complaints to drive quality improvement: an exploratory study in Taiwan. Health Serv Manage Res 2010;23(1):5-11.
28. Sağlık Bakanlığı. Sağlık İstatistikleri Yıllığı 2013. Accessed 21st January 2020. https://www.saglik.gov.tr/TR,4743/saglik-istatistikleri-yilligi-2013.html

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Original Article / Orijinal Araştırma

Incidences of Terminal Zones of Myelination: An Evaluation of Patients aged 3–30 Years

Terminal Myelinasyon Zonlarının Görülme Sıklığı: 3-30 Yaş Arası Değerlendirme

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Abstract

Aim: Studies on terminal zones of myelination (TZM) generally focus on the infant to early childhood periods. Information concerning the incidence and localization in adulthood is rare and controversial. Our aim is to determine the localization and frequency TZM in patients aged 3–30 years using magnetic resonance imaging (MRI).

Material and Method: Images of 560 patients aged 3-30 years, whose cranial MRIs were reported as normal, were re-evaluated by two radiologists using a double-blind, retrospective method. Five different white matter (WM) regions (parietal peritrigonal WM; frontal, temporal, parietal, and insular subcortical WM) were reviewed for TZM. Turbo spin echo T2- and T1-weighted imaging and T2 fluid-attenuated inversion recovery sequences were used. The binary logistic regression analysis was used for the relationship of TZM with age and sex. The inter-observer agreement was evaluated by the kappa statistic.

Results: The incidences of TZM in all age groups were 28.7% in the insula, 14.6% in the temporal lobes, and 5.2% in the peritrigonal region. TZM were localized most commonly in the insula, followed by the temporal poles. The presence of peritrigonal TZM after five years of age was very rare (2.6%). Inter-observer agreement was significant for all regions (Kappa value < 0.05).

Conclusion: We detected TZM most often in the insular subcortical WM. It should be noted that insular and temporal TZM can be observed quite frequently, even in third decade.

Keywords: Insula, subcortical white matter, myelination, MRI

Öz

Amaç: Terminal miyelinasyon zonları (TMZ) ile ilgili çalışmalar genellikle infant-erken çocukluk dönemlerini kapsayacak şekilde yapılmıştır. Erişkinlikte insidans ve lokalizasyonu ile ilgili bilgiler nadirdir ve tartışmalıdır. Amacımız, manyetik rezonans görüntüleme (MRG) ile 3-30 yaş arası hastalarda TMZ lokalizasyonunu ve sıklığını belirlemektir.

Gereç ve Yöntem: Kranial MRG'leri normal olarak raporlanan, yaşları 3-30 arasında değişen 560 hastanın görüntüleri, iki radyolog tarafından çift kör, retrospektif yöntemle tekrar değerlendirildi. TMZ için beş farklı beyaz cevher (BC) bölgesi (parietal peritrigonal BC; frontal, temporal, parietal ve insular subkortikal BC) tekrar gözden geçirildi. T2 ve T1 ağırlıklı turbo spin eko ve T2-FLAIR (fluid-attenuated inversion recovery) sekansları kullanıldı. TMZ'nin yaş ve cinsiyet ile ilişkisi ikili lojistik regresyon analizi, gözlemciler arası uyum ise kappa istatistiği ile değerlendirildi

Bulgular: Tüm yaş gruplarında TMZ insidansı insulada %28.7, temporal loblarda %14.6 ve peritrigonal bölgede %5.2 idi. TMZ, en sık insulada lokalizeydi, bunu temporal poller izliyordu. Beş yaşından sonra peritrigonal TMZ varlığı çok nadirdi (%2.6). Gözlemciler arası uyum tüm bölgeler için anlamlıydı (Kappa değeri < 0.05).

Sonuç: TMZ'yi, en sık insular subkortikal BC'de saptadık. Insular ve temporal TMZ'lerin, üçüncü dekatta bile oldukça sıklıkla izlenebileceği unutulmamalıdır.

Anahtar Kelimeler: İnsula, subkortikal beyaz cevher, miyelinasyon, MRG

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INTRODUCTION

Magnetic resonance imaging (MRI) is the most commonly used non-invasive imaging method for evaluation of white matter myelination (WM). Persistent T2 hyperintensity on MRI images after 2 years of age is considered to be terminal zones of myelination (TZM). TZMs can easily be mistaken for pathology by the inexperienced. Therefore, it is important to distinguish it from WM lesions. Studies on TZM, which represent the late phase of myelination, generally focus on the infant to early childhood periods. Although TZM can be found in people up to the age of 40 years,[1] information concerning the incidence and localization in adulthood is rare and controversial. We aimed to determine the localization and frequency of TZM in patients aged 3–30 years using MRI.

MATERIAL AND METHOD

Study population

Between September 2019 and February 2020, 560 patients aged 3–30 years (median age 16 years) with completely normal cranial MRI scans were included in the study. MRI examinations that had not an optimal quality (due to motion artifacts etc.) were not included in the study. The cranial MRI scans were evaluated retrospectively. Therefore, we did not obtain consent from the subjects. None of the patients examined were premature or had perinatal hypoxic-ischemic encephalopathy, a systemic or neurological disease affecting the WM, a history of drug use, or any other chronic diseases. The ethics committee's approval was received (Approval Date: 29.04.2021; Approval Number: 386)

MRI Protocol

MRI was performed using a 1.5 Tesla (T) system (Aera, Siemens, Erlangen, Germany) with a 20-channel head coil. Intravenous sedation (ketamine 1 mg/kg) was performed when necessary (especially in children under 7 years of age) to prevent motion artifacts. Intravenous contrast material was not used for any of the patients. TZM evaluation was conducted using transverse and coronal plane turbo spin echo T2-weighted imaging (T2WI), transverse plane turbo spin echo T1-weighted imaging (T1WI), and T2 fluid-attenuated inversion recovery (T2-FLAIR) sequences (**Table 1**).

Image analysis

Image evaluations were conducted by two radiologists with at least 8 years of experience, one of whom was a pediatric radiologist. Five different WM regions (parietal peritrigonal WM; frontal, temporal, parietal, and insular subcortical WM) were evaluated in the MRI scans for TZM. The TZM inclusion criteria were the presence of T2WI hyperintensity with T1WI and T2-FLAIR isointensity according to the WM, and T2WI hyperintensity had to be present in at least two sections in both coronal–axial planes.

Statistical Analysis

Analyses were performed using IBM SPSS Statistics 22. The relationship of TZM with age and sex was evaluated by binary logistic regression analysis, and inter-observer agreement was evaluated using the kappa statistic.

RESULTS

A total of 560 patients (242 males, 318 females) aged 3–30 years (median age 16 years) were included in this study. The number of patients in each age group ranged from 14 to 44 (**Figure 1**).

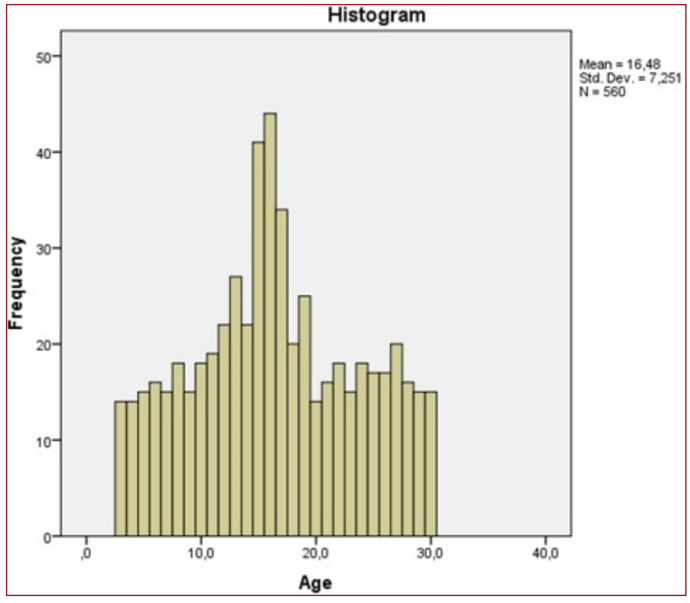

Figure 1. Histogram showing the number of patients according to age

The insula was the most common area of TZM localization in each age group (**Figure 2**). The incidences of TZM in all age groups were 28.7% in the insula (**Figure 3**), 14.6% in the temporal lobes (**Figure 4**), and 5.2% in the peritrigonal region. The presence of peritrigonal TZM after 5 years of age was very rare (in 56.6% of those aged 3–5 years, 1.4% of those aged 6–10 years, 1.2% in second decade, 0% in third decade). TZM were not detected in the frontal or parietal lobe. The incidences of TZM in the insula and temporal lobes were 13.8% and 9.8%, respectively, among in third decade.

Table 1: Magnetic resonance imaging sequence parameters.

	TR	TE	FOV	Matrix	Voxel	NEX	Interslice Gap
T2WI	3000–4000 msn	80–90 msn	175×200	280×320	0.62×0.62	3	0%
T1WI	550–600 msn	8–15 msn	175×200	280×320	0.62×0.62	2	0%
T2-FLAIR	7000–9000 msn (TI 2200 msn)	90–100 msn	175×200	280×320	0.62×0.62	3	0%

Note: TR: time repetition; TE: time echo; TI; time inversion; FOV: field of view; NEX: number of excitations; T2WI: T2-weighted images; T1WI: T1-weighted images; T2-FLAIR: T2 fluid-attenuated inversion recovery sequences.

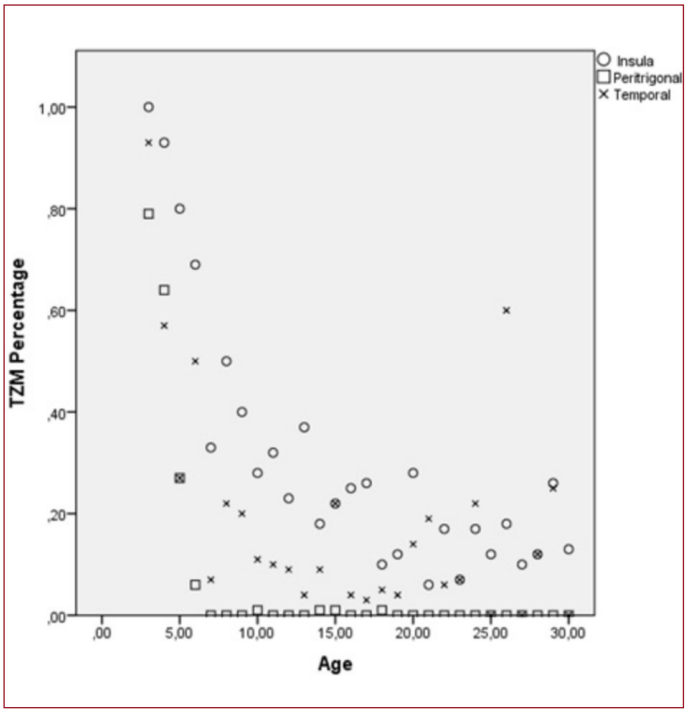

Figure 2. The distribution of insular, temporal, and peritrigonal TZM by age. TZM: terminal zones of myelination.

Based on binary logistic regression analysis, a significant correlation was found between age and TZM ($P < 0.0001$). There was no significant correlation with sex ($P > 0.1$). Cohen's kappa statistic was significant for inter-rater agreement (Kappa value < 0.05).

DISCUSSION

Myelination is a dynamic process. It begins in the cranial nerves during the 5th month of fetal life and continues throughout life.[2-4] Myelination progresses inferior to superior and posterior to anterior and centrifugal. MRI is a safe and non-invasive imaging method used to follow the process of myelination.[5,6] Myelination that similar to adults on MRI scans appears from age 1 year onwards on T1WI and from 2 years onwards on T2WI.[7,8] Persistent T2 hyperintensity on MR images after 2 years of age is considered to be TZM. However, complete myelination of the terminal zones may not be complete until fourth decade.[1] T2WIs are the most frequently used sequences to evaluate TZM.[9]

Most previous studies on TZM focused on the infant and early childhood periods. In those studies, TZM were detected in the parietal peritrigonal WM[10,11] or frontotemporoparietal subcortical WM.[12] Our findings concord with those of

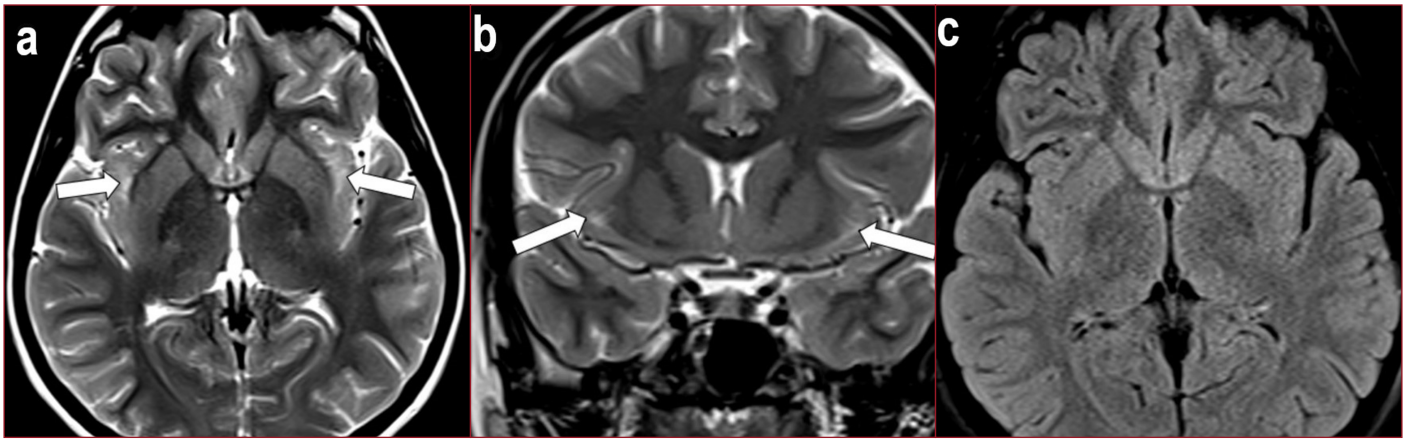

Figure 3. 16-years-old girl complains of dizziness. Hyperintense TZM (arrows) is present in bilateral insular subcortical WM in transverse (a) and coronal T2WI (b). Transvers T2-FLAIR (c) show isointensity according to white matter in same section. (TZM: Terminal zones of myelination, WM: White matter)

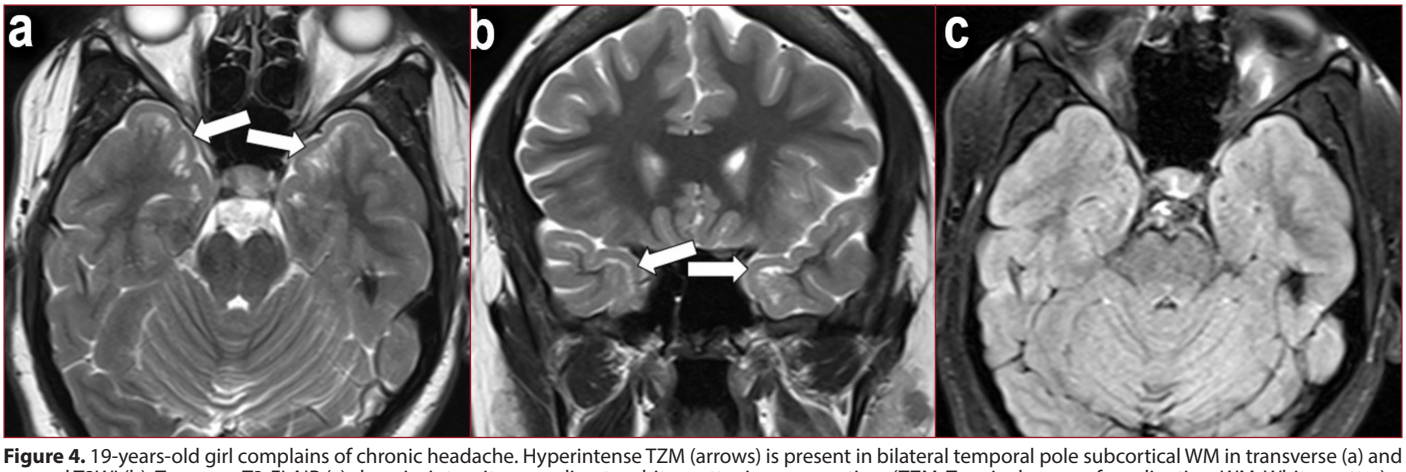

Figure 4. 19-years-old girl complains of chronic headache. Hyperintense TZM (arrows) is present in bilateral temporal pole subcortical WM in transverse (a) and coronal T2WI (b). Transvers T2-FLAIR (c) show isointensity according to white matter in same section. (TZM: Terminal zones of myelination, WM: White matter)

Parazzini et al.[12] in that TZM often occur in the subcortical WM; however, we found that the most common location was the insula, followed by the temporal poles. TZM in the peritrigonal WM were very rare after the age of 5–6 years.

Several autopsy studies showed that myelination of the frontal, parietal, and temporal subcortical association fibers was completed during early adulthood, and this may indicate completion of the higher intellectual functions.[13-15] Unlike these studies, our results showed that TZM occurred even during late adulthood (> 25 years old) and were most commonly localized in the insular subcortical association fibers.

Dennis et al.[16] stated that connection of the insula with other lobes continues until early adulthood. He suggested that this relationship decreased with age in the frontal and parietal lobes and increased in the temporal lobes. This may explain the later completion of myelination in the temporal and insular subcortical WM in our study.

We had some limitations. Our study was retrospective and all examinations in our study were obtained with 1.5 T MRI which has lower signal-to-noise ratio according to high-field MRIs. Studies with high-field MRIs (3T and above) will further reduce the contradictions on this subject.

CONCLUSION

Our results showed that, unlike other studies, TZM were most common in the insular subcortical WM. It should be remembered that insular and temporal subcortical TZM can occur at a significant rate, even in third decade. It should not be confused with pathological WM lesions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date: 29.04.2021, Decision No: 386).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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REFERENCES

1. Yakovlev PI, Lecours AR. The myelogenetic cycles of regional maturation of the brain. In: Minkowski A, ed. Regional development of the brain in early life. Oxford, UK: Blackwell, 1967:3–70.
2. Dietrich RB, Bradley WG, Zaragoza E J, et al. MR evaluation of early myelination patterns in normal and developmentally delayed infants. AJNR Am J Neuroradiol 1988;9:69–76
3. Martin E, Kikinis R, Zuerrer M, et al. Developmental stages of human brain: an MR study. J Comput Assist Tomogr 1988;12:917– 922
4. Staudt M, Schropp C, Staudt F, Obletter N, Bise K, Breit A. Myelination of the brain in MR: a staging system. Pediatr Radiol 1993;23:169–176
5. Barkovich AJ. MR of the normal neonatal brain: assessment of deep structures. AJNR Am J Neuroradiol 1998;19:1397–1403
6. Staudt M, Schropp C, Staudt F, et al. MRI assessment of myelination: an age standardization. Pediatr Radiol 1994:24:122–127
7. Barkovich AJ, Kjos BO, Jackson DE, Norman D. Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. Radiology 1988;166:173–180
8. Bird CR, Hedberg M, Drayer BP, Keller PJ, Flom RA, Hodak JA. MR assessment of myelination in infants and children: usefulness of marker sites. AJNR Am J Neuroradiol 1989;10:731–740
9. Curnes JT, Burger PC, Djang WT, Boyko O B. MR imaging of compact WM pathways. AJNR Am J Neuroradiol 1988;9:1061–1068
10. Barkovich AJ. Normal development of the neonatal and infant brain, skull, and spine. In: Pediatric neuroimaging. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2000:13–69
11. Maricich SM, Azizi P, Jones JY, et al. Myelination as assessed by conventional MR imaging is normal in young children with idiopathic developmental delay. AJNR Am J Neuroradiol. 2007;28(8):1602-1605. doi:10.3174/ajnr.A0602
12. Parazzini C, Baldoli C, Scotti G, Triulzi F. Terminal zones of myelination: MR evaluation of children aged 20-40 months. AJNR Am J Neuroradiol. 2002;23(10):1669-1673.
13. Kinney HC, Brody BA, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy: patterns of myelination in autopsied infants. J Neuropathol Exp Neurol 1988;47:3, 217–234
14. Baierl P, Forster CH, Fendel H, Naegele M, Fink U, Kenn W. Magnetic resonance imaging of normal and pathological WM maturation. Pediatr Radiol 1988;18:183–189
15. Curnes JT, Burger PC, Djang WT, Boyko O B. MR imaging of compact WM pathways. AJNR Am J Neuroradiol 1988;9: 1061–1068.
16. Dennis EL, Jahanshad N, McMahon KL, de Zubicaray GI, Martin NG, Hickie IB, Toga AW, Wright MJ, Thompson PM (2014) Development of insula connectivity between ages 12 and 30 revealed by high angular resolution diffusion imaging. Hum Brain Mapp 35(4):1790–1800.

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Original Article / Orijinal Araştırma

The Effect of Exercise on Serum Resistin and Leptin Values in Rats Fed with a High Fat Diet

Yüksek Yağlı Diyetle Beslenen Ratlarda Egzersizin Serum Resistin ve Leptin Değerlerine Etkisi

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Abstract

Aim: This study was performed to investigate the effect of exercise on serum resistin and leptin values in rats fed with a high-fat diet.

Material and Method: 24 Wistar albino male rats were used in the study. They were randomly divided into 4 groups, with 6 rats in each group. The groups were determined as the control group (C), exercise group (E), high-fat diet (HFD) group, and high-fat diet + exercise (HFDE) group.

Results: In this study, resistin values were found to be similar in the C, E, and HFDE groups, but different in the HFD group. It was determined that the resistin value in the HFD group was higher than the other groups. It was observed that exercise decreased the value of rising resistin. When evaluated in terms of leptin levels, the C and E groups showed similarity, while the HFD and HFDE groups showed similarity with each other. Although exercise slightly decreased the leptin level, which was highly increased with a high-fat diet, it was not statistically significant.

Conclusion: It has been determined that feeding with a high-fat diet causes an increase in serum resistin and leptin levels, and exercise provides a significant decrease in resistin values, but is not effective in leptin levels.

Keywords: Resistin, Leptin, Exercise, High-fat diet

Öz

Amaç: Bu çalışma, yüksek yağlı diyetle beslenen ratlarda egzersizin serum resistin ve leptin değerlerine nasıl bir etkisinin olacağını araştırmak için yapıldı.

Gereç ve Yöntem: Çalışmada 24 adet Wistar albino ırkı erkek rat kullanıldı. Her grupta 6 adet rat olacak şekilde rastgele 4 gruba ayrıldı. Gruplar kontrol grubu (C), egzersiz grubu (E), yüksek yağlı diyet (HFD) grubu ve yüksek yağlı diyet + egzersiz (HFDE) grubu olarak belirlendi.

Bulgular: Bu araştırmada resistin değerleri C, E, ve HFDE gruplarında benzer, HFD grubunda ise farklı bulunmuştur. HFD grubunda resistin değerinin, diğer gruplara göre yüksek olduğu tespit edilmiştir. Egzersizin yükselen resistin değerini düşürdüğü görülmüştür.

Leptin seviyeleri açısından değerlendirildiğinde C ve E grubu benzerlik gösterirken, HFD ve HFDE grupları da birbiri ile benzerlik göstermektedir. Yüksek yağlı diyet ile oldukça artan leptin seviyesini egzersiz bir miktar düşürse de, istatistiksel açıdan anlamlı bulunmamıştır.

Sonuç: Yüksek yağlı diyet ile beslenmenin serum resistin ve leptin düzeylerinde artışa sebep olduğu, egzersizin resistin değerlerinde anlamlı bir düşüş sağladığı fakat leptin düzeylerinde etkili olmadığı tespit edilmiştir.

Anahtar Kelimeler: Resistin, Leptin, Egzersiz, Yüksek yağlı diyet

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INTRODUCTION

The phenomenon of high-fat dietary nutrition and related obesity observed in Western societies has become a worldwide recognized problem. It is a well-known fact that high-fat dietary nutrition and obesity are the triggers and causes of many diseases.[1] High-fat diets cause disruption of energy balance and increase in adipose tissue mass. Regular exercise reduces the amount of fat in the body. It is known that exercise reduces deaths due to heart diseases, prevents osteoporosis and hypertension, as well as plays an important role in protecting against diseases such as diabetes and obesity.[2-4]

Resistin has been defined as a special hormone belonging to adipose tissue and has been reported to be associated with obesity, metabolic syndrome and diabetes. It is known that the release of resistin increases in obesity caused by diet. Resistin both prevents glucose from entering the cell and causes insulin resistance.[5,6] Leptin is a peptide hormone that has protein structure. Its rate in the body is directly proportional to the amount of adipose tissue. Leptin is known to be effective on growth and development, determining the metabolic rate and activating the sympathetic nervous system.[7,8] Leptin levels decrease with weight loss and increase with weight gain. As the number and size of fat cells in the body increase, leptin production increases and begins to be released into the circulation. When increased leptin reaches the hypothalamus, it reduces food intake.[9]

MATERIAL AND METHOD

This study was carried out with the permission dated 31/03/2022 and numbered 2022/03-05 given by Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee. 24 Wistar albino male rats were used in the study. All conditions were met according to laboratory animal care standards. Rats were randomly divided into 4 groups, with 6 rats in each group.

1. Control (C) Group: Standard nutrition program was applied to this group. During the experiment, normal pellet rat food and tap water were given.[10]

2. Exercise (E) Group: Along with the standard nutrition program, an exercise program was applied 3 days a week.

3. High-Fat Diet (HFD) Group: In the high-fat diet group, 300 g/kg margarine was melted and added to the standard pellet meal. The prepared mixture was applied daily for 8 weeks.[11]

4. High Fat Diet + Exercise (HFDE) Group: In this group, 300 g/kg margarine was melted and added to standard pellet feed. The prepared mixture was applied daily for 8 weeks. At the same time, an exercise program was applied 3 days a week.[10,11]

Exercise testing was performed on a Rat-specific treadmill. In order for the rats in the exercise group to adapt to the treadmill, after running at the lowest speed of the protocol for a period of 2 weeks (15 min/day), the treadmill protocol was adapted for 17 cm/sec speed to be 40 cm/sec at medium intensity (30 mins/day), 3 days a week.[10]

Test animals were anesthetized with Ketamine HCL (50 mg/kg) at the end of the 8th week. The blood taken from the hearts of the animals with the help of syringes were transferred to biochemistry tubes. After the tubes were centrifuged, serums were obtained. Commercial kits used in the study were determined by ELISA in accordance with the kit procedure.

Statistical Analysis: One-way Anova test was used for the analysis because the groups for resistin were normally distributed, and the group variances were homogeneous. Since the groups for leptin were not normally distributed and the group variances were not homogeneous, the Kruskal wallis test, one of the non-parametric tests, was used for analysis. Tukey test, one of the Post-Hoc tests, was used to determine the significant groups. The statistical significance level was taken as 5% in the calculations and the SPSS (ver.21) statistical package program was used for the calculations.

RESULTS

The effect of exercise on serum resistin and leptin values and statistical data in rats fed with a high-fat diet are given in **Table 1**.

Table 1. Resistin and leptin levels of the groups used in the study.

Groups	N	Resistin	Leptin
Control (C) Group	6	4.34±0.20^{b}	613.76±18.97^{b}
Exercise (E) Group	6	4.26±0.22^{b}	607.24±12.95^{b}
High-Fat Diet (HFD) Group	6	4.87±0.24^{a}	1690.76±201.81^{a}
High Fat Diet + Exercise (HFDE) Group	6	4.42±0.18^{b}	1584.16±140.55^{a}

* Different letters in the same column indicate statistical significance at p≤ 0.05. a,b: Shows the difference between groups (Tukey)

When the findings obtained in this study were evaluated statistically, it was determined that the resistin values were similar in the C, E and HFDE groups, and higher in the HFD group compared to the other groups. It was observed that resistin value increased with high-fat diet and decreased with exercise. When evaluated in terms of leptin levels, the K and E groups show similarity, while the HFD and HFDE groups show similarity with each other. Although exercise slightly decreased the leptin level, which was highly increased with a high-fat diet, it was not found to be statistically significant.

DISCUSSION

In this study conducted to examine the effects of high-fat diet and exercise on serum resistin and leptin values in rats, it was determined that feeding a high-fat diet increased the level of resistin in rats. Pagano et al. (2005) found in their study that serum resistin level was directly related to obesity.[12] It is known that serum resistin levels increase in rats set up with an experimental diet.[13] Steppan et al. showed in their study in 2001 that resistin is a hormone belonging to adipose tissue and its amount in the body is directly proportional to the amount of fat.[5] In another study, they reported that obesity

and resistin were related, and body fat mass and serum resistin level were related.[14] Koerner et al. (2005) stated in their study that the nutritional character had an effect on the level of resistin, the amount decreased with hunger, and increased again with food intake.[15] In a study, they found that 12 weeks of exercise and a low-calorie diet decreased the level of resistin.[16] The reason for this decrease in resistin level was also reported as weight loss. It has been found that exercise performed 4 times a week for 4 months causes a decrease in the level of serum resistin.[17] In studies on test animals, it has been reported that resistin causes changes in insulin metabolism in cells and increases glucose production in the liver, resulting in insulin resistance.[18] It was determined that in mice fed a high-fat diet, insulin resistance developed, and with the subsequent resistin oligonucleotide treatment, insulin resistance decreased.[19] In another study, it was shown that resistin is effective in liver cells and causes insulin resistance.[20] It can be considered that in this study, serum resistin level increased in rats fed a high-fat diet, and this was due to the weight gain in rats. As in the literature, it has been determined that the diet that causes weight gain increases the serum resistin level, and there is no increase in rats that are not fed with a high-fat diet. Resistin values were similar in the C, E and HFDE groups, but higher in the HFD group. When HFDE and HFD groups were compared, the difference between the resistin values was found to be statistically significant. Resistin values did not increase in the HFDE group, in which both high-fat diet and exercise were applied, and showed parallelism with the control group. When the studies conducted in recent years are examined, it has been reported that regular exercise is beneficial in diseases such as diabetes, high blood pressure and cardiovascular diseases, and reduces the risks.[21] In this study, it was determined that the increase in serum resistin levels caused by high-fat diet decreased with exercise.

When this study was examined in terms of leptin levels, the C and E groups were found to be statistically similar to each other, but different when compared with the HFD and HFDE groups. When HFD and HFDE groups were compared with each other, the difference between leptin levels was not found to be significant. In other words, it was observed that feeding with a high-fat diet increased the leptin level, and although exercise slightly decreased the increased leptin level, it was not statistically significant. As it is known, the most important task of leptin in the organism is to reduce the risk of obesity by regulating food intake and energy metabolism.[22] Severe obesity has been reported in leptin-deficient mice.[23] In another study, it was shown that leptin levels were quite high in obese mice, and this ratio did not change with exercise.[24] Although prolonged and heavy exercise reduces leptin level by approximately 1/3, it was observed that leptin level increased to the level before the exercise 18-24 hours after the exercise.[25] It is considered that this is not related with weight loss and rather the long-term fasting or exercise reduces leptin secretion by affecting fatty acids in the blood. In the study by Olive et al., it was reported that the leptin level did not decrease immediately after the exercise, but decreased after a day or two. Another study found that leptin levels did not decrease even one day after exercise, but a decrease of approximately 30% was found after two days of exercise.[26] When the literature was searched, quite different opinions were found about the relationship between leptin and exercise. Generally, studies have reported that short-term exercise does not reduce leptin levels, and decreased leptin levels are also associated with circadian rhythm.[27,28] It has been determined that long-term exercises significantly reduce leptin levels, and the duration and form of exercise are important.[25,29,30] In this study, it was observed that feeding a high-fat diet significantly increased leptin levels, but exercise was not very effective in reducing leptin levels. It is considered that longer and more intense exercises can reduce leptin levels by affecting body fat ratio and free fatty acids in the blood.

CONCLUSION

As a result, significant increases were observed in both resistin and leptin levels in rats fed with a high-fat diet. It was observed that a 12-week exercise was effective in reducing the serum resistin level, but the duration and form of this exercise was not effective in reducing the leptin level. It is considered that longer and more vigorous exercises may produce different results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee (Dater: 31/03/2022, Decision No: 2022/03-05).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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REFERENCES

1. Mosby TT, Cosgrove M, Sarkardei S, et al. Nutrition in adult and childhood cancer:role of carcinogens and anti-carcinogens. Anticancer Res 2012;32(10):4171-92.
2. Toumilehto J, Lindström J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343-50.
3. Swinburn BA, Caterson I, Seidell JC, et al. Diet, nutrition and the prevention of excess weight gain and obesity. Public Health Nutr 2004;7(1a):123-46.

4. Kodama S, Tanaka S, Heianza Y, et al. Association between physical activity and risk of all-cause mortality and cardiovascular disease in patients with diabetes:a meta-analysis. Diabetes Care 2013;36(2):471-9.
5. Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. Nature 2001;409(6818):307-12.
6. Ukkola O. Resistin-a mediator of obesity-associated insulin resistance or an innocent bystander?. Eur J Endocrinol 2002;147(5):571-4.
7. Lee GH, Proenca R, Montez JM, et al. Abnormal splicing of the leptin receptor in diabetic mice. Nature 1996;379(6566):632-5.
8. Fantuzzi G, Faggioni R. Leptin in the regulation of immunity, inflammation, and hematopoiesis. J Leukocyte Biol 2000;68(4):437-46.
9. Keleş V, Büyükgüzel K, Büyükgüzel E. Leptin ve Metabolik Düzenlenmedeki Rolü. Türkiye Diyabet ve Obezite Derg 2018;2(1):17-22.
10. Yaşar S, Günbatar N, Yüksek S, et al. Effect of exercise on erythrocyte osmotic fragility in high fat diet fed rats during intermittent fasting. Eastern J Med 2017;22(4):176.
11. Günbatar, N, Bayıroğlu, F. The Effect of a Highly Saturated Fat Diet and Intermittent Fasting Diet on Experimental Colon Cancer Development and Some Serum Inflammation Markers in Rats, 1 Adiponectin and Lipid Metabolism . Van Veterinary J 2015;26 (3):123-7 .
12. Pagano C, Marin O, Calcagno A, et al. Increased serum resistin in adults with prader-willi syndrome is related to obesity and not to insulin resistance. J Clin Endocrinol Metab 2005;90(7):4335-40.
13. Steppan CM, Lazar MA. Resistin and obesity-associated insulin resistance. Trends Endocrinol Metab 2002;13(1):18-23.
14. Eminler AT, Aygun C, Konduk T, et al. The relationship between resistin and ghrelin levels with fibrosis in nonalcoholic fatty liver disease. J Res Med Sci 2014;19 (11):1058.
15. Koerner A, Kratzsch J, Kiess W. Adipocytokines:leptin the classical, resistin the controversical, adiponectin—the promising, and more to come. Best Pract Res Clin Endocrinol Metab 2005;19(4):525-46.
16. Jung SH, Park HS, Kim KS, et al. Effect of weight loss on some serum cytokines in human obesity:increase in IL-10 after weight loss. J Nutrition Biochem 2008;19(6):371-5.
17. Kadoglou NP, Perrea D, Iliadis F, et al. Exercise reduces resistin and inflammatory cytokines in patients with type 2 diabetes. Diabetes Care 2007;30(3):719-21.
18. Rajala MW, Obici S, Scherer PE, et al. Adipose-derived resistin and gut-derived resistin-like molecule–β selectively impair insulin action on glucose production. J Clin Invest 2003;111(2):225-30.
19. Muse ED, Obici S, Bhanot S, et al. Role of resistin in diet-induced hepatic insulin resistance. J Clin Invest 2004;114(2):232-9.
20. Palanivel R, Sweeney G. Regulation of fatty acid uptake and metabolism in L6 skeletal muscle cells by resistin. FEBS letters 2005;579(22):5049-54.
21. Kraemer RR, Castracane VD. Exercise and humoral mediators of peripheral energy balance:ghrelin and adiponectin. Experiment Biol Med 2007;232(2):184-94.
22. Lin TC, Huang KW, Liu CW, et al. Leptin signaling axis specifically associates with clinical prognosis and is multifunctional in regulating cancer progression. Oncotarget 2018;9(24):17210.
23. Correia ML, Haynes WG. Obesity-related hypertension:is there a role for selective leptin resistance?. Curr Hypertens Rep 2004;6(3):230-5.
24. Pagano C, Marzolo M, Granzotto M, et al. Acute Effects of Exercise on Circulating Leptin in Lean and Genetically Obesefa/faRats. Biochem Biophysic Res Communicat 1999;255(3):698-702.
25. Landt M, Lawson GM, Helgeson JM, et al. Prolonged exercise decreases serum leptin concentrations. Metabolism 1997;46(10):1109-12.
26. Essig DA, Alderson NL, Ferguson MA, et al. Delayed effects of exercise on the plasma leptin concentration. Metabolism 2000;49(3):395-9.
27. Weltman A, Pritzlaff CJ, Wideman L, et al. Intensity of acute exercise does not affect serum leptin concentrations in young men. Med Sci Sports Exercise 2000;32(9):1556-61.
28. Kraemer R., Acevedo E, Synovitz L, et al. Leptin and steroid hormone responses to exercise in adolescent female runners over a 7-week season. Eur J Applied Physiol 2001;86(1):85-91.
29. Olive JL, Miller GD. Differential effects of maximal-and moderate-intensity runs on plasma leptin in healthy trained subjects. Nutrition 2001;17(5):365-9.
30. Gökbel H., et al. "Ratlarda zorlu egzersizde serum leptin düzeylerindeki değişme ve çinko eksikliği/takviyesiyle ilişkisi. I." Leptin Sempozyumu 2003;20-2.

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Original Article / Orijinal Araştırma

Could Uric Acid to High-Density Lipoprotein-Cholesterol Ratio be Considered as a Marker of Hemodialysis Sufficiency?

Ürik Asit Yüksek Yoğunluklu Lipoprotein-Kolesterol Oranı, Hemodiyaliz Yeterliliğinin Bir Belirteci Olarak Kabul Edilebilir Mi?

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Abstract

Aim: Hemodialysis (HD) is one of the most widely utilized renal replacement therapies in individuals with end-stage chronic kidney disease (CKD). The purpose of this study was to compare the Uric acid to HDL cholesterol ratio (UHR) levels of well-treated HD patients to those of those who had inadequate HD therapy.

Material and Method: In the research, 60 participants had sufficient HD, and 24 had insufficient HD. 31 men (52%) and 29 women (48%) had adequate HD, whereas 17 men (71%) and seven women (29%) did not. Data on HD patients were acquired from patient files and the institution's database. A URR value of more than 70% designated the sufficient HD group, whereas less than 70% defined the insufficient HD group. Furthermore, laboratory data, such as the UHR of the study groups, were compared.

Results: The UHRs for adequate and inadequate HD were 0.160±04 and 0.20±0.07, respectively. The UHR of patients with insufficient HD was substantially greater than that of the subjects with sufficient HD (p=0.004). Besides, UHR was substantially and positively connected with urea before HD (r=0.37, p=0.001), urea after HD (r=0.39, p=0.001), serum creatinine before HD (r=0.48, p0.001), serum creatinine after HD (r=0.45, p0.001), and negatively correlated with URR (r=-0.29, p=0.008), according to correlation analyses. In individuals with chronic renal disease, a UHR value higher than 0.16 exhibited 67% sensitivity and 57% specificity in detecting inadequate HD.

Conclusion: We propose that UHR, in addition to URR, might be used to determine HS sufficiency in CKD patients undergoing HD therapy.

Keywords: Hemodialysis, uric acid to HDL cholesterol ratio, urea reduction ratio

Öz

Amaç: Hemodiyaliz (HD), son dönem kronik böbrek hastalığı (KBH) olan bireylerde en yaygın kullanılan renal replasman tedavilerinden biridir. Bu çalışmanın amacı, iyi tedavi edilen HD hastalarının Ürik asit / HDL kolesterol oranı (UHR) düzeylerini, yetersiz HD tedavisi almayanlarınkilerle karşılaştırmaktı.

Gereç ve Yöntem: Araştırmada 60 katılımcının HD'si yeterli, 24'ünün HD'si yetersizdi. 31 erkek (%52) ve 29 kadın (%48) yeterli HD'ye sahipken, 17 erkek (%71) ve yedi kadın (%29) değildi. HD hastalarına ilişkin veriler, hasta dosyalarından ve kurumun veri tabanından elde edildi. URR değerinin %70'in üzerinde olması yeterli HD grubunu, %70'in altında olması ise yetersiz HD grubunu tanımlamıştır. Ayrıca, çalışma gruplarının UHR'si gibi laboratuvar verileri karşılaştırıldı.

Bulgular: Yeterli ve yetersiz HD için UHR'ler sırasıyla 0,160±04 ve 0,20±0,07 idi. Yetersiz HD'si olan hastaların UHR'si, yeterli HD'si olan deneklerden önemli ölçüde daha yüksekti (p=0.004). Ayrıca UHR, HD öncesi üre (r=0,37, p=0,001), HD sonrası üre (r=0,39, p=0,001), HD öncesi serum kreatinin (r=0,48, p0,001), serum Korelasyon analizlerine göre HD sonrası kreatinin (r=0.45, p0.001) ve URR ile negatif korelasyon (r=-0.29, p=0.008). Kronik böbrek hastalığı olan bireylerde, 0,16'dan yüksek bir UHR değeri, yetersiz HD'yi saptamada %67 duyarlılık ve %57 özgüllük sergilemiştir.

Sonuç: HD tedavisi gören KBH hastalarında HS yeterliliğini belirlemek için URR'ye ek olarak UHR'nin kullanılabileceğini öneriyoruz.

Anahtar Kelimeler: Hemodiyaliz, ürik asit HDL oranı, üre düşüş oranı

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INTRODUCTION

Hemodialysis (HD) is one of the most widely utilized renal replacement therapies in individuals with end-stage chronic kidney disease (CKD). Urea reduction ratio (URR) and normalized treatment ratio (Kt/V) are two indicators used to calculate HD dosage (1). Inflammation is critical in the progression of CKD. According to the scientists, inflammatory markers and indicators of oxidative stress are higher in patients with grade 3-5 CKD than in healthy participants (2). Furthermore, inflammation is linked to the development of CKD (3). Many inflammatory markers have been investigated and discovered to be elevated in the HD population. C-reactive protein (CRP), tumor necrosis factor (TNF)-alpha, and adiponectin are examples (4; 5). Therefore, effective HD has a pivotal role in decreasing the inflammatory burden in CKD.

Uric acid is the byproduct of purine metabolism. The uric acid elevation is linked to oxidative damage and inflammation (6). Subjects with high uric acid levels are more likely to develop CKD (7). It also rises in people with diabetes with inadequate metabolic control (8; 9). The uric acid to HDL-cholesterol ratio (UHR) has recently been proposed as a potential metabolic and inflammatory measure in specific situations. It was hypothesized that UHR predicted metabolic syndrome better than any other metric (10).

Furthermore, it was linked to HbA1c levels in type 2 diabetes patients (11). Furthermore, individuals with non-alcoholic fatty liver disease had greater UHR levels than healthy controls (12). Because metabolic syndrome, type 2 diabetes, and non-alcoholic fatty liver disease are all illnesses with a low-grade chronic inflammatory burden, UHR has been acknowledged as a metabolic and inflammatory marker. Therefore, in the present study, we aimed to determine UHR levels of the sufficiently treated HD patients according to URR level and compare them to those who received poor HD treatment.

MATERIAL AND METHOD

Study Design

A total of 84 subjects enrolled in the study; 60 were in the sufficient HD group and 24 in the insufficient HD group. There were 31 (52%) men and 29 (48%) women in the sufficient HD group, while there were 17 (71%) men and 7 (29%) women in the insufficient HD group. The mean age of the subjects in sufficient and insufficient HD groups were 62±15 and 58±14 years, respectively. This study was designed retrospectively, and after approval from the institutional review board, the data about HD patients were obtained from the patient's files and the institution's database. A sufficient HD group was determined with a URR value greater than 70%. The subjects with a URR value equal to or below 70% were grouped as insufficient HD subjects. The age and gender of the sufficient and insufficient HD groups were recorded. Urea, creatinine, and potassium (K) levels were recorded before and after dialysis. Complete blood count parameters, leukocyte count (WBC), hemoglobin (Hb), hematocrit (Htc), and platelet count (Plt) of the study groups were obtained. Fasting plasma glucose, alanine transaminase, sodium (Na), phosphorus (P), bicarbonate (HCO3), parathyroid hormone (PTH), total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, c-reactive protein (CRP), serum iron, iron-binding capacity, and ferritin levels were also obtained and recorded. In addition, KTV and URR levels were calculated. UHR was calculated by simple division of serum uric acid by HDL cholesterol. Data from the sufficient and insufficient HD groups were compared. All procedures were carried out under the ethical rules and the principles of the Declaration of Helsinki. Our study was approved by the XXX University Non-Interventional Clinical Researches Ethics Committee (Date: 20.05.2021, Decision No: 16318).

Statistical Analyses

The SPSS software (SPSS 18.0 for Windows, IBM Co., Chicago, IL, USA) is used to conduct the statistical analyses. The distribution of the variables between study groups was analyzed with the Shapiro-Wilk test. Variables with normal distribution were expressed as mean ± standard deviation (SD) and compared with independent samples t-test. Variables without normal distribution were expressed as median (min.-max.) and compared with the Mann-Whitney U test. A comparison of categorical variables was conducted with the X2 test. Pearson's correlation analysis test revealed a possible correlation between study variables. Receiver operative characteristics (ROC) analysis is used to observe the sensitivity and specificity of UHR in determining HD sufficiency. A p-value lower than 0.05 was considered statistically significant.

RESULTS

Age was not significantly different among the study groups (p=0.21). Gender was also not statistically different among study groups.

Urea before HD (p=0.11), K before HD (p=0.15), Na (p=), Ca (p=0.97), total protein (p=0.52), albumin (p=0.31), FPG (p=0.73), HCO3 (p=0.35), total cholesterol (p=0.08), HDL cholesterol (p=0.12), CRP (p=0.13), WBC (p=0.053), Plt (p=0.88), PTH (p=0.95), serum iron (p=0.42) and iron binding capacity (p=0.08) of the sufficient and insufficient HD groups were not statistically different.

Serum creatinine before (p=0.01) and after (p<0.001) HD, urea after HD (p<0.001), K after HD (p=0.02), P (p=0.01), uric acid (p=0.01) and ferritin (p=0.03) levels of the sufficient and insufficient HD groups were statistically different. **Table 1** and **Table 2** show the general data and laboratory findings of the study population. **Table 3** demonstrates descriptive statistics.

Table 1. Demographic characteristics of the patients

	n	%
Age (year)		
Min-Max	23-88	
Mean±SD	60,75±14,3	
Gender		
Female	36	(42,9)
Male	48	(57,1)
Dialysis way of entry		
Permanent right subclavian catheter	7	8,3
Right AVF	19	22,6
Right Femoral catheter	1	1,2
Permanent right femoral catheter	1	1,2
Right juguler catheter	5	6,0
Left AVF	51	60,7
Primary etiological cause		
Idiopathic	16	19,0
Atrophic kidney	1	1,2
Diabetes Mellitus	14	16,7
Diabetes Mellitus + hypertension	17	20,2
Diabetes Mellitus + hypertension + Nephrolithiasis	2	2,4
FMF	2	2,4
FMF + Amyloidosis	2	2,4
Glomerulonephritis	3	3,6
Hypertension	13	15,5
Hypertension + Nephrolithiasis	1	1,2
Cystic kidney disease	1	1,2
Contrast nephropathy	1	1,2
Nephrolithiasis	3	3,6
Nephrotic syndrome	1	1,2
Polycystic kidney	3	3,6
Renal cancer	1	1,2
Systemic lupus erythematosus	1	1,2
Tuberculosis	1	1,2
Wegener granulomatosis	1	1,2

AVF: Arteriovenous fistula, FMF: Familial Mediterranean Fever

Table 2. Laboratory data of the study population

Laboratory Findings	Minimum-Maximum	Mean- Std. Deviation
Urea (Dialysis entrance)	6-206	125,61±32,19
Urea (Dialysis exit)	9-96	33,39±14,96
Creatin (Dialysis entrance)	3,39-14,6	7,89±2,37
Creatin (Dialysis exit)	0,81-6,6	2,64±1,15
Potassium (Dialysis entrance)	3,7-7,03	5,46±0,7
Potassium (Dialysis exit)	2,15-5,03	3,6±0,47
Ferritin	9,4-1867	633,05±481,48
PTH	17-2000	505,44 ±358,99
CRP	0,21-84	9,63±11,35
Uric acid	3,8-9,2	5,83±1,09
HDL	20-76	37±9,9
KTV	0,86-20,8	1,89±2,11
URR	49-86	74,26±6,34

PTH: Parathormone, CRP: C-Reactive Protein, HDL: High-Density Lipoprotein, URR: Urea reduction ratio KTV(Kt/V): normalized treatment ratio

Table 3. Descriptive analysis of patients.

Descriptive Statistics

		Median	Mean	Std. Error	Std. Deviation	Min.	Max.
Age	F	64.500	61.882	2.475	14.432	23.000	82.000
Age	M	61.000	59.980	2.034	14.383	26.000	88.000
Dialysis time (month)	F	16.000	16.029	0.143	0.834	15.000	17.000
Dialysis time (month)	M	16.000	16.160	0.108	0.766	15.000	17.000
Uric acid	F	5.400	5.582	0.162	0.945	3.800	7.600
Uric acid	M	5.900	5.998	0.163	1.152	4.000	9.200
CRP	F	5.000	6.986	1.137	6.633	0.210	35.000
CRP	M	7.020	11.437	1.899	13.426	0.880	84.000
HDL	F	40.000	41.000	1.862	10.857	20.000	76.000
HDL	M	34.000	34.240	1.153	8.156	21.000	60.000
LDL	F	93.000	101.676	6.118	35.675	38.000	184.000
LDL	M	73.000	76.180	3.665	25.916	25.000	159.000
T.KOL	F	164.000	170.706	7.800	45.482	101.000	289.000
T.KOL	M	138.500	139.560	4.769	33.722	79.000	219.000
KT/V	F	1.830	2.371	0.561	3.269	1.250	20.800
KT/V	M	1.535	1.566	0.036	0.256	0.860	2.100
URR %	F	79.000	77.265	0.905	5.276	66.000	86.000
URR %	M	73.000	72.220	0.884	6.248	49.000	85.000

CRP: C-Reactive Protein, HDL: High-Density Lipoprotein, URR: Urea reduction ratio KTV(Kt/V): normalized treatment ratio. Min.: Minimum, Max.: Maximum

The UHR of the sufficient and insufficient HD groups were 0.16±0.04 and 0.20± 0.07, respectively. UHR of the subjects with insufficient HD was significantly higher than that of the sufficient HD group (p=0.004). **Table 4** reveals independent sample statistical results.

Correlation analyses revealed that UHR was significantly and positively correlated with urea before HD (r=0.37, p=0.001), urea after HD (r=0.39, p=0.001), serum creatinine before HD (r=0.48, p<0.001), serum creatinine after HD (r=0.45, p<0.001), and inversely correlated with URR (r=-0.29, p=0.008). **Table 5** indicates correlation analyses.

In ROC analysis, a UHR value greater than 0.16 had 67% sensitivity and 57% specificity in determining insufficient HD in patients with chronic kidney disease (**Figure**).

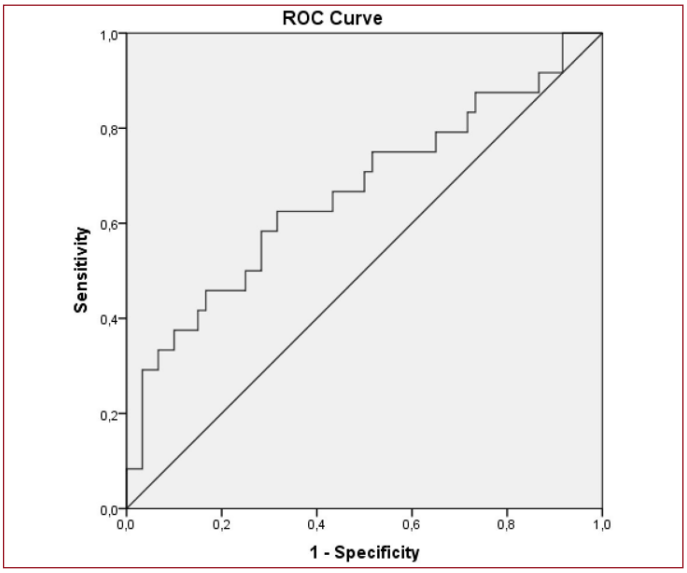

Figure: ROC curve of UHR in predicting insufficient HD

Table 4. Statistical analysis of independent samples test results.

Independent Samples Test

	Levene's Test for Equality of Variances		t-test for Equality of Means						
			t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
								Lower	Upper
AGE	0,005	0,947	1,267	82	0,209	4,375	3,452	-2,493	11,243
			1,303	45,049	0,199	4,375	3,358	-2,388	11,138
ureaentrance	0,211	0,647	-1,617	82	0,110	-12,450	7,700	-27,768	2,868
			-1,659	44,844	0,104	-12,450	7,504	-27,566	2,666
Creaentrance	3,193	0,078	-2,678	82	0,009	-1,4791667	0,5524128	-2,5780916	-0,3802417
			-2,342	33,215	0,025	-1,4791667	0,6316584	-2,7639687	-0,1943647
Kexit	0,066	0,798	-2,425	82	0,017	-0,2677500	0,1104071	-0,4873849	-0,0481151
			-2,251	36,710	0,030	-0,2677500	0,1189556	-0,5088413	-0,0266587
UA	7,604	0,007	-2,670	82	0,009	-0,6760000	0,2531996	-1,1796947	-0,1723053
			-2,236	31,122	0,033	-0,6760000	0,3023790	-1,2926076	-0,0593924
HCO3	2,720	0,103	0,935	82	0,353	0,5768333	0,6171685	-0,6509113	1,8045780
			1,077	59,117	0,286	0,5768333	0,5355606	-0,4947767	1,6484434
HDL	0,189	0,665	1,567	82	0,121	3,700	2,362	-0,998	8,398
			1,563	42,210	0,126	3,700	2,367	-1,077	8,477
Chol	1,103	0,297	1,788	82	0,077	17,733	9,916	-1,993	37,460
			2,005	55,197	0,050	17,733	8,846	0,008	35,459
UHR	5,392	0,023	-2,950	82	0,004	-0,04175	0,01415	-0,06990	-0,01360
			-2,471	31,133	0,019	-0,04175	0,01690	-0,07620	-0,00730

UA: Uric Acid, HCO3: Bicarbonate, HDL: High-Density Lipoprotein, UHR: Uric acid to HDL cholesterol ratio

Table 5. Pearson correlation analyses.

Correlations

	AGE	ureaentrance	ureaexit	Creaentrance	Creaeaexit	CRP	KTV	URR	UHR
	1	-0.227*	-0.215*	-0.477**	-0.374**	0.016	0.121	0.084	-0.205
AGE		0.038	0.049	0.000	0.000	0.888	0.272	0.449	0.062
	84	84	84	84	84	84	84	84	84
	-0.227*	1	0.790**	0.398**	0.482**	-0.004	-0.103	-0.255*	0.365**
ureaentrance	0.038		0.000	0.000	0.000	0.972	0.351	0.019	0.001
	84	84	84	84	84	84	84	84	84
	-0.215*	0.790**	1	0.460**	0.742**	0.079	-0.274*	-0.726**	0.386**
ureaexit	0.049	0.000		0.000	0.000	0.473	0.012	0.000	0.000
	84	84	84	84	84	84	84	84	84
	-0.477**	0.398**	0.460**	1	0.873**	0.080	-0.104	-0.354**	0.477**
Creaentrance	0.000	0.000	0.000		0.000	0.468	0.346	0.001	0.000
	84	84	84	84	84	84	84	84	84
	-0.374**	0.482**	0.742**	0.873**	1	0.106	-0.183	-0.697**	0.450**
Creaeaexit	0.000	0.000	0.000	0.000		0.335	0.095	0.000	0.000
	84	84	84	84	84	84	84	84	84
	0.016	-0.004	0.079	0.080	0.106	1	-0.092	-0.123	0.067
CRP1	0.888	0.972	0.473	0.468	0.335		0.403	0.266	0.545
	84	84	84	84	84	84	84	84	84
	0.121	-0.103	-0.274*	-0.104	-0.183	-0.092	1	0.265*	-0.098
KTV1	0.272	0.351	0.012	0.346	0.095	0.403		0.015	0.376
	84	84	84	84	84	84	84	84	84
	0.084	-0.255*	-0.726**	-0.354**	-0.697**	-0.123	0.265*	1	-0.288**
URR1	0.449	0.019	0.000	0.001	0.000	0.266	0.015		0.008
	84	84	84	84	84	84	84	84	84
	-0.205	0.365**	0.386**	0.477**	0.450**	0.067	-0.098	-0.288**	1
UHR	0.062	0.001	0.000	0.000	0.000	0.545	0.376	0.008	
	84	84	84	84	84	84	84	84	84

CRP: C-Reactive Protein, UHR: Uric acid to HDL cholesterol ratio, URR: Urea reduction ratio KTV(Kt/V): normalized treatment ratio

DISCUSSION

We showed for the first time in the medical literature that UHR could predict HD sufficiency in CKD patients receiving HD treatment. Significant inverse correlation between UHR and URR and considerable sensitivity and specificity of UHR in selecting subjects with insufficient HD are essential outcomes of the present study.

The role of UHR was foremost proposed by Aktas et al. (10) and Kocak et al. (11) in subjects with type 2 diabetes mellitus and metabolic syndrome. It was considered a metabolic predictor and, thus, an inflammatory marker in chronic conditions characterized by continuous low-grade inflammation. Chronic kidney disease is also related to a chronic inflammatory burden (19;20). Therefore, the relationship between UHR and dialysis sufficiency reported in the present study is not surprising. Indeed, the authors reported an inverse correlation between glomerular filtration rate and UHR (11).

The present study correlated serum creatinine levels before and after dialysis with UHR. Similar studies have been reported in the literature (21;22). Impaired renal functions have been reported in subjects with high normal uric acid levels (13), a component of the UHR. Similar results have been reported by Cai et al. (14). There was a weak but significant inverse correlation between serum uric acid and glomerular filtration rate in a study from Taiwan (15). Per the literature knowledge, we reported a significant correlation between UHR and serum creatinine levels, the most important determinant of glomerular filtration rate.

Various reasons may cause chronic inflammation in the CKD population. Bio-incompatible dialysis membranes, infections of the fistula or graft used as HD access, endotoxin exposure, malnutrition, poor dental hygiene, dialysate, and back filtration are possible components of inflammatory burden in these patients (5; 16-18). Although CRP is nearly a universal marker of inflammation, our study showed that CRP levels of sufficient and insufficient HD groups were not statistically different (23-25). Moreover, there was no significant correlation between UHR and CRP levels. We consider that this was mainly due to the small study population of the present report.

Limitations

Limitations of our study are a retrospective design which may cause difficulties in interpreting the study results and a relatively small study population. The second limitation could be the lack of investigation of the other laboratory parameters, such as TNF alpha and interleukins. However, to our knowledge, this is the first study in the literature that pointed out an association between UHR and HD sufficiency.

CONCLUSION

In conclusion, we suggest that UHR could be an auxiliary tool to URR in determining HS sufficiency in CKD patients receiving HD treatment. However, prospective studies with a larger cohort may be required to suggest the relationship between UHR and inflammation in this population.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Amasya University Non-interventional Clinical Research Ethics Committee (Date: 20.05.2021, Decision No: 16318).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Li Z, Lew NL, Lazarus JM, Lowrie EG. Comparing the urea reduction ratio and the urea product as outcome-based measures of hemodialysis dose. Am J Kidney Dis 2000;35(4):598-605.
2. Oberg BP, McMenamin E, Lucas FL, et al. Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. Kidney Int 2004;65(3):1009-16.
3. Ruiz S, Pergola PE, Zager RA, Vaziri ND. Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. Kidney Int 2013;83(6):1029-41.
4. Kir HM, Eraldemir C, Dervisoglu E, Caglayan C, Kalender B. Effects of chronic kidney disease and type of dialysis on serum levels of adiponectin, TNF-alpha and high sensitive C-reactive protein. Clin Lab 2012;58(5-6):495-500.
5. Brito F, Almeida S, Figueredo CM, Bregman R, Suassuna JH, Fischer RG. Extent and severity of chronic periodontitis in chronic kidney disease patients. J Periodontal Res 2012;47(4):426-30.
6. Glantzounis GK, Tsimoyiannis EC, Kappas AM, Galaris DA. Uric acid and oxidative stress. Curr Pharm Des 2005;11(32):4145-51.
7. Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol 2008;19(12):2407-13.
8. Duman TT, Kocak MZ, Atak BM, Erkus E. Serum uric acid is correlated with HbA1c levels in type 2 diabetes mellitus. Exp Bio Res 2018;1(1):6-9.
9. Atak BM, Duman TT, Kocak MZ, Savli H. Serum uric acid level is associated with type 2 diabetes mellitus and diabetic regulation. Exp Bio Res 2018;1(4):135-9.
10. Kocak MZ, Aktas G, Erkus E, Sincer I, Atak B, Duman T. Serum uric acid to HDL-cholesterol ratio is a strong predictor of metabolic syndrome in type 2 diabetes mellitus. Rev Assoc Med Bras 2019;65(1):9-15.
11. Aktas G, Kocak MZ, Bilgin S, Atak BM, Duman TT, Kurtkulagi O. Uric acid to HDL cholesterol ratio is a strong predictor of diabetic control in men with type 2 diabetes mellitus. Aging Male 2020;23(5):1098-102.
12. Zhang Y-N, Wang Q-Q, Chen Y-S, Shen C, Xu C-F. Association between serum uric acid to hdl-cholesterol ratio and non-alcoholic fatty liver disease in lean chinese adults. Int J Endocrinol 2020;2020:1-6.
13. Rosolowsky ET, Ficociello LH, Maselli NJ, et al. High-normal serum uric acid is associated with impaired glomerular filtration rate in nonproteinuric patients with type 1 diabetes. Clin J Am Soc Nephrol 2008;3(3):706-13.
14. Cai XL, Han XY, Ji LN. High-normal serum uric acid is associated with albuminuria and impaired glomerular filtration rate in Chinese type 2 diabetic patients. Chin Med J (Engl) 2011;124(22):3629-34.
15. See LC, Kuo CF, Chuang FH, et al. Serum uric acid is independently associated with metabolic syndrome in subjects with and without a low estimated glomerular filtration rate. J Rheumatol 2009;36(8):1691-8.

16. Nadeem M, Stephen L, Schubert C, Davids MR. Association between periodontitis and systemic inflammation in patients with end-stage renal disease. SADJ : journal of the South African Dental Association = tydskrif van die Suid-Afrikaanse Tandheelkundige Vereniging 2009; 64: 470-3.
17. Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JJ, De Nardin E. Periodontal infections contribute to elevated systemic C-reactive protein level. J Periodontol 2001;72(9):1221-7.
18. Pejcic A, Kesic LJ, Milasin J. C-reactive protein as a systemic marker of inflammation in periodontitis. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clin Microbiol 2011; 30: 407-14.
19. Stenvinkel P, Chertow GM, Devarajan P, et al. Chronic Inflammation in Chronic Kidney Disease Progression: Role of Nrf2. Kidney Int Rep 2021;6(7):1775-87.
20. Brennan E, Kantharidis P, Cooper ME, Godson C. Pro-resolving lipid mediators: regulators of inflammation, metabolism and kidney function. Nat Rev Nephrol 2021;17(11):725-39.
21. Agraharkar M, Nair V, Patlovany M. Recovery of renal function in dialysis patients. BMC Nephrol 2003;4:9.
22. Bani-Hani S, Showkat A. Renal function recovery in dialysis dependent patients. Tenn Med 2013;106(8):36-40.
23. Valga F, Monzón T, Vega-Diaz N, Rodriguez-Perez JC, Ruiz-Santana S. Inflammation and hemodialysis adequacy: Are C-reactive protein levels influenced by dialysis dose? Nefrologia (Engl Ed) 2021:S0211-6995(21)00112-0.
24. Hajji M, Khedher R, Mrad M, et al. Effects of Zinc supplementation on serum copper to Zinc and CRP to albumin ratios in hemodialysis patients. J Med Biochem 2021;40(2):193-8.
25. Ridker PM, Rane M. Interleukin-6 Signaling and Anti-Interleukin-6 Therapeutics in Cardiovascular Disease. Circ Res 2021;128(11):1728-46.

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Original Article / Orijinal Araştırma

Immunohistochemical Expression of B Cell Transcription Factors in Hodgkin's Lymphoma and Their Use in Differential Diagnosis

Hodgkin Lenfomada B Hücre Transkripsiyon Faktörlerinin İmmünohistokimyasal İfadesi ve Ayırıcı Tanıda Kullanımı

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Abstract

Aim: Classical Hodgkin lymphoma is common; it is one of the lymphomas whose differential diagnosis can be difficult. It is thought that Hodgkin's cell may originate from the germinal centre. Our aim in this study was to determine the germinal centre transformation markers OCT-2, BOB.1, BCL-6, PAX-5, CD20 and MUM-1 in Classic Hodgkin Lymphoma (CHL), Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) and Diffuse Large B-cell Lymphoma (DLBCL) to evaluate the expressions of by immunohistochemical method and chromogenic in-situ hybridization (ISH) of EBV early RNAs (EBER).

Material and Method: 49 biopsies diagnosed with Hodgkin lymphoma (HL), 5 with NLPHL and 19 with DLBCL were evaluated for CD30, PAX-5, OCT-2, BOB.1, MUM-1, BCL-6, and CD20, and EBER positivity. SPSS 18 was used for statistical analysis.

Results: 73 lymphoma cases were included in the study: 61.6% males and 38.4% females. The median age of patients was 50 years. CHL (67.1%) was the most common type, and mixed cellular Hodgkin lymphoma (MCHL) was the most common subtype. There was a statistically significant difference in CD30, OCT-2, BOB.1, MUM-1, PAX-5, CD20, BCL-6, EBER expression between CHL and DLBCL cases (p<0,001). In addition, there was a statistically significant difference between CHL and NLPHL for all antibodies except BCL-6 and EBER.

Conclusion: It would be beneficial to use a panel consisting of CD30, PAX-5, OCT-2, BOB.1, MUM-1, BCL-6, and CD20, and EBER in the differential diagnosis of CHL from NLPHL and DLBCL.

Keywords: Hodgkin's Lymphoma, OCT-2, BOB.1, PAX-5, EBER

Öz

Amaç: Klasik Hodgkin lenfoma (KHL) Sık görülmek ile birlikte ayrıcı tanısı zor olabilen lenfomalardandır. Hodgkin hücresinin germinal merkezli olabileceği düşünülmektedir. Bu çalışmadaki amacımız, KHL, nodular lenfosit baskın Hodgkin lenfoma (NLBHL) ve diffuse büyük B hücreli lenfomada (DBBHL) germinal merkez transformasyon belirteçleri olan OCT-2, BOB.1, BCL-6, PAX-5, CD20 ve MUM-1'in ekspresyonlarını immünohistokimyasal yöntem ile, EBV early RNAs (EBER)'in kromojenik in-situ hibridizasyon (KISH) ile değerlendirmektir.

Gereç ve Yöntem: 49 KHL, 5'i NLBHL ve 19'u DBBHL tanılı biyopsi, CD30, PAX-5, OCT-2, BOB.1, MUM-1, BCL-6 ve CD20 ve EBER pozitifliği açısından değerlendirildi. İstatistiksel analiz için SPSS 18 kullanıldı.

Bulgular: Çalışmaya %61,6 erkek ve %38,4 kadın olmak üzere 73 lenfoma olgusu dahil edildi. Hastaların medyan yaşı 50 idi. En sık görülen lenfoma tipi KHL (%67,1), en sık görülen alt tip mikst hücreli Hodgkin lenfoma (MSHL) idi. KHL ve DBBHL olguları arasında CD30, OCT-2, BOB.1, MUM-1, PAX-5, CD20, BCL-6, EBER ekspresyonu açısından istatistiksel olarak anlamlı fark vardı (p<0,001). Ek olarak BCL-6 ve EBER haricinde diğer tüm antikorlarda KHL ve NLBHL arasında istatistiki olarak anlamlı fark mevcuttu.

Sonuç: KHL'nin NLBHL ve DBBHL'dan ayırıcı tanısında CD30, PAX-5, OCT-2, BOB.1, MUM-1, BCL-6 ve CD20 ve EBER'den oluşan bir panelin kullanılması çok faydalı olacaktır.

Anahtar Kelimeler: Hodgkin Lenfoma, OCT-2, BOB.1, PAX-5, EBER

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INTRODUCTION

Lymphoid neoplasms are clonal in origin. The World Health Organization (WHO) updated the classification of lymphoid neoplasms in 2022, and approximately 80 types of lymphoid neoplasia have been defined. Lymphomas are divided into two major groups: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). Hodgkin lymphomas constitute approximately 20% of all lymphomas. Hodgkin lymphoma is divided into two groups: Classic Hodgkin Lymphoma (CHL) and Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) (1-3). At the same time, CHL is divided into four subgroups: mixed cellular (MSHL), nodular sclerosing (NSHL), lymphocyte-rich type (LRHL), and lymphocyte-poor (LPHL).

Although there is still controversial information about the origin of the Hodgkin cell, it is emphasized that it originates from the germinal centre in the lymph node but has undergone some changes and lost its B cell characteristics. In addition, the marker on the Hodgkin cell is CD30. Hodgkin cells show CD20 expression in NLPHL. Hodgkin cells have quite different morphologies. Therefore, it can be confused with many lymphomas. Sometimes it can be quite challenging to distinguish between non-Hodgkin and classic Hodgkin lymphomas from the other group. In this case, some cell antigen expressions are used; Germinal centre transformation markers are (1, 2). These markers are OCT-2 and BOB.1 (4), BCL-6, PAX5 (5), and MUM-1 (6), and these markers are upregulated on the lymphocyte in the germinal centre during the plasma cell differentiation stage of the lymphocyte. These markers are expressed by cells forming the germinal center. Hodgkin cells also express some of these markers. But they are usually either weakly or partially expressed. This feature can be used in the differential diagnosis (7-10).

Epstein-Barr virus (EBV) is an oncogenic virus from the herpes virus family. It has been proven to be associated with lymphoid malignancies in children and adults. There are geographical differences between lymphoma types and EBV positivity (7, 8).

In our study, we wanted to look at the expression of germinal center transformation markers (OCT-2, BOB.1(2), BCL-6, PAX5 (3), and MUM-1) and EBV positivity in HL, NLPHL, and and diffuse large B-cell lymphoma (DLBCL) and the differential diagnosis of HL from the other two groups.

MATERIAL AND METHOD

This retrospective study included 54 biopsies diagnosed with HL and 19 diagnosed with DLBCL between 2016 and 2021. All cases were diagnosed from the lymph node. The age, gender, and clinical information of the patients were obtained from the hospital information system. Hematoxylin-eosin (HE) stained preparations prepared by embedding in paraffin after 10% formaldehyde fixation from the tissues were examined. CD30, PAX-5, OCT-2, BOB.1, MUM-1, BCL-6, and CD20 immunohistochemical (IHC) studies and EBER staining of all biopsies were performed.

The Method Used in the Immunohistochemical Studies and Chromogenic In-situ Hybridization

Four micron-thick sections from tissues in appropriate paraffin blocks for each antibody were taken on poly-L-lysine coated slides. The antigen retrieval technique was used in IHC studies; the avidin-biotin-peroxidase complex method was applied. Antibodies were stained on a Leica band max automated immunohistochemical staining device. A Bond Polymer Refine Detection kit (Leica, DS9800) was used for each antibody. The necessary staining procedure was performed according to the datasheet of each antibody, and appropriate positive and negative controls were used for each antibody. The characteristics of the primary antibodies used in the immunohistochemical study are listed in **Table 1**. After covering them with a coverslip ultra-mount, the prepared samples were examined under an Olympus BX51 model microscope. EBV early RNAs (EBER) and chromogenic in-situ hybridisation (ISH) method were used for EBV. 4 µm thick sections were taken from the paraffin-embedded tissue. Chromogenic ISH with Leica brand EBV RNA probe and ISH kit on the Leica band max device were performed automatically according to the manufacturer's recommendations using standard procedure. Examined under the Olympus BX51 model microscope.

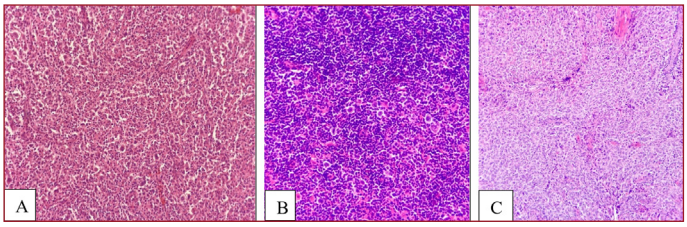
Table 1: The characteristics of the antibodies used in the immunohistochemical study

Primary Antibody	Clone	Dilution Rate	Incubation Time	Antigen Revealing	Company
CD30	JCM182	1:100	20 minute	ER2	Novocastra
Pax-5	Polycylonal	1:80	40 minute	ER2	Thermo
OCT-2	ZM90	1:50	30 minute	ER2	Zeta
BOB.1	TG14	1:20	30 minute	ER2	Novocastra
MUM-1	EAU32	1:200	20 minute	ER1	Novocastra
BCL-6	LN22	1:60	40 minute	ER2	Leica
CD20	L26	1:200	40 minute	ER2	Leica

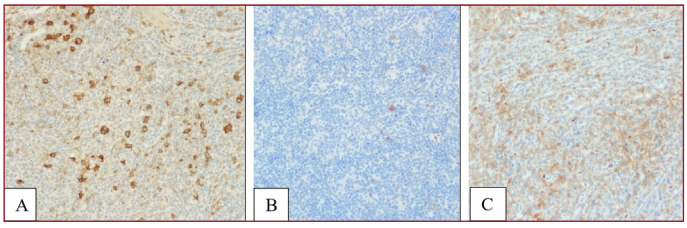
ER1 : Citrat Buffer, pH:6; ER2 : EDTA Buffer, pH:9

2.2 Immunohistochemical and Chromogenic In-situ Hybridization Evaluation

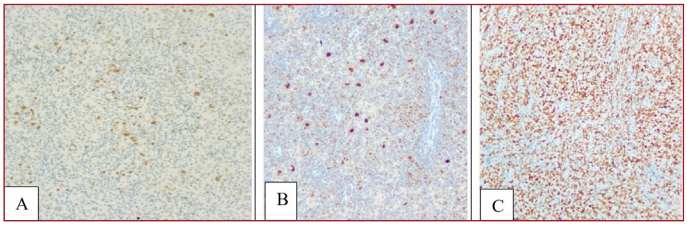
The severity and diffusiveness of expression were taken into account when evaluating IHC studies with CD30, PAX5, OCT-2, BOB.1, MUM-1, BCL-6 and CD20. The germinal center in the tissue is used as the internal positive control and the external negative control tissue. Absence of staining was scored as 0, weak and focal staining as 1, and strong and diffuse staining as 2. EBER was recorded as positive and negative (11). **Table 1** presents the characteristics of the antibodies used in the immunohistochemical study. The images of the results of the immunohistochemical studies of the lymphoma groups included in the study are in **Figure 1-7**. Positive staining with EBER in CHL (**Figure 8**).



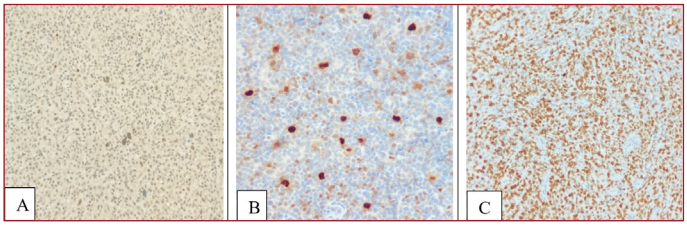
Figüre 1. In classical Hodgkin lymphoma, mixed cellular and nodular lymphocyte predominant Hodgkin lymphoma, there is an infiltration consisting of hodgkin and reed-sternberg cells in the nonneoplastic cellular background, while mass-forming lymphoma cells are present in diffuse large B-cell lymphoma (A, B, C , respectively x200 HE)



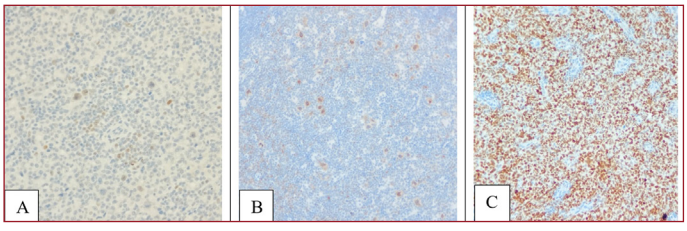
Figüre 2. In classical Hodgkin lymphoma, membranous-golgi zone CD30 antibody expression is present, whereas expression is not observed in nodular lymphocyte predominant Hodgkin lymphoma. Cytoplasmic CD30 antibody expression is observed in diffuse large B-cell lymphoma (A, B, C , respectively x200)



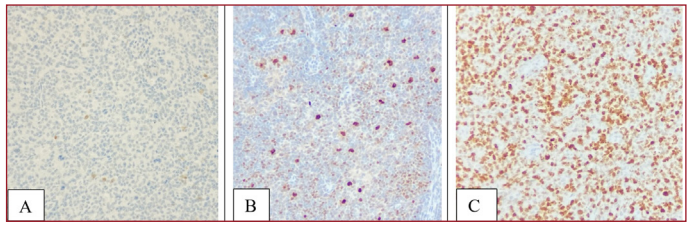
Figüre 3. Strong expression by BCL-6 antibody in all lymphoma groups (x200).



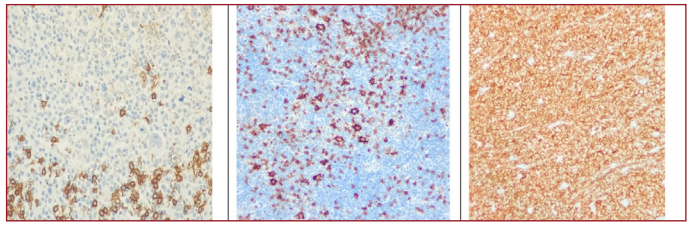
Figüre 4. While weak nuclear expression is detected with PAX-5 antibody in classical Hodgkin lymphoma (A), strong nuclear expression is observed in nodular lymphocyte predominant Hodgkin lymphoma (B) and diffuse large b-cell lymphoma (C) (X200).



Figüre 5. While OCT-2 antibody has weak and sparse nuclear expression in classical Hodgkin lymphoma (A), strong nuclear expression is observed in nodular lymphocyte predominant Hodgkin lymphoma (B) and diffuse large b-cell lymphoma (C) (X200).



Figüre 6. There was no reaction with BOB-1 antibody in classical Hodgkin lymphoma (A), while strong nuclear expression was present in nodular lymphocyte predominant Hodgkin lymphoma (B) and diffuse large b-cell lymphoma (C) (X200).



Figüre 7. There was no reaction with CD20 antibody in classical Hodgkin lymphoma (A), while strong cytoplasmic expression was present in nodular lymphocyte predominant Hodgkin lymphoma (B) and diffuse large b-cell lymphoma (C) (X200).

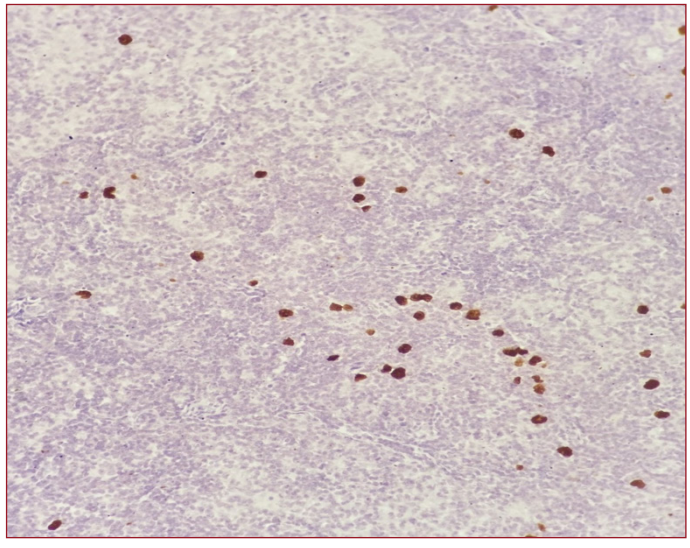


Figure 8. Nuclear positivity of EBER (CISH) in classical Hodgkin lymphoma (x200).

Ethics Committee Approval

The study was approved by the Clinical Research Ethics Committee number: 2021/408. dated 06.08.2021.

Statistical analysis

The immunohistochemical studies and the EBER results of the lymphomas included in the study were divided into three groups, and statistics were made. Three main groups are divided into Classical Hodgkin Lymphoma, Nodular Lymphocyte Predominant Hodgkin Lymphoma, and Diffuse Large B Cell Lymphoma. SPSS 18 was used for statistical analysis. Continuous data were expressed as median, minimum, and maximum values. Categorical variables were defined as percentage frequency. The

distribution characteristics of continuous data were evaluated with the Shapiro-Wilk test, and it was found that it did not fit the normal distribution. The Kruskal Wallis H test was used to compare the ordinal and continuous variables with more than two groups. Mann Whitney U test with Bonferroni correction was used in post hoc analyses. In statistical analysis, the level of significance was accepted as $p<0.05$.

RESULTS

Of the 73 lymphoma cases included in the study, 61.6% were male, and 38.4% were female. The median age of patients was 50, the youngest was 18, and the largest was 83. The most common lymphoma type included in the study was CHL (67.1%), and the most common subtype of CHL was MCHL (57.2%) (**Table 2**).

Table 2. Distribution of Lymphoma Types

Types of lymphoma	N	%
Classical Hodgkin Lymphoma	49	67.1
Nodular Lymphocyte Predominant Hodgkin Lymphoma	5	6.8
Diffuse Large B-cell Lymphoma	19	26.1
Classical Hodgkin Lymphoma Subtypes	N	%
Mixed Cellular	28	57.2
Nodular Sclerosing	16	32.6
Lymphocyte Rich	5	10.2

When lymphoma types were compared according to their age, it was observed that there was a statistically significant difference between the ages (p=0.001). In addition, as a result of in-group comparisons, the age of the diffuse large B-cell lymphoma group was found to be statistically significantly higher than the other disease groups ($p<0.001$) (**Table 3**).

Table 3: Comparison of the types of lymphoma and the mean age of patients

Group	Median	25-75	p
Classical Hodgkin Lymphoma, Mixed Cellular	43.5	43.50-58.25	0.001*
Diffuse large B-cell lymphoma	68.0	68.00-78.00	
Classical Hodgkin Lymphoma, Nodular Sclerosing	52.5	52.50-61.75	
Nodular Lymphocyte Predominant Hodgkin Lymphoma	44.0	44.00-55.00	
Classical Hodgkin Lymphoma, Lymphocyte Rich	29.0	29,00-42,00	

Kruskal Wallis H Test, *p<0,05

Table 4 presents the results of immunohistochemical staining and EBER for CD20, CD30, OCT.1, OCT.2, BOB.1, BCL-6, PAX-5 and MUM.1 in CHL, NLPHL, DLBCL. The results of the same immunohistochemical staining and EBER in CHL subtypes are shown in **Table 5**. Finally, the comparison of immunohistochemical staining results between lymphoma groups is presented in **Table 6**.

OCT-2

28.6% of CHL cases showed weakly positive, 8.2% positive, and 63.3% negative reactions with OCT-2. In CHL subtypes, independent of the degree of positivity, the highest OCT-2 expression was seen in 60 % in LRHL, and the lowest OCT-2 expression was 18.8% in NSHL. OCT-2 expression was positive in 80% and negative in 20% of NLPHL cases. OCT-2 expression was positive in 94.7% and weakly positive in 5.3% of DLBCL cases. A statistically significant difference was found between CHL, NLPHL (p=0.006), and DLBCL cases regarding OCT-2 expression ($p<0.001$). No statistically significant difference was found between NLPHL and DLBCL cases following OCT-2 expression (p=0.226).

Table 4: An immunohistochemical study and EBER results based on lymphoma types

	Classical Hodgkin Lymphoma		Nodular Lymphocyte Predominant Hodgkin Lymphoma		Diffuse Large B-cell Lymphoma		Total	
	n	%	n	%	n	%		
Oct-2								
0 (Negative)	31	63.3	1	20.0	0	0.0	32	43.8
1 (Weakly Positive)	14	28.6	0	0.0	1	5.3	15	20.5
2 (Strong Positive)	4	8.2	4	80.0	18	94.7	26	35.6
BOB.1								
0 (Negative)	46	93.9	0	0.0	1	5.3	47	64.4
1 (Weakly Positive)	3	6.1	2	40.0	4	21.1	9	12.3
2 (Strong Positive)	0	0.0	3	60.0	14	73.7	17	23.3
Pax-5								
0 (Negative)	6	12.2	0	0.0	0	0.0	6	8.2
1 (Weakly Positive)	43	87.8	1	20.0	1	5.3	45	61.6
2 (Strong Positive)	0	0.0	4	80.0	18	94.7	22	30.1
BCL-6								
0 (Negative)	34	69.4	2	40.0	0	0.0	36	49.3
1 (Weakly Positive)	13	26.5	2	40.0	3	15.8	18	24.7
2 (Strong Positive)	2	4.1	1	20.0	16	84.2	19	26.0
MUM-1								
0 (Negative)	6	12.2	4	80.0	4	21.1	14	19.2
1 (Weakly Positive)	8	16.3	1	20.0	10	52.6	19	26.0
2 (Strong Positive)	35	71.4	0	0.0	5	26.3	40	54.8
CD20								
0 (Negative)	36	73.5	1	20.0	0	0.0	37	50.7
1 (Weakly Positive)	10	20.4	1	20.0	0	0.0	11	15.1
2 (Strong Positive)	3	6.1	3	60.0	19	100.0	25	34.2
CD30								
0 (Negative)	0	0.0	5	100.0	13	68.4	18	24.7
1 (Weakly Positive)	2	4.1	0	0.0	3	15.8	5	6.8
2 (Strong Positive)	47	95.9	0	0.0	3	15.8	50	68.5
EBER								
Negative	28	57.1	5	100.0	19	100.0	52	71.2
Positive	21	42.9	0	0	0	0.0	21	28.8
Total	49	100.0	5	100.0	19	100.0	73	100.0

EBER: EBV early RNAs

Table 5: Results of İmmunohistochemical Studies in Classical Hodgkin Lymphoma Subgroups

	Classical Hodgkin Lymphoma, Mixed Cellular		Classical Hodgkin Lymphoma, Nodular Sclerosing		Classical Hodgkin Lymphoma Lymphocyte Rich	
	n	%	n	%	n	%
Oct-2						
0 (Negatif)	16	57.1	13	81.3	2	40.0
1 (Weakly Positive)	9	32.1	2	12.5	3	60.0
2 (Strong Positive)	3	10.7	1	6.3	0	0.0
BOB.1						
0 (Negatif)	26	92.9	15	93.8	5	100.0
1 (Weakly Positive)	2	7.1	1	6.3	0	0.0
2 (Strong Positive)	0	0.0	0	0.0	0	0.0
Pax-5						
0 (Negatif)	2	7.1	3	18.8	1	20.0
1 (Weakly Positive)	26	92.9	13	81.3	4	80.0
2 (Strong Positive)	0	0.0	0	0.0	0	0.0
BCL-6						
0 (Negatif)	16	57.1	14	87.5	4	80.0
1 (Weakly Positive)	10	35.7	2	12.5	1	20.0
2 (Strong Positive)	2	7.1	0	0.0	0	0.0
MUM-1						
0 (Negatif)	2	7.1	3	18.8	1	20.0
1 (Weakly Positive)	5	17.9	1	6.3	2	40.0
2 (Strong Positive)	21	75.0	12	75.0	2	40.0
CD20						
0 (Negatif)	23	82.1	12	75.0	1	20.0
1 (Weakly Positive)	3	10.7	4	25.0	3	60.0
2 (Strong Positive)	2	7.1	0	0.0	1	20.0
CD30						
0 (Negatif)	0	0.0	0	0.0	0	0.0
1 (Weakly Positive)	0	0.0	2	12.5	0	0.0
2 (Strong Positive)	28	100	14	87.5	5	100.0
EBER						
Negative	16	57.1	9	56.3	3	60.0
Positive	12	42.9	7	43.8	2	40.0
Total	28	100.0	16	100.0	5	100.0

Table 6. An analysis of the statistical results between lymphoma types and antibodies

ANTIBODY	CHL/ NLPHL/ DLBCL1	CHL/ NLPHL2	CHL/ DLBCL2	NLPHL / DLBCL2
		P Value		
Oct-2	<0.001*	0.006#	<0.001#	0.226
BOB.1	<0.001*	<0.001#	<0.001#	0.622
Pax-5	<0.001*	<0.001#	<0.001#	0.229
BCL-6	<0.001*	0.143	<0.001#	0.003#
MUM-1	<0.001*	<0.001#	0.002#	0.019
CD20	<0.001*	0.004#	<0.001#	0.005#
CD30	<0.001*	<0.001#	<0.001#	0.299
EBER	0.001*	0.064	0.001#	0.160

1 Kruskal Wallis H Test.*p<0.05, 2 Mann Whitney U test was used as posthoc analysis. Bonferroni With the correction. statistical significance was taken as #p<0.017. CHL: Classical Hodgkin Lymphoma ; NLPHL: Nodular Lymphocyte Predominant Hodgkin Lymphoma ; DLBCL: Diffuse Large B-cell Lymphoma.

BOB.1

Of the CHL cases, 93.9% were negative with BOB.1, and 6.1% had weak expression. Strong expression was not observed in any case. The highest expression of BOB.1 in CHL subtypes was seen in MCHL at 7.1 %. There was no statistically significant difference between CHL subtypes regarding BOB.1 expression (p=0.837).

BOB.1 showed positive expression in 60% of NLPHL cases and weakly positive expression in 40%. On the other hand, it showed positive expression in 73.7% of DLBCL cases, weakly positive expression in 21.1%, and negative expression in 5.3%.

Regardless of the degree of staining, lower BOB.1 expression was detected in CHL cases compared to NLPHL and DLBCL cases. This difference was also statistically significant (p<0.001). On the other hand, no statistically significant difference between NLPHL and DLBCL cases regarding BOB.1 expression (p=0.622) was found.

PAX-5

87.8% of (CHL cases showed weak positive and 12.2% negative expression with PAX-5. No strong expression was detected. The highest weak positive expression of CHL subtypes was in MCHL, 92.9%.

Strong positive expression in 80% of NLPHL cases and weak positive expression in 20%. Strong positive expression was observed in 94.7% of DLBCL cases, and weakly positive expression was observed in 5.3% of DLBCL cases.

A statistically significant difference was found between CHL, NLPHL, and DLBCL cases regarding PAX-5 expression (p<0.001). However, there was no statistically significant difference in PAX-5 expression between NLPHL and DLBCL cases (p=0.229).

BCL-6

CHL cases showed weak positive, 69.4% negative, and 4.1% strong positive reactions with BCL-6. Regardless of the degree of staining, the highest BCL-6 expression was seen in MCHL, 42.8 %, and the lowest BCL-6 expression was 12.5% in NSHL, in CHL subtypes.

BCL-6 showed positive expression in 20%, weakly positive in 40%, and negative in 40% of NLPHL cases. It showed positive expression in 84.2% of DLBCL cases and weakly positive expression in 15.8%.

Considering the BCL-6 expressions regardless of the staining degree, the lowest expression was found in CHL cases, and the highest was found in DLBCL cases. A statistically significant difference was found between CHL and DLBCL cases in BCL-6 expression (p<0.001). No statistically significant difference between CHL and NLPHL cases was found in BCL-6 expression (p=0.143).

MUM1

71.4% of CHL cases had a positive reaction with MUM1, 16.4% had a weak positive reaction, and 12.2% had a negative response. Regardless of the staining degree, the

highest MUM1 expression was seen in MCHL, 92.8%, and the lowest MUM1 expression was 80% in LRHL, in CHL subtypes. Weakly positive MUM1 expression was detected in 20% of NLPHL cases and negative in 80%. No negative reaction was observed in any of the cases. It showed positive expression in 26.3% of DLBCL cases, weakly positive expression in 52.6% and negative expression in 21.1%.

The highest MUM1 expression was seen in CHL cases, and the lowest MUM1 expression was seen in DLBCL cases. A statistically significant difference was found between CHL and DLBCL and between CHL and NLPHL cases in MUM1 expression ($p=0.002$, $p<0.001$). There was no statistically significant difference in MUM1 expression between NLPHL and DLBCL cases ($p=0.019$).

CD20

73.5% of CHL cases showed negative expression, 20.4% weakly positive, and 6.1% positive expression reaction with CD20. Regardless of the degree of staining, the highest CD20 expression in CHL subtypes was 80% in LZHL.

Strong and weakly positive CD20 expression was detected in 80% of NLPHL cases. CD20 expression was seen in all DLBCL cases.

The highest MUM1 expression was seen in CHL cases, and the lowest MUM1 expression was seen in DLBCL cases. A statistically significant difference was found between CHL and DLBCL and between CHL and NLPHL cases in CD20 expression ($p<0.001$). There was no statistically significant difference in CD20 expression between NLPHL and DLBCL cases ($p=0.140$).

CD30

CD30 expression was present in all CHL cases. Expression was not observed in any of the NLPHL cases. A varying degree of positive words was observed in 31.6% of DLBCL cases.

A statistically significant difference was found between CHL and DLBCL and between CHL and NLPHL cases in CD20 expression ($p<0.001$). There was no statistically significant difference in CD45 expression between NLPHL and DLBCL cases ($p=0.299$).

EBER

EBER was positive in 42.9% of CHL cases. The highest EBER positivity in CHL subtypes was NSHL, with 43.8%. EBER was negative in all NLPHL and DLBCL cases.

A statistically significant difference was found between CHL and DLBCL cases regarding EBER expression ($p=0.001$). There was no statistically significant difference in EBER expression between NLPHL and DLBCL cases ($p=0.160$).

DISCUSSION

CHL is one of the lymphomas of which nearly 100 types have been defined so far; the origin of the Hodgkin cell, a malignant cell, is still controversial. It is stated that it originates from the germinal center but has lost some of its characteristics (1-3).

CHL subtype MSHL accounted for the majority of cases in our study, with 28 (57.2%) cases. Contrary to our study, the most common subtype was found to be NSHL in some studies, 52.5% (12) and 75% (13), respectively. Similar to our study another research have reported MSHL (50%) as the most prevalent subtype of CHL (5).

PAX-5 is the gene family that encodes the nuclear transcription factor; it regulates B cells' development, differentiation, and migration (4). PAX-5 CHL generally shows weak expression in Reed- Sternberg cells (5). In our study, we found 87.8% of CHL cases to have weak positive reactions with PAX-5 and 12.2% to negative reactions; we did not observe strong positivity in any of the cases. In the study, which included 60 CHLs previously performed in the literature, a weak reaction was obtained with PAX-5 in all cases, but no strong response was received. A moderate reaction was obtained in a patient with NLPHL, and a strong reaction was found in 26 cases, except for one DLBCL (5, 14).

Furthermore, our study did not find strong positivity for PAX-5 in CHL cases. In contrast, in our study, negative reactions were obtained in 12.2% of CHL cases, positive expression was found in 80% of NLPHL cases and weak positive expression in 20%. Our study found a strong reaction in almost all cases, similar to DLBCL cases.

An interaction between transcription factors and the octamer regions of the immunoglobulin promoter is required for immunoglobulin gene expression during the development of B cells. Two of these transcription factors, BOB.1 and OCT-2, belong to the POU family of transcription factors (15). Surprisingly, OCT-2 expressed in B cells can be expressed in Hodgkin cells in CHL together with the co-transcription factor BOB.1 (16-18).

BOB.1 has been studied very little in the context of CHL, and little recent literature has been published about it. A previous study conducted with 57 CHL cases found a weak positive reaction in 28% (16/57 patients) (18). Our study had a few cases of BOB.1 (6.1%), but the staining pattern was the same.

In the same study, a strong positive reaction was obtained with BOB.1 in all DLBCL and NLPHL cases: 73.7% (14) of 19 DLBCL cases were strongly positive, 21.1% (4) weakly positive, 5.3% (1) showed a negative reaction. A strong positive reaction was observed in 60% (5) of NLPHL cases and a weak positive reaction in 40% (2).

In various studies, OCT-2 expression in CHL ranges from 0% (19) to 33% (18). In our study, 28.6% of CHL cases showed a weak positive reaction, 8.2% a strong reaction, and 63.3% a negative reaction with OCT-2. The expression pattern was like in previous studies (18). In NLPHL, OCT-2 showed 100% strong expression in almost all previous studies (4). Most cases, except for one case, showed a strong positive reaction. The OCT-2 expression in DLBCL was found to be over 90% in our study, similar to other studies (7, 18, 20).

B-cell lymphoma 6 protein (BCL-6) is a follicular helper T cell (TFH) related marker and is involved in the transformation of B cells in the germinal center (21). BCL-6 expression is particularly expressed in T-cell lymphomas of follicular origin. It is also expressed in many B-cell lymphomas, including DLBCL (22). It is expressed at rates ranging from 83-100% in NLPHL (23, 24). In this study, we found 60% expression in NLPDHL. Studies with Bcl-6 in CHL are very limited. Generally, no expression was detected or very few and weak positivity was detected (25). Although expressions were low in CHL, our study found higher positivity than previous studies.

Multiple myeloma-1/interferon regulatory factor-4 (MUM1/IRF-4), a lymphocyte-specific member of the IRF family, is expressed in the final stage of B cell differentiation in the germinal center (26). MUM-1 expression is present in almost all CHL, regardless of type (27). This study detected positive expression in 87.8% of our CHL cases, regardless of the staining pattern. The lowest expression of CHL subtypes was NSHL, and it was negative in 18.8%. We detected weak positive expression with MUM-1 in only one of our NLPHL cases, while the others were negative. Our results were similar to previous studies (26, 27). MUM-1 positive expression was 78.9% in our DLBCL cases, and in one of the earlier studies, 92% was found in 92 cases (28).

CD30 is expressed in various inflammatory conditions and malignancies and is described as a transmembrane glycoprotein receptor (120kd) of the tumours necrosis factor receptor superfamily 8 (TNFRSF8) (29). CD30 expression is reported between 90-100% in CHL (30, 31). In our study, all our CHL cases showed CD30 positive expression. CD30 expression in de nova DLBCL varies between 10-25% (29). This study shows CD30 expression is slightly higher in DLBCL, 31.6%. Similar to the literature (32), in our study, CD30 expression was not seen in NLPHL.

CD20, a pan- B cell marker, can be expressed in Hodgkin's cells and Reed Sternberg cells in CHL. These rates generally vary between 19-28% regardless of the subgroup (18, 30). Results similar to previous studies were obtained in our study. As reported in the previous study, it was found to be positive in nearly all cases of DLBCL and NLPHL CD20 (7, 18). All cases of DLBCL in our study showed strong expression. Three of our five NLPHL cases showed a strong positive reaction. One case resulted in a negative reaction. CD20 expression may be negative or weakly positive, depending on the location of NLPHL, especially in the mediastinal area.

Epstein-Barr virus (EBV) is a herpes virus that causes lymphoid neoplasms. The prevalence of EBV positivity in HL varies between countries (33). HL positivity was detected in 45.4% of cases in Turkey, most frequently in the NSHL subtype and none in the NLPHL subtype (34). The results of our study are in agreement with those of this study. There is a low level of EBER positivity in DLBCL (35). All cases of DLBCL in our study were negative.

Our immunohistochemical study revealed significant differences between CHL and the other two types of lymphoma, except for BCL-6, regardless of the staining intensity. Based on previous publications, only the frequency of antibodies has been reported (18), and no statistical comparison has yet been conducted.

CONCLUSION

Regardless of their type, lymphomas are challenging to diagnose neoplasms. For their treatment, they should be typified. In addition to morphology, immunophenotyping by the immunohistochemical method should be a must. Aberrant expressions or loss of expression seen in lymphomas make diagnosing difficult, necessitating reliable immunohistochemical markers. As a result of our study, we demonstrated that CD30 positivity, BOB.1 negativity, PAX-5 weak positivity, MUM-1 strong positivity, and EBER positivity could be used to diagnose CHL effectively.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee Sayı (2021/408), Date 06.08.2021

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. de Leval L, Jaffe ES. Lymphoma classification. The Cancer Journal. 2020;26(3):176-85.
2. Swerdlow SH CE HN, Jaffe ES, Pileri SA, Stein H, Thit Rele J, Arber DA, Hasserjian RP, Le Beau MM, Orazi A, Sieber. . WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: International Agency for Research on Cancer2017.
3. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-48.
4. McCune RC, Syrbu SI, Vasef MA. Expression profiling of transcription factors Pax-5, Oct-1, Oct-2, BOB. 1, and PU. 1 in Hodgkin's and non-Hodgkin's lymphomas: a comparative study using high throughput tissue microarrays. Modern Pathol 2006;19(7):1010-8.
5. Khan MR, Ahmad A, Kayani N, Minhas K. Expression of PAX-5 in B cell hodgkin and non hodgkin lymphoma. APJCP. 2018;19(12):3463.
6. Torlakovic E, Tierens A, Dang HD, Delabie J. The transcription factor PU. 1, necessary for B-cell development is expressed in lymphocyte predominance, but not classical Hodgkin's disease. Am J Pathol 2001;159(5):1807-14.

7. Browne P, Petrosyan K, Hernandez A, Chan JA. The B-cell transcription factors BSAP, Oct-2, and BOB.1 and the pan-B-cell markers CD20, CD22, and CD79a are useful in the differential diagnosis of classic Hodgkin lymphoma. Am J Clin Pathol. 2003;120(5):767-77.
8. O'Malley DP, Fedoriw Y, Weiss LM. Distinguishing classical Hodgkin lymphoma, gray zone lymphoma, and large B-cell lymphoma: a proposed scoring system. Applied Immunohistochemistry & Molecular Morphology. 2016;24(8):535-40.
9. Watanabe T, Kitazawa R, Mizuno Y, Kuwahara N, Ito C, Sugita A, et al. BOB. 1-positive classical Hodgkin's Lymphoma carries hypermethylation of its promoter as epigenetic marker of gene-silencing memory. Acta Histochemica et Cytochemica. 2014;47(3):125-31.
10. O'Malley DP, Fedoriw Y, Weiss LM. Distinguishing Classical Hodgkin Lymphoma, Gray Zone Lymphoma, and Large B-cell Lymphoma: A Proposed Scoring System. Appl Immunohistochem Mol Morphol. 2016;24(8):535-40.
11. García-Cosío M, Santón A, Martín P, Camarasa N, Montalbán C, García JF, et al. Analysis of transcription factor OCT. 1, OCT. 2 and BOB. 1 expression using tissue arrays in classical Hodgkin's lymphoma. Modern pathology. 2004;17(12):1531-8.
12. Şeker M, Mengi A, Bilici A, Ustaalioğlu BB, Kefeli U, Özşeker NI, et al. Hodgkin lenfoma olgularının retrospektif değerlendirilmesi ve prognostik faktörlerin saptanması. Turkish Journal of Oncology/Türk Onkoloji Dergisi. 2011;26(3).
13. Ferrarini I, Rigo A, Zamò A, Vinante F. Classical Hodgkin lymphoma cells may promote an IL-17-enriched microenvironment. Leukemia & lymphoma. 2019;60(14):3395-405.
14. Khan MR, Ahmad A, Kayani N, Minhas K. Expression of PAX-5 in B Cell Hodgkin and Non Hodgkin Lymphoma. Asian Pac J Cancer Prev. 2018;19(12):3463-6.
15. Theil J, Laumen H, Marafioti T, Hummel M, Lenz G, Wirth T, et al. Defective octamer-dependent transcription is responsible for silenced immunoglobulin transcription in Reed-Sternberg cells. Blood. 2001;97(10):3191-6.
16. Latchman DS. The Oct-2 transcription factor. Int J Biochem Cell Biol. 1996;28(10):1081-3.
17. Chang JF, Phillips K, Lundbäck T, Gstaiger M, Ladbury JE, Luisi B. Oct-1 POU and octamer DNA co-operate to recognise the Bob-1 transcription co-activator via induced folding. J Mol Biol. 1999;288(5):941-52.
18. Browne P, Petrosyan K, Hernandez A, Chan JA. The B-cell transcription factors BSAP, Oct-2, and BOB. 1 and the pan–B-cell markers CD20, CD22, and CD79a are useful in the differential diagnosis of classic Hodgkin lymphoma. American journal of clinical pathology. 2003;120(5):767-77.
19. Torlakovic E, Tierens A, Dang HD, Delabie J. The transcription factor PU.1, necessary for B-cell development is expressed in lymphocyte predominance, but not classical Hodgkin's disease. Am J Pathol. 2001;159(5):1807-14.
20. Torlakovic E, Torlakovic G, Nguyen PL, Brunning RD, Delabie J. The value of anti-pax-5 immunostaining in routinely fixed and paraffin-embedded sections: a novel pan pre-B and B-cell marker. Am J Surg Pathol. 2002;26(10):1343-50.
21. Abukhiran I, Syrbu SI, Holman CJ. Markers of Follicular Helper T Cells Are Occasionally Expressed in T-Cell or Histiocyte-Rich Large B-Cell Lymphoma, Classic Hodgkin Lymphoma, and Atypical Paracortical HyperplasiaA Diagnostic Pitfall For T-Cell Lymphomas of T Follicular Helper Origin. Am J Clin Pathol. 2021;156(3):409-26.
22. Zhang Y, Wang H, Ren C, Yu H, Fang W, Zhang N, et al. Correlation Between C-MYC, BCL-2, and BCL-6 Protein Expression and Gene Translocation as Biomarkers in Diagnosis and Prognosis of Diffuse Large B-cell Lymphoma. Front Pharmacol. 2018;9:1497.
23. Uherova P, Valdez R, Ross CW, Schnitzer B, Finn WG. Nodular lymphocyte predominant Hodgkin lymphoma. An immunophenotypic reappraisal based on a single-institution experience. Am J Clin Pathol. 2003;119(2):192-8.
24. Fromm JR, Thomas A, Wood BL. Characterization and Purification of Neoplastic Cells of Nodular Lymphocyte Predominant Hodgkin Lymphoma from Lymph Nodes by Flow Cytometry and Flow Cytometric Cell Sorting. Am J Pathol. 2017;187(2):304-17.
25. Carbone A, Gloghini A, Gaidano G, Franceschi S, Capello D, Drexler HG, et al. Expression status of BCL-6 and syndecan-1 identifies distinct histogenetic subtypes of Hodgkin's disease. Blood, The Journal of the American Society of Hematology. 1998;92(7):2220-8.
26. Carbone A, Gloghini A, Aldinucci D, Gattei V, Dalla-Favera R, Gaidano G. Expression pattern of MUM1/IRF4 in the spectrum of pathology of Hodgkin's disease. Br J Haematol. 2002;117(2):366-72.
27. Huang W, Xie J, Xu X, Gao X, Xie P, Zhou X. MUM-1 expression differentiates AITL with HRS-like cells from cHL. Int J Clin Exp Pathol. 2015;8(9):11372-8.
28. Irawan C, Iskandar M, Harahap AS, Rumende CM, Ham MF. MUM1 Expression versus Hans Algorithm to Predict Prognosis in Indonesian Diffuse Large B-Cell Lymphoma Patients Receiving R-CHOP. Cancer Manag Res. 2022;14:925-35.
29. Xu ML, Gabali A, Hsi ED, Fedoriw Y, Vij K, Salama ME, et al. Practical Approaches on CD30 Detection and Reporting in Lymphoma Diagnosis. Am J Surg Pathol. 2020;44(2):e1-e14.
30. Hoeller S, Zihler D, Zlobec I, Obermann EC, Pileri SA, Dirnhofer S, et al. BOB.1, CD79a and cyclin E are the most appropriate markers to discriminate classical Hodgkin's lymphoma from primary mediastinal large B-cell lymphoma. Histopathology. 2010;56(2):217-28.
31. Nam-Cha SH, Montes-Moreno S, Salcedo MT, Sanjuan J, Garcia JF, Piris MA. Lymphocyte-rich classical Hodgkin's lymphoma: distinctive tumor and microenvironment markers. Mod Pathol. 2009;22(8):1006-15.
32. Eichenauer DA, Engert A. Nodular lymphocyte-predominant Hodgkin lymphoma: a unique disease deserving unique management. Hematology Am Soc Hematol Educ Program. 2017;2017(1):324-8.
33. O'Malley DP, Dogan A, Fedoriw Y, Medeiros LJ, Ok CY, Salama ME. American Registry of Pathology Expert Opinions: Immunohistochemical evaluation of classic Hodgkin lymphoma. Ann Diagn Pathol. 2019;39:105-10.
34. Gulen G, ÖZCAN MA, ÖZKAL S. EBER In Situ Hybridization Experience In Hodgkin Lymphoma. Journal of Basic and Clinical Health Sciences. 2021;5(3):201-4.
35. ÇOKBANKİR Ö. Diffüz büyük b hücreli lenfomalarda sitogenetik olarak alt tiplerin ve bunların prognostik özelliklerinin araştırılması: Dokuz Eylül Üniversitesi Tıp Fakültesi; 2013.

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Original Article / Orijinal Araştırma

Evaluation of Cardiac Arrhythmia Susceptibility in Pediatric Familial Mediterranean Fever Patients

Pediatrik Ailevi Akdeniz Ateşi Hastalarında Kardiyak Aritmi Yatkınlığının Değerlendirilmesi

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Abstract

Aim: Familial Mediterranean fever is an autoinflammatory disease characterized by attacks of inflammation. Despite treatment, there is evidence of subclinical persistence of inflammation with normal laboratory values. This study was conducted to investigate the cardiac effects of continued subclinical inflammation in children and the predisposition towards arrhythmia in familial Mediterranean fever.

Material and Method: Age and sex-matched familial Mediterranean fever patients and healthy controls were compared in terms of demographic, laboratory, echocardiographic and electrocardiographic data. The patients with familial Mediterranean fever were grouped according to disease severity scores and compared in terms of electrocardiographic data that could indicate arrhythmogenesis. Correlation analysis was used to examine the relationship between the electrocardiographic measurements and the clinical and laboratory data.

Results: In the comparison of the two groups, no significant difference was found in the echocardiographic measurements in terms of left ventricular systolic and diastolic functions. According to these data, QT and Tp-e intervals were significantly longer in those with familial Mediterranean fever (p=0.002, p=0.046, respectively). When the patients were classified according to the 3 separate disease severity scores, QT dispersion in the moderate-severe disease group was significantly longer than in the mild disease group (p<0.001, p=0.002, p=0.013, respectively). In correlation analysis, weak correlations were found between and QT dispersion, disease duration and P wave dispersion, and frequency of attacks and QT dispersion.

Conclusion: Our study results indicate that the predisposition to ventricular arrhythmia is greater in children with familial Mediterranean fever and that this can be associated with the severity of the disease.

Keywords: Arrhythmia, electrocardiography, familial Mediterranean fever

Öz

Amaç: Ailevi Akdeniz ateşi inflamasyon atakları ile karakterize otoinflamatuar bir hastalıktır. Tedaviye rağmen, normal laboratuvar değerleri ile subklinik inflamasyonun devam ettiğine dair kanıtlar vardır. Bu çalışma, çocuklarda devam eden subklinik inflamasyonun kardiyak etkilerini ve ailevi Akdeniz ateşinde aritmiye yatkınlığı araştırmak için yapılmıştır.

Gereç ve Yöntem: Yaş ve cinsiyet açısından eşleştirilmiş ailevi Akdeniz ateşi hastaları ve sağlıklı kontroller demografik, laboratuvar, ekokardiyografik ve elektrokardiyografik veriler açısından karşılaştırıldı. Ailevi Akdeniz ateşi hastaları hastalık şiddeti skorlarına göre gruplandırıldı ve aritmogenezi gösterebilecek elektrokardiyografik veriler açısından karşılaştırıldı. Elektrokardiyografik ölçümler ile klinik ve laboratuvar verileri arasındaki ilişkiyi incelemek için korelasyon analizi kullanıldı.

Bulgular: İki grup karşılaştırıldığında, ekokardiyografik ölçümlerde sol ventrikül sistolik ve diyastolik fonksiyonları açısından anlamlı bir fark bulunmadı. Bu verilere göre QT ve Tp-e intervalleri ailesel Akdeniz ateşi olanlarda anlamlı olarak daha uzundu (sırasıyla p=0.002, p=0.046). Hastalar 3 ayrı hastalık şiddeti skoruna göre sınıflandırıldığında, orta-şiddetli hastalık grubunda QT dispersiyonu hafif hastalık grubuna göre anlamlı olarak daha uzundu (sırasıyla p<0.001, p=0.002, p=0.013). Korelasyon analizinde, QT dispersiyonu ile QT dispersiyonu, hastalık süresi ile P dalga dispersiyonu ve atak sıklığı ile QT dispersiyonu arasında zayıf korelasyonlar bulunmuştur.

Sonuç: Çalışma sonuçlarımız ailevi Akdeniz ateşi olan çocuklarda ventriküler aritmiye yatkınlığın daha fazla olduğunu ve bunun hastalığın şiddeti ile ilişkili olabileceğini göstermektedir.

Anahtar Kelimeler: Aritmi, elektrokardiyografi, ailevi Akdeniz ateşi

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INTRODUCTION

Familial Mediterranean fever (FMF) is an inherited autosomal recessive disorder and the most common monogenic and autoinflammatory disease that is characterized by recurrent and self-limited attacks of polyserositis.[1] It is believed that the disease is caused by mutations in the MEFV gene that encodes pyrin protein on the short arm of chromosome 16. The mutated pyrin activates pyrin inflammasome, causing the uncontrolled secretion of cytokines that leads to inflammation.[2] There is evidence suggesting that patients with FMF have continued subclinical inflammation even in periods when they are not experiencing attacks.[3] Chronic inflammation and its sequels can cause anemia and splenomegaly, continuously high acute phase reactants, and the most feared complication of amyloidosis.[2]

Cardiovascular system involvement is among the causes of high morbidity and mortality in FMF. While FMF-related pericarditis and cardiac amyloidosis are the most commonly expected complications, recent studies have reported that FMF patients can suffer sudden cardiac death or malign arrhythmias that are caused by cardiac repolarization abnormalities, even without the presence of amyloidosis.[4,5] This has been linked to the chronic inflammation occurring in FMF. It is believed that the chronic inflammation observed in FMF can lead to endothelial injury and ischemic cardiovascular damage.[6-9] It is considered that this condition can occur not only during periods of attack but also in patients who do not experience attack.[10,11]

There are various parameters that indicate myocardial repolarization in an electrocardiogram. The abnormalities in these parameters may foresee a tendency toward arrhyrthmia. The most commonly known of these are the T wave, Tp-e interval, corrected Tp-e interval, the QT interval, corrected QT interval, Q wave dispersion, P wave dispersion. It has been found that prolonged Tp-e, corrected QT rates are associated with life-threatening ventricular arrhythmias such as life-threatening polymorphic ventricular tachycardia, torsades de pointes, and ventricular fibrillation.[12,13] There are many studies in the literature which have used these new indices that indicate ventricular repolarization in FMF.[4,5,14-16] Studies have revealed that the Tp-e interval is superior to QT dispersion in foreseeing sudden cardiac death and ventricular arrhythmia.[17]

Our aim in this study was to evaluate the longstanding as well as the newly developed electrocardiogram parameters indicating myocardial repolarization and to assess the QT interval, corrected QT interval, Tp-e interval, corrected Tp-e, Tp-e/corrected QT, P wave dispersion to see whether pediatric patients diagnosed with FMF have a predisposition toward arrhythmia.

MATERIAL AND METHOD

Study Population

Between September 2017 and September 2019, 44 pediatric patients aged <18 years who were treated with a diagnosis of FMF in our Pediatric Rheumatology unit were included in the study. FMF was diagnosed according to the diagnostic criteria proposed by Yalçınkaya and Özen.[18] Those with congenital or acquired heart disease, problems in cardiac conduction, electrolyte imbalance, those who have had an attack in the last 3 months, smokers, those with concomitant diseases (diabetes, hypertension, hypothyroidism, anemia, obesity, chronic kidney disease, chronic lung disease, etc.) and those who were not followed up regularly were excluded from the study.

The control group consisted of 44 children who were of the same age and gender as those patients with FMF, had no chronic disease, who had presented to the pediatric cardiology outpatient clinic for an innocent heart murmur or for a health report needed for participating in sports, or who had presented to the pediatric rheumatology outpatient clinic for growth pains.

The patients and the control group were matched one-to-one in terms of age and gender. There was no difference between the two groups in terms of body mass index.

Study Design

The blood pressure of the patients and the control group was taken. Blood samples were drawn for a complete blood count, glucose, creatinine, electrolyte and albumin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urinalysis, and thyroid function tests. Electrocardiography and transthoracic echocardiography were taken. Body mass index was calculated by dividing body weight (kilograms) by height squared (meters). C-reactive protein was assessed by nephelometric and ESR Westergreen methods. Laboratory devices that were regularly monitored for accuracy and calibration were used for the biochemistry tests and complete blood count.

The laboratory and cardiac investigations of the patients were evaluated for a period of at least 3 months in which there were no attacks.

Also, the patients were divided into three groups according to their disease severity scores–mild, moderate and severe. Pras et al.'s scoring system[19], Mor et al.'s scoring system[20], and the International Severity Score for Familial Mediterranean Fever (ISSF)[21] were employed in the scoring. The patients were divided into groups according to these three scoring systems and were assessed to find out whether there were any differences between them in terms of myocardial repolarization parameters.

The local ethics committee approved the study with its decision of 2020/274.

Electrocardiography

An electrocardiogram was taken at 50mm/s speed and 1mV / cm standardization with a 12-lead electrocardiography device after each child had rested for 10 minutes and had been placed in a supine position (Nihon Kohden electrocardiogram, Cardiofax GEM, Model 9022K, Tokyo, Japan). All electrocardiography recordings were transferred to a computer via a scanner, after which Adobe Photoshop software was used for a x400 enlargement. To reduce the margin of error, the measurements were made with an electronic digital caliper. All measurements were taken by two researchers who were blinded to the clinical condition of the patients and controls. An average value of two measurements was calculated for each parameter. Heart rate, rhythm, R-R interval, P wave interval, QT interval, corrected OT interval, QT dispersion, Tp-e interval, corrected Tp-e, Tp-e/corrected QT were calculated.

The QT interval was calculated as from the start of the Q wave to the point where the T wave returned to the isoelectric line, using the corrected QT Modified Bazett formula (corrected QT=QT/√ R-R interval). The Tp-e interval was measured as the distance between the peak and end of the T wave. First a V5 derivation was used for the measurement and when this was not appropriate (concentrated artifacts or T wave amplitude of ≤ 1.5mV), V4 and V6 leads were used respectively. QT dispersion was found by calculating the difference between the longest QT interval at derivation 12 and the shortest QT interval. P wave dispersion was found by calculating the difference between the p wave time calculated to be the longest at derivation 12 and the P wave time calculated to be the shortest. To adjust Tp-e time according to the corrected QT and heart rate defined in the literature, the following formulas were used: Tp-e corrected QT: Tp-e/corrected QT and corrected Tp-e: Tp-e/√R-R. The intra-observer and inter-observer variations for all measurements were <5%, and therefore insignificant.

Transthoracic Echocardiographic Examination

All echocardiographic and Doppler assessments were performed by a single pediatric cardiology expert who was blinded to the clinical and laboratory results of the study group. Epiq 7 echocardiography equipment (Philips Healthcare, Minnesota, United State) with a 3MHz phased-array transducer was used for each subject. The echocardiographic evaluation from the parasternal long-axis view included left ventricular end-diastolic and end-systolic diameters, septum and left ventricular posterior wall thicknesses in diastole and systole, and left ventricular ejection fraction and fractional shortening. Teichholz's M-mode formula was used to calculate left ventricular ejection fraction and fractional shortening. All data were obtained according to the recommendations of the American Society of Echocardiography.[22] The left atrial dimension was measured from the parasternal long-axis window in M-mode echocardiograph.

Statistical Analysis

All data were analyzed with the SPSS 15.0 (SPSS Inc., Chicago, IL, USA) program. Mean±standard deviation was used for numerical variables, and percentages for categorical data. If the numerical data showed normal distribution in the comparison of the data of children with FMF and healthy children, the Student-t test was employed; if the data did not display normal distribution, the Mann Whitney-U test was used. The chi-square test was used in the comparison of categorical data. If the correlational variables between the parameters were normally distributed, Pearson's correlation analysis was used, while Spearman's correlation analysis was employed if they were not normally distributed. A correlation coefficient and p values were obtained. Statistical significance was accepted as $p<0.05$.

RESULTS

Demographic and Clinical Characteristics

Forty-four patients with FMF and 44 healthy children were included in the study. In both groups, there was a total of 25 girls (56.8%) and 19 boys (43.2%). The mean age of the patients was 11.38±4.21 years; that of the control group was 11.61±4.16 years.

The mean age at which FMF started was 6.2±3.4; the duration of the disease was a mean 5.40±3.68 years. The frequency of attacks was at a median of once every 5 months (minimum 3 months, maximum 12 months). The duration of attacks were at a median of 2 (minimum 2-maximum 3) days. The median dose of colchicine taken by the patients was 0.5 mg (minimum 0.25 mg-maximum 2 mg).

In the classification of the patients according to their disease severity scores in line with the scoring system of Pras et al., 9 patients (20.4%) displayed mild, 29 patients (65.9%) showed moderate, and 6 patients (13.6%) severe forms of the disease. According to the scoring system of Mor et al., 23 patients (52.2%) displayed mild, 13 patients (29.5%) showed moderate, and 8 patients (18.1%) severe disease. The ISSF scoring showed that 20 patients (45.4%) exhibited mild, 18 patients (40.9%) moderate, and 6 patients (13.6%) severe disease.

Demographical and clinical characteristics are shown in **Table 1**. Comparison of Laboratory Features

Laboratory findings and comparisons of the patients and the control group can be seen in **Table 1**. Although ESR, potassium, phosphorus, creatinine values were within the reference range in both the FMF group and the controls, a statistically significant difference for each value was detected between the two groups (p values: p=0.038, p=0.019, p=0.019, p=0.04, respectively). While creatinine and potassium were statistically and significantly high in the control group, the patient group displayed high levels of phosphorus and ESR.

Table 1: Demographic, clinical and laboratory characteristics of the pediatric familial Mediterranean fever patients

	FMF patients n=44	Control n=44	p value
Gender			
Male (n, %)	19 (43.2%)	19 (43.2%)	1
Female (n, %)	25 (56.8%)	25 (56.8%)	
Age, mean (SD)	11.38 (4.21)	11.61 (4.16)	0.80
BMI	21.40 (1.32)	22.12 (2.11)	0.64
Clinical Manifestations	**Mean (SD) or Median (min-max)**		
Age at onset (year)	6.20 (3.42)		
Disease duration (year)	5.40 (3.68)		
Attack frequency (month)	5 (3-12)*		
Attack duration (day)	2 (2-3)*		
Dose of colchicines (Tb)	1.00 (0.5-3)		
Severity Scores	**n (%)**		
Pras et al			
Mild	9 (20.5)		
Moderate	29 (65.9)		
Severe	6 (13.6)		
Mor at al			
Mild	23 (52.2)		
Moderate	13 (29.5)		
Severe	8 (18.1)		
ISSF			
Mild	20 (45.4)		
Moderate	18 (40.9)		
Severe	6 (13.6)		
Laboratory features	**Mean (SD) or Median (min-max)**	**Mean (SD) or Median (min-max)**	**p value**
CRP	1.44 (1.09-2.64)*	1.52 (1.25-2.32)*	0.34†
ESR	6 (3-13)	4 (2-9)	0.038†
Wbc	7.27 (2.17)	7.14 (2.31)	0.79
Hb	13.23 (1.33)	13.45 (1.35)	0.45
Plt	313.00 (74.79)	296.50 (67.58)	0.29
Neuthrophil	8.28 (1.03)	3.75 (2.13)	0.71
Na	138.90 (1.84)	138.71 (2.32)	0.68
K	4.30 (0.29)	4.46 (0.33)	0.019
Cl	104 (103-105)*	104 (103-105)*	0.37†
Ca	9.9 (9.6-10.2)*	9.9 (9.7-10.1)*	0.99†
P	4.75 (0.51)	4.45 (0.63)	0.019
Mg	2.02 (0.13)	2.03 (0.15)	0.76
Albumine	4.45 (4.30-4.60)*	4.40 (4.30-4.60)*	0.44†
Creatinine	0.49 (0.14)	0.59 (0.15)	0.004

FMF: Familial Mediterranean fever, SD: Standart deviation, Min: minimum, Max: maximum, BMI: Body mass index, Tb: Tablet, ISSF: International severity score of Familial Mediterranean Fever, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Wbc: White blood cell, Hb: Hemoglobulin, Plt: Platelet, Na: Sodium, K: Potassium, Cl: Chlorine, Ca: Calcium, P: Phosphorus, Mg: Magnesium
*Non-normally distributed values
† Mann-Whitney -U test, p<0.05 is statistically significant

Comparison of Cardiovascular Parameters

No difference was found between the FMF and control groups in terms of heart rate, systolic-diastolic blood pressure and echocardiographic parameters. The RR, QT and Tp-e intervals were statistically and significantly higher in the patient group compared to the controls (p values: p=0.020, p=0.002, p=0.046, respectively). A comparison of cardiovascular parameters can be found in **Table 2**.

Table 2: Comparison between cardiovascular, electrocardiographic and echocardiographic measurements of patients and controls

	FMF	Control	p value
Blood pressures	Mean (SD)	Mean (SD)	
Systolic blood pressure (mmHg)	106.15 (11.93)	100 (0.0)	0.49
Diastolic blood pressure (mmHg)	58.08 (8.30)	60 (0.0)	0.76
Electrocardiographic measurements	**Mean (SD)**	**Mean (SD)**	
Hearth rate (beat/min)	88.34 (13.78)	83.74 (12.76)	0.11
RR interval (msec)	486.05 (122.59)	435.07 (70.35)	0.020
QT interval (msec)	235.98 (50.81)	208.49 (22.99)	0.002
QTc interval (msec)	340.98 (45.29)	324.12 (41.36)	0.074
QT dispersion(msec)	36.64 (16.12)	35.30 (12.45)	0.67
Tp-e interval (msec)	52.84 (15.12)	47.37 (9.31)	0.046
cTp-e interval (msec)	2.39 (0.56)	2.29 (0.48)	0.34
Tp-e/QTc (ratio)	0.15 (0.03)	0.15 (0.03)	0.33
P dispersion (msec)	23.18 (6.69)	25.58 (10.93)	0.22
Echocardiographic measurements	**Mean (SD)**	**Mean (SD)**	
EF (%)	68.98 (4.80)	68.15 (4.08)	0.39
FS (%)	37.59 (3.80)	36.43 (5.47)	0.25
IVSd thickness (mm)	7.40 (1.19)	7.13 (1.33)	0.31
IVSs thickness (mm)	8.69 (1.37)	9.83 (9.78)	0.44
LVEDd (mm)	35.33 (3.98)	43.51 (47.47)	0.26
LVEDs (mm)	22.01 (3.26)	22.44 (4.08)	0.59
LA dimension (mm)	22.03 (2.72)	21.49 (5.11)	0.56
LVPWd (mm)	7.38 (1.42)	7.43 (2.13)	0.89
LVPWS (mm)	9.43 (2.39)	9.65 (2.27)	0.65
Aorta diameter (mm)	19.63 (2.87)	19.57 (3.96)	0.95
Mitral E (m/s)	0.90 (0.08)	1.48 (3.20)	0.28
Mitral A (m/s)	0.61 (0.10)	1.74 (6.69)	0.28
E/A ratio	1.51 (0.25)	1.55 (0.39)	0.62

SD: Standart deviation, EF: LV ejection fraction, FS: LV fractional shortening, IVSd: Interventricular septal diameter in diastole, IVSs: Interventricular septal diameter in systole, LVEDd: LV end-diastolic diameter, LVEDs: LV end-systolic diameter, LVPWd : LV posterior wall diameter in diastole, LVPWS: LV posterior wall diameter in systole, LA: Left atrial dimention, Aort: Aortic dimension, mitralE: Mitral peak early diastolic wave (E), mitralA: Mitral peak late diastolic wave (A), EA: Mitral peak early diastolic wave/peak late diastolic wave ratio, p<0.05 is statistically significant

Correlation between Patients' Electrocardiography Parameters and Clinical Features

A weak positive correlation was found between disease duration and P wave dispersion (p=0.039, correlation coefficient=0.331). A weak correlation was found between attack frequency and QT dispersion (p=0.032, correlation coefficient=-0.345), while a weak negative correlation was found between attack duration and RR and QT intervals (p=0.003, correlation coefficient=-0.461; p=0.019, correlation coefficient=-0.365, respectively). There was also a weak positive correlation between ESR and QT dispersion (p=0.030, correlation coefficient=0.240) (**Table 3**).

The Relationship Between Disease Severity and Electrocardiography Parameters

Since the size of the patient group was small, the groups were classified as mild and moderate-severe in all three scoring systems. When evaluated in this way, it was found that according to all three scoring systems, QT dispersion was longer in the group with moderate-severe disease compared to the group with mild disease (p<0.001, p=0.002, p=0.013, respectively). The correlation between disease severity scores and electrocardiograph data is reviewed in **Table 4**.

Table 3: Correlation between electrocardiography parameters of the patients and their clinical/laboratory features

Clinical features	RR interval	QT interval	QT dispersion	QTc interval	Tpe interval	cTpe interval	Tpe/QTc ratio	P wave dispersion
Age at disease onset								
Coefficient corelation	0.139	0.113	-0.039	0.006	0.15	0.105	0.161	-0.065
p value	0.400	0.492	0.814	0.973	0.363	0.524	0.327	0.695
Disease duration								
Coefficient corelation	0.287	0.186	0.054	0.028	0.085	-0.013	0.151	0.331
p value	0.076	0.256	0.745	0.868	0.609	0.94	0.36	0.039
Attack frequency								
Coefficient corelation	0.007	-0.041	0.345	-0.059	-0.016	-0.01	-0.041	-0.078
p value	0.968	0.805	0.032	0.721	0.922	0.953	0.803	0.635
Attack duration								
Coefficient corelation	-0.461	-0.375	-0.024	-0.216	-0.282	-0.196	-0.411	-0.057
p value	0.003	0.019	0.882	0.187	0.082	0.233	0.090	0.729
ESR								
Coefficient corelation	-0.078	0.063	0.240	0.091	-0.25	0.00	-0.115	0.093
p vavlue	0.484	0.571	0.030	0.416	0.824	0.999	0.303	0.405
K								
Coefficient corelation	0.039	-0.66	0.024	-0.164	-0.081	-0.107	0.053	-0.043
p value	0.726	0.549	0.825	0.136	0.464	0.333	0.634	0.638
P								
Coefficient corelation	0.010	0.159	0.141	0.153	0.081	0.078	-0.017	-0.180
p value	0.932	0.153	0.208	0.175	0.571	0.487	0.877	0.106
Cre								
Coefficient corelation	0.184	-0.050	0.131	-0.119	-0.074	-0.162	-0.025	0.201
p value	0.096	0.654	0.239	0.285	0.505	0.144	0.815	0.069

K: Potassium, P: Phosphorus, Cre: Creatinin, ESR: Erythrocyte sedimentation rate, QTc: Corrected QT, cTp-e: Corrected Tp-e, p<0.05 is statistically significant

Table 4: Comparison of electrocardiographic measurements among familial Mediterranean fever patients according to disease severity scores

Electrocardiographic measurements	Pras et al severity score		p value
	Mild (n=9) Mean (SD)	Moderate-Severe (n=35) Mean (SD)	
RR interval	90.78 (13.16)	93.29 (17.22)	0.74
QT interval	208.49 (22.99)	235.17 (51.93)	0.84
QTc interval	343.11 (35.50)	340.43 (47.92)	0.88
QT dispersion	32.40 (9.41)	53.11 (25.23)	<0.001
Tpe interval	50.44 (13.61)	53.46 (15.61)	0.60
cTpe interval	2.27 (0.42)	2.43 (0.60)	0.46
Tpe/QTc ratio	0.15 (0.04)	0.15 (0.03)	0.56
P dispersion	25.44 (6.58)	22.60 (6.69)	0.26
	Mor et al severity score		
	Mild (n=23) Mean (SD)	Moderate-Severe (n= 21) Mean (SD)	p value
RR interval	516.43 (128.67)	482.94 (113.62)	0.08
QT interval	244.52 (49.24)	226.62 (52.03)	0.25
QTc interval	345.09 (40.67)	336.48 (50.51)	0.54
QT dispersion	29.19 (6.70)	43.43 (19.12)	0.002
Tpe interval	55.52 (14.92)	49.90 (15.14)	0.22
cTpe interval	2.45 (0.57)	2.33 (0.56)	0.50
Tpe/QTc ratio	0.16 (0.03)	0.15 (0.03)	0.33
P dispersion	24.39 (7.01)	21.86 (6.22)	0.21
	ISSF		
	Mild (n=20) Mean (SD)	Moderate-Severe (n=24) Mean (SD)	p value
RR interval	501.40 (137.54)	473.25 (109.98)	0.45
QT interval	237.10 (51.42)	235.04 (51.39)	0.90
QTc interval	340.35 (41.07)	341.50 (49.41)	0.93
QT dispersion	31.25 (8.66)	43.10 (20.41)	0.013
Tp-e interval	53.10 (15.64)	52.63 (15.01)	0.92
cTp-e interval	2.37 (0.59)	2.41 (0.55)	0.83
Tpe/QTc ratio	0.15 (0.03)	0.15 (0.03)	0.75
P dispersion	24.15 (6.96)	22.38 (6.50)	0.39

ISSF: International severity score of familial Mediterranean fever, QTc: Corrected QT, cTp-e: Corrected Tp-e, SD: Standart deviation, p<0.05 is statistically significant

DISCUSSION

We found in our study that RR, QT and Tp-e intervals were significantly longer in FMF patients. Since prolongations in these parameters on the electrocardiography could be related to ventricular arrhythmia, we considered that FMF patients may have increased cardiac arrhythmia risk compared to the control group. We examined the correlation between ESR and the cardiac repolarization parameters of QT and Tp-e. We could not find any correlation between ESR and these parameters, but we did detect a weak correlation with QT dispersion. We also found that QT dispersion duration was significantly longer in the group with moderate and severe disease compared to those with mild disease. In many studies, QT dispersion has been found to be associated with cardiac arrhythmias.[23,24] In our study, the fact that the QT and Tpe intervals were longer in the FMF group compared to the controls, and that the prolongation of the QT dispersion was also associated with the severity of the disease suggested that subclinical inflammation predisposes to ventricular arrhythmia in patients with FMF.

Familial Mediterranean fever is a disease that is characterized by recurrent attacks of inflammation.[25] Controlling inflammation is the most effective way of preventing the mortality and morbidity caused by the disease. Despite this, however, some studies have shown that the effects of FMF persist even in the absence of inflammation.[26,27] Many markers have been studied, especially in hemograms, in order to detect subclinical inflammation, but as yet no clear conclusions have been drawn.[28,29] It was interesting to note that although ESR values were in the normal range in both our patients and in the control group, these values were significantly higher in the FMF group. This may be discussed as an indication of subclinical inflammation, but this is not the aim of our study.

It has been shown that continued subclinical inflammation leads to endothelial dysfunction in the heart muscle and that endothelial dysfunction leads to vasculitis and in turn, to ischemia-related focal fibroses.[30-33] In our study, no difference was detected between the patients with FMF and the healthy controls in terms of echocardiographic measurements, left ventricular systolic and diastolic functions. Since we worked with pediatric patients in our study, we considered that the duration of the disease may not be enough to spot potential changes in coronary microvascular circulation.

Cardiac arrhythmia is a serious condition that can result in sudden death. It is thought that transmission problems and rhythm disorders are associated with continued inflammation-related ischemia and/or local fibrosis in FMF.[15,34] The myocardial repolarization QT duration, QT dispersion and transmural repolarization can be calculated and evaluated.[35-37] While the peak point of the T wave on the electrocardiography signifies the end of the epicardial action potential and the earliest completed repolarization on the ventricular wall, the end of the T wave corresponds to the end of the mid myocardial action potential; this distance is thought to indicate total repolarization.[13] It is therefore believed that Tp-e reflects transmural repolarization distribution. Furthermore, because the Tp-e/ corrected QT ratio is not affected by dynamic changes in heart rate in terms of indicating ventricular repolarization and arrhythmogenesis, it is believed it is more sensitive to indicating ventricular repolarization.[38] Yamaguchi et al. have observed that the Tp-e interval is more valuable than QT dispersion in terms of predicting torsades de pointes in patients with acquired long QT syndrome.[39] It has been noted in other studies that the Tp-e interval is prolonged in diseases such as rheumatoid arthritis, systemic lupus erythematosus.[40,41] Studies with adult patients have shown that the Tp-e interval and corrected Tp-e/QT ratio is statistically and significantly prolonged compared to healthy controls in FMF.[14,15] In our study, we observed that the QT and Tp-e intervals displaying ventricular repolarization in the FMF group were significantly more prolonged than in the control group.

QT dispersion is an index that is newly being introduced as a measure of arrhythmogenicity.[42] Akçay found increased QT dispersion in individuals with FMF compared to healthy controls.[4] On the other hand, there are also studies that have not indicated any significant difference between FMF and healthy groups in terms of QT dispersion.[32,33] In pediatric cases, Fidancı et al. reported increased QT dispersion in pediatric FMF patients compared to healthy controls.[16] In a study by Koca et al., the authors did not find a difference between FMF and control groups in terms of QT dispersion and corrected QT dispersion.[43]

The increase in P wave dispersion is correlated with heterogeneity in atrial transmission and it is assumed that this is a risk for atrial fibrillation and relapse.[44,45] In the present study, we found a positive and weak correlation between P wave dispersion and disease duration. On the other hand, no difference was found between the FMF group and the healthy controls in terms of P wave dispersion.

Differing from other studies, our research included the evaluation of electrocardiographic parameters in terms of patients' disease severity scores. For a more accurate statistical analysis, the patients were divided into two groups of mild and moderate-severe and according to all 3 scoring systems, QT dispersion was seen to be significantly longer in the moderate-severe group compared to the group with mild disease. QT dispersion's sensitivity in determining arrhythmogenesis and the fact that similar results were found in all 3 scoring systems suggests that even though there may be no apparent sign of inflammation in FMF, the subclinical inflammation occurring as disease severity progresses will increase arrhythmogenesis.

The present study had some limitations, the most important of which was that the sampling consisted solely of pediatric patients and the number of patients was limited. Another limitation was that because the follow-up periods had to be made at short intervals due to the younger ages of the individuals, it was not possible to work with definitive data. We believe it will be of much more benefit from a scientific point of view if this type of study can be carried on into the children's adult phase so that 5- and 10-year comparisons can be made.

CONCLUSION

In conclusion, the adverse effects of inflammation on transmission systems are known. We detected significant changes in our study in individuals with FMF compared to the healthy controls, noting that moderate-severe FMF disease showed more significant changes in terms of predicting arrhythmogensis than in individuals with mild disease. This led us to think that subclinical inflammation in FMF can be the cause of ventricular arrhythmias. The correlation between the increase in the severity of the disease and the widening of QT dispersion reinforced our thesis. We believe that studies with longer follow-ups and larger patient populations will enable the collection of more accurate results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University local ethics committee (Decision No: 2020/274).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus:the molecular pathophysiology of autoinflammatory disease. Annu Rev Immunol 2009;27:621-68
2. Ben-Zvi I, Livneh A. Chronic inflammation in FMF:markers, risk factors, outcomes and therapy. Nat Rev Rheumatology 2011;7(2):105.
3. Lachmann H. Clinical immunology review series:an approach to the patient with a periodic fever syndrome. Clin Exp Immunol 2011;165(3):301-9.
4. Akcay A, Acar G, Sayarlioglu M et al. QT dispersion and transmural dispersion of repolarization in patients with familial Mediterranean fever. Mod Rheumatol 2009;19(5):550-5.
5. Nussinovitch U, Livneh A. Late ventricular potentials in familial Mediterranean fever with and without AA amyloidosis. Eur J Rheumatol 2017;4(3):184-8.
6. Nussinovitch U, Shoenfeld Y. Autoimmunity and heart diseases:pathogenesis and diagnostic criteria. Arch Immunol Ther Exp 2009;57(2):95-104.
7. Polachek A, Touma Z, Anderson M, Eder L. Risk of cardiovascular morbidity in patients with psoriatic arthritis:a meta-analysis of observational studies. Arthritis Care Res 2017;69(1):67-74.
8. Kaya EB, Yorgun H, Akdogan A, et al. Heart-rate recovery index is impaired in Behçet's disease. Tex Heart Inst J 2009;36(4):282-6.
9. Rozenbaum M, Naschitz JE, Yudashkin M, et al. Cardiovascular autonomic dysfunction in familial Mediterranean fever. J Rheumatol 2002;29(5):987-9.
10. Ocal AG, Ocal L, Kup A, Eren H, Tezcan ME. Colchicine's Effects on Electrocardiographic Parameters in Newly Diagnosed Familial Mediterranean Fever Patients: Colchicine may have Favorable Effects on Parameters Related to Ventricular Arrhythmias in New Diagnosed Familial Mediterranean Fever. Z Rheumatol 2020;79(2):210-5.
11. Arslan D, Oran B, Yazılıtas F, Peru H, Cimen D, Vatansev H. P-wave duration and dispersion in children with uncomplicated familial Mediterranean fever. Mod Rheumatol 2013;23(6):1166-71.
12. Antzelevitch C, Shimizu W, Yan G-X, Sicouri S. Cellular basis for QT dispersion. J Electrocardiol 1998;30:168-75.
13. Kors JA, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. J Electrocardiol 2008;41(6):575-80.
14. Ahbap E, Sakaci T, Kara E, et al. Familial Mediterranean Fever is associated with abnormal ventricular repolarization indices. Rev Med Chil 2015;143(12):1560-8.
15. Karaman K, Karayakali M, Erken E, et al. Assessment of myocardial repolarisation parameters in patients with familial Mediterranean fever. Cardiovasc J Afr 2017;28(3):154-8.
16. Fidancı MK, Kilic A, Gülgün M, et al. QT and JT dispersion in children with familial Mediterranean fever. Arch Rheumatol 2015;30(4):343-8.
17. Shimizu M, Ino H, Okeie K, et al. T-peak to T-end interval may be a better predictor of high-risk patients with hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion. Clin Cardiol 2002;25(7):335-9.
18. Yalçinkaya F, Ozen S, Ozçakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford) 2009;48(4):395-8.
19. Pras E, Livneh A, Balow JE Jr, et al. Clinical differences between North African and Iraqi Jews with familial Mediterranean fever. Am J Med Genet 1998;75(2):216-9.
20. Mor A, Shinar Y, Zaks N, et al. Evaluation of disease severity in familial Mediterranean fever. Semin Arthritis Rheum 2005;35(1):57-64.
21. Demirkaya E, Acikel C, Hashkes P, et al;FMF Arthritis Vasculitis and Orphan disease Research in pediatric rheumatology (FAVOR). Development and initial validation of international severity scoring system for familial Mediterranean fever (ISSF). Ann Rheum Dis 2016;75(6):1051-6.
22. Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults:Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2019;32(1):1-64.
23. Alp H, Baysal T, Altın H, Karataş Z, Karaarslan S. QT and P-wave dispersions in rheumatic heart disease:prospective long-term follow up. Pediatr Int 2014;56(5):681-8.
24. Kittnar O, Lechmanová M. Disperze QT intervalu [QT interval dispersion]. Cesk Fysiol 2001;50(3):125-33.
25. Ben-Chetrit E, Levy M. Familial Mediterranean fever. The Lancet 1998;351(9103):659-64.
26. Uslu AU, Deveci K, Korkmaz S, et al. Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial Mediterranean fever? Biomed Res Int 2013;2013:185317.
27. Lachmann HJ, Sengül B, Yavuzşen TU, et al. Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology (Oxford) 2006;45(6):746-50.
28. Marzouk H, Mostafa N, Khalifa I, et al. Red Cell Distribution Width (RDW) as a Marker of Subclinical Inflammation in Children with Familial Mediterranean Fever. Curr Rheumatol Rev 2020;16(4):298-303.
29. Özer S, Yılmaz R, Sönmezgöz E, et al. Simple markers for subclinical inflammation in patients with Familial Mediterranean Fever. Med Sci Monit 2015;21:298-303.
30. Shoenfeld Y, Gerli R, Doria A, et al. Accelerated atherosclerosis in autoimmune rheumatic diseases. Circulation 2005;112(21):3337-47.
31. Karaman K, Karayakalı M, Sağlam E, et al . Evaluation of Tp-e Interval and Tp-e/QT Ratio in Patients with Familial Mediterranean Fever. Am J Cardiol 2016;117:90-1.
32. Giese A, Ornek A, Kurucay M, et al. P wave dispersion and QT dispersion in adult Turkish migrants with familial mediterranean fever living in Germany. Int J Med Sci 2014;11(11):1140-6.
33. Caliskan M, Gullu H, Yilmaz S, et al. Impaired coronary microvascular function in familial Mediterranean fever. Atherosclerosis 2007;195(2):161-7.
34. Coronel R, Wilders R, Verkerk AO, Wiegerinck RF, Benoist D, Bernus O. Electrophysiological changes in heart failure and their implications for arrhythmogenesis. Biochim Biophys Acta Mol Basis Dis 2013;1832(12):2432-41.
35. Antzelevitch C, Sicouri S, Di Diego JM, et al. Does Tpeak-Tend provide an index of transmural dispersion of repolarization? Heart Rhythm 2007;4(8):1114-6.
36. Sicouri S, Antzelevitch C. A subpopulation of cells with unique electrophysiological properties in the deep subepicardium of the canine ventricle. The M cell. Circ res 1991;68(6):1729-41.
37. Yan G-X, Wu Y, Liu T, Wang J, Marinchak RA, Kowey PR. Phase 2 early afterdepolarization as a trigger of polymorphic ventricular tachycardia in acquired long-QT syndrome:direct evidence from intracellular recordings in the intact left ventricular wall. Circulation 2001;103(23):2851-6.
38. Gupta P, Patel C, Patel H, et al. Tp-e/QT ratio as an index of arrhythmogenesis. J Electrocardiol 2008;41(6):567-74.
39. Yamaguchi M, Shimizu M, Ino H, et al. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome:a new index for arrhythmogenicity. Clin Sci (Lond) 2003;105(6):671-6.
40. Acar GR, Akkoyun M, Nacar AB, et al. Evaluation of Tp-e interval and Tp-e/QT ratio in patients with rheumatoid arthritis. Turk Kardiyol Dern Ars 2014;42(1):29-34.
41. Avci A, Demir K, Altunkeser BB, et al. Assessment of inhomogeneities of repolarization in patients with systemic lupus erythematosus. Ann Noninvasive Electrocardiol 2014;19(4):374-82.
42. Bazoukis G, Yeung C, Wui Hang Ho R, et al. Association of QT dispersion with mortality and arrhythmic events-A meta-analysis of observational studies. J Arrhythm 2019;36(1):105-15.
43. Koca B, Kasapçopur O, Bakari S, et al. QT dispersion and cardiac involvement in children with Familial Mediterranean fever. Cardiol Young 2012;22(4):404-9.
44. Okutucu S, Aytemir K, Oto A. P-wave dispersion:What we know till now?. JRSM Cardiovasc Dis 2016;5:2048004016639443.
45. Boos CJ, Anderson RA and Lip GY. Is atrial fibrillation an inflammatory disorder? Eur Heart J 2006;27:136–49

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Investigation of Supplement Products Preferred by Healthcare Professionals During COVID-19 Pandemic Process

COVID-19 Pandemi Sürecinde Sağlık Profesyonelleri Tarafından Tercih Edilen Takviye Ürünlerin Araştırılması

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Abstract

Aim: Various products are used to strengthen immunity in prevention and treatment during the COVID-19 pandemic affecting the whole world, which has no cure yet, and the vaccine has just been used. This study was planned to learn about the supplements used by healthcare professionals.

Material and Method: A questionnaire was applied to the physicians, nurses, technicians, secretaries, and staff working in the operating room, intensive care, ward, and outpatient clinic by e-mail, WhatsApp, or face-to-face interview method.

Results: There was no difference between the groups in terms of being COVID-19-positive. The most used products were primarily Mg and vitamin D, and vitamin C, ginger, Zn, turmeric, green tea, vitamin complex, thyme, black elderberry (sambucus nigra), propolis, prebiotic/probiotic, acetylsalicylic acid (ASA), black cumin (niger sativa), N-acetyl cysteine (NAC), selenium (Se), Coenzyme-Q10, cinnamon, glutathione (GSH) and quercetin respectively. No one had used alpha lipoic acid (ALA). The products that showed significant differences between the groups with and without COVID-19 were vitamin C, prebiotic/probiotic, propolis and ASA.

Conclusion: Since it is not asked when the product is used, although it is not possible to evaluate its effectiveness for preventive or therapeutic purposes, known to be natural, inexpensive, and easily accessible antiviral products may be preferred.

Keywords: COVID-19, healthcare workers, boosting immunity, supplement products

Öz

Amaç: Henüz tedavisi bulunmayan ve aşının da yeni kullanıma girdiği, tüm dünyayı etkileyen COVID-19 pandemi sürecinde korunma ve tedavide bağışıklığı güçlendirmek için çeşitli ürünler kullanılmıştır. Bu anket sağlık çalışanlarının kullandığı takviyeleri öğrenmek amacıyla planlanmıştır.

Gereç ve Yöntem: Ameliyathane, yoğun bakım, servis ve poliklinikte çalışan doktor, hemşire, tekniker, sekreter ve personele elektronik posta, whatsapp veya yüzyüze görüşme yöntemiyle anket uygulandı.

BULGULAR: Gruplar arasında COVID-19 pozitif olma açısından fark yoktu. En çok kullanılan ürünler başta Mg ve D vitamini olmak üzere sırasıyla C vitamini, zencefil, Zn, zerdeçal, yeşil çay, vitamin kompleksi, kekik, kara mürver (sambucus nigra), propolis, prebiyotik/probiyotik, asetilsalisilik asit (ASA), çörek otu (niger sativa), N-asetil sistein (NAC), selenyum (Se), Koenzim-Q10, tarçın, glutatyon (GSH) ve kuersetin idi. Hiç kimse alfa lipoik asit (ALA) kullanmamıştı. COVID-19 olan ve olmayan gruplar arasında anlamlı farklılık gösteren ürünler C vitamini, prebiyotik/probiyotik, propolis ve ASA idi.

Sonuç: Ürünün ne zaman kullanıldığı sorulmadığı için koruyucu veya tedavi amaçlı etkinliğini değerlendirmek mümkün olmasa da doğal, ucuz ve kolay erişilebilir olduğu bilinen antiviral ürünler tercih edilebilir.

Anahtar Kelimeler: COVID-19, sağlık çalışanları, bağışıklığı artırmak, takviyeler

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INTRODUCTION

In December 2019, the outbreak of the new coronavirus disease (COVID-19), caused by SARS coronavirus 2 (SARS-CoV-2), in the city of Wuhan, China, was declared a pandemic on March 11, 2020, by the World Health Organization. During the pandemic period, especially the health workers used very different supportive products as well as personal protective equipment to protect themselves from the disease.

Quite a lot of healthcare workers in the world and Turkey have been infected with the virus, and there have been those who lost their lives during the pandemic. Healthcare professionals have preferred to use products such as vitamin D, vitamin C, Zn, Se, Mg, green tea, elderberry (sambucus nigra), quercetin, propolis, probiotic/prebiotic, ginger(zingiber), turmeric(curcumin), thyme, cinnamon, Coenzyme Q10, acetylsalicylic acid (ASA), N-acetyl cysteine (NAC), glutathione (GSH), and alpha lipoic acid (ALA) to strengthen the immune system in order not to get sick or to be asymptomatic or mildly symptomatic.

This survey study was designed to identify the vitamins, minerals, herbs, and supplements used by healthcare professionals during the pandemic and determine their virus positivity.

MATERIAL AND METHOD

Hospital ethics committee approval (Decision no: 19.04.2021, 109/07) and Ministry of Health (2021-02-08T12-14-16) of the Republic of Turkey were obtained for this survey study. Our study was carried out in accordance with the Helsinki Declaration principles. The questionnaire consisting of 10 questions prepared in February 2021 was administered to physicians, nurses, anesthesia technicians, secretaries, and staff working in different hospitals in April 2021 through e-mail, WhatsApp, or face-to-face interview method. In the first part of the questionnaire, information about the purpose of the study was presented, and consent was obtained. They were asked to fill out the questionnaire form without obtaining specific information such as their identity and the name of the institution they work for. The study reached 288 participants.

Age, gender, working unit, title, duration of professional experience, comorbidity, anxiety about COVID-19, support products used to prevent infection (antioxidant, immunomodulatory, and anti-inflammatory), and COVID-19 test positivity history were evaluated.

Statistical Review

"Statistical Package for Social Sciences-SPSS 17" (Chicago, USA) program was used to evaluate the results.

The descriptive properties of the variables were presented as numbers and percentages. The Chi-square test was used to compare categorical variables. P<0.05 was considered statistically significant.

RESULTS

The data of 288 participants included in the survey were analyzed. No questionnaire form was excluded from the study. 51.38% of the participants were physicians, 19.79% nurses, 17.01% technicians, 7.98% secretaries, and 3.81% personnel (**Figure 1**).

Age, gender, working unit, and professional experience period of the participants were significantly different between physicians, nurse technicians, secretaries, and personnel (p<0.001) (**Table 1**).

Table 1. Demographic data

	Physician (n=148)	Nurse (n=57)	Technician (n=49)	Secretary (n=23)	Personnel (n=11)	p
Sex						<0.001
Female	90	38	26	14	1	
Male	58	19	23	9	10	
Age (year)						<0.001
<30	14 (9.5%)	34 (59.6%)	12 (24.5%)	4 (17.4%)	0 (0)	
30-40	37 (25%)	13 (22.8%)	12 (24.5%)	13 (56.5%)	0 (0)	
40-50	66 (44.6%)	10 (17.5%)	22 (44.9%)	5 (21.7%)	7 (63.6%)	
50-60	31 (20.9%)	0 (0)	3 (6.1%)	1 (4.3%)	4 (36.4%)	
Workplace						<0.001
Operating room	79 (53.4%)	19 (33.3)	43 (87.8)	1 (4.3%)	9 (81.8%)	
Ward	14 (9.5%)	0 (0)	2 (4.1%)	8 (34.8%)	1 (9.1%)	
Outpatient clinic	29 (19.6%)	2 (3.5%)	4 (8.2%)	12 (52.2%)	0 (0)	
Intensive care	26 (17.6%)	36 (63.2%)	0 (0)	2 (8.7%)	1 (9.1%)	
Professional Experience (year)						<0.001
1-5	21 (14.2%)	25 (43.9%)	6 (12.2%)	3 (13%)	0 (0)	
6-10	17 (11.5)	9 (15.8)	7 (14.3)	6 (26.1)	2 (18.2)	
11-15	26 (17.6)	7 (12.3)	5 (10.2)	7 (30.4)	5 (45.5)	
16-20	24 (16.2)	5 (8.8)	9 (18.4)	6 (26.1)	1 (9.1)	
>20	60 (40.5)	11 (19.3)	22 (44.9)	1 (4.3)	3 (27.3)	

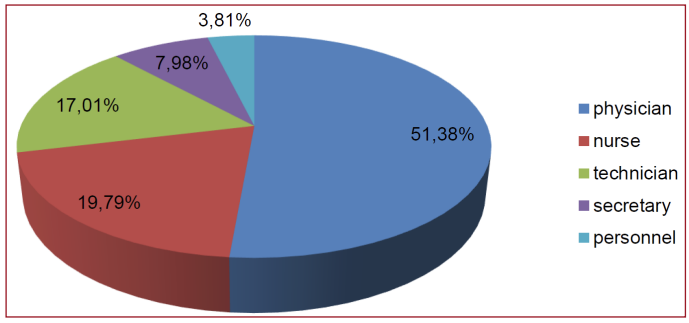

Figure 1. Distribution of the participants by occupational groups

Anxiety levels were significantly different between the groups (p<0.001), as it was the most among physicians (89.9%) and the least among the secretary group (56.5%) (**Figure 2**).

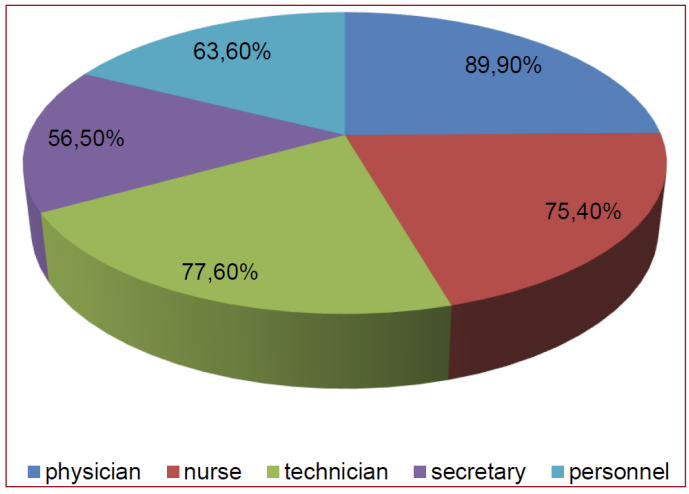

Figure 2. Anxiety rates by occupational groups

The presence of comorbid diseases was not different between the physician, nurse, anesthesia technician, secretary, and personnel groups (27%, 19.3%, 18.4%, 21.7%, and 45.5%, respectively) (p=0.280).

The presence of comorbid diseases was significantly different between groups with and without COVID-19 (p=0.031), while anxiety rates were similar. The products that showed significant differences between the groups with and without COVID-19 were vitamin C, prebiotic/probiotic, propolis and ASA (**Table 2**).

COVID-19 transmission rates were not different between occupational groups (p>0.05), but those with 1-5 years of employment and 16-20 years of employment had higher rates of COVID-19 transmission (p=0.021). There was a comorbid disease in 24.4% (n=70) of the participants, and the incidence increased with age and occupational duration (p<0.001). It was reported that 38.6% (n=27) of those with comorbidities had COVID-19 (p=0.031).

In our study, most common used products by healthcare professionals during the COVID-19 pandemic were primarily Mg and vitamin D, and vitamin C, ginger, Zn, turmeric, green tea, vitamin complex, thyme, black elderberry, propolis, prebiotic/probiotic, respectively.

Table 2. Comparison of groups with and without COVID-19

	COVID-19 (-) (n=206)	COVID-19 (+) (n=82)	p
Physician	111 (53.9%)	37 (45.1%)	
Nurse	36 (17.5%)	21 (25.6%)	
Technician	35 (17%)	14 (17.1%)	0.297
Secretary	18 (8.7%)	5 (6.1%)	
Personnel	6 (52.9%)	5 (6.1%)	
Comorbid disease	43 (20.9%)	27 (32.9%)	0.031*
Anxiety	166 (80.6%)	68 (82.9%)	0.646
Vitamin C	22 (10.7%)	17 (20.7%)	0.024*
Pre/Probiotic	5 (2.4%)	7 (8.5%)	0.019*
Propolis	6 (2.9%)	7 (8.5%)	0.038*
ASA	3 (1.5%)	6 (7.3%)	0.010*

*p <0.05

The usage rate of green tea was high, and the rate of black cumin use was low in those with COVID-19 anxiety (p=0.048 and p=0.001). The use of glutathione and ASA was significant in patients with comorbidities (p=0.012 and 0.003).

Products that were significantly different between groups were Vitamin D, Vitamin C was turmeric, ginger, green tea, black cumin, ASA and vitamin complex (p=0.003, 0.020, 0.008, <0.001, 0.001, <0.001, 0.008, and 0.003, respectively).

The group that received the vitamin complex the most was the secretaries, and the group that received the least was the technicians (p=0.003). It was observed that 12.8% of the physicians and 39.1% of the secretaries used vitamin D, and the difference was significant (p=0.003).

It was seen that vitamin C was used mostly by nurses (24.6%) and least by personnel (9.1%), and the difference between the groups was significant (p=0.020).

The use of turmeric and ginger was significantly different according to occupational groups (p= 0.008 and p<0.001). Both products were mostly used by the personnel group. Green tea was consumed the most by the personnel (18.2%) and the physicians and anesthesia technicians (2%) the least (p<0.001). Those working in the intensive care unit consumed more vitamin C and green tea (p= 0.022 and p<0.001).

Black cumin was consumed mostly by secretaries and least by anesthesia technicians (p<0.001).

None of the participants preferred to use ALA (**Figure 3**).

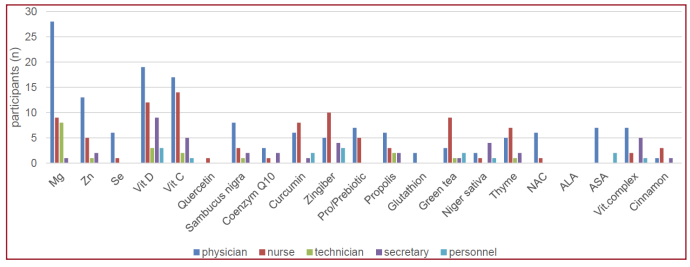

Figure 3. Products used by occupational groups

The group that consumed thyme the most was those working in the wards (p=0.008).

The consumption of vitamin D, vitamin C, turmeric, ginger, probiotic/prebiotic, and green tea was mostly in those who worked for 1-5 years (p=0.004, <0.001, 0.002, 0.020, 0.014, and 0.001, respectively).

Vitamin C, turmeric, green tea, and prebiotic/probiotic use were mostly in the group below the age of 30 (p=0.045, 0.008, 0.009, and 0.024, respectively).

Those who consumed black elderberry the most were those who worked for 16-20 years (p=0.030).

DISCUSSION

Healthcare workers at risk used a wide variety of products besides masks, distance, and personal protective equipment to protect themselves from COVID-19 when there was no cure yet, and vaccination had just begun. In our study, we searched for the supportive products and drugs used by physicians, nurses, anesthesia technicians, secretaries, and personnel working in the operating room, intensive care units, wards, and outpatient clinics to prevent and treat COVID-19 during the pandemic process. The most preferred products by occupational groups respectively, were Mg, vitamin D, vitamin C, Zn and black elderberry in physicians, vitamin C, vitamin D, ginger, Mg, green tea and turmeric in nurses, Mg, vitamin D, vitamin C and propolis in technicians, vitamin D, vitamin C, complex vitamin, ginger and black cumin in secretaries, vitamin D, ginger, turmeric, green tea and ASA were observed in the personnel.

Bioactive substances obtained from immunomodulatory, anti-inflammatory, antioxidant vitamins (A, B, C, D, and E), minerals (Se and Zn), and polyphenols such as turmeric, propolis, green tea have been evaluated as promising nutritional approaches in the fight against COVID-19.[1] It was observed that the combination of vitamin D, magnesium, and vitamin B12 in elderly COVID-19 patients significantly reduces conditions requiring oxygen and intensive care support.[2] The present study determined that the anxiety level was highest in physicians, and they also used Mg, vitamin D, and vitamin C more than other products. Vitamins that also have antiviral effects have also been demonstrated to have a potential role in the management of COVID-19, supplementation is necessary to protect against COVID-19 or relieve symptoms as doses are required too high to come from the diet, but further research is recommended to determine the effective dose.[3] Vitamin D insufficiency increased hospitalization and mortality from COVID-19, and a positive correlation was observed between its deficiency and the severity of the disease and increasing the vitamin D concentration above 40-60 ng/mL should be the target.[4,5] Evidence to date in COVID-19 indicates that oral vitamin C (2-8 g/day) can reduce the incidence and duration of respiratory tract infections, and IV (intravenous) vitamin C (6-24 g/day) may decrease mechanical ventilation and intensive care length of stay and mortality.[6] It has also been predicted that vitamin C which has antithrombotic properties, may reduce the risk of ARDS due to COVID-19.[7,8] However, it is recommended to optimize the high dose IV vitamin C dose.[9,10] In our survey, the rates of vitamin D, vitamin C, and complex vitamin use were significantly higher between the groups.

Mg is known to be a cofactor in many enzymatic reactions in the body. In clinical practice, Mg supplementation protects against SARS-CoV-2 infection and reduces the severity of symptoms while facilitating recovery after the acute phase.[11] In our study, Mg was the most used product together with vitamin D. Although Mg preference was not statistically significant between the groups, it was higher in physicians, technicians, and nurses.

Zn is necessary to protect natural tissue barriers such as respiratory epithelium, prevent pathogen entry, and maintain the immune system's balanced function. Zn deficiency is a predisposing factor to severe COVID-19.[12] Recent studies on COVID-19 patients have revealed that vitamin D and Se deficiencies are evident in patients with acute respiratory tract infections. Vitamin D improves the physical barrier against viruses and stimulates the production of antimicrobial peptides. Se is essential for T-cell-dependent antibody production, while vitamin C has increased the survival rate of COVID-19 patients by reducing the overactivation of the immune response. The combination of these micronutrients can help boost the immune system, prevent the spread of the virus and reduce disease progression.[13] In another study, serum Zn and Se concentrations in the patient group were statistically lower than in the control group.[14] In our study, while the use of Se was significant in the physician group, the use of Zn was not significantly different between the groups. There was no mineral used in the personnel group.

Although there is no standard effective treatment against SARS CoV-2, nutraceuticals such as Zn, Se, vitamin D, and vitamin C are recommended for both prophylaxis and treatment.[15,16]

Spices and herbs with antioxidant and antiviral properties (turmeric, ginger, thyme, cinnamon, green tea, black cumin, elderberry) have also been frequently used during the pandemic. Some herbs and their components, such as turmeric and green tea, have been shown to have promising antiviral properties against SARS-CoV-2.[17] It has been demonstrated that turmeric and ginger, together with their anti-fibrotic effects on the lung, can be helpful in both prophylaxis and treatment in reversing the cytokine storm in severe cases.[18,19] Ninety-three agents, including natural products such as turmeric, green tea, and ginger, have been reported as potential antiviral (for SARS and other viruses) drug candidates.[20]

The phenolic compounds in elderberry have an immunomodulatory effect by increasing macrophage activity and releasing cytokines (TNF-alpha, IL-1, IL-6, and IL-8) from

monocytes. Elderberry has been determined to significantly reduce upper respiratory tract symptoms associated with viral infections but is recommended in the early infection phase as it increases proinflammatory cytokines.[21,22]

The use of vitamin C, pre/probiotic, propolis, and ASA in patients with COVID-19 infection was statistically significantly different.

There is evidence that an aromatherapy blend, including thyme, can significantly improve energy levels in women experiencing fatigue after COVID-19.[23]

Publications support the effectiveness of black cumin and its oil against COVID-19.[24] Although black cumin was used more in secretaries, it was a less preferred product in those with anxiety.

Cinnamon can effectively treat SARS-CoV-2 with its anti-obstructive, diuretic, and tonic effects. There is also pharmacological evidence for its anti-depressant effects.[25]

Green tea-epigallocatechin gallate (EGCG) and black tea-theaflavin plants contain copper (Cu), iron (Fe), manganese (Mn), selenium (Se), and zinc (Zn) from the soil. It is recommended for the prophylaxis and treatment of COVID-19 due to the antiviral, antibacterial, immunomodulatory, antioxidant, and anti-inflammatory effects of the polyphenols it contains.[26-28]

A survey conducted in India found that 93.6% of respondents thought spices were helpful in curing coronavirus or other viral infections and strengthening immunity, and most of them used a mixture of vitamin C and spices to strengthen their immunity. Therefore, it has been concluded from research and available literature that spices and herbs play an important role in enhancing immunity against viral infections.[29] According to our survey results, ginger, turmeric, green tea, thyme, black elderberry, black cumin, and cinnamon were the most preferred herbal products, respectively.

Propolis contains more than 300 chemical components (e.g., terpenes, flavonoids, phenolic acids) and is beneficial in curing symptoms (dry cough, shortness of breath, sore throat, chest pain, fever, dizziness, headache, abdominal pain, and diarrhea) with its antiviral activity against SARS-CoV-2.[30-32] In addition to potent antiviral activity, apitherapy plays a role in stimulating antibody production and maturation of immune cells.[33]

Probiotics can help balance the gut-lung axis and manage the mortality and morbidity rates associated with SARS-CoV-2 infection.[34] The use of probiotics in SARS-CoV-2 virus infection, which was also detected in stool samples, has been suggested as an adjunct treatment for the modulation of microbiota.[35] In our study, we received the answer that the physician and nurse groups used probiotics.

Co-Q10, Quercetin, ALA, ASA, NAC, and GSH are also supplements preferred by healthcare professionals.

Quercetin synergizes antiviral and immunomodulatory properties with vitamin C in both prophylaxis and therapy in high-risk populations in COVID-19.[36] Quercetin is also recommended to alleviate and shorten the duration of the post-COVID-19 syndrome.[37] In addition, both anti-inflammatory and thrombin inhibitory effects of quercetin in COVID-19 should be considered.[38] The rate of quercetin use was very low, and it was determined that only one nurse took it.

Co-Q10 is a cell protective supplement effective on mitochondrial dysfunction and useful in cardiovascular diseases and obesity. Studies have revealed that Co-Q10 has anti-inflammatory and antioxidant effects. It reduces viral load and has been suggested as adjuvant therapy in infectious diseases.[39] Six participants (three doctors, one nurse, and two secretaries) stated that they use it.

The endogenous platelet CoQ10 level decreased in patients after COVID-19. Mitochondrial support is suggested, assuming this may partially block electron transfer in the respiratory chain, resulting in decreased adenosine triphosphate (ATP) production. Platelet mitochondrial function and CoQ10 content may be useful post-COVID-19 health biomarkers.[40]

Based on evidence confirming the ability of glutathione to inhibit viral replication and lower IL-6 levels in human immunodeficiency virus (HIV) and tuberculosis patients, as well as the beneficial effects of GSH on other lung diseases, it has been suggested that its liposomal form may be beneficial in patients with COVID-19.[41] Only two physicians in our study group stated that they used GSH.

GSH and NAC may be beneficial in the prophylaxis and treatment of SARS-Cov-2 with their antioxidant, anti-inflammatory, and immunomodulatory properties.[42] The thiols contained in NAC block the angiotensin-converting enzyme 2 (ACE-2) and prevent SARS-CoV-2 from entering the cells. The benefit of oral intake in influenza-like illnesses has been demonstrated. Moreover, high-dose IV NAC could be expected to play an adjuvant role in treating severe cases of COVID-19 and controlling complications.[43] NAC can reduce cytokine storm, and its antiviral effect on other respiratory viruses suggests its role in the treatment of COVID-19 is worthy of further investigation.[44] It improved clinically by significantly reducing CRP and ferritin in patients infected with COVID-19 on mechanical ventilator.[45] Six out of 7 people using NAC were doctors.

Oxidative stress is considered to play a pathogenic role in viral infections such as COVID-19. Alpha-lipoic acid (ALA) is one of the most studied and used antiviral natural compounds because it has a well-defined antioxidant and immunomodulatory profile.[46] However, no one in our study group used it.

ASA has both anti-inflammatory and antithrombotic effects. Its antiviral activity has been documented against DNA and RNA viruses, including different human coronaviruses. The use of ASA in patients with different infections has been associated with reduced thromboinflammation, lower complication rates, and in-hospital mortality.[47] In hospitalized

COVID-19 patients, prior ASA therapy was associated with less respiratory support and better in-hospital outcomes.[48] It was observed that those with COVID-19 (+) had used ASA. Seven doctors and two personnel from the participants used ASA.

Grouping some plant foods such as Zn, vitamin D, vitamin C, curcumin, cinnamaldehyde, probiotics, Se, and quercetin in the right combination as supplements strengthens the immune system. It inhibits the progression of the disease to the severe stage by suppressing hyper-inflammation in COVID-19.[49]

Natural products such as ginger, turmeric, cinnamon, and green tea have been proven to have therapeutic benefits against acute respiratory infections. These homemade, inexpensive, easily accessible products can be used prophylactically against COVID-19 while stopping the progression of infection in symptomatic patients. In advanced patients, it can alleviate complications and reduce mortality.[19]

Less anxiety in secretaries can be explained by working from a longer distance to the patient.

The limitations of our study and the forms of use of the products (tea, drops, oral, IV, dermal patch) were asked, but they could not be evaluated since the answers were mixed and not regular. The COVID-19's clinical presentation was not questioned; only the test positivity was based on. Chronic disease types were not questioned. At the time the questionnaire was prepared, no questions were asked in this direction, as the vaccination program had just started for healthcare workers.

CONCLUSION

As a result, all health workers, especially physicians, were experiencing anxiety.

While the presence of comorbid diseases differed significantly between groups with and without COVID-19, rates of anxiety were similar.

Use of vitamin C, prebiotic/probiotic, propolis, and ASA differed significantly between groups with and without COVID-19.

One of the reasons for the low use of supplements may be their cost, but natural herbal products known to be antiviral effective and easily accessible can be preferred for prevention and treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Diskapi Yildirim Beyazit Training and Research Hospital Ethics Committee (Date: 19.04.2021, Decision No: 109/07).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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REFERENCES

1. Keflie TS, Biesalski HK. Micronutrients and bioactive substances:Their potential roles in combating COVID-19. Nutrition 2021;84:111103.
2. Tan CW, Ho LP, Kalimuddin S, et al. Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). Nutrition 2020;79-80:111017.
3. Shakoor H, Feehan J, Al Dhaheri AS, et al. Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? Maturitas 2021;143:1–9.
4. Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19:systematic review and meta-analysis. Crit Rev Food Sci And Nutr 2022;62(5):1308–16.
5. Grant WB, Lahore H, McDonnell SL, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients 2020;12(4):988.
6. Holford P, Carr AC, Jovic TH, et al. Vitamin C-An Adjunctive Therapy for Respiratory Infection, Sepsis and COVID-19. Nutrients 2020;12(12):3760.
7. Carr AC, Rowe S. The Emerging Role of Vitamin C in the Prevention and Treatment of COVID-19. Nutrients 2020; 12(11):3286.
8. Liu F, Zhu Y, Zhang J, Li Y, Peng Z. Intravenous high-dose vitamin C for the treatment of severe COVID-19:study protocol for a multicentre randomised controlled trial. BMJ open 2020;10(7):e039519.
9. Feyaerts AF, Luyten W. Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19? Nutrition 2020;79-80.
10. Koçyiğit A. Is the Use of High-Dose Intravenous Vitamin C Safe in the Treatment of SARS-CoV-2? Bezmialem Science 2020.
11. Trapani V, Rosanoff A, Baniasadi S, et al. The relevance of magnesium homeostasis in COVID-19. Eur J Nutr 2022;61(2):625–636.
12. Wessels I, Rolles B, Rink L. The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis. Front Immunol 2020; 11:1712.
13. Bae M, Kim H. Mini-Review on the Roles of Vitamin C, Vitamin D, and Selenium in the Immune System against COVID-19. Molecules 2020;25(22):5346.
14. Kocak OF, Ozgeris FB, Parlak E, et al. Evaluation of Serum Trace Element Levels and Biochemical Parameters of COVID-19 Patients According to Disease Severity. Biol Trace Elem Res 2022;200(7):3138–46.
15. Giovane RA, Di Giovanni-Kinsley S, Keeton E. Micronutrients for potential therapeutic use against COVID-19; a review. Clin Nutr ESPEN 2021;46:9–13.
16. Alexander J, Tinkov A, Strand TA, Alehagen U, Skalny A, Aaseth J. Early Nutritional Interventions with Zinc, Selenium and Vitamin D for Raising Anti-Viral Resistance Against Progressive COVID-19. Nutrients 2020;12(8):2358.
17. Anand AV, Balamuralikrishnan B, Kaviya M, et al. Medicinal Plants, Phytochemicals, and Herbs to Combat Viral Pathogens Including SARS-CoV-2. Molecules 2021;26(6):1775.
18. Zahedipour F, Hosseini SA, Sathyapalan T, et al. Potential effects of curcumin in the treatment of COVID-19 infection. Phytother Res 2020;34(11):2911–20.

19. Thota SM, Balan V, Sivaramakrishnan V. Natural products as home-based prophylactic and symptom management agents in the setting of COVID-19. Phytother Res 2020;34(12):3148–67.
20. Adhikari B, Marasini BP, Rayamajhee B, et al. Potential roles of medicinal plants for the treatment of viral diseases focusing on COVID-19:A review. Phytother Res 2021;35(3):1298–312.
21. Hawkins J, Baker C, Cherry L, Dunne E. Black elderberry (Sambucus nigra) supplementation effectively treats upper respiratory symptoms: A meta-analysis of randomized, controlled clinical trials. Complement Ther Med 2019;42:361–5.
22. Alschuler L, Weil A, Horwitz R, et al. Integrative considerations during the COVID-19 pandemic. Explore 2020;16(6):354–6.
23. Hawkins J, Hires C, Keenan L, Dunne E. Aromatherapy blend of thyme, orange, clove bud, and frankincense boosts energy levels in post-COVID-19 female patients:A randomized, double-blinded, placebo controlled clinical trial. Complement Ther Med 2022;67:102823.
24. Imran M, Khan SA, Abida, et al. Nigella sativa L. and COVID-19:A Glance at The Anti-COVID-19 Chemical Constituents, Clinical Trials, Inventions, and Patent Literature. Molecules 2022; 27(9):2750.
25. Yakhchali M, Taghipour Z, Mirabzadeh Ardakani M, Alizadeh Vaghasloo M, Vazirian M, Sadrai S. Cinnamon and its possible impact on COVID-19:The viewpoint of traditional and conventional medicine. Biomed pharmacother 2021;143:112221.
26. Mhatre S, Srivastava T, Naik S, Patravale V. Antiviral activity of green tea and black tea polyphenols in prophylaxis and treatment of COVID-19: A review. Phytomedicine 2021;85:153286.
27. Chowdhury P, Barooah AK. Tea Bioactive Modulate Innate Immunity:In Perception to COVID-19 Pandemic. Front Immunol 2020; 11:590716.
28. 28.Tallei TE, Fatimawali, Niode NJ, et al. A Comprehensive Review of the Potential Use of Green Tea Polyphenols in the Management of COVID-19. Evid Based Complement Alternat Med 2021;7170736.
29. Singh NA, Kumar P, Jyoti, Kumar N. Spices and herbs:Potential antiviral preventives and immunity boosters during COVID-19. Phytother Res 2021;35(5):2745–57.
30. Yosri N, Abd El-Wahed AA, Ghonaim R, et al. Anti-Viral and Immunomodulatory Properties of Propolis: Chemical Diversity, Pharmacological Properties, Preclinical and Clinical Applications, and In Silico Potential against SARS-CoV-2. Foods 2021;10(8):1776.
31. Güler Hİ, Ay Şal F, Can Z, et al. Targeting CoV-2 spike RBD and ACE-2 interaction with flavonoids of Anatolian propolis by in silico and in vitro studies in terms of possible COVID-19 therapeutics. Turk J Biol 2021;45(4):530–48.
32. Kosari M, Noureddini M, Khamechi SP, et al. The effect of propolis plus Hyoscyamus niger L. methanolic extract on clinical symptoms in patients with acute respiratory syndrome suspected to COVID-19:A clinical trial. Phytother Res 2021; 35(7):4000–6.
33. Lima WG, Brito J, da Cruz Nizer WS. Bee products as a source of promising therapeutic and chemoprophylaxis strategies against COVID-19 (SARS-CoV-2). Phytother Res 2021;35(2):743–50.
34. Baradaran Ghavami S, Pourhamzeh M, Farmani M, et al. Cross-talk between immune system and microbiota in COVID-19. Expert Rev Gastroenterol Hepatol 2021;15(11):1281–94.
35. de Oliveira G, Oliveira C, Pinzan CF, de Salis L, Cardoso C. Microbiota Modulation of the Gut-Lung Axis in COVID-19. Front Immunol 2021;12:635471.
36. Colunga Biancatelli R, Berrill M, Catravas JD, Marik PE. Quercetin and Vitamin C:An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19). Front Immunol 2020;11:1451.
37. Bardelčíková A, Miroššay A, Šoltýs J, Mojžiš J. Therapeutic and prophylactic effect of flavonoids in post-COVID-19 therapy. Phytother Res 2022;36(5):2042–60.
38. Derosa G, Maffioli P, D'Angelo A, Di Pierro F. A role for quercetin in coronavirus disease 2019 (COVID-19). Phytother Res 2021; 35(3):1230–6.
39. Sifuentes-Franco S, Sánchez-Macías DC, Carrillo-Ibarra S, Rivera-Valdés JJ, Zuñiga LY, Sánchez-López VA. Antioxidant and Anti-Inflammatory Effects of Coenzyme Q10 Supplementation on Infectious Diseases. Healthcare 2022;10(3):487.
40. Sumbalova Z, Kucharska J, Palacka P, et al. Platelet mitochondrial function and endogenous coenzyme Q10 levels are reduced in patients after COVID-19. Bratisl Lek Listy 2022;123(1):9–15.
41. Guloyan V, Oganesian B, Baghdasaryan N, et al. Glutathione Supplementation as an Adjunctive Therapy in COVID-19. Antioxidants 2020; 9(10):914.
42. Shi Z, Puyo CA. N-Acetylcysteine to Combat COVID-19:An Evidence Review. Ther Clin Risk Manag 2020;16:1047–55.
43. De Flora S, Balansky R, La Maestra S. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. FASEB J 2020;34(10):13185–93.
44. Zhou N, Yang X, Huang A, Chen Z. The Potential Mechanism of N-acetylcysteine in Treating COVID-19. Curr Pharm Biotechnol 2021; 22(12):1584–90.
45. Ibrahim H, Perl A, Smith D, et al. Therapeutic blockade of inflammation in severe COVID-19 infection with intravenous N-acetylcysteine. Clin Immunol 2020;219:108544.
46. Dragomanova S, Miteva S, Nicoletti F, et al. Therapeutic Potential of Alpha-Lipoic Acid in Viral Infections, including COVID-19. Antioxidants 2021; 10(8):1294.
47. Bianconi V, Violi F, Fallarino F, Pignatelli P, Sahebkar A, Pirro M. Is Acetylsalicylic Acid a Safe and Potentially Useful Choice for Adult Patients with COVID-19? Drugs 2020;80(14):1383–96.
48. Sisinni A, Rossi L, Battista A, et al. Pre-admission acetylsalicylic acid therapy and impact on in-hospital outcome in COVID-19 patients:The ASA-CARE study. Int J Cardiol 2021;344:240–5.
49. Mrityunjaya M, Pavithra V, Neelam R, Janhavi P, Halami PM, Ravindra PM. Immune-Boosting, Antioxidant and Anti-inflammatory Food Supplements Targeting Pathogenesis of COVID-19. Front Immunol 2020;11:570122.

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Maternal Characteristics and Complications in Pregnancies Complicated with Diabetes

Diyabetle Komplike Olmuş Gebeliklerde Maternal Özellikler ve Komplikasyonlar

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Abstract

Aim: Pregnancies complicated with diabetes are risky pregnancies with different maternal characteristics and increased maternal complications compared to the normal pregnant group. In this study, it is aimed to determine maternal characteristics and maternal complications in pregnant women with different glucose intolerance or blood glucose levels, and to compare them with the information in the literature and to investigate the effectiveness of our follow-up and treatment protocols.

Material and Method: This study is carried out with 223 patients at **XXXXXX** Training and Research Hospital between May 2009 and March 2010. Group 1 in the study, normal glycemic group; Group 2, group with 1 value higher in 100 g oral glucose tolerance test (OGTT); Group 3, gestational diabetes mellitus (GDM), is the blood sugar regulated group; Group 4, the uncontrolled group diagnosed with GDM and whose blood sugar is not regulated; Group 5 consisted of patients with pregestational diabetes mellitus, with or without regulated blood sugar.

Results: Considering the maternal characteristics, it is seen that the age, gravida, parity, body mass index (BMI) of Group 3, Group 4 and Group 5 patients are significantly higher than the patients in Group 1 and Group 2. The rates of preeclampsia, macrosomic baby and preterm birth are significantly higher in groups 4 and 5. In terms of delivery types, normal birth rate is high in Group 1, while cesarean section rates are high in Groups 4 and 5. According to the groups, the cases with a 1st minute apgar score less than 7 are significantly higher in Group 4 and Group 5.

Conclusion: It is revealed that different glucose intolerances cause some problems in pregnancy, increase complications, and uncontrolled blood glucose levels increase these problems and complications. In pregestational and gestational periods; In such cases, it should be aimed and ensured that these problems and complications are reduced to the lowest possible level with appropriate diagnosis and treatment approaches.

Keywords: Gestational diabetes mellitus, high risk pregnancy, maternal outcomes

Öz

Amaç: Diyabetle komplike olmuş gebelikler normal gebe grubuna göre farklı maternal özellikler ve artmış maternal komplikasyonların olduğu riskli gebeliklerdir. Biz bu çalışmada farklı glukoz intoleransları veya kan glukoz düzeylerine sahip gebelerde maternal özellikleri ve maternal komplikasyonları saptamayı, bunları literatürdeki mevcut bilgilerle kıyaslıyarak takip ve tedavi protokollerimizin etkinliğini araştırmayı amaçladık.

Gereç ve Yöntem: Bu çalışma Mayıs 2009 ve Mart 2010 tarihleri arasında **XXXXXX** Eğitim ve Araştırma Hastanesi'nde 223 hasta ile gerçekleştirildi. Çalışmada Grup 1, normal glisemik grub; Grup 2, 100 gr oral glukoz tolerans testinde (OGTT) 1 değer yüksek grup; Grup 3, gestasyonel diyabetes mellitüs (GDM) olup kan şekeri regüle grup; Grup 4, GDM tanısı alıp kan şekeri regüle olmayan kontrolsüz grup; Grup 5, Pregestasyonel diyabetes mellitüslu, kan şekeri regüle veya regüle olmayan hastalardan oluşmaktaydı.

Bulgular: Maternal özelliklere bakıldığında Grup 3, Grup 4 ve Grup 5 hastaların Grup 1 ve Grup 2'de ki hastalara göre yaş, gravida, parite, vücut kitle indeksleri (VKİ)'leri, karşılaştırıldığında anlamlı yüksek olduğu görüldü. Grup 4 ve 5'te preeklampsi, makrozomik bebek, preterm doğum görülme oranları anlamlı derecede yüksekti. Doğum şekilleri açısından normal doğum oranı Grup 1'de yüksekken, sezaryan oranları Grup 4 ve 5'te yüksekti. Gruplara göre Grup 4 ve Grup 5'te 1. Dakika apgar skoru 7'den küçük olgular anlamlı yüksekti.

Sonuç: Farklı glukoz intoleranslarının gebelikte bir takım sorunlara yol açtığı, komplikasyonları artırdığı, kontrolsüz kan glukoz düzeylerinin bu sorun ve komplikasyonları daha da artırdığını ortaya koyduk. Pregestasyonel ve gestasyonel dönemlerde; bu tür olgularda, uygun tanı ve tedavi yaklaşımları ile bu sorun ve komplikasyonların mümkün olabilecek en düşük düzeye indirilmesi hedeflenmeli ve sağlanmalıdır.

Anahtar Kelimeler: Gestasyonel diabetes mellitus, yüksek riskli gebelik, maternal sonuçlar

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INTRODUCTION

Gestational Diabetes Mellitus; It is any degree of glucose intolerance that is diagnosed for the first time during pregnancy or that occurs during pregnancy.[1,2] If it is diagnosed before pregnancy, it is called pregestational diabetes mellitus.[3] About 7% of all pregnancies are complicated by diabetes, and 86% of them occur as GDM. [2] The prevalence of GDM varies according to social characteristics as well as the diagnostic tests and criteria used.

Two different approaches can be used in GDM screening: single (75 g OGTT) and two-step (50 g scan and 100 g OGTT) methods.[4] The two-step approach frequently used in GDM screening is based on the detection of venous blood glucose at 1 hour following ingestion of 50 g of oral glucose solution at the initial screening. Women whose glucose levels reach or exceed the laboratory threshold value are then given a 3-hour 100 g OGTT as a diagnostic test. The diagnosis of GDM is usually made with 2 or more abnormal values in the 3-hour OGTT.[5,6]

Decreased insulin sensitivity during pregnancy; It is attributed to the increase in placental and maternal hormones such as human placental lactogen, progesterone, estrogen, cortisol and prolactin, leptin, tumor necrosis factor-alpha (TNF-alpha) and resistin.[7]

As a result of increasing insulin resistance during pregnancy, the amount of insulin secreted from the pancreas to provide maternal euglycemia increases more than two times compared to non-pregnant women. While this situation can be tolerated physiologically in normal pregnant women, it cannot be compensated during pregnancy in diabetic women and many women who are not known to have diabetes before, and the balance of carbohydrate metabolism is disturbed.[8]

Pregnancies complicated by diabetes are risky pregnancies that require close follow-up from both maternal and fetal aspects. After the discovery of insulin by Banting and Best in 1921, maternal and perinatal mortality in diabetic women, which is quite high until that day, has now approached the levels in normal pregnancies, especially except for malformations.[9] GDM has negative effects on maternal health such as increased risk of preeclampsia, increased cesarean delivery rate and increased risk of type 2 diabetes in later life.[10,11]

In this study, it is aimed to determine the maternal characteristics and maternal complications related to a total of 5 groups of pregnant women with different glucose intolerance or blood glucose levels, whose births are performed in our clinic, and to compare these with the existing information in the literature and to investigate the effectiveness of our follow-up and treatment protocols.

MATERIAL AND METHOD

This study is carried out between 11 May 2009 and 11 March 2010 at **XXXXXX** Training and Research Hospital, Gynecology Clinic. The study was carried out with the permission of Ümraniye Training and Research Hospital Ethics Committee (Date: 10.03.2010). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study includes a total of 223 pregnant women and their babies, who are followed up and treated in the obstetrics clinic and delivery room, and delivered in our hospital. In order to investigate maternal characteristics and complications in different levels of glucose intolerance, 5 groups of pregnant women are compared.

Group 1 (normoglycemic) consisted of 85 patients with normol glucose level. Pregnant women with 50 g glucose screening test above 140 mg/dl but not exceeding any threshold value in 100 g OGTT are included in this group. Group 2 consisted of 44 patients with only one elevation in 100 g OGTT, exceeding 140 mg/dl in the 50 g glucose screening test. Group 3, those whose 50 g glucose screening test result is 140 mg/dl and above, 100 g OGTT is performed, and those who have at least two values higher or those whose 50 g scan result is above 180 mg/dl are followed up and treated in our clinic and their blood sugar is regulated with diet or insulin. It consisted of 52 patients. The values suggested by Carpenter and Causton are taken as the basis for the threshold values in OGTT.[5] Group 4 consisted of 24 uncontrolled patients who are diagnosed with gestational DM and delivered in our clinic, but did not have follow-up and treatment and blood sugar regulation is not provided. Group 5 consisted of 18 patients with pregestational DM, blood glucose control or uncontrolled due to lack of follow-up.

Diabetic pregnant women are started on a diet in consultation with a dietitian. Patients with persistently high blood glucose levels for 1-2 weeks although diet and exercise are hospitalized. Insulin therapy is started for the patients whose fasting blood glucose is 95 mg/dl and 1 hour postprandial blood glucose is above 140 mg/dl.

No treatment is given to the pregnant women in group 1 and group 2. The pregnant women included in the study are randomly selected among those who applied to the obstetric follow-up outpatient clinics and have singleton pregnancy. Those with chronic hypertension and high blood pressure in the first trimester, those with a history of drug use that may cause deterioration in glucose metabolism, and those with multiple pregnancies are not included in the study.

While evaluating the findings obtained in the study, NCSS (Number Cruncher Statistical System) 2007&PASS 2008 Statistical Software (Utah, USA) program is used for statistical analysis. While evaluating the study data, in addition to descriptive statistical methods (Mean, Standard deviation), the Oneway Anova test is used for the comparison of the normally distributed parameters in the comparison of the quantitative data, and the Tukey HSD test is used to determine

the group that caused the difference. The Kruskal Wallis test is used for the comparison of the parameters that did not show normal distribution, and the Mann-Whitney U test is used to determine the group that caused the difference. Chi-square test is used to compare qualitative data. Significance is evaluated at the p<0.05 level.

RESULTS

There is a statistically significant difference between the groups according to the ages (p<0.01). As a result of the Post-Hoc Tukey HSD test, which is conducted to determine which group the significance originated from; It is determined that the mean age of Group 1 and Group 2 is significantly lower than Group 3, Group 4 and Group 5 (p:0.043; p:0.009).

There is a statistically significant difference between pre-pregnancy BMI measurements according to the groups (p<0.01). As a result of the Post-Hoc Tukey HSD test, which is conducted to determine which group the significance originated from; The mean BMI of Group 1 is significantly lower than the other groups (p:0.019; p:0.001; p:0.001; p:0.001); Group 2 is also found to be significantly lower than Group 5 (p:0.006).

There is a statistically significant difference between the numbers of gravida according to the groups (p<0.05). As a result of the pairwise comparisons made in order to determine which group the difference originates from; The number of gravida in Group 1 is significantly lower than Group 3, Group 4 and Group 5 (p:0.026; p:0.034; p:0.009); The number of gravida in Group 2 is also found to be significantly lower than Group 5 (p:0.029).

There is a statistically significant difference between the parity numbers according to the groups (p<0.05). As a result of the pairwise comparisons made in order to determine which group the difference originates from; It is determined that the parity number of Group 1 and Group 2 is significantly lower than Group 3, Group 4 and Group 5 (p:0.022; p:0.026; p:0.023).

There is no statistically significant difference between the number of abortions according to the groups (p>0.05). (**Table 1**)

There is a statistically significant difference between the groups with a family history of DM (p<0.01); The rate of family history in Group 3, Group 4 and Group 5 is significantly higher than the other groups.

According to the groups, there is no statistically significant difference between the incidence of large babies in previous pregnancy (p>0.05).

There is a statistically significant difference between the incidence of stillbirth in previous pregnancies according to the groups (p<0.05); In Group 3 and Group 4, the rate of stillbirth in previous pregnancies is significantly higher than the other groups. (**Table 2**)

There is a statistically significant difference between the weeks of birth according to the groups (p<0.01). As a result of the Post-Hoc Tukey HSD test, which is conducted to determine which group the significance originated from; It is determined that the birth week of group 4 is significantly lower than the other groups (p:0.001; p:0.024).

There is a statistically significant difference between the birth weight averages according to the groups (p<0.05). As a result of the Post-Hoc Tukey HSD test, which is conducted to determine which group the significance originated from; It is determined that the mean birth weight of Group 5 is significantly higher than Group 1, Group 2 and Group 3 (p:0.017; p:0.026; p:0.039).

There is no statistically significant difference between the cases of presentation anomaly according to the groups (p>0.05).

Table 1. Evaluation of pregnancy characteristics according to groups

	Group 1	Group 2	Group 3	Group 4	Group 5	p
	Mean±SD (Median)	Mean±SD (Median)	Mean±SD (Median)	Mean±SD (Median)	Mean±SD (Median)	
Age (years)	28.65±5.28	28.06±5.93	31.88±5.61	32.21±5.57	33.5±7.47	0.001**
BMI Pre-Pregnancy	23.74±3.68	26.0±4.22	27.98±4.41	28.04±3.23	29.78±3.68	0.001**
Gravida	2.47±1.68 (2)	2.43±1.42(2)	2.86±1.34 (3)	3.16±2.03 (3)	3.05±0.99 (3)	0.015*
Parity	2.16±1.14 (2)	2.09±1.19(2)	2.59±1.22(2.5)	2.83±1.57 (3)	2.71±1.04 (3)	0.010*
Abortion history	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Yes	15 (17.6%)	9 (20.5%)	10 (19.2%)	5 (20.8%)	6 (33.3%)	0.679
No	70 (82.4%)	35 (79.5%)	42 (80.8%)	19 (79.2%)	12 (66.7%)	

Kruskal Wallis test is used, aChi-Square test, *p<0.05, **p<0,01

Table 2. Evaluation of previous pregnancy histories according to groups

	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	Group 5 n (%)	p
DM Family History	12 (14.1%)	8 (18.2%)	28 (53.8%)	12 (50%)	13 (72.2%)	0.001**
Big baby in previous pregnancy	4 (4.7%)	4 (9.1%)	7 (13.5%)	3 (12.5%)	4 (22.2%)	0.158
Stillbirth in a previous pregnancy	1 (1.2%)	0	6 (11.5%)	3 (12.5%)	1 (5.6%)	0.013*

Chi-square test is used., *p<0.05, **p<0.01

Table 3. Evaluation of descriptive features by groups

	Group 1	Group 2	Group 3	Group 4	Group 5	p
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Birth Week	39.26±1.35	38.99±1.94	38.94±1.24	37.71±2.79	38.94±1.21	0.003**
Birth Weight (gr)	3277.8±456.1	3262.9±647.8	3298.8±560.7	3312.1±1037.0	3786.1±750.2	0.033*
	n (%)	n (%)	n (%)	n (%)	n (%)	
Presentation anomaly	2 (2.4%)	4 (9.1%)	4 (7.7%)	4 (16.7%)	2 (11.1%)	0.141
Type of Birth						
Cesarean section	28 (33.3%)	22 (50%)	25 (48.1%)	17 (70.8%)	11 (61.1%)	0.010*
Normal	56 (66.7%)	22 (50%)	27 (51.9%)	7 (29.2%)	7 (38.9%)	

Oneway ANOVA test is used, aChi-square test, *p<0,05, **p<0,01

There is a statistically significant difference between the delivery types according to the groups (p<0.05); While the rate of Group 1 is high in cases with normal delivery, the rate of Group 4 and Group 5 is high in cases with cesarean section. (**Table 3**)

There is a statistically significant difference between the cesarean section indications according to the groups (p<0.05); While the rate of old cesarean section is high in Group 1, Group 2 and Group 3, the rate of large babies is high in Group 4 and Group 5. (**Table 4**)

Table 4. Evaluation of cesarean section indications according to groups

	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	Group 5 n (%)
Old cesarean section	17 (58.)	9 (40.9)	16 (64)	1 (6.3)	5 (45.4)
Fetal distress	3 (10.3)	2 (9.1)	2 (8)	3 (18.8)	1 (9.1)
Big baby	1 (3.4)	4 (18.2)	4 (16)	7 (43.8)	3 (27.2)
Presentation anomaly	2 (6.9)	4 (18.2)	3 (12)	4 (25)	1 (9.1)
Other	6 (20.7)	2 (9.1)	0	0	0

Chi-square test is used, *p<0,05

There is a statistically significant difference between the incidence of prematurity according to the groups (p<0.01); The incidence of prematurity in Group 4 and Group 5 is significantly higher than the other groups.

There is a statistically significant difference between the incidence of macrosomia according to the groups (p<0.01); The incidence of macrosomia in Group 4 and Group 5 is significantly higher than the other groups.

There is a statistically significant difference between the incidence of preeclampsia according to the groups (p<0.01); The incidence of preeclampsia in Group 4 and Group 5 is significantly higher than the other groups.

There is a statistically significant difference between the stillbirth cases according to the groups (p<0.05); The stillbirth rate in Group 5 is significantly higher than the other groups. (**Table 5**)

Table 5. Evaluation of some results by groups

	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	Group 5 n (%)	p
Prematurity	2 (2.4)	3 (6.8)	3 (5.8)	6 (25)	2 (11.1)	0.006**
Macrosomia	1 (1.2)	5 (11.4)	5 (9.6)	9 (37.5)	7 (38.9)	0.001**
Preeclampsia	1 (1.2)	3 (6.8)	4 (7.7)	6 (25)	5 (27.8)	0.001**
Stillbirth	1 (1.2)	1 (2.3)	0	0	2 (11.1)	0.033*

Chi-square test is used, *p<0,05, **p<0,01

DISCUSSION

In general, some features are seen more frequently in diabetic pregnant women than in pregnant women with normal glucose levels. Advanced age, increased prepregnancy body mass index (BMI), parity, family history of diabetes, bad obstetric history and macrosomic baby delivery are more common in diabetic pregnant women.[12-14]

In our study, it is determined that the mean age of Group 1 and Group 2 is significantly lower than Group 3, Group 4 and Group 5. This result is similar to the opinion of selective screening for people over 25 years old in the absence of other risk factors suggested in the Fourth International Gestational Diabetes Workshop.[12] In our study, the gravida and parity numbers of Group 1 are determined from Group 3, Group 4 and Group 5; In Group 2, the number of gravida and parity is found to be significantly lower than Group 5, in parallel with the increased mean age.

The familial history in people with type 2 diabetes is remarkable. Co-occurrence of monozygotic twins is 100%. Abnormal glucose tolerance or overt diabetes develops in 40% of siblings and one-third of children. If both parents are diabetic, this rate rises to 60-75%. There is a similar familial predisposition in GDM, which progresses with insulin resistance in target tissues.[4,15] In our study, we investigated the history of diabetes in first-degree relatives of pregnant women. As the degree of glucose intolerance increased, we found a higher family history. The incidence of family history for diabetes in Group 3, Group 4 and Group 5 is significantly higher than Group 1 and Group 2. 14% of Group 1, 18% of Group 2, 53% of Group 3, 50% of Group 4, 72% of Group 5 have a positive family history.

Another feature of diabetic pregnant women is that obesity rates in these pregnant women are higher than those with normol glycemic level. The American Diabetes Association and ACOG recommend that all women who are obese and overweight and have one or more of the specified risk factors should have a screening test planned at the first antepartum visit.[16] As BMI increases, the risk of developing Type 2 diabetes and varying degrees of glucose intolerance increases. While this risk is approximately 4-5 times higher at 27 kg/m², it becomes 40 times higher at 35 kg/m².[17,18] Parallel to the studies performed, there is a statistically significant difference between pre-pregnancy BMI measurements according to the groups in our study. We found that the mean BMI of Group

1 is significantly lower than the other groups, and Group 2 is significantly lower than Group 5. Group 1 mean BMI is 23.7 kg/m², Group 2 mean BMI is 26.0 kg/m², Group 3 mean BMI is 27.9 kg/m², Group 4 mean BMI is 28.0 kg/m², mean BMI of Group 5 is 29.7 kg/m².

Insufficient glycemic control in the periconceptional period and in the first trimester has been found to be associated with spontaneous abortions in some prospective studies.[9,19] In our study, we questioned the history of abortion in the previous pregnancies of the pregnant women and we did not find a significant difference between the groups. In this study, when it is investigated that the history of giving birth to a large baby in previous pregnancies in the groups, it is found that the history of giving birth to a baby of 4000 g and above increased as the degree of glucose intolerance increased. It is found a statistically significant difference between the groups with a history of stillbirth in the previous pregnancy. The rate of stillbirth in Group 3, Group 4 and Group 5 is significantly higher than the other groups.

In pregnancies complicated with diabetes, especially in the presence of overt diabetes before pregnancy, some fetal and maternal complications are observed more frequently and many pregnancies are terminated in earlier weeks due to these complications. In addition, since the incidence of macrosomia and unexplained fetal losses gradually increases in the advancing gestational weeks, most of the physicians do not expect spontaneous labor and generally terminate the pregnancy with induction or cesarean section.[19-22] These reasons explain the increased cesarean and preterm birth rates in pregnancies accompanied by diabetes. On the other hand, regardless of diabetes-related complications, Monique M. Hedderson et al. found different degrees of glucose intolerance to be associated with spontaneous preterm delivery.[23] In our study, mean week of delivery is 39.2 weeks in Group 1, mean week of delivery is 38.9 weeks in Group 2, mean week of delivery is 38.9 weeks in Group 3, mean week of delivery is 37.7 weeks in Group 4, mean week of delivery is found to be 38.9 weeks in Group 5. It is determined that the birth week of group 4 is significantly lower than the other groups.

Preeclampsia is seen in approximately 6% of the general pregnant population and is one of the most important complications of pregnancy. Sibai et al. reported that preeclampsia is encountered 2-3 times more frequently in pregnant women w ith pregestational diabetes.[24] Preeclampsia is seen in up to 50% of patients with diabetic nephropathy.[9] Many studies suggest that varying degrees of insulin resistance and glucose intolerance may play a role in the pathogenesis of pregnancy-induced hypertension.[9,19,25,26] In this study, it is found a statistically significant difference between the incidence of preeclampsia according to the groups. The incidence of preeclampsia in Group 4 and Group 5 is significantly higher than the other groups. It is found that preeclampsia of 1.2% of Group 1, 6.8% of Group 2, 7.7% of Group 3, 25% of Group 4, 27% of Group 5.

In our study, there is no statistically significant difference between the presentation anomaly according to the groups ($p>0.05$). This result is consistent with what Noraihan et al. reported.[21] Yang et al., published in 2002, reported that presentation anomaly rates are more common in pregnancies with impaired glucose tolerance compared to normoglycemic pregnancies.[27]

In our study, a statistically significant difference is found between the delivery types according to the groups, while the rate of Group 1 is found to be high in cases who have normal delivery, while the rate of Group 4 (70.8%) and Group 5 (61.1%) is found to be high in cases who have cesarean section.

One of the most important complications in diabetic pregnancies is fetal macrosomia. While it is seen in 8-14% of non-diabetic patients, it is seen in 25-40% of diabetics.[19,28] In this study, it is considered that babies born 4000 g and over to be macrosomic, regardless of the week of birth. Macrosomia is 3.5% in Group 1, 11.4% in Group 2, 13.3% in Group 3, 37.5% in Group 4, 38.9% in Group 5 detected. Accordingly, it is found that the incidence of macrosomia in Group 4 and Group 5 is significantly higher than the other groups. In parallel with our study, many clinical series revealed that the incidence of macrosomia decreased with tight maternal glucose control. Kitzmiller and Cloherty reported the rate of infants with a birth weight over 4000 g in 134 women with fasting blood glucose levels between 105-121 mg/dl as 11%.[29] This rate drops more dramatically when physiological control is achieved. Roversi and Gargiulo applied the maximum tolerated insulin administration program and found a 6% macrosomia rate. [30] Using capillary glucose values at the 2nd and 3rd months, Landon et al. determined the rate of macrosomia as 3% in women with an average glucose level of 110 mg/dl, and 34% in those with less control.[31]

Overt diabetes existing before pregnancy is a risk factor for preterm birth. In this study, it is found a statistically high level of significance between the incidence of prematurity according to the groups, and the rate of prematurity in Group 4 and Group 5 is significantly higher than the other groups. Sibai et al. analyzed the pregnancy outcomes of 461 women with pregestational diabetes and found that 9% of the women gave birth spontaneously at or before 34 weeks. This rate is 2% in non-diabetic women.[32]

The most feared complication in diabetic pregnancies is the unexplained death of the baby in the womb in the later weeks of pregnancy. A total of 4 stillbirths occurred in our study groups. 1 (1.2%) of these occurred in Group 1, 1 (2.3%) in Group 2, and 2 (11.1%) in Group 5. The stillbirth rate in group 5 is significantly higher than the other groups. The reason for the increase in stillbirth rate in diabetic pregnant women is unknown. Chronic intrauterine hypoxia has been reported as the cause of intrauterine death, since extramedullary hematopoiesis is common in stillborn infants of diabetic mothers. Studies performed on fetal umbilical cord blood

samples of pregnant women with type 1 diabetes have shown the presence of relative fetal erythremia and lactic acidemia. Salvasen et al. reported that fetal pH decreased and CO_2, lactate and erythropoietin values increased in diabetic pregnancies.[33] Maternal diabetes can alter erythrocytes oxygen release and placental flow. It has been stated that changes in fetal carbohydrate mechanism may cause intrauterine asphyxia.[34]

As a result, in this descriptive prospective study, it is demonstrated again with this study that different glucose intolerances cause some problems in pregnancy, increase complications, and uncontrolled blood glucose levels increase these problems and complications. When we compile and collectively present the data of these pregnant women, whom we frequently follow in our hospital, it has been understood much more clearly that pregnant women complicated with diabetes are indeed in the high-risk pregnancies class. It should be kept in mind that various complications such as preeclampsia, fetal death, prematurity, macrosomia, higher cesarean section rates are more common in these pregnancies complicated with diabetes, and risky pregnant women should be screened and treated at early gestational weeks. In pregestational and gestational periods; In such cases, it should be aimed and ensured to minimize the problems and complications that may be encountered with appropriate diagnosis and treatment approaches.

ETHICAL DECLARATIONS

Ethics Committee Approval: The local ethics committee approved this study of Umraniye Training and Research Hospital, Turkey (10.03.2010)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. American Diabetes Association:Diagnosis and Classification of Diabetes Mellitus;Diabetes Care 2005;28:37-42.
2. American Diabetes Association:Gestational Diabetes Mellitus;Diabetes Care 2003;26(1):103-5.
3. İsmail D, Özlem O. Diabetes Mellitus ve Gebelik. Kadın Hastalıkları ve Doğum Bilgisi. 1. baskı. Güneş Kitabevi. Sayfa:435-450, 2006
4. Stephan C, Elizabeth S. Diabetes mellitus. İn:Michael T. Mc. Dermott eds. The Endocrine Secrets. 1th ed. Hanley and Belfus Medical Publishers:1-61, 2004
5. American College of Obstetricians and Gynecologists:Diabetes and pregnancy. ACOG Technical Bulletin. Washington, DC 1994
6. Gestational diabetes mellitus. ACOG Practice Bulletin No. 190. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;131:e49–64
7. Kirwan JP, Hauguel-de Mounzon S, et al. TNF –α is a predictor of insülin resistance in human pregnancy. Diabetes 2002;51:2207
8. Carla J, Jeffrey S. Diabetes Mellitus and Pregnancy. İn:Alan H. De Cherney, Lauren Nathan eds. Current Obstetric and Gynecologic Diagnosis and Treatment. 9th. Ed. Lange Medical Boks/McGraw Hill Companies:326-337,2003
9. Cunningham FG:Diabetes. İn:Cunningham FG, Mac Donald PC, Gant NF, et al. Eds. Williams Obstetrics 21th ed. Appleton & Lange:567-618, 2001
10. Abebe KZ, Scifres C, Simhan HN, Day N, Catalano P, Bodnar LM, et al. Comparison of two screening strategies for Gestational Diabetes (GDM²) Trial:Design and rationale. Contemp Clin Trials. 2017;62(1):43-9.
11. Sugiyama MS, Cash HL, Roseveare C, Reklai R, Basilius K, Madraisau S. Assessment of gestational diabetes and associated risk factors and outcomes in the Pacific Island Nation of Palau. Matern Child Health J. 2017;21(10):1961-6.
12. Metzger BE, Couston DR:Summary and recommendations of the fourth international workshop-conference on gestational diabetes mellitus. Diabetes Care 1998;21:B161.
13. Berkus MD, Langer O:Glucose tolerance test:Degree of glucose abnormality correlates with neonatal outcome. Obstet Gynecol 1993;81:344,
14. Owen J, Phelan ST, Landon MB, Gabbe SG. Gestational diabetes survey. Am J Obstet Gynecol 1995;172:615-20.
15. Foster DW:Diabetes Mellitus. İn Fauci AS, Braunwald E, İsselbacher KJ, Wilson JD:Harrison's Principles of İnternal Medicine, 14th ed. 1998
16. Gestational diabetes mellitus. ACOG Practice Bulletin No. 190. American College of Obstetricians and Gynecologists. Obstet Gyne- col 2018;131:e49–64.
17. George A. Bray:Medical Consequences of Obesity. The Journal of Clinical Endocrinology and Metabolism 2004;89(6):2583-89.
18. Colditz GA, Willett WC, Rotnitzky A, Manson JE:Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995;122:481–6.
19. Thomas R. Moore. Diabetes in pregnancy. In Creasy RK, Resnik R, eds. Maternal-Fetal Medicine. 5th ed. Philadelphia:WB Saunders Company, 2004;1023-61.
20. Sibai BM, Caritis S, Hauth J, et al. Risks of preeclampsia and adverse neonatal outcomes among women with pregestational diabetes mellitus. Am J Obstet Gynecol 2000;182:364
21. Noraihan MN, Justen WHW, Nyi NN, et al. Comparison of maternal-fetal outcomes in gestational diabetes and lesser degrees of glucose intolerance. J Obstet Gynecol Res 2006;32:1:107-14
22. Gunton JE, McElduff A, Sulway M, et al. Outcome of pregnancies complicated by pre-gestational diabetes mellitus. Aust N Z J Obstet Gynaecol 2000;40(1):38-43.
23. Monique M.H, Assiamira Ferrara, et al. Gestational Diabetes Mellitus and Lesser Degrees of Pregnancy Hyperglycemia:Association With Increased Risk of Spontaneous Preterm Birth. Obstetr Gynecol 2003;102:850-856,
24. American Diabetes Association:Standards of Medical Care in Diabetes. Diabetes Care 2005;28:4-36.
25. Caren G. Solomon, Steven W. Graves, et al. Glucose intolerance as a predictor of hypertension in pregnancy. Hypertension 1994;23:6:717-72.
26. Vambergue A, Nuttens MC, Goeusse P, et al. Pregnancy induced hypertension in women with gestational carbohydrate intolerance:the diagest study. European J of Obstetrics and Gynecology and Reproductive Biology 2002;102(1):31-5.
27. Caren G. Solomon, Steven W. Graves, et al. Glucose intolerance as a predictor of hypertension in pregnancy. Hypertension 1994;23:6:717-21.
28. Janice Falls, Lorraine Milio. Endocrine Disease in Pregnancy. İn:Brandon J.B, Amy E. H eds. The Johns Hopkins Manuel of Gynecology and Obstetrics. 2th ed. philadelphia:Lippincott Williams and Wilkins:162-182,2002

29. Kitzmiller JL, Gloherty JP:Diabetic pregnancy and perinatal morbidity. Am J Obstet Gynecol 1978;131:560.
30. Roversi GD, Gargiulo M:A new aproach to the treatment of diabetic pregnant women. Am Obstet Gynecol 1979;135:567.
31. Landon MB, Gabbe SG, Piana R, et al. neonatal morbidity in pregnancy complicated by diabetes mellitus predictive value of maternal glycemic profiles. Am J Obstet Gynecol 1987;156:1089.
32. Dashe JS, Nathan L, Leveno KJ:Correlation between amniotic fluid glucose correlation and amniotic fluid volume in pregnancy complicated by diabetes. Am J Obstet Gynecol 2000;182:901.
33. Salvesen DR, Brudenel MJ, Nicholaides KH:Fetal polycythemia and trombocitepenia in pregnancies complicated by maternal diabetes. Am J Obstet Gynecol 1992;166:1987.
34. Salvasen DR, Brudenell MJ, Snijders JM, et al. Fetal plasma erythropoietin in pregnancies complicated by maternal diabetes mellitus. Am J Obstet Gynecol 1993;168:88.

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Original Article / Orijinal Araştırma

Evaluation of the Relationship Between Intraoperative Cerebral Oxygen Saturation and Postoperative Cognitive Functions in Laparoscopic Hysterectomy Surgery

Laparaskopik Histerektomi Cerrahisinde İntraoperatif Serebral Oksijen Saturasyonu ile Postoperatif Kognitif Fonksiyonların İlişkisinin Değerlendirilmesi

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Abstract

Aim: Laparoscopic surgery has become more popular than traditional open surgery because it is less invasive, provides faster recovery, and provides better cosmetic success. This procedure requires insufflation of an inert gas into the peritoneal cavity. This may be an increase in arterial carbon dioxide pressure, changes in cerebral blood flow, an increase in intra-abdominal pressure (IAP), a decrease in cardiac output. The primary outcome of this study is to show the effect of IAP levels on cerebral oxygen saturation (COS) in patients who underwent total laparoscopic abdominal hysterectomy (TLH), and the secondary outcome is to reveal the relationship between IAP and COS and the recovery of postoperative cognitive functions.

Material and Method: Demographic data of the cases were recorded and mini-mental test (MMT) was applied to evaluate the preoperative cognitive functions of the cases before surgery. COS monitoring were performed with standard anesthesia procedure for all patients. The MMT was repeated 30 minutes after the operation.

Results: A total of 40 female patients were included in the study. Those with IAP level 12 mmHg and below were defined as Group Low-Pressure, and those above 12 mmHg were defined as Group High-Pressure. There was no statistical difference between the anesthesia times and recovery times of the two groups. While there was no statistical difference in the preoperative MMT evaluation, it was found to be significantly lower in Group H in the postoperative MMT evaluation.

Conclusion: In this study, we evaluated the effect of intraoperative IAP levels on intraoperative COS. It is seen that high IAP level does not have a negative effect on COS. In addition, this study has evidence that high IAP affects postoperative cognitive functions. In intraoperative management for TLH surgery, we recommend maintaining the IAP level at the lowest appropriate pressure that does not impair surgical comfort.

Keywords: Cerebral oxygen saturation, cognitive functions, laparoscopic hysterectomy, general anesthesia

Öz

Amaç: Laparoskopik cerrahi, daha az invaziv olması, daha hızlı iyileşme sağlaması ve daha iyi kozmetik başarı sağlaması nedeniyle geleneksel açık cerrahiden daha popüler hale gelmiştir. Bu prosedür, inert bir gazın periton boşluğuna üflenmesini gerektirir. Karın içersine gaz insufilasyonu, arteriyel karbondioksit basıncında bir artış, serebral kan akışında değişiklikler, intraabdominal basınçta (İAB) bir artış, kalp debisinde azalmaya neden olabilir. Bu çalışmanın birincil sonucu, total laparoskopik abdominal histerektomi (TLH) uygulanan hastalarda İAB düzeylerinin serebral oksijen satürasyonu (SOS) üzerindeki etkisini göstermek ve ikincil sonuç, İAB ve SOS ile postoperatif bilişsel işlevlerin iyileşmesi arasındaki ilişkiyi ortaya koymaktır.

Gereç ve Yöntem: Olguların demografik verileri kaydedildi ve olgulara ameliyat öncesi kognitif fonksiyonlarını değerlendirmek için ameliyat öncesi mini-mental test (MMT) uygulandı. Tüm hastalar için standart anestezi prosedürü ile SOS monitörizasyonu yapıldı. MMT ameliyattan 30 dakika sonra tekrarlandı.

Bulgular: Çalışmaya toplam 40 kadın hasta dahil edildi. İAB seviyesi 12 mmHg ve altında olanlar Grup Düşük-Basınç (Grup L), 12 mmHg'nin üzerinde olanlar Grup Yüksek-Basınç (Grup H) olarak tanımlandı. İki grubun anestezi süreleri ve derlenme süreleri arasında istatistiksel fark yoktu. Preoperatif MMT değerlendirmesinde istatistiksel olarak fark bulunmazken, postoperatif MMT değerlendirmesinde Grup H'de anlamlı olarak düşük bulundu.

Sonuç: Yüksek İAB düzeyinin SOS'a olumsuz etkisinin olmadığı görüldü. Ayrıca bu çalışmada yüksek İAB'nin ameliyat sonrası kognitif fonksiyonları etkilediğine dair kanıtlar var. TLH cerrahisi için intraoperatif yönetimde, İAB seviyesinin cerrahi konforu bozmayan uygun en düşük basınçta tutulmasını öneririz.

Anahtar Kelimeler: Serebral oksijen saturasyonu, kognitif fonksiyonlar, laparaskopik histerektomi, genel anestezi

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INTRODUCTION

Laparoscopic surgery has become more popular than traditional open surgery because it is less invasive, provides faster recovery, and provides better cosmetic success. This procedure requires insufflation of an inert gas into the peritoneal cavity. Often this gas is carbon dioxide (CO_2). Although CO_2 is used, which is optimal for insufflation, there may be an increase in arterial CO_2 ($PaCO_2$) and changes in cerebral blood flow. In addition, peritoneal insufflation leads to an increase in intra-abdominal pressure (IAP), which leads to a decrease in cardiac output.[1]

Atelectasis may develop due to the effect of pneumoperitoneum and oxygenation may be affected, therefore it is recommended to apply prophylactic positive end-expiratory pressure (PEEP) intraoperatively to patients. Since standard monitoring may not be sufficient to determine the conditions in which cerebral oxygenation is affected, monitors such as cerebral oximetry (SO_2) by near-infrared spectroscopy (NIRS), which are used to measure SO_2, have been used in recent times. Thanks to NIRS, if cerebral oxygenation is adversely affected, it can be detected early and before tissue hypoxia occurs.[2-5]

In the literature, the number of studies using NIRS in gynaecological laparoscopy surgeries with Trendelenburg and pneumoperitoneum is limited, and no study evaluating its relationship with intra-abdominal pressure has been found.

The primary outcome of this study is to show the effect of intra-abdominal pressure levels on cerebral oxygenation in patients who underwent total laparoscopic hysterectomy (TLH), and the secondary outcome is to reveal the relationship between IAP and cerebral oxygen saturation (COS) and the recovery of postoperative cognitive functions.

MATERIAL AND METHOD

Study designed as a prospective and observational. The study was carried out with the permission of Necmettin Erbakan University Ethics Committee (Date: 16.04.2021, Decision No: 2021/3209). The study was carried out in accordance with the Declaration of Helsinki, in the gynaecology operating room of our hospital, between January and June 2022. Among the patients who will undergo total hysterectomy surgery with the laparoscopic approach, 40 patients whose physical status is 'I' or 'II' according to the American Society of Anesthesiology (ASA) classification, aged 18-65 years, and whose informed consent was obtained, were included in the study.

Cases with disorientation and cooperation disorders, cases with severe psychiatric disorders, emergency cases, cases with cardiac dysrhythmia and a history of heart failure, cases with drug dependence, cases who needed intraoperative inotropic drug use, and cases who refused to volunteer were excluded from the study. Demographic data of the cases were recorded and mini-mental test was applied to evaluate the preoperative cognitive functions of the cases before surgery.

Electrocardiography (ECG), noninvasive arterial blood pressure measurement, pulse oximetry (SpO_2), Train of Four (TOF) with neuromuscular transmission and NIRS monitoring were performed as standard anesthesia procedure for all patients. All patients were given 0.15 mg/kg midazolam, 2 mg/kg propofol induction, 0.2 mcg/kg/min remifentanil infusion and 0.6 mg/kg rocuronium muscle relaxation. Intubation was performed when the TOF ratio reached zero. For maintenance anesthesia, 0.5-1 MAC sevoflurane and 0.2 mcg/kg/min remifentanil were used.

After obtaining abdominal access for insufflation, a 300-degree trendelenburg position was given. IAP was increased to the level that the surgical area could be adequately visualized (min 8-max 14). IAP level 12 and below were defined as Group Low-Pressure (Group L), and those above 12 were defined as Group High-Pressure (Group H).

Hemodynamic data was recorded throughout the operation. Tramadol 2 mg/kg for postoperative analgesia and ondansetron 4 mg for nausea were administered.

At the end of the surgery, the maintenance of anesthesia was terminated and the patient was awakened. The time from anesthesia induction to extubation was recorded as the duration of anesthesia. The patient was taken to the recovery unit and followed up until the Aldrete score reached 9. The time from extubation to an Aldrete score of 9 was recorded as recovery time.

The mini-mental test was repeated 30 minutes after the end of the operation to evaluate the cognitive functions.

Statistical Analysis

SPSS 18.00 (Statistical Package for Social Sciences, Inc., Chicago, IL) program was used for the analysis of the collected data. Obtained continuous variables were expressed as mean±SD or number (%). Number and % values were used in the presentation of categorical variables. The conformity of the obtained data to the normal distribution was evaluated using the "Kolmogorov-Smirnov test". The "Mann-Whitney-U" test was used in the analysis of continuous variables (age, weight, etc.). Chi-square test was used to compare two groups and to analyse categorical variables. A p value of <0.05 was considered significant in the analyses.

RESULTS

A total of 40 female patients were included in the study. The age, height and weight values of the groups were examined, there was no statistical difference (**Table 1**). The ASA distributions of the groups were also similar (**Table 2**).

Table 1: ASA distributions of the groups

		Group L	Group H	Total	P value
ASA	I	5	7	12	0.529
	II	13	15	28	
Total		18	22	40	

ASA: American Society of Anesthesiology classification, Group L: Intra Abdominal Pressure level 12 mmHg and below, Group H: Intra Abdominal Pressure above 12 mmHg

Table 2: Age, height and weight values of the groups

	Group L	Group H	P Value
Age	48.89±10.00	50.46±8.27	0.591
Height	163.61±5.41	163.59±6.10	0.991
Weight	75.00±7.52	73.27±17.99	0.706

Group L: Intra Abdominal Pressure level 12 mmHg and below, Group H: Intra Abdominal Pressure above 12 mmHg

In intraoperative hemodynamic follow-up, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) were compared between the groups and there was no statistical difference (**Table 3**). NIRS monitoring findings were similar (**Table 4**).

There was no statistical difference between the anesthesia times and recovery times of the two groups (**Table 5**).

Table 5: Comparison of the anesthesia and recovery times of the groups

	Group L	Group H	P Value
Anesthesia Duration (min)	75.00±21.83	77.05±21.36	0.767
Recovery Duration (min)	20.56±12.47	17.50±7.52	0.344

Group L: Intra Abdominal Pressure level 12 mmHg and below, Group H: Intra Abdominal Pressure above 12 mmHg

While there was no statistical difference in the preoperative mini-mental test (MMT) evaluation, it was found to be significantly lower in Group H in the postoperative MMT evaluation (**Table 6**).

Table 6: Comparison of the MMT scores of the groups

	Preoperative-MMT	Postoperative-MMT	P Value
Group L	23.61±3.17	21.89±2.27	0.055
Group H	23.18±3.23	19.46±3.32	0.001*

MMT: Mini Mental Test, Group L: Intra Abdominal Pressure level 12 mmHg and below, Group H: Intra Abdominal Pressure above 12 mmHg

DISCUSSION

In this study, we evaluated the effect of intraoperative IAP levels on intraoperative COS. Our findings show that there is no difference between the IAP levels oxygen saturation with NIRS monitoring. While no difference was observed in terms of recovery after anesthesia, a negative effect of high pressure level on postoperative cognitive functions was determined.

Conditions such as advanced age, bleeding-transfusion, major orthopedic traumas, prolonged surgeries, infection, and pulmonary complications in the perioperative period may increase the risk of cognitive dysfunction.[6,7] Additionally, intraoperative cerebral oxygen desaturation has been found to be associated with cognitive dysfunction and prolonged hospitalization.[8] When this study was designed, patients with advanced age, transfusion status, and perioperative complications were not included in the study. In a study in which only the early period was evaluated, the researchers reported that postoperative cognitive dysfunction (POCD)

Table 3: Comparison of hemodynamic values of the groups

	Heart Rate			Systolic Blood Pressure			Diastolic Blood Pressure		
	Group L	Group H	P Value	Group L	Group H	P Value	Group L	Group H	P Value
Basic	83.61±17.93	80.87±14.53	0.421	143.22±18.53	136.96±15.48	0.710	83.39±7.86	80.68±8.71	0.763
3.min intubation	69.83±15.32	71.96±13.51	0.914	99.6±19.20	104.82±17.57	0.445	55.28±13.91	60.59±12.32	0.503
5.min TP	61.56±10.26	64.00±9.06	0.415	107.44±15.40	108.18±15.12	0.718	62.33±10.27	61.32±13.90	0.465
15.min TP	63.94±8.74	63.60±7.60	0.200	107.78±12.52	112.32±14.99	0.204	63.83±6.7	63.36±11.16	0.044
30.min TP	63.83±9.24	64.05±11.26	0.522	110.00±±13.08	108.55±±16.27	0.162	64.83±9.22	59.96±12.87	0.074
45.min TP	65.67±10.49	64.36±9.467	0.513	109.28±14.43	112.64±17.42	0.502	62.83±9.22	62.14±14.54	0.138
60.min TP	63.06±11.78	63.50±9.23	0.502	103.56±13.37	104.46±16.22	0.545	59.00±8.70	59.23±12.62	0.243
Position	59.78±12.98	62.55±11.51	0.874	101.94±16.2	99.27±18.12	0.819	57.83±10.02	54.46±12.58	0.493
End Of Operation	86.39±17.72	88.14±13.33	0.101	125.89±19.99	119.68±20.56	0.988	75.06±13.06	71.14±14.66	0.278

RTP: 300 Trendelenburg Position, Group L: Intra Abdominal Pressure level 12 mmHg and below, Group H: Intra Abdominal Pressure above 12 mmHg

Table 4: Comparison of NIRS values of the groups

	Right Cerebral Oxygen Saturation			Left Cerebral Oxygen Saturation		
	Group L	Group H	P Value	Group L	Group H	P Value
Basic	67.06±7.35	62.23±6.38	0.669	65.61±6.75	62.96±6.13	0.652
3.min intubation	70.61±9.48	65.55±8.59	0.311	69.11±10.74	66.09±9.60	0.337
5.min TP	66.83±8.33	66.96±8.87	0.799	64.11±8.51	65.64±7.80	0.502
15.min TP	73.33±7.59	70.59±8.23	0.911	71.44±8.57	67.77±8.76	0.900
30.min TP	71.67±7.55	68.09±9.58	0.730	70.50±9.15	65.87±9.40	0.819
45.min TP	73.33±7.59	66.73±10.08	0.419	71.44±8.57	67.32±9.16	0.691
60.min TP	70.33±7.72	65.41±8.62	0.951	68.44±8.76	66.68±10.20	0.660
Position	70.22±8.60	64.91±8.09	0.603	67.06±8.54	64.27±8.36	0.625
End Of Operation	73.56±9.65	71.46±9.20	0.435	72.56±9.49	70.41±10.73	0.680

RTP: 300 Trendelenburg Position Group L: Intra Abdominal Pressure level 12 mmHg and below Group H: Intra Abdominal Pressure above 12 mmHg

was detected in one third of the patients at the postoperative 3rd hour, and this situation improved after 24 hours.[9] It is recommended to perform early postoperative cognitive function evaluation within the first week.[6,7] Considering this recommendation, cognitive function evaluation was performed on the operation day.

Hemodynamics may be adversely affected due to pneumoperitoneum. Bradycardia with vagal reflex due to pneumoperitoneum has been reported, especially during insufflation. This bradycardia was treatable with atropine. Cardiac arrest developed in resistant cases. Cerebral oxygenation monitoring values performed in bariatric surgeries are not affected by hemodynamic changes, and hemodynamic changes are generally well tolerated in terms of cerebral perfusion.[10] No statistically significant finding was obtained in a study evaluating the effect of hemodynamic events on cerebral oxygenation.[11] Consistent with the literature, no hemodynamic changes requiring medical intervention were recorded in cerebral oxygenation values. In addition, despite the difference in intra-abdominal pressure, no statistically significant difference was observed between the groups in terms of hemodynamics.

It has been reported that trendelenburg position and carbon dioxide pneumoperitoneum increase intracranial pressure (ICP)[12,13] and change cerebral blood flow (CBF) or volume (CBV).[14,15] Therefore, gynaecological laparoscopic surgery may affect brain oxygenation by altering cerebral hemodynamics. The head-down position causes an increase in ICP, CBF, and CBV[16,17] and a decrease in carotid artery blood flow.[18,19] All of these factors may impair cerebral tissue oxygenation by decreasing cerebral perfusion pressure.[20]

Intracranial, intrathoracic and intraabdominal compartment pressures are interrelated. They concluded that neurologic follow-up should include minimizing intrathoracic and intra-abdominal pressures as much as clinically possible, as well as ICP control.[21] Another indication of the link between cerebral venous outflow and ICP is the beneficial effect of raising the head of the bed in lowering ICP.[22]

The first well-conducted clinical study evaluating the relationship between IAP and ICP was published in 2001 by Citerio et al. They conducted a prospective, nonrandomized observational study that systematically measured the effect of increased IAP by placing a 15 L soft water bag on the patient's abdomen. The authors found that weight bearing on the patient's abdomen resulted in a significant increase in IAP, accompanied by a rapid increase in ICP, central venous pressure (CVP), and jugular bulb pressure (IJP).[23]

Ventilation maneuvers to treat respiratory failure (e.g., recruitment) may increase intrathoracic pressure, limit venous return, and thereby increase ICP and decrease cerebral perfusion pressure.[22]

Available information indicates that there are two pathways by which IAP can be delivered to the central nervous system. First, the reflux flow from the venous plexus of the spinal canal and intracranial veins. The valveless nature of the venous plexus provides a direct anatomical route from the pelvis to the eyes and brain. This is a pathway involving multiple anastomoses to the systemic venous circulation, including the venous circulation of the lungs, renal veins, and thoracic veins. The second pathway is a direct effect through an increase in IAP causing cranial extension of the diaphragm. Increased intrathoracic pressure and increased central venous pressure causes decreased venous drainage from the central nervous system via the jugular system.[24]

Intra-abdominal hypertension (IAH) is usually determined by three consecutive measurements taken at 4-to-6 hour intervals and is defined as 12 mmHg or higher.[25] Based on this information, patients with IAP values above 12 were considered high pressure, and patients with IAP values below 12 were considered low pressure and were divided into two groups.

Intraoperative cerebral hypoperfusion and desaturation are important factors in the development of neurological complications, and cerebral monitoring is known to provide significant benefits in determining this. With the use of NIRS, low regional COS has been shown to be associated with neurological complications and cognitive impairment.[26,27] NIRS monitoring was applied to all patients included in the study and there was no finding that required intervention during monitoring. In addition, the groups were similar in terms of duration of anesthesia and recovery times. However, a difference was observed in the cognitive assessment of patients exposed to different IAP. We believe that this is due to the increase in intracranial pressure due to high IAP.

In the light of this information, we believe that the negative movement in cognitive functions in the group with high intra-abdominal pressure in our study is due to the deterioration of cerebral venous return due to high intra-abdominal pressure, the increase in central venous pressures and the increase in intracranial pressure.

This study has several limitations. Initially, only patients aged 19 to 65 years with ASA physical status 1 or 2 were included in the study. Considering the physiological and pathological changes in the elderly population, worse outcomes may be seen. Secondly, as long as patients are normocapnic, pneumoperitoneum has no effect on cerebral oxygenation. On the other hand, cerebral oxygenation is impaired when hypercapnic.[28] In our study, while carbon dioxide monitoring was not performed, no deterioration in cerebral oxygenation occurred in any of the patients. Finally, although the patient was treated to provide pain control during postoperative care, the data of the patients for this period were not examined.

CONCLUSION

In this study, it is seen that high intra-abdominal pressure level does not have a negative effect on cerebral oxygenation. In addition, this study has evidence that high IAP negatively affects postoperative cognitive functions. In intraoperative

management for TLH surgery, we recommend maintaining the IAP level at the lowest appropriate pressure that does not impair surgical comfort.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Necmettin Erbakan University Ethics Committee (Date: 16.04.2021, Decision No: 2021/3209).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Gibson CL, Johnson GA, Fisher R, et al. Changes in cerebral oximetry during peritoneal insufflation for laparoscopic procedures. J Minim Access Surg 2006;2:67-72.
2. Pasch T, Zalunardo M. Intraoperatives Monitoring. Notwendiges, sinnvolles und überflüssiges. Anaesthetist 2000;49 (1):2-6.
3. Hoppenstein D, Zohar E, Ramaty E, Shabat S. The effects of general vs spinal anesthesia on frontal cerebral oxygen saturation in geriatric patients undergoing emergency surgical fixation of the neck of the femur. J Clin Anesth 2005;17 (6):431-8.
4. Carron E. Positive end-expiratory pressure in obese patients during general anaesthesia. The role of intraabdominal pressure. Br J Anaesth 2018;120 (2):409-10.
5. Han S, Moon H, Oh Y, Lee J. Cerebral oxygenation during gynecologic laparoscopic surgery. Anesthesiology 2003;99:A277.
6. Pappa M, Theodosiadis N, Tsounis A, Sarafis P. Pathogenesis And Treatment of Post-Operative Cognitive Dysfunction. Electronic Physician (ISSN:2008-5842). February 2017, Volume:9, Issue:2, Pages:3768-3775.
7. Somprakit P, Lertakyamanee J, Satraratanamai C, et al. Mental state change after general and regional anesthesia in adults and elderly patients, a randomized clinical trial. J Med Assoc Thai 2002;85(Suppl 3):S875–83.
8. Slater JP, Guarino T, Stack J, et al. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. Ann Thorac Surg 2009;87(1):36-44.
9. Tang L, Kazan R, Taddei R, Zaouter C, Cyr S, Hemmerling TM. Reduced cerebral oxygen saturation during thoracic surgery predicts early postoperative cognitive dysfunction. Br J Anaesth 2012;108(4):623-9.
10. Turan E. Laparoskopik Bariatrik Cerrahinin. Serebral Oksijenizasyon Üzerine Etkisi. Turkiye Klinikleri J Med Sci 2019;39(2):135-43.
11. Ay N. The retrospective evaluation of cerebral oxygenation monitorization in patients undergoing gynecologic laparoscopy. Ege J Med 2019;58 (3):239-245
12. Uzzo RG,Bilsky M, Mininberg DT, Poppas DP. Laparoscopic surgery in children with ventriculo peritoneal shunts:effect of pneumoperitoneum on intracranial pressure–preliminary experience. Urology 1997;49:753-7.
13. Moncure M, Salem R, Moncure K, et al. Central nervous system metabolic and physiologic effects of laparoscopy. Am Surg1999;65:168–72.
14. Abe K, Hashimoto N, Taniguchi A, Yoshiya I. Middle cerebral artery blood flow velocity during laparoscopic surgery in head-down position. Surg Laparosc Endosc1998;8:1–4.
15. Huettemann E, Terborg C, Sakka SG, et al. Preserved CO(2) reactivity andincrease in middle cerebral arterial blood flowvelocity during laparoscopic surgery in children. Anesth Analg 2002;94:25– 258.
16. Magnaes B:Body position and cerebrospinal fluid pressure. Par 1:clinical studies on the effect of rapid postural changes. J Neurosurg1976;44:687 – 697.
17. Lovell AT, Marshall AC, Elwell CE, Smith M, Goldston JC. Changes in cerebral bloodvolume with changes in position in awake andanesthetized subjects. Anesth Analg 2000;90:372–376.
18. Loeppky JA, Hirshfield DW, Eldridge MW. The effects of head-down tilt on carotid blood flow and pulmonary gas exchange. Aviat Space Environ Med 1987;58:637–44
19. Hu Z, Zhao G, Xiao Z, Chen X, Zhong C, Yang J. Different responses of cerebral vessels to –30 degrees head-dow tilt in humans. Aviat Space Environ Med 1999;70:674680.
20. Goetz CG. Textbook of Clinical Neurology, 2nd edn. Chicago:Elsevier, 2003;pp511–529.
21. Citerio G, Vascotto E, Villa F, Celotti S, Pesenti A. Induced abdominal compartment syndrome increases intracranial pressure in neurotrauma patients:a prospective study. Crit Care Med 2001:29;1466–71.
22. Lauerman MH, Stein DM. Multicompartment management of patients with severe traumatic brain injury. Curr Opin Anaesthesiol 2014:27;219–24
23. Scalea TM, Bochicchio GV, Habashi N, et al. Increased intra-abdominal, intrathoracic, and intracranial pressure after severe brain injury:multiple compartment syndrome. J Trauma 2007:62;647–656
24. Depauw PRAM, Groen RJM, Van Loon J, Peul WC, Malbrain MLNG, De Waele JJ. The significance of intra-abdominal pressure in neurosurgery and neurological diseases:a narrative review and a conceptual proposal. Acta Neurochir (Wien) 2019 May;161(5):855-864.
25. Kirkpatrick AW, De Waele JJ, De Laet I, et al. WSACS–the abdominal compartment society. A society dedicated to the study of the physiology and pathophysiology of the abdominal compartment and its interactions with all organ systems. Anaesthesiol Intensive Ther 2015:47;191–194
26. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001:344;395– 402.
27. Canet J, Raeder J, Rasmussen LS, et al. Cognitive dysfunction after minor surgery in the elderly. Acta Anaesthesiol Scand 2003;47:1204–10.
28. Park CG, Jung WS, Park HY, Kim HW, Kwak HJ, Jo YY. Comparison of the Effects of Normocapnia and Mild Hypercapnia on the Optic Nerve Sheath Diameter and Regional Cerebral Oxygen Saturation in Patients Undergoing Gynecological Laparoscopy with Total Intravenous Anesthesia. J Clin Med 2021;10:4707

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Original Article / Orijinal Araştırma

Evaluation of Special Needs Reports for Children

Çocuklar İçin Özel Gereksinim Raporlarının Değerlendirilmesi

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Abstract

Aim: This study aims to evaluate of the reports of children who applied to the Medical Board for special needs reports regarding gender, age, diagnosis, and special needs area.

Material and Method: The special needs reports of 269 children aged 0-18, who applied to Kahta State Hospital Medical board between January 1 and December 31, 2022, were analyzed retrospectively, together with their sociodemographic characteristics.

Results: The mean age of the cases was 7.4±4.9 years, of which 109 (40.5%) were female, and 59.5% were male. When the areas of the reports were examined, the highest rate was the cognitive area, with 42.4%. When the suggested special needs were examined, 43.9% stated the need for rehabilitation/early intervention to support cognitive functions. The highest level of special needs in both girls and boys was the presence of special conditions needs. There was no significant difference between the genders regarding the level of special needs. However, the rate of child and adolescent psychiatry area in boys (22.5%) was found to be significantly higher than the rate of girls (12.8%) (p=0.046). There was no significant difference between genders in other areas (p>0.05)

Conclusion: Special needs reports provide financial, social, and exceptional education support to the needs of children and families. For this reason, medical boards must be organized to make the fastest and most objective decisions. Examination of the reports as a whole guides health professionals for quality service, social scientists, and lawmakers for permanent solutions.

Keywords: Special needs, disability evaluation, disability medical board, medical board, health board, health committee

Öz

Amaç: Bu çalışma, sağlık kuruluna çocuklar için özel gereksinim raporu (ÇÖZGER) için başvuran çocukların raporlarının cinsiyet, yaş, tanı ve özel gereksinim alanı açısından değerlendirilmesini amaçlamaktadır.

Gereç ve Yöntem: Kahta Devlet Hastanesi Sağlık Kurulu'na 1 Ocak-31 Aralık 2022 tarihleri arasında başvuran 0-18 yaş arası 269 çocuğun ÇÖZGER ve sosyodemografik özellikleri retrospektif olarak incelendi.

Bulgular: Olguların yaş ortalaması 7,4±4,9 olup, bunların 109'u (%40,5) kadın, %59,5'i erkekti. Rapor alanları incelendiğinde en yüksek oranın %42,4 ile bilişsel alan olduğu görüldü. Önerilen özel gereksinimler incelendiğinde %43,9'u bilişsel işlevleri desteklemek için rehabilitasyon/erken müdahale gerektiğini belirtmiştir. Hem kızlarda hem de erkeklerde en yüksek özel gereksinim düzeyi özel durum gereksinimlerinin varlığıydı. Özel gereksinim düzeyi açısından cinsiyetler arasında anlamlı fark yoktu. Ancak erkek çocuklarda çocuk ve ergen psikiyatrisi bölümü oranı (%22,5) kız çocukların oranından (%12,8) anlamlı olarak yüksek bulunmuştur (p=0,046). Diğer alanlarda cinsiyetler arasında anlamlı fark yoktu (p>0,05).

Sonuç: ÇÖZGER, çocukların ve ailelerin ihtiyaçlarına mali, sosyal ve istisnai eğitim desteği sağlar. Bu nedenle sağlık kurullarının en hızlı ve en objektif kararları verecek şekilde düzenlenmesi gerekmektedir. Raporların bir bütün olarak incelenmesi kaliteli hizmet için sağlık profesyonellerine, kalıcı çözümler için sosyal bilimcilere ve kanun koyuculara yol göstermektedir.

Anahtar Kelimeler: Özel ihtiyaçlar, engellilik değerlendirmesi, engelli sağlık kurulu, sağlık kurulu, sağlık kurulu, sağlık kurulu

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INTRODUCTION

One in every six people worldwide has a significant disability.[1] Although the disabled individual has been defined with different words in the historical process in Turkey and the world, the concept of "individual with special needs" has been adopted more recently.[2]

An individual with special needs; is a person who experiences inadequacy due to impairment, limitations, and restrictions in his/her physical, mental, spiritual, sensory, and social abilities due to various congenital or acquired reasons. These people need help meeting their daily needs and adapting to social life.[3,4]

Disability Medical boards are established in the health institutions determined by the Ministry of Health in Turkey to have specialist physicians in certain branches. In line with the decision of medical boards, individuals achieve gains for their needs arising from their diseases and/or disabilities. While there was only one disability regulation before, with the "Regulation on Special Needs Assessment for Children" dated February 20, 2019, published in the Official Gazette, it has become possible for children to be evaluated on boards formed only for children. There are at least six permanent members in the boards established to issue "Special Needs Reports for Children" (SNRFC), including at least four different specialist physicians, the chairman of the board, and the SNRFC-authorized physician. In addition to the child's disability, the board's decision is reported in 23 different categories, indicating the area of special needs (2) and degree.[4,5]

MATERIAL AND METHOD

Study Design

The study was conducted in Kahta State Hospital, the only hospital in the Kahta district of Adıyaman, a southeastern province of Turkey. During 2022, records of children aged 0-18 who applied for a special needs report for children were retrospectively reviewed one by one. The study was carried out with the permission of Fırat University Non-Interventional Clinical Researches Ethics Committee (Date: 01.12.2022, Decision No: 2022/14-26).

Statistical Analysis

Analyzes were evaluated in 22 package programs of SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). In the study, descriptive data were shown as n and % values in categorical data, and mean±standard deviation (mean±SD) and median, interquartile range (25-75 percentile values) in continuous data. Chi-square analysis (Pearson Chi-square) was used to compare categorical variables between groups. The Kolmogorov-Smirnov test evaluated the conformity of continuous variables to normal distribution. In comparing paired groups, Student's t-test was used for normally distributed variables, and Mann Whitney U-test was used for non-normally distributed variables. In comparing more than two variables, One Way ANOVA analysis was performed for those with normal distribution and the Kruskal Wallis test for those who did not. The Pearson correlation test was used for those with normal distribution, and the Spearman correlation test was used for those with non-normal distribution to examine the relationship between continuous variables. Linear regression analysis was performed to determine the predictor of the dependent variable. The statistical significance level in the analysis was accepted as $p<0.05$.

RESULTS

Two hundred sixty-nine cases who applied for SNRFC were included in the study. Only one of those included in the study applied to SNRFC to benefit from law no. 2828 (caregiver salary) and all of the other patients to benefit from the disability rights.

The mean age of the cases in the reports included in the study was 7.4±4.9 years, of which 109 (40.5%) were female, and 59.5% were male. When the special needs levels were examined, 7.4% had no special needs, and 27.9% had special needs. 2.2% had mild special needs, 7.8% had moderate special needs, 1% 0.9 of them had advanced special needs, and 3.3% had very advanced special needs. 4.5% had significant special needs, and 45% had special conditional needs (**Table 1**).

Table 1. Demographic and special needs levels of reports

	Number	%
Age, Mean±SD	7.4±4.9	
Gender		
Girl	109	40.5
Boy	160	59.5
Special needs level		
No special needs	20	7.4
Have special needs (HSN): 20-39%	75	27.9
Mild special needs: 40-49%	6	2.2
Moderate special needs: 50-59%	21	7.8
Advanced special needs: 60-69%	5	1.9
Very advanced special needs: 70-79%	9	3.3
Have significant special needs (HSSN): 80-89%	12	4.5
Have special conditions needs (HSCN): 90-99%	121	45.0

When the areas of the reports were examined, 42.4% were cognitive, 40.1% were movement development, 20.4% were nervous system, 18.6% were a child and adolescent psychiatry, and 10% were language-speech-communication development area, 8.2% were hereditary-congenital diseases area, 7.4% visual function area, 5.9% endocrine system area, 4.5% hearing function-ear nose throat area, digestive system area in 2.2%, heart and circulatory system areas in 1.5%, metabolism area in 0.7%, genitourinary system area in 0.4% and hematology- oncology area was seen (**Figure 1**).

When the recommended special needs are examined, 43.9% are rehabilitation/early intervention to support cognitive functions, 41.3% require physiotherapy, occupational therapy, and rehabilitation, and 22.7% have a device, orthosis, prosthesis, or wheelchair and other equipment. 19.3% require rehabilitation at home or hospital, and 10.8% require speech and language therapy/rehabilitation. 10.8% require

therapy/rehabilitation for autism spectrum disorder, 7.1% received therapy/rehabilitation need for visual impairment/loss, 5.2% therapy/rehabilitation need for specific learning disability, and 4.1% therapy/rehabilitation needed for hearing impairment/loss (**Table 2**).

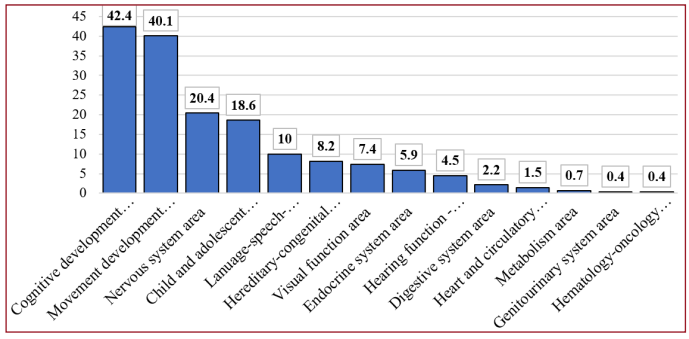

Figure 1. Distribution of the areas of the reports

Table 2. Recommended special needs*

	Number	%
Need for rehabilitation/early intervention to support cognitive functions	118	43.9
Need for physiotherapy, occupational therapy, rehabilitation	111	41.3
Need for devices, orthoses, prostheses, wheelchairs, and other equipment	61	22.7
Need for rehabilitation at home or hospital	52	19.3
Need for speech and language therapy/rehabilitation	29	10.8
Need for therapy/rehabilitation for autism spectrum disorder	29	10.8
Need for therapy/rehabilitation for visual function limitation/loss	19	7.1
Need for therapy/rehabilitation for specific learning disability	14	5.2
Need for therapy/rehabilitation for hearing impairment/loss	11	4.1

*some patients are recommended for more than one special need.

The highest level of special needs in both girls and boys was the presence of special conditions needs, and there was no significant difference between the genders in terms of the level of special needs (p=0.645) (**Table 3**).

Table 3. Comparison of special needs levels by gender

	Girl		Boy		p*
	Number	%	Number	%	
No special needs	11	10.1	9	5.6	0.645
Have special needs (HSN): 20-39%	25	22.9	50	31.3	
Mild special needs: 40-49%	2	1.8	4	2.5	
Moderate special needs: 50-59%	10	9.2	11	6.9	
Advanced special needs: 60-69%	2	1.8	3	1.9	
Very advanced special needs: 70-79%	5	4.6	4	2.5	
Have significant special need (HSSN): 80-89%	4	3.7	8	5.0	
Have special conditions needs (HSCN): 90-99%	50	45.9	71	44.4	

* Chi-square analysis was applied.

Table 4. Comparison of special needs areas by gender

	Girl		Boy		p*
	Number	%	Number	%	
Cognitive development area	50	45.9	64	40.0	0.339
Child and adolescent psychiatry area	14	12.8	36	22.5	0.046
Language-speech-communication development area	11	10.1	16	10.0	0.980
Endocrine system area	7	6.4	9	5.6	0.786
Genitourinary system area	1	.9	0	.0	0.405
Visual function area	6	5.5	14	8.8	0.319
Movement development area	48	44.0	60	37.5	0.283
Hematology-oncology area	0	.0	1	.6	0.408
Hearing function-ear nose, throat area	7	6.4	5	3.1	0.236
Hereditary-congenital diseases area	10	9.2	12	7.5	0.623
Hearth and circulatory system area	2	1.8	2	1.3	0.697
Metabolism area	1	.9	1	.6	0.784
Digestive system area	3	2.8	3	1.9	0.689
Nervous system area	23	21.1	32	20.0	0.826

* Chi-square analysis was applied.

Table 5. Number of patients evaluated on an area basis and evaluation results

	HSN	Mild HSN	Moderate HSN	Advanced HSN	Very advanced HSN	HSSN	HSCN
Cognitive development area	23	2	17	2	9	4	57
Child and adolescent psychiatry area	18	1	1	0	0	3	27
Language-speech-communication development area	17	0	1	1	0	1	7
Endocrine system area	1	0	0	1	0	4	10
Genitourinary system area	0	0	0	0	0	0	1
Visual function area	6	2	0	2	0	0	10
Movement development area	25	3	10	3	3	5	59
Hematology-oncology area	0	0	0	0	0	0	1
Hearing function-ear nose, throat area	2	0	0	0	0	0	10
Hereditary-congenital diseases area	0	0	0	0	0	1	21
Hearth and circulatory system area	0	0	0	0	0	0	4
Metabolism area	0	0	0	0	0	0	2
Digestive system area	0	0	0	0	0	2	4
Nervous system area	12	1	5	2	3	2	30

HSN, Have special needs; HSSN, Have significant special need; HSCN, Have special conditions needs

DISCUSSION

In a study conducted across Turkey by the State Institute of Statistics in 2002, the disability rate was 12.29% in all age groups.[4] Ministry of Family and Social Services 2022 statistical data remarks that the rate of people over the age of 3 with at least one disability in Turkey is 6.9%. Adıyaman is one of the provinces with a ratio of 6.37% to 7.85%. When examined in terms of gender, the disability rate is 56% for men and 44% for women. The disability rate for children aged 3-9 across the country is 6.7. The highest rate of disability; is a physical disability in the form of difficulty walking, climbing / descending stairs, and holding and carrying things.[6]

According to the Turkish Statistical Institute data, 27.2% of Turkey's population is children.[7] The needs of children due to disability are different from those of adults. So, social and institutional solutions should be produced with the child and family at the center. While SNRFC produces solutions for the needs of the disabled child and their families, it also enables physicians to make objective decisions without experiencing legal problems.[3,8]

Most studies[2,9] on the SNRFC examined psychiatric development. However, many new multi-faceted studies will be carried out in this regard, with the complete disappearance of the negative effect of the COVID-19 pandemic on medical boards.

In the present study, the mean age of the cases was 7.4±4.9 years, 109 (40.5%) were female, and 59.5% were male. The ratio between genders was similar to the Baykara et al.[2] study in 472 patients with a mean age of 8.5 (girls 39%, boys 61%). In addition, the high disability rate in men was consistent with studies in the literature.[2,4,8,9] This may be because some disorders, such as autism spectrum disorder or specific learning disorders, are more common in males. When the special needs levels of the patients were examined, it was reported that 7.4% had no special needs, and 3.3% had very advanced special needs. These rates coincide with the 7.2% and 3.2% of Baykara et al. However, in the study by Mehmet Kayhan &Yusuf Öztürk in 2020,[9] unlike both studies, no special needs were reported at the rate of 3.6%, while there was a very high level of special needs at a rate of 7.2%.

The highest level of special needs in both girls and boys is the presence of special conditions, which is consistent with other studies in the literature.[2-4,8] Similar to most studies, the most common area was the cognitive development area (42.4%), and the second was disability in the movement development area (40.1%).[4,8,9]

The rate of child and adolescent psychiatry area in boys (22.5%) was found to be significantly higher than the rate of girls (12.8%) (p=0.046). There was no significant difference between the genders in other areas (p>0.05). In the study conducted by Deniz Yıldız and Mahmut Cem Tarakçıoğlu,[4] the diagnoses of borderline cognitive delay and mild cognitive delay were significantly higher in girls. In contrast, the diagnosis of autism spectrum disorder was found to be higher in boys.

The need for devices, orthoses, prostheses, wheelchairs, and other equipment was determined at a rate of 22.7%. This situation shows that more than one-fifth of the children who apply to the medical board need serious rehabilitation. These data reveal the vital importance of SNRFC, as demonstrated by other studies.[2,10]

Only one person benefited from the law numbered 2828 (caregiver salary); All of the other patients applied to SNRFC to benefit from their disability rights. However, when the studies in the literature[8,9,11] are examined, the rates of application reasons in no study do not match each other showing us that each region has different needs. The economic situation of families, education levels, the social environment of children with special needs, physical conditions in their places of residence, and differences in the perspectives of different cultures towards the disabled may be the reason for this situation. Foreign nationals were not evaluated separately in the present study. We think that the number of children who are victims of war in cities with a large number of Syrian guests may affect the reasons for applying to medical boards and the results of the report need area. New studies will clarify this issue.

Objections to the medical board are substantial. Losing family time due to objections is exhausting for both the child and the family. For this reason, medical boards should be standardized in the same situation, with the same diagnoses, to determine the same need areas. The way to achieve this is to carry out other studies on the objections in the medical board and evaluate the results of the objections by a central commission established by the Ministry of Health. A platform can also be created where physicians can exchange information with this commission about the issues they need help with on medical boards.

After switching to SNRFC, there was a 90-99% disability rate in the group, which increased more than three times compared to the old regulation.[12] So, it can be said that medical boards established only for children reduce the victimization that may occur in children and families due to late detection. However, on this issue, Güller and Yaylacı,[12] contrary to our prediction,[12] stated that the increase in the rate of disability after switching to SNRFC would put families with already high-stress levels more stressed and hopeless. Accordingly, it is stated that families will refrain from applying to hospitals to get a medical board report. In our opinion, the financial and moral support provided by the special needs reports from the medical board for the child and family will reduce the stress of the families and increase the applications for SNRFC.

Creating free time for children and adolescents with special needs will contribute to their personal development.[13] For this reason, it is essential to identify the special needs of children and young people as soon as possible and eliminate the deficiencies that cause time loss as soon as possible. Because as the age increases, the quality of the needs may change while the quantity may also increase. This study it is aimed to reveal the problem with different indicators so that society can produce solutions by examining the special needs of children.

CONCLUSION

It is necessary to ensure that all individuals with special needs, especially children, participate in social life at the highest rate. One of the most important ways to achieve this is that medical boards for children in hospitals work with a standardized algorithm consisting of fast, effective, and objective criteria. Special needs reports for children from these boards provide financial, social, and special education support to the needs of children and families. Examination of the reports as a whole guides health professionals for more accessible and qualified services and social scientists and lawmakers for permanent solutions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Fırat University Non-Interventional Clinical Researches Ethics Committee (Date: 01.12.2022, Decision No: 2022/14-26).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. World Health Organization. Disability. Available online: https://www.who.int/news-room/fact-sheets/detail/disability-and-health (accessed on December 2022)
2. Aydoğan Baykara R, Pıhtılı Taş N, Taşcı İ. Investigation of Movement Development Area of Patients Applying to Health Board for Special Needs Report for Children (SNRC) to Special Needs Report for Children Regulations: A Cross-Sectional Study. J PMR Sci. 2022;25:189-96
3. Uygun SD, Çetinkaya M, Efe A, et al. The Difficulties Encountered in Practice for the Field of Child and Adolescent Psychiatry After the Regulation on Assessment of Special Needs for Children (RASNC). Turk J Child Adolesc Ment Health. 2021;28:191-9.
4. Yıldız D, Tarakçıoğlu MC. Evaluation of clinical characteristics and comorbidities of children applied for special requirement report and comparison of diagnosis and disability rates according to old and new regulations. Istanbul Kanuni Sultan Süleyman Med J. 2020;12:144-50.
5. Resmi Gazete. Çocuklar İçin Özel Gereksinim Değerlendirmesi Hakkinda Yönetm. Available online: https://www.resmigazete.gov.tr/eskiler/2019/02/20190220-1.htm (accessed on December 2022)
6. TC. Aile ve Sosyal Politikalar Bakanlığı. Engelli ve yaşlı istatistik bülteni Ocak 2022. Available online: https://www.aile.gov.tr/media/98625/eyhgm_istatistik_bulteni_ocak_2022.pdf (accessed on December 2022)
7. Türkiye Istatistik Kurumu İstatistik Veri Portalı. Availanle online: https://data.tuik.gov.tr/Search/Search?text=engelli&dil=1 (accessed on December 2022)
8. Kumbul YÇ, Sivrice ME, and Akın V. The Importance of Otorhinolaryngology and Evaluation of Clinical Features of the Admitted Patients in Special Need Report for Children (SNRC). Süleyman Demirel University J Health Sci 2020;11:348-52.
9. Kayhan M, Öztürk Ö. Clinical and Sociodemographic Characteristics of Cases Presenting to an Unıversity Hospital for Special Need Reports for Children. Osmangazi J Med 2020;42:240-8.
10. Oral A, Aydın R, Ketenci A, Akyüz G, Sindel D, Yalıman A. World Report on Disability: analysis of the disability issues and contributions of physical medicine and rehabilitation medical specialty in Turkey/Dunya Engellilik Raporu: Turkiye'de engellilik ile ilgili konuların analizi ve fiziksel tıp ve rehabilitasyon tıp uzmanlığının katkıları. Turk J Phys Med Rehab. 2016;1:83-97.
11. Şahin N, Altun H, and Kara B. Assessment of Disabled Child Health Council Reports. Kocatepe Med J 2014;15:48-53.
12. Barış G, Yaylacı F. The evaluation of medical board report datas for one year period after the transition to special s report for children. J Clin Psychiatry. 2021;24:207-16.
13. Powrie B, Kolehmainen N, Turpin M, Ziviani J, Copley J. The meaning of leisure for children and young people with physical disabilities: a systematic evidence synthesis. Dev Med Child Neurol. 2015;57:993-1010.

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Original Article / Orijinal Araştırma

Attitudes of Preschool Children and Their Families Towards Face Mask During the COVID-19 Pandemic

COVID-19 Pandemisinde Okul Öncesi Çocukların ve Ailelerinin Maske Kullanım Tutumları

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Abstract

Aim: The use of face masks, compliance with hygiene and distance rules were among the leading measures during pandemic. But some authorities didn't recommend face masks to preschool children. In this study we aimed to evaluate the attitudes of preschool children and their families towards face masks.

Material and Method: We performed a survey between February-March 2022 to 189 volunteer participants who have preschool children, in Pediatric Health and Diseases Outpatient Clinics in two different centers. Survey was consisted of 40 questions and 4 parts: 1. Demographic characteristics 2. COVID-19 3. Use of face mask 4.Compliance with hygiene and distance rules

Results: Fifty three percent of the children used face mask. It was observed that the presence of a family member obsessed with cleaning caused a statistically higher increase in the number of handwashing in children (p:0,019). Mothers who were university graduates taught the children more distance rules (p:0.014), the number of handwashing increased in their children (p:0.001) and the rate of using face masks was higher (p:0.036). Having a family member who have had COVID-19 was inversely proportional to the use of face mask in children (p:0.001) and correct use (p:0.033). It was observed that the rate of wearing mask was higher in children who used glasses (92%, p:0.006).

Conclusion: Half of the preschool children used face masks regularly. COVID-19 rate was higher in the families whose children didn't use face masks in community. Face masks can be recommended to preschool children who can use it, during the pandemic.

Keywords: Children, COVID-19, face mask

Öz

Amaç: Pandemi sürecinde yüz maskesi kullanımı, hijyen ve mesafe kurallarına uyulması başta gelen önlemler arasında yer almıştır. Ancak bazı otoriteler okul öncesi çocuklara yüz maskesi kullanımını önermemektedir. Bu çalışmada okul öncesi çocukların ve ailelerinin yüz maskelerine yönelik tutumlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Şubat-Mart 2022 tarihleri arasında iki farklı merkezde Çocuk Sağlığı ve Hastalıkları Poliklinikler'inde okul öncesi çocuğu olan 189 gönüllü katılımcıya anket uygulandı. Anket 40 soru ve 4 bölümden oluşuyordu: 1. Demografik özellikler 2. COVID-19 3. Yüz maskesi kullanımı 4. Hijyen ve mesafe kurallarına uygunluk.

Bulgular: Çocukların yüzde elli üçü yüz maskesi kullanmıştı. Ailede temizlik takıntısı olan bir bireyin varlığının çocuklarda el yıkama sayısında istatistiksel olarak daha fazla artışa neden olduğu görüldü (p:0,019). Üniversite mezunu annelerin çocuklarına daha fazla mesafe kuralı öğrettiği(p.0.014), çocuklarında el yıkama sayısının arttığı (p:0.001) ve yüz maskesi kullanma oranlarının daha yüksek olduğu (p:0.036) belirlendi. Ailede COVID-19 geçirmiş bir birey olması, çocuklarda yüz maskesi kullanımı (p:0,001) ve doğru kullanım (p:0,033) ile ters orantılıydı. Gözlük kullanan çocuklarda maske takma oranının daha yüksek olduğu görüldü (%92, p:0,006).

Sonuç: Okul öncesi çocukların yarısı düzenli olarak yüz maskesi kullanmıştı. Çocukları toplum içinde yüz maskesi kullanmayan ailelerde COVID-19 oranı daha yüksekti. Pandemi döneminde, okul öncesi çocuklardan kullanabilenlere yüz maskesi önerilebileceğini düşünmekteyiz.

Anahtar Kelimeler: Çocuk, COVID-19, maske

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INTRODUCTION

Sars-Cov 2 virus, which emerged in Wuhan, China at the end of 2019, has caused a pandemic all over the world. [1] While adults had the disease more severely, the rate of asymptomatic transmission was higher in children. But even if the children were asymptomatic, they were at risk of infecting their families.[2] In addition, it was observed that the frequency of symptomatic infections in children increased with the emergence of new variants. Children also developped a Kawasaki Like Disease called Multisystem Inflamatory Disease in Children ,after due to COVİD 19.

In this process, many countries had to take various measures. The use of face masks, compliance with hygiene and distance rules were among the leading measures. The World Health Organization (WHO) advised the use of face masks as part of prevention and control measures to limit the spread of SARS-CoV-2, but it didn't recommend the use of face masks for children aged up to five years.[3] In this study we aimed to evaluate the attitudes of preschool children and their families towards face masks during the SARS-CoV 2 pandemic.

MATERIAL AND METHOD

We performed a survey between February-March 2022 to 189 volunteer participants who have preschool children, in Pediatric Health and Diseases Outpatient Clinics in two different centers. The surveys were filled by the researchers face to face during the children's outpetient clinic visits. Survey was consisted of 40 questions and 4 parts: 1. Demographic characteristics 2. COVID-19 3. Use of face mask 4.Compliance with hygiene and distance rules. The study was approved by our hospitals local ethics committee.

Statistical analyses were performed using the Statistical Package for Social Sciences version 20. Results are presented as percentage and mean or median. Comparisons between groups were analyzed using the chi-squared test. P<0.05 was taken as a criterion for statistically significant differences.

RESULTS

Most of the participants were mothers (81%). Demographic characteristics of the children were shown in **Table 1**. COVID-19 infection rate among children was 4,8% even if it was 43,4% in their family. Fourteen percent of the participants had a relative who died due to COVID-19.

Fifty three percent of the children used face mask (**Figure 1**). **Figure 2** showed the reason of children who didn't use face mask. Only 31,7% of the children and 51,9% of the participants used the face mask correctly. Thirteen percent of the children had a problem (itching 5.3%, rash 2.6%, sneezing 4.6%) with face mask. Half of the children (49,2%) used face mask with their wish. Children prefered patterned, colorful and cartoon-heroic face masks. While surgical mask was preferred 83.4%, fabric mask was preferred by 15.3%.

Table 1: Demographic characteristics of children

Characteristic	
Gender	
Male	52.4%
Female	47.6 %
Avarge age	42.8±19.5 months (4-72)
Mother's education	
Primary school	17.5%
Secondary school	23.3%
High school	23.8%
University	34.9%
Father's education	
Primary school	13.8%
Secondary school	22.2%
High school	22.8%
University	40.7%
Chronic diseases of children	11.6%
Chidren's care during pandemic	
Going to kindergarten when it is open	23.3%
Being cared for at home by a baby sitter	46.6%
Being cared for at home by mother	20%
Being cared for at baby sitter's home	10.1%

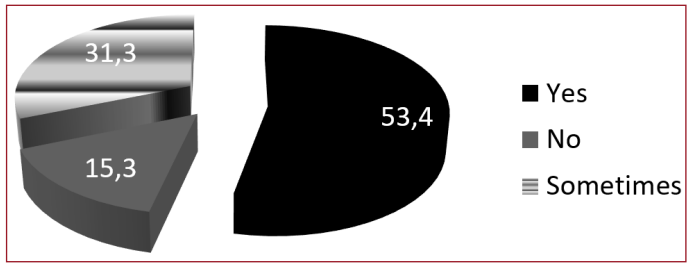

Figure 1: Face mask use rates of children

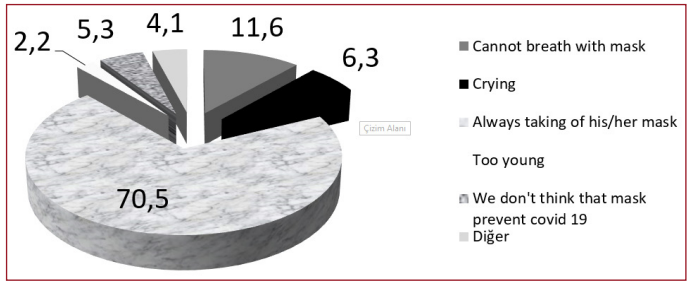

Figure 2: Distribution of the reasons for not using face masks

There was an increase in hand washing frequency of 43.9% of the children. Sixty four percent of the participants taught their children distance rules.

It was observed that the presence of a family member obsessed with cleaning caused a statistically higher increase in the number of handwashing in children (p:0,019). Mothers who were university graduates taught the children more distance rules (p:0.014), the number of handwashing increased in their children (p:0.001) and the rate of using face mask was higher (p:0.036). Having a family member who have had COVID-19 was inversely proportional to the use of face masks in children (p:0.001) and correct use (p:0.033). It was observed that the rate of wearing masks was higher in children who used glasses (92%, p:0.006).

DISCUSSION

Since face masks are known to reduce virus transmission, it was one of the most prominent protective methods during the COVID-19 pandemic.[1,4] With the suggestion of the WHO, face mask have started to be used around the world and its use still continues in countries where the spread of the virus continues. But WHO didn't recommend the face mask use for children up to five years whereas centers for disease control and prevention recommended it to children two years and older and the use of face mask in this age group differed according to countries.[3,5] For example Italian Pediatric Society recommended face mask protection in children over three years old.[6] In our country authorities recommended the use of face masks for children aged two and over if they could use them, but there was no official obligation for preschool children. In this study we evaluated the attitudes of preschool children and their families towards face masks.

Fifty three percent of the children used face mask, 31.7% used the mask correctly and 49,2% used face mask with their wish. Mickells et al. conducted a study evaluating adherence to face mask in early elementary school children which also included pre kindergarten and kindergarten children. In this study adherence rate increased by age and it was 56.2%, 73.5% respectively in pre-kindergarten and kindergarten childre.[7] The use of face mask in pre kindergarten children was nearly similar to our study but in our study the age of the children differed between 4-72 months. In a study adherence of adolecents in United States was found 89.2% and in a French study the adherence rate was 59.7 % in children of all ages.[8,9]

When the reasons for not wearing a mask were evaluated, it was seen that the most common reason was that although the mother wore the mask to the child, the child constantly took off the mask because he did not want to wear it. 11 percent of the children did not use masks because they could not breathe properly. Even if there isn't any child study, adult studies reported that face masks commonly used during the pandemic did not impair gas exchange during rest or mild exercise.[10]

Thirteen percent of the children had a problem with face mask. Among those itching was the most common problem whereas sneezing was second and rash was the third common problem. Assathiany et all. reported headache (49%), difficulties to speak (45.1%) and breathing discomfort (28.1%) as the most common side effects in their study. None of the children in our study had headache or difficulties to speak.[9] There are facial dermatoses cases due to face masks reported in the litarature.[11,12]

There was an increase in hand washing frequency of nearly half of the children. The presence of a family member obsessed with cleaning caused a statistically higher increase in the number of handwashing in children. Sixty four percent of the participants taught their children distance rules. Mothers who were university graduates taught the children more distance rules, the number of handwashing increased in their children and the rate of using face masks was higher. Naam et al. also found that face mask use incresed with education level in adults.[13]

COVID-19 rate among children was 4,8% and 43,4% in their family. This wide difference can be explained by the fact COVID-19 in children is lower or the rate of false negatives is higher.

One of the most important findings of the study was that COVID-19 was higher in the families whose children didn't use face mask or didn't use it correctly. These results suggested that children are important transporters for their families. It was observed that the rate of wearing mask was higher in children who used glasses. This suggested that children who have the habit of affixing something to their faces such as glasses adopt mask more easly.

The strength of the study is that mask use of preschool children was evaluated with a comprehensive 40 question survey. The fact that this study is a survey may create a limitation due to recall bias.

CONCLUSION

Half of the preschool children used face mask regularly. COVID-19 rate was higher in the families whose children didn't use face mask in community. Face masks can be recommended to preschool children who can use it, during the pandemic.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by ethics committee of Sami Ulus Maternity and Children Training and Research Hospital. Number: 2020-KAEK-141/276

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declare that he has all participated in the design, execution, and analysis of the paper, and that he has approved the final version.

REFERENCES

1. Bubbico L, Mastrangelo G, Larese-Filon F, et al. Community use of face masks against the spread of covid-19. Int J Environ Res Public Health 2021;18:1–13.
2. Su L, Ma X, Yu H, et al. The different clinical characteristics of corona virus disease cases between children and their families in China–the character of children with COVID-19. Emerg Microbes Infect 2020;9:707–13.
3. World Health Organization. Mask use in the context of COVID-19. Who 2020:1–10. Available from:https://www.who.int/publications/i/item/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak

4. Abboah-offei M, Salifu Y, Adewale B, Bayuo J. A rapid review of the use of face mask in preventing the spread of COVID-19 Mary. Int J Nurs Stud Adv J 2021;3:100013.
5. Esposito S, Principi N. To mask or not to mask children to overcome COVID-19. Eur J Pediatr 2020;179:1267–70.
6. Villani A, Bozzola E, Staiano A, et al. Facial masks in children:The position statement of the Italian pediatric society. Ital J Pediatr 2020;46:1–2.
7. Mickells GE, Figueroa J, West KW, Wood A, McElhanon BO. Adherence to Masking Requirement During the COVID-19 Pandemic by Early Elementary School Children. J Sch Health 2021;91:555–61.
8. Dejonckheere M, Ph D, Waselewski M, et al. Views on COVID-19 and Use of Face Coverings Among U.S. Youth. J Adolesc Heal 2021;68:873–81.
9. Assathiany R, Salinier C, Béchet S, et al. Face Masks in Young Children During the COVID-19 Pandemic:Parents' and Pediatricians' Point of View. Front Pediatr 2021;9.
10. Eberhart M, Orthaber S, Kerbl R. The impact of face masks on children—A mini review. Acta Paediatrica, International Journal of Paediatrics 2021;110:1778-1783.
11. Olisova OY, Teplyuk NP, Grekova EV, Lepekhova AA. Dermatoses caused by face mask wearing during the COVID-19 pandemic. J Eur Acad Dermatology Venereol 2021;1:1–3.
12. Schwensen JF, Simonsen AB, Zachariae C, Johansen JD. Facial dermatoses in healthcare professionals induced by the use of protective masks during the COVID -19 pandemic . Contact Dermatitis 2021:2–6.
13. Al Naam YA, Elsafi SH, Alkharraz ZS, Alfahad OA, Al-Jubran KM, Al Zahrani EM. Community practice of using face masks for the prevention of COVID-19 in Saudi Arabia. PLoS One 2021;16:1–12.

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Original Article / Orijinal Araştırma

Primary Lung Tumors Invading the Chest Wall

Göğüs Duvarını İnvaze Eden Primer Akciğer Tümörleri

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Abstract

Aim: Lung cancer remains the leading cause of cancer deaths worldwide. The surgical approach to locally advanced non-small cell lung cancer (NSCLC) goes beyond the classical approach and requires a multidisciplinary approach both preoperatively and postoperatively. In addition to the tumor size, the location of T3 and T4 tumors affects the extent of the surgery.

Material and Method: Patients who underwent lung resection for cancer between March 2019 and October 2022 were retrospectively reviewed. Patients who underwent chest wall resection were evaluated in terms of age, gender, pathology, type of operation, survival, recurrence, complications, receipt of preoperative chemotherapy, tumor node metastasis (TNM) stage, whether or not mediastinoscopy was performed, STAS (The spread through air spaces) positivity, visceral pleural invasion, parietal pleural invasion, lymphovascular invasion, perineural invasion, and alveolar/bronchial wall invasion.

Results: Thoracic wall resection was performed in nine patients with locally advanced NSCLC. The use of prolene mesh was required in eight patients. All patients complained of pain in the thoracic wall in the preoperative period. Postoperative pathology results showed STAS positivity in four patients; alveolar/bronchial wall invasion in four; and visceral, parietal, pleural, and lymphovascular invasion in seven. The mean survival of the patients was 24.20 months (0.63–39). No patient developed recurrence during the follow-up period.

Conclusion: Chest wall resection and reconstruction for lung cancer is a surgical treatment method that should be performed without violating respiratory physiology and by using a small amount/number of synthetic materials.

Keywords: Cancer, lung, thoracic surgery,thoracic wall

Öz

Amaç: Akciğer Kanseri dünya çapında kanser ölümlerinin önde gelen nedeni olmaya devam etmektedir. Lokal ileri küçük hücreli dışı akciğer kanserinde (KHDAK) cerrahi yaklaşım klasik yaklaşımın ötesine geçerek hem preoperatif hem de postoperatif multidisipliner yaklaşım ihtiyacını doğurur. Tümörün boyutunun büyüklüğüne ek olarak, T3 ve T4 tümörlerin yerleşim yeri uygulanacak cerrahinin büyüklüğünü etkiler.

Gereç ve Yöntem: Mart 2019 ile Ekim 2022 yılları arasında akciğer kanseri nedeniyle rezeksiyon yapılan hastalar retrospektif olarak incelendi. Göğüs duvarı rezeksiyonu uygulanan hastalar yaş, cinsiyet, patoloji, operasyon şekli, sağkalım, nüks, komplikasyonlar, preoperatif kemoterapi alıp-almadığı, TNM evresi, mediastinoskopi yapılıp-yapılmadığı, STAS (The spread through air spaces) pozitifliği, visseral plevra invazyonu, paryetal plevra invazyonu, lenfovasküler invazyon, perinöral invazyon ve alveol/bronş duvarı invazyonu açısından değerlendirildi.

Bulgular: Lokal ileri küçük hücreli dışı akciğer kanseri nedeniyle 9 hastaya toraks duvarı rezeksiyonu uygulanmıştır. Hastaların 8'inde prolen mesh kullanma ihtiyacı doğmuştur. Tüm hastalarda preoperatif dönemde toraks duvarında ağrı şikayeti mevcuttu. Postoperatif patoloji sonuçlarında hastaların 4'ünde STAS pozitifliği, 4'ünde alveol/bronş duvarı invazyonu, 7'sinde visseral, paryetal plevra ve lenfovasküler invazyon tespit edilmiştir. Hastaların ortalama sağ kalım süresi 24,20 ay (0,63-39) olarak tespit edilmiştir. Takip süresi içerisinde nüks gelişen hasta olmamıştır.

Sonuç: Akciğer kanseri nedeniyle gerçekleştirilen göğüs duvarı rezeksiyonu ve rekonstrüksiyonu solunum fizyolojisine aykırı davralınmadan ve az miktarda/sayıda sentetik materyal tercih edilerek gerçekleştirilmesi gereken bir cerrahi tedavi yöntemidir.

Anahtar Kelimeler: Akciğer, göğüs cerrahisi, kanser, toraks duvarı

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INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide. According to the 2020 data of the World Health Organization, the incidence rate of lung cancer is 22.4/100000 and it is the deadliest cancer, with a rate of 18/100000. The 5-year survival rate of lung cancer is 10%–20%.[1] Surgical resection is the best treatment option for non-small cell lung cancer.

The chest wall is involved in approximately 5% of all primary lung neoplasms, and this clinical condition is more common than primary chest wall tumors that invade the lung.[2] According to the 8th tumor node metastasis (TNM) classification, lung tumors invading the chest wall are classified as T3, and they account for approximately 45% of all T3 lung cancers.[3] Surgical resection consisting of excision of the primary lung cancer with associated chest wall resection and lymph node dissection is the treatment of choice for locally advanced tumors. The success of treatment depends on achieving R0 resection and the involvement of lymph nodes by the tumor. This study aimed to take a critical look at lung cancers invading the chest wall, focusing on the preoperative evaluation of patients, surgical techniques, postoperative complications, and overall outcomes.

MATERIAL AND METHOD

The Ethics committee approval was obtained for this study from the hospital's ethics committee. (Received from the Ankara City Hospital Ethics Committee with the number E1-20-817 on 25.06.2022)

All persons included in the study signed the informed consent form. Patients who underwent lung resection for malignancy between March 2021 and October 2022 were retrospectively reviewed. Patients who underwent chest wall resection were evaluated in terms of age, gender, pathology, type of operation, survival, recurrence, complications, receipt of preoperative chemotherapy, TNM stage, whether or not mediastinoscopy was performed, STAS (The spread through air spaces) positivity, visceral pleural invasion, parietal pleural invasion, lymphovascular invasion, perineural invasion, and alveolar/bronchial wall invasion. TNM stages were determined according to the American Joint Committee on Cancer/Union for International Cancer Control8th TNM staging classifications. Prior to surgical resection, the patients were preoperatively examined. For a routine preoperative examination, the patients were asked to undergo a positron emission tomography-computed tomography (PET-CT) scan and a pulmonary function test, along with hemograms and biochemical blood tests. High fluorodeoxyglucose uptake in the mediastinal lymph nodes during PET-CT indicated mediastinal lymph node metastasis.

Statistical analyses were performed using IBM Corp. (Released in 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: software). STAS, age groups, gender, type of operation, visceral pleural invasion, parietal pleural invasion, lymphovascular invasion, perineural invasion, alveolar/bronchial invasion, and TNM stages are presented using contingency tables. The chi-square test or Fisher's exact test (when the values observed in the cells did not meet the assumptions of the chi-square test) were used as appropriate to determine whether there was a difference between the groups in terms of these frequencies. The Mann–Whitney U test was used to compare age and survival between the groups. While investigating the associations between age and survival the Spearman test was used. A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

Of the nine patients with lung cancer who underwent surgical treatment for thoracic wall invasion, one was a female and eight were males. The mean age of the patients was 62.6 years (45–74). All patients in the preoperative period had a pathological diagnosis. Pathological examination revealed squamous cell carcinoma in six patients, adenocarcinoma in two patients, and neuroendocrine carcinoma in one patient. All patients reported thoracic wall pain. All patients were active smokers. None of the patients who underwent PET-CT evaluation underwent mediastinoscopy before resection. Three patients with suspected mediastinal lymph node involvement on PET-CT evaluation underwent endobronchial ultrasound (EBUS). No patient received preoperative chemoradiotherapy.

The surgical procedures performed on the patients are shown in **Table 1**. One patient with limited respiratory reserve underwent wedge resection.

Patients were staged by the TNM system according to postoperative pathology reports. The prolene mesh used in thoracic wall reconstruction is shown in **Figure 2**.

T4 tumors invading the thoracic wall have also been discussed in our study (**Figure 1**). Of the patients with T4 disease, two had vertebral body invasion with thoracic wall invasion and one had a tumor greater than 7 cm.

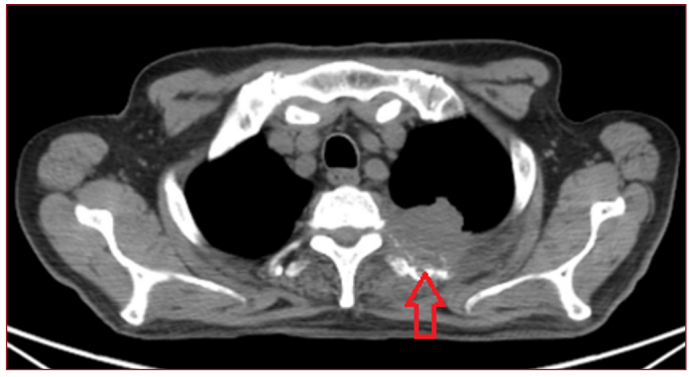

Figure 1: Lung cancer invading the paravertebral portion of the rib and the vertebral body (arrow).

Table 1: Surgical approaches and distribution of patients by pathology

Patient	Operation	Pathology	Parietal pleura status	TNM	Stage
1	Right lower lobectomy + anterolateral thoracic wall resection, including ribs 4, 5, and 6, and reconstruction using prolene mesh	Sqcc	+	T3N0M0	2B
2	Right lower lobectomy + anterolateral thoracic wall resection, including ribs 4, 5, and 6, and reconstruction using prolene mesh	Adenoca	+	T3N0M0	2B
3	Right upper lobe wedge resection + Posterior thoracic wall resection, including the ribs 2, 3.	Sqcc	-	T3N0M0	2B
4	Right upper lobectomy + Anterolateral thoracic wall resection, including the ribs 3, 4, 5, and reconstruction using prolene mesh	Sqcc	+	T4N1M0	3A
5	Right upper lobectomy + Anterolateral thoracic wall resection, including the ribs 3, 4, 5, and reconstruction using prolene mesh	Sqcc	+	T4N0M0	3A
6	Left lower lobectomy + anterolateral thoracic wall resection, including the 4th, 5th, 6th ribs, and reconstruction	Adenoca	+	T3N0M0	2B
7	Left upper lobectomy + Anterolateral thoracic wall resection, including the ribs 3, 4, 5, and reconstruction using prolene mesh	Sqcc	+	T4N2M0	3B
8	Right upper lobectomy + Resection of the posterolateral thoracic wall, including the ribs 2,3,4,5, and reconstruction using prolene mesh	Sqcc	+	T3N0M0	2B
9	Right upper lobectomy + Resection of the posterolateral thoracic wall, including the ribs 3, 4, 5, and reconstruction using prolene mesh	Neuro ca	-	T3N0M0	2B

Sqcc Squamous cell carcinoma, Adenoca Adenocarcinoma, Neuro ca Neuroendocrine carcinoma

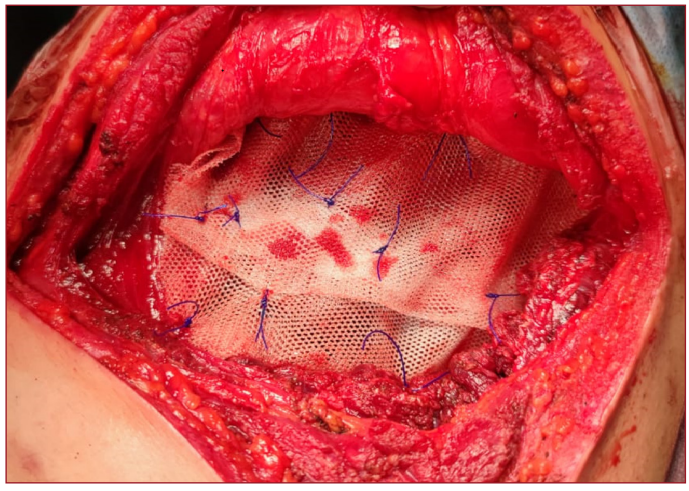

Figure 2: Appearance of the prolene patch used on the reconstruction of the thoracic wall

STAS positivity was detected in four patients; alveolar/bronchial wall invasion was detected in four; and visceral, parietal pleural invasion was detected in seven, and lymphovascular invasion was detected in six patients. There was no statistically significant difference between disease stages in terms of the rate of STAS positivity; parietal and visceral pleural invasion; and lymphovascular, perineural, and alveolar/bronchial invasion (p=0.232, p=0.526, p=0.526, p=0.325, p=0.455, p=0.455). There was no statistically significant difference in the rate of STAS positivity between histological groups (p=0.455). The recurrence rate and survival were not different between STAS-positive and STAS-negative groups (p=0.343, p=0.858),

One patient died on postoperative day 25 due to coronavirus disease 2019, and one patient died on postoperative day 19 due to cardiac complications. The mean survival of the patients was 24.20 months (0.63–39). One patient developed recurrence during the follow-up period. There was no statistically significant relationship between age and survival (p=0.897). The survival was not significantly different between patients with and without lymphovascular invasion, parietal pleural invasion, perineural invasion, alveolar/bronchial wall invasion, and visceral pleural invasion (p=0.571, p=0.391, p=0.858, p=0.858, p=0.858).

DISCUSSION

Coleman described the first surgical management of a primary lung cancer invading the chest wall in 1947.[4] The chest wall is involved in approximately 5% of all primary lung tumors.[2]

Chest wall infiltration is usually caused by peripherally located tumors and develops slowly. The tumor invades the parietal pleura, followed by the soft tissues and intercostal muscles, and finally the ribs. Extrapleural resection is sufficient only if the parietal pleura is infiltrated, whereas deeper invasion requires a complete chest wall resection. Tumor size and depth of invasion are not always directly correlated. In general, lung cancers invading the chest wall originate from the apico-posterior part of the upper or lower lobes.[5,6] The majority of our patients had tumors originating from the upper lobes. Considering the location, the best surgical approach is posterolateral thoracotomy. In our study, a traditional posterolateral thoracotomy was performed. In our patients with vertebral invasion, a high posterolateral thoracotomy was required and hemivertebrectomy was performed by a neurosurgeon.

In addition to symptoms secondary to lung malignancy, the most common clinical symptom at presentation is chest pain (>60%), which is highly specific for chest wall infiltration (>90%).[3] All of our patients complained of chest pain. The diagnosis is usually made radiologically. Tomography has an accuracy of 50%–91% in the diagnosis of T3 tumors.[7,8] Dynamic magnetic resonance imaging (MRI) may be useful to rule out a possible invasion of the parietal pleura.[9]

PET-CT scanning is recommended for the detection of preoperative hilar/mediastinal lymph node involvement.[3] In our study, patients underwent chest radiography, thoracic tomography, MRI for suspected vertebral body invasion and brain metastasis, and PET-CT for staging. Further invasive examinations, such as mediastinoscopy or EBUS, are indicated to exclude suspected nodal metastases. No patient underwent mediastinoscopy in our study. Three patients underwent EBUS for staging, and lymph node involvement was ruled out. The incidence of lymph node involvement is not related to the depth of chest wall infiltration or tumor size.[3] Similar results were obtained in our study.

Patients with locally advanced lung cancer are at high risk for postoperative complications and therefore require careful preoperative evaluation of comorbid conditions. All of our patients were evaluated preoperatively for comorbid diseases, and some patients required a multidisciplinary approach.

Preoperative pulmonary and cardiac evaluations should be performed. Pulmonary function tests, ventilation–perfusion scintigraphy, and echocardiography should be performed.

A differential diagnosis of lung cancer should be made, and diagnostic procedures such as transthoracic fine needle aspiration biopsy and bronchoscopy should be performed to make a preoperative tumor diagnosis. Preoperative histopathological diagnosis was made by transthoracic fine needle aspiration biopsy and bronchoscopy in eight patients and by intraoperative frozen section examination in one patient.

The goal of surgery must be to achieve R0 resection. Lung resection, systemic lymph node dissection, and chest wall resection are the surgical methods. All patients underwent R0 resection.

Chest wall reconstruction can be performed depending on the size and location of the chest wall defect. In general, small posterior defects closed by the scapula do not require reconstruction. Large defects and defects located in the anterior chest wall usually require reconstruction. If the defect is below the tip of the scapula, reconstruction is recommended to avoid potential compression of the scapula within the defect. The basic principles of reconstruction are preservation of chest wall stability and protection of vital organs and respiratory mechanics.[3] The need for reconstruction in chest wall resections ranges from 40% to 60%.[10,11]

For reconstruction, autologous live tissue extraction and moldable titanium rods or synthetic patches may be preferred. Firm materials are not recommended because they have a high risk of damaging the surrounding tissues and tend to break due to respiratory movements.[2] All synthetic materials used for reconstruction carry the risk of causing a foreign body reaction in the body. Infection at the operation site and allergic reactions due to the material used may be observed. We used prolene mesh in all of our patients and avoided the excessive use of synthetic material as much as possible. Complications such as foreign body reaction, loss of function, infection, and bleeding were not seen in any of our patients.

CONCLUSION

We believe that the anatomical and physiologic structures of the thorax should be preserved as much as possible in chest wall resection and reconstruction for lung cancer. Excessive and unnecessary use of synthetic materials may cause loss of respiratory function, infections, allergic reactions, and anatomical distortion. In reconstruction, the surgical procedure should be performed by resecting the tissues as much as possible while adhering to the principles of malignancy surgery.

ETHICAL DECLARATIONS

Ethics Committee Approval: The Ethics committee approval was obtained for this study from the hospital's ethics committee. (Received from the Ankara City Hospital Ethics Committee with the number E1-20-817 on 25.06.2022)

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Allemani C, Weir HK, Carreira H et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet 2015;385(9972):977-1010.
2. Stoelben E, Ludwig C. Chest wall resection for lung cancer: indications and techniques. Eur J Cardiothorac Surg 2009;35(3):450-6.
3. Filosso PL, Sandri A, Guerrera F et al. Primary lung tumors invading the chest wall. J Thorac Dis 2016;8(Suppl 11):S855-62.
4. Coleman FP. primary carcinoma of the lung, with invasion of the ribs: pneumonectomy and simultaneous block resection of the chest wall. Ann Surg 1947;126(2):156-68.
5. Elia S, Griffo S, Gentile M, Costabile R, Ferrante G. Surgical treatment of lung cancer invading chest wall: a retrospective analysis of 110 patients. Eur J Cardiothorac Surg 2001;20(2):356-60.
6. Martin-Ucar AE, Nicum R, Oey I, Edwards JG, Waller DA. En-bloc chest wall and lung resection for non-small cell lung cancer. Predictors of 60-day non-cancer related mortality. Eur J Cardiothorac Surg 2003;23(6):859-64.
7. Cangemi V, Volpino P, Drudi FM, D'Andrea N, Cangemi R, Piat G. Assessment of the accuracy of diagnostic chest CT scanning. Impact on lung cancer management. Int Surg 1996;81(1):77-82.

8. Gdeedo A, Van Schil P, Corthouts B, Van Mieghem F, Van Meerbeeck J, Van Marck E. Comparison of imaging TNM [(i)TNM] and pathological TNM [pTNM] in staging of bronchogenic carcinoma. Eur J Cardiothorac Surg 1997;12(2):224-7.
9. Bandi V, Lunn W, Ernst A, Eberhardt R, Hoffmann H, Herth FJ. Ultrasound vs. CT in detecting chest wall invasion by tumor: a prospective study. Chest 2008;133(4):881-6.
10. Doddoli C, D'Journo B, Le Pimpec-Barthes F, Dujon A, Foucault C, Thomas P et al. Lung cancer invading the chest wall: a plea for en-bloc resection but the need for new treatment strategies. Ann Thorac Surg 2005;80(6):2032-40.
11. Akay H, Cangir AK, Kutlay H, Kavukçu S, Okten I, Yavuzer S. Surgical treatment of peripheral lung cancer adherent to the parietal pleura. Eur J Cardiothorac Surg 2002;22(4):615-20.

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Original Article / Orijinal Araştırma

First Aid in Snakebites: an Evaluation of the Usefulness and Quality of Youtube Videos

Yılan Isırıklarında İlk Yardım: YouTube Videolarının Faydası ve Kalitesi Üzerine Değerlendirme

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Abstract

Aim: YouTube has become an increasingly used platform for obtaining health information such as first aid knowledge of snake bites rescuers in recent years. Aim of the study is to evaluate the quality of existing YouTube videos on first aid interventions for snake bites and whether they are of an educational nature.

Material and Method: Descriptive study. On February 20, 2021, determined search terms such as; "Snake bite emergency aid, Snake bite treatment medicine, first aid in snake bite" were searched separately on YouTube (https://youtube.com). A total of 360 YouTube videos were listed. It was analyzed according to the Global Quality Scale (GQS) developed to evaluate internet-based resources and the DISCERN scale developed to determine reliability.

Results: A total of 72 videos meeting the criteria were identified. The median duration of the videos were 292 seconds. The median number of views were 13.8, the number of comments were 0.01, likes were 0.11, and the number of dislikes were 0.01. When the DISCERN scores and uploaded sources were compared, significant differences were found (p=0.031). DISCERN scores of videos shared by doctors were found to be significantly higher than other sources (p <0.05). While 4.2% (n=3) of the videos gave incorrect information such as sucking with mouth, cutting, it was suggested to apply a tourniquet incorrectly in 5.6%. Limb immobilization and bandage application was shown in 73.6% of all videos.

Conclusions: YouTube videos uploaded by doctors and health-related websites on first aid practices on snake bites contain useful first aid information.

Keywords: First aid, snake bites, quality, YouTube videos

Öz

Amaç: YouTube, son yıllarda yılan ısırığına müdahale edenlerin ilk yardım bilgisi gibi sağlık bilgilerinin elde edilmesi için giderek daha fazla kullanılan bir platform haline gelmiştir. Çalışmanın amacı, yılan ısırmalarında ilk yardım müdahaleleri ile ilgili mevcut YouTube videolarının kalitesini ve eğitici nitelikte olup olmadığını değerlendirmektir.

Gereç ve Yöntem: Tanımlayıcı çalışma. 20 Şubat 2021 tarihinde; YouTube (https://youtube.com) internet sitesinde "Yılan ısırması acil yardımı, Yılan sokması tedavisi, yılan ısırmasında ilk yardım" ayrı ayrı tarandı. Toplam 360 YouTube videosu listelendi. İnternet tabanlı kaynakları değerlendirmek için geliştirilen Global Kalite Ölçeği (GQS) ve güvenilirliği belirlemek için geliştirilen DISCERN ölçeğine göre analiz edilmiştir.

Bulgular: Kriterleri karşılayan toplam 72 video belirlendi. Videoların medyan süresi 292 saniyeydi. Ortalama görüntülenme sayısı 13.8, yorum sayısı 0.01, beğeni sayısı 0.11 ve beğenilmeyen sayısı 0.01 olarak gerçekleşti. DISCERN puanları ve yüklenen kaynaklar karşılaştırıldığında anlamlı bir fark saptandı (p=0.031). Doktorların paylaştığı videoların DISCERN puanları diğer kaynaklara göre anlamlı olarak yüksek bulundu (p<0.05). Videoların %4,2'si (n=3) ağızdan emme, kesme gibi yanlış bilgi verirken, %5,6'sında yanlış turnike uygulanması önerilmiştir. Ekstremite sabitleme ve bandaj uygulaması tüm videoların %73,6'sında gösterildi.

Sonuç: Doktorlar ve sağlıkla ilgili web siteleri tarafından yüklenen yılan sokmalarında ilk yardım uygulamalarıyla ilgili YouTube videoları yararlı ilk yardım bilgileri içermektedir.

Anahtar Kelimeler: İlk yardım, yılan sokması, kalite, YouTube videoları

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INTRODUCTION

Snake bites are a medical emergency encountered all over the world. Since exposure mostly occurs in rural areas, first aid is carried out outside the hospital and by the general public. Lack of first aid knowledge of rescuers is one of the leading causes of death from bite.[1-2] However, for those at risk, such as agricultural workers, nature travelers and wildlife enthusiasts, there are limited sources of accurate information in such emergencies.

Considering that nearly half of the adult population today uses the internet to obtain medical information, it can be said that online platforms are an important source of information in such cases.[3] Especially YouTube has become an increasingly used platform for obtaining health information in recent years.[4] However, it does not have a mechanism to control and regulate the content quality of uploaded videos. This is a cause for concern about the quality of online health information.[5] Although obtaining health information online is considered to be low risk, damaged cases have been reported.[6] For this reason, it has become popular to evaluate medical information contained in YouTube videos. Researchers have so far conducted studies evaluating YouTube videos for some disease and medical applications. [7,8] However, as far as we know, there is no study evaluating treatment and first aid videos in snake bites in the literature. Therefore, in this study, the authors aimed to evaluate the quality of existing YouTube videos on first aid interventions for snake bites and whether they are educational.

The authors wanted to determine the distribution of video sources and identify sources that provide high quality and accurate information. Finally, the authors aimed to compare the number of views, likes, dislikes and comments among video quality groups.

MATERIAL AND METHOD

Study design

This is a descriptive study. First, key terms for search were determined. On February 20, 2021, determined search terms such as; "Snake bite emergency aid, Snake bite treatment medicine, first aid in snake bite, Snake bite emergency medicine, what to do if a snake bites you, what to do if a rattle snake bite you? "were searched separately on YouTube (https: // youtube.com). Browser search history was deleted before research to minimize the impact of past internet usage on search results. The video lists were made according to the number of views, which made the most viewed videos listed on the first page. As previous research showed that the vast majority of users evaluated videos on the first three pages, videos on the first three pages (60 videos) were evaluated for each search term.[9,10] 360 videos were listed for a total of 6 search terms, and as YouTube data is constantly changing, the listed videos were saved for analysis. The sources used in the study are YouTube videos. These resources are open to everyone. In addition, no patient or experimental animals were used in the study. Therefore, ethics committee approval is not required for the study. Ethics committee approval was not obtained in similar studies.

Videos and advertisements that were uploaded in different languages other than English, had duplicate content, had problems with picture or sound quality, were not educational, and were for demonstration purposes were excluded. The videos taken into the evaluation were examined in terms of simplified intervention and first aid applications in accordance with the recommendations of WHO.[1] In the video content;

- Whether he took safety precautions against a new snake bite after exposure
- Whether rings and similar jewelry, if any, have been removed from the bite site.
- Whether wrong practices such as sucking with mouth, cutting, herbal products, mud, egg application have been made,
- Whether a turnstile is recommended or not,
- Whether the bitten limb was immobilized and bandaged applied;

Information was examined.

Measurements:

Global Quality Scale (GQS) is a scale developed to evaluate internet-based resources. GQS has been used in some recent studies to evaluate the quality of information on the Internet. [5,7] The educational features of the videos examined in the study were evaluated according to this scale. The GQS is a five-point Likert-type scale:

1=poor quality, poor flow, most information missing and not helpful to patients;
2=generally poor, some information provided but limited use to patients;
3=medium quality, some vital information sufficiently discussed;
4=good quality, good flow, most relevant information covered, useful for patients;
5=excellent quality and flow, beneficial for patients.

Of the videos, those rated as 1 or 2 were considered low-quality, rated 3 as medium-quality, and those rated 4 or 5 as high-quality.[5,7]

In addition, a modified version of the DISCERN scale was used to determine reliability.[11] The scale includes five closed-ended questions:

1. 'Is the video clear, concise and understandable?',
2. 'Are valid sources quoted?',
3. 'Is the information provided balanced and unbiased?'
4. 'Are sources of information listed for patient reference?',
5. "Does the video address discussion / uncertainty areas?"

Each parameter was scored with 1 point for a yes response and 0 points for a no response.

The duration in seconds of the videos and the number of days from the upload date to the evaluation date were recorded. In addition, the daily number of views, likes, dislikes and comments were calculated and recorded.

Videos were divided into eight groups in terms of resources: (1) Non-profit organization (2) Doctor (3) Health-related website, (4) University / academic institution, (5) Independent user, (6) Non-physician medical staff, (7)) Commercial health institutions and (8) Media-Documentary-News agency

All evaluations were done independently by two researchers, MS and HG, who had previous experience with snakebite. The videos that were found to be inconsistent between the evaluations of these two researchers were evaluated by a third researcher, MMO, and the final decision was made.

Statistical analysis

The compliance of the data to normal distribution was examined using the Shapiro Wilks test. Kruskal Wallis test and Dunn test as post hoc test were used for quality and loading source comparisons of non-normally distributed features. Qualitative variables were compared using Exact and Pearson Chi-square tests. Descriptive statistics of numerical variables are given as median (min-max) and number and% values for categorical variables. Relationships between numerical variables were tested with Spearman rank correlation coefficient. p <0.05 was considered statistically significant.

RESULTS

288 of the total 360 videos; because they were off-topic, had advertisement and entertainment content (n=137), repeated video (n=51), broadcast in a language other than English (n=86), poor image or sound (n=14) not included. After the inclusion and exclusion criteria were applied, a total of 72 videos were identified for evaluation in the study.

The median duration of the videos is 292 seconds (21 - 11235). The median number of views is 13.8, the number of comments is 0.01, likes is 0.11, and the number of dislikes is 0.01. General characteristics of the videos are shown in **Table 1**.

Table 1. General characteristics of the videos

Video features	Median	Minimum-Maximum
Number of days	1201.5	4-4582
Duration (seconds)	292	21-11235
Number of daily viewing	13.8	0.03-8381.98
Daily comments	0.01	0-1.4
Number of daily likes	0.11	0-24.27
Number of daily dislikes	0.01	0-5.37

Videos were produced by non-profit organizations 18.05% (n=13), universities and academic institutions 18.05% (n=13), doctors 13.88% (n=10). 40.23% (n=29) of these videos are high quality, 38.84% (n=28) medium quality 20.83% (n=15) low quality. While 6 (8.33%) of 10 (13.88%) videos produced by doctors were of high quality, no low-quality video was detected. 5 (6.94%) of 11 (15.27%) videos produced by health-related websites are high quality and 2 (2.77%) are low quality. While 6 (8.33%) of 13 (18.05%) videos produced by non-profit organizations are of low quality, 4 (5.55%) of them are of high quality. 3 (4.16%) out of 9 (12.5%) videos produced by independent users are of low quality. Quality distributions according to the sources are shown in **Table 2**.

Table 2. Categorization of the videos according to sources

Source	Total N (%)	GQS low quality N (%)	GQS medium quality N (%)	GQS high quality N (%)
Non-profit organization	13 (18.05)	6 (8.33)	3 (4.16)	4 (5.55)
Physician	10 (13.88)	0 (0)	4 (5.55)	6 (8.33)
Health-related web	11 (15.27)	2 (2.77)	4 (5.55)	5 (6.94)
Academic / University	13 (18.05)	2 (2.77)	8 (11.11)	3 (4.16)
Independent user	9 (12.5)	3 (4.16)	4 (5.55)	2 (2.77)
Non-physician medical staff	3 (4.16)	0 (0)	1 (1.38)	2 (2.77)
Commercial Health Organization	6 (8.33)	1 (1.38)	2 (2.77)	3 (4.16)
Media / documentary	7 (9.72)	1 (1.38)	2 (2.77)	4 (5.55)
Total	72 (100)	15 (20.83)	28 (38.84)	29 (40.23)

GQS: Global Quality Score

In our study, a statistically significant difference was found when the duration of the uploaded videos and their sources were compared (p=0.010). Accordingly, the sharing time of videos produced by academic institutions and doctors is significantly longer (p <0.05) (**Table 3**). When the Discern scores (DS) of the evaluated videos were compared with the uploaded sources, a statistically significant difference was found (p=0.031). Accordingly, the DS of the videos shared by academic institutions and doctors is significantly higher than the DS of the videos shared by independent users. In addition, the DS of the videos shared by doctors were found to be significantly higher than other sources (p <0.05) (**Table 3**).

A statistically significant difference was found between the high, medium and low-quality groups in terms of DS (p <0.001). The highest median DS is in the high-quality group. On the other hand, there is no statistically significant difference between the quality groups in terms of other video parameters (p> 0.05) (**Table 4**).

When the videos are evaluated in terms of content, providing environmental safety in case of snakebite is stated in the publication only 18% (n=13). Removing jewellery from the extremity has been shown or suggested in 33% of the videos. On the other hand, while 4.2% (n=3) were given incorrect information such as mouth sucking and cutting, 5.6% (n=4) were also suggested to apply a tourniquet incorrectly. On the other hand, 38.9% (n=28) emphasized the inaccuracy of applications such as suction cutting in the video, while 37.5% (n=27) emphasized the inaccuracy of tourniquet application in the video. Correct practices such as immobilization and bandaging of the injured extremity were suggested in 73.6% of all videos (n=53). The distribution of other applications is shown in **Table 5**. The kappa score of the study was calculated as 0.81.

Table 3. Comparison of the video Parameters between the source groups

Source	*Day	†Time (sec)	*Watch	*Comment	*Like	*Dislike	‡DS
Non-profit organization	1753	174	14.07	0.01	0.24	0.01	3
Physician	1669.5	517.5	8.14	0.01	0.11	0.01	4.5
Health-related web	1386	280	66.18	0.02	0.63	0.03	3
Academic / university	402.5	1343.5	8.15	0	0.15	0	4
Independent user	2434	249	5.89	0.01	0.03	0	3
Non-physician medical staff	506	197	3.78	0	0.01	0	4
Commercial Health Organization	1201.5	120.5	27.79	0	0.11	0	3
Media / documentary	1017	327	24.06	0.02	0.11	0.02	4
Total	0.170	0.010	0.159	0.412	0.519	0.335	0.031

*p> 0.05, †p< 0.05, ‡p < 0.001, Quantitative data re-expressed as median DS: Discern Score

Table 4. Comparison table of GQS category and video monitoring parameters

GQS	*DS	‡Number of Days	‡Viewing	‡Video duration	‡Comment	‡Like	‡Dislike
Low	2 (1-5)	1193	13.81	289	0.03	0.18	0.01
İntermediate	3 (2-4)	1339	12.8	336	0.01	0.07	0.01
High	p<0.001 4 (2-5)	1192	18.91	292	0.01	0.12	0.01

*p< 0.05, ‡p> 0.05, Quantitative data re-expressed as median, DS: DISCERN Score, GQS: Global Quality Score

Table 5. Distribution of video content

Attempt	Recommended n (%)	Not-recommended n (%)	Not-mentioned n (%)
Ensuring security	13 (18.1)	-	59 (81.9)
Removal of jewellery	24 (33.3)	-	48 (66.7)
Mouth sucking, cutting, misinformation	3 (4.2)	28 (38.9)	41 (56.9)
Recommending tourniquet	4 (5.6)	27 (37.5)	41 (56.9)
Limb immobilization and bandage-splint	53 (73.6)	-	19 (26.4)
Limb elevation	15 (20.8)	-	57 (79.2)

DISCUSSION

The widespread use of the internet today enables people to access information easily and quickly. The fact that YouTube is a free and easily accessible platform makes it widely preferred for both users and producers. Especially users who have difficulties in applying to a health institution often turn to online information in emergency situations. In this case, YouTube is preferred, where applications can be learned visually through videos. However, in addition to high quality videos containing useful information, there are also videos containing misleading and false information on YouTube.[5,7] So, to what extent should we trust YouTube videos for snake bites with fatal consequences?

Almost half (40%) of the videos produced with snake bites are of high quality. With similar evaluation criteria, Koçyiğit et al.[12], in the study on Covid-19 and rheumatological diseases, the rate of high-quality video was shown as 41.4%. Again, Koçyiğit et al.[5] in another study, 46% of the videos were of high quality, while in the study of Ahmad et al.[13] 41.4% of the videos were found to be high quality. In a study on YouTube where Retinopathy of Premature videos were examined, it was shown that two-thirds of the videos consisted of high quality or useful videos.[14] Our study is consistent with the results of these studies. However, there are also studies in the literature reporting low rates of high-quality video.[9,15] These different results in the evaluation of the videos may be related to the different study subjects or the different evaluation criteria.

In our study, high-quality videos were mostly produced by doctors and health-related websites (**Table 2**). Ahmad et al.[13] in his study, it was revealed that videos uploaded to YouTube by healthcare professionals or organizations contain quality and reliable information. Studies in the literature have reported that the main sources of high-quality videos are academicians / universities, followed by doctors and health professionals.[5,14,16] In our study, the videos produced by academicians and universities were mostly evaluated as medium quality. The reason for this is that most of these productions are conference or lecture presentations. These kinds of presentations appeal to people with academic formation rather than public users. Therefore, it seems unlikely that people other than healthcare professionals will benefit from these videos.

In our study, it has been shown that low quality videos are produced by non-profit organizations and our affiliated users. Similarly, other studies have shown that low-quality videos are produced by independent users.[5,14,16] On the other hand, there are studies in the literature reporting that they are not educative enough, even if uploaded by healthcare professionals.[17] However, in terms of resources, it is possible to say that the videos uploaded by doctors and health professionals are quality productions.

The number of views, likes, dislike and comments can also be preferred in YouTube video selections. High rates can affect the viewing preferences of the general public. However,

the most important problem in this regard is that videos that provide misleading information may also have a large number of views.[5] On the other hand, there are studies in the literature showing that "useful" videos have more views and likes.[14] In our study, no significant relationship was found between other parameters such as watching, commenting, and liking, and the video content and GQS level. However, it has been determined that there is a significant relationship between the GQS level of the videos and their DS. Accordingly, the DS of the videos with a high GQS level is significantly higher than the videos at the other level ($p < 0.001$) (**Table 4**). When our study is evaluated in terms of information content, it can be said that the videos mostly contain correct information. Limb immobilization and bandage application, which is strongly emphasized by WHO, has been shown in two-thirds of all videos (**Table 5**). On the other hand, in a study conducted in Myanmar, where the risk of snakebite is high, it was shown that 72% of the participants had no idea about this practice.[18] In the literature, there are studies reporting high rate of wrong practices such as casting spells after a snake bite, putting a snake stone, tying a tourniquet, sucking the wound, and cutting.[19,20] There are a small number of productions that give such false information in the YouTube videos we have reviewed. In the light of these data, it can be said that the information content of the videos uploaded to YouTube on snake bites is mostly in accordance with the WHO recommendations. However, it is an important deficiency that 18% (n=13) of an important application such as ensuring environmental security against a new snake attack was stated in the publication.

The low number of videos uploaded to YouTube on snake bite is the most important factor limiting our study universe. On the other hand, the fact that videos produced outside of English could not be examined, has also restricted our study. Since the evaluation of the content is observational, the perspective of the researchers may have affected the evaluation results.

Limitation

The limitations of the study are the examination of videos in a certain time period due to being a constantly updated channel, the exclusion of languages other than English, limited research on keyword, and also the intervention information on snake bites in the content of the videos containing general first aid information.

CONCLUSION

It is possible to say that YouTube videos on snake bites contain useful first aid information. However, information on ensuring crime scene security against a new snake attack has been highlighted in a small number of videos. People who encounter snakebites and rescuers from public can benefit from videos produced by doctors, health-related websites, and healthcare professionals, in particular. The number of views, like, dislike and comment counts that determine user preferences on YouTube cannot be used as an indicator of correct practices.

ETHICAL DECLARATIONS

Ethics Committee Approval: The sources used in the study are YouTube videos. These resources are open to everyone. Therefore, ethics committee approval is not required for the study. Ethics committee approval was not obtained in similar studies.

Referee Evaluation Process: Externally peer-reviewed.

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

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REFERENCES

1. David Warrell. Snakebites. World Health Organization, Guidelines for the management of snakebites. 2nd Edition. WHO/Regional Office for South-East Asia. 2016.[Cited 20 March 2021] Available from https://www.who.int/publications/i/item/9789290225300
2. Bhargava S, Kumari K, Sarin RK, Singh R. First-hand knowledge about snakes and snake-bite management:an urgent need. Nagoya J Med Sci 2020;82(4):763-74.
3. Amante DJ, Hogan TP, Pagoto SL, English TM, Lapane KL. Access to care and use of the Internet to search for health information:results from the US National Health Interview Survey. J Med Internet Res 2015;17(4):e106.
4. Madathil KC, Rivera-Rodriguez AJ, Greenstein JS, Gramopadhye AK. Healthcare information on YouTube:A systematic review. Health Informatics J 2015;21:173- 94.
5. Koçyiğit FB, Akaltun MS, Şahin AR. YouTube as a source of information on COVID-19 and rheumatic disease link. ClinRheumatol 2020;39(7):2049-54.
6. Crocco AG, Villasis-Keever M, Jadad AR. Analysis of cases of harm associated with use of health information on the internet. JAMA 2002;287:2869-71.
7. Akyol A. Karahan İ. Is YouTube a quality source of information on sarcopenia? Eur Eur Geriatr Med 2020;11:693-697.
8. Yaylaci S, Serinken M, Eken C, et al. Are YouTube videos accurate and reliable on basic life support and cardiopulmonary resuscitation? Emerg Med Australas 2014;26:474-7.
9. Rittberg R, Dissanayake T, Katz SJ. A qualitative analysis of methotrexate self-injection education videos on YouTube. Clin Rheumatol 2016;35:1329-33.
10. Kocyigit BF, Nacitarhan V, Koca TT, Berk E. YouTube as a source of patient information for ankylosing spondylitis exercises. Clin Rheumatol 2019;38(6):1747-51.
11. Charnock D, Shepperd S, Needham G, Gann R. DISCERN:an instrument for judging the quality of written consumer health information on treatment choices. J Epidemiol Community Health 1999;53(2).
12. Kocyigit FB, Tuba Tulay Kocal, Mazlum Serdar Akaltun. Quality and readability of online information on ankylosing spondylitis. Clin Rheumatol 2019;38:3269-74.
13. Ahmad T, Sattar K, Akram A. Medical professionalism videos on YouTube:Content exploration and appraisal of user engagement. Saudi J. Biol. Sci. 2020;27:2287-92.

14. Şahin A, Şahin M, Türkcü FM. YouTube as a source of information in retinopathy of prematurity. Ir J Med Sci. 2019;188(2):613-7.
15. Villafañe JH, Cantero-Tellez R, Valdes K, Usuelli FG, Berjano P. Educational Quality of YouTube Videos in Thumb Exercises for Carpometacarpal Osteoarthritis:A Search on Current Practice. HAND 2018;13(6):715-9.
16. Bora K, Das D, Barman B, Borah P. Are internet videos useful sources of information during global public health emergencies? A case study of YouTube videos during the 2015-16 Zika virus pandemic. Pathog Glob Health 2018;112(6):320-8.
17. Bae SS, Baxter S. YouTube videos in the English language as a patient education resource for cataract surgery. Int Ophthalmol 2018, 38:1941-5.
18. Mahmood MA, Halliday D, Cumming R, et al. Inadequate knowledge about snakebite envenoming symptoms and application of harmful first aid methods in the community in high snakebite incidence areas of Myanmar. PLoS Negl Trop Dis. 2019;13(2):e0007171.
19. Michael GC, Aliyu I, Grema BA, Paul De-Kaa NL. Prehospital care practices for venomous snakebites in resource-limited settings:A narrative review. Arch Med Health Sci 2017;5:237-41.
20. Kularatne AM, Silva A, Maduwage K, et al. Victims' response to snakebite and socio-epidemiological factors of 1018 snakebites in a tertiary care hospital in Sri Lanka. Wilderness Environ Med. 2014;25(1):35-40.

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Original Article / Orijinal Araştırma

Evaluation of the Short-Term Effects on Bone Mineral Metabolism and the Adrenal Pathway of Adrenocorticotropic Hormone Therapy Used in Epileptic Encephalopathy

Epileptik Ensefalopatide Kullanılan Adrenokortikotropik Hormonun Kemik Mineral Metabolizması ve Adrenal Yolak Üzerine Kısa Dönem Etkilerinin Değerlendirilmesi

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Abstract

Aim: We aimed to investigate the short-term effects of adrenocorticotropic hormone (ACTH) treatment on the adrenal pathway and bone metabolism in patients with epileptic encephalopathy.

Material and Method: Two groups with 16 patients and 16 controls were formed. Before the treatment, all patients and controls were tested for bone and adrenal metabolism. Twenty doses of ACTH therapy were given to the patient group over 3 months. The tests on the patient group were repeated 1 month after the end of the treatment.

Results: In the patient group, serum calcium, phosphorus and parathyroid hormone levels increased significantly after treatment compared with before treatment. Comparing the bone metabolism of the patient and control groups, urinary calcium/creatinine ratio was higher before treatment; serum phosphorus level, bone-specific alkaline phosphatase level and the urinary calcium/creatinine ratio were higher after treatment in the patient group. In the evaluation of the adrenal pathway, no significant differences were found between fasting serum glucose, sodium, potassium, cortisol and ACTH levels before and after treatment and in the comparison of the patient and control groups.

Conclusion: Our study investigated the short-term effect of ACTH on the adrenal pathway and bone metabolism. The results show that ACTH treatment did not have a negative effect on the adrenal pathway in the early period but, its effects on bone metabolism have not been adequately clarified.

Keywords: Epileptic encephalopathy, West syndrome, adrenocorticotropic hormone

Mesut Güngör and bengü Altınordu contributed equally to the study.

Öz

Amaç: Epileptik ensefalopatili hastalarda adrenokortikotropik hormon (ACTH) tedavisinin adrenal yolak ve kemik metabolizması üzerine kısa dönemli etkilerini araştırmayı amaçladık.

Gereç ve Yöntem: 16 hasta ve 16 kontrolden oluşan iki grup oluşturuldu. Tedavi öncesi tüm hasta ve kontrollere kemik ve adrenal metabolizma testleri yapıldı. Hasta grubuna 3 ay boyunca 20 doz ACTH tedavisi verildi. Hasta grubundaki testler tedavi bitiminden 1 ay sonra tekrarlandı.

Bulgular: Hasta grubunda tedavi öncesine göre tedavi sonrası serum kalsiyum, fosfor ve paratiroid hormon düzeyleri anlamlı olarak yükseldi. Hasta ve kontrol gruplarının kemik metabolizması karşılaştırıldığında, tedavi öncesi idrar kalsiyum/kreatinin oranı daha yüksekti; hasta grubunda tedavi sonrası serum fosfor düzeyi, kemiğe özgü alkalin fosfataz düzeyi ve idrar kalsiyum/kreatinin oranı daha yüksekti. Adrenal yolun değerlendirilmesinde, tedavi öncesi ve sonrası açlık serum glukozu, sodyum, potasyum, kortizol ve ACTH düzeyleri arasında ve hasta ve kontrol grupları karşılaştırıldığında anlamlı fark bulunmadı.

Sonuç: Çalışmamız ACTH'nin adrenal yol ve kemik metabolizması üzerindeki kısa vadeli etkisini araştırdı. Sonuçlar, ACTH tedavisinin erken dönemde adrenal yolak üzerinde olumsuz bir etkisinin olmadığını ancak kemik metabolizması üzerindeki etkilerinin yeterince aydınlatılmadığını göstermektedir.

Anahtar Kelimeler: Epileptik ensefalopati, West sendromu, adrenokortikotropik hormon

Mesut Güngör ve Bengü Altınordu çalışmaya eşit oranda katkıda bulunmuştur

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INTRODUCTION

Epileptic encephalopathy is a group of diseases and epileptic syndromes, that epileptic activity itself cause severe cognitive and behavioral disorders, beyond what is expected from the underlying pathology (such as cortical malformation) accompanied by epileptiform electroencephalography (EEG) changes.[1] Conventional antiepileptic drugs, immunomodulatory treatments (steroids, intravenous immunoglobulin, plasmapheresis, etc.), ketogenic diet or surgical treatments have been tried in the treatment of these patients.[1,2]

Adrenocorticotropic hormone (ACTH) is a treatment option shown to have short-term efficacy in epileptic encephalopathy.[3] Although its exact mechanism of action is not known, it is suggested that it reduces neuronal hyper-excitability by suppressing corticotropin-releasing hormone (CRH) metabolism and secretion and suppresses seizures with this mechanism. Side effects of ACTH treatment such as weight gain, hypertension, restlessness, and infection have been reported.[4,5] There are limited data in the literature regarding the effects of ACTH on the steroid-dependent adrenal pathway and bone metabolism.

In our study, we aimed to investigate the short-term effects of ACTH treatment on the adrenal pathway and bone metabolism in patients with epileptic encephalopathy.

MATERIAL AND METHOD

The study was carried out with the permission of Kocaeli University Clinical Research Ethics Committee (Date: 09.04.2013, Decision No: 8/16). Every patient who was diagnosed with epileptic encephalopathy in our clinic and who was scheduled for ACTH treatment due to insufficient response to antiepileptic medication was included in the study. Exclusion criteria included previous ACTH treatment, systemic disease-causing adrenal pathway involvement other than epileptic encephalopathy and bone metabolism disorders.

We aimed to investigate the effect of ACTH treatment on the adrenal pathway and bone metabolism in the short term by performing tests on the patients in the study group before and after treatment. A control group consisted 16 children with a diagnosis of idiopathic or familial epilepsy, no mental or motor development retardation, no other systemic disease and receiving conventional antiepileptic treatment for at least 3 months. After obtaining family consent for these children, tests on the adrenal pathway and bone metabolism were performed on the children in the patient group according to the same protocol and in the same laboratory.

To evaluate the bone metabolism of the children in the patient group, determinants such as whether they received vitamin D supplements, level of sun exposure, and the degree of mobility were recorded by asking their families. Before treatment, serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathyroid hormone (PTH), 25-OH vitamin D level, serum C-terminal collagen (CTx), osteocalcin, bone-specific alkaline phosphatase, urinary calcium and creatinine (in 3 different spot urine samples), renal ultrasonography examinations were performed. For evaluation of the adrenal pathway, the patients and children in the control group were invited to the hospital and serum fasting glucose, sodium, potassium, cortisol and ACTH values were measured at 08:00 hours. If the serum cortisol level was below 10 µg/dl, the basal cortisol test was repeated at the same time on another day. A low-dose ACTH stimulation test was performed to exclude adrenal insufficiency in children with control serum cortisol levels below 10 µg/dl. In the patient group, synthetic ACTH was administered intramuscularly at a dose of 0.035 mg/kg, giving a total of 20 doses over a 3-month treatment period. One month after the ACTH treatment was finished, the tests were repeated, except for 25-OH-D vitamin. Only baseline evaluations were done in children in the control group, and unlike children in the patient group, renal ultrasonography was not performed in children in this group.

The Statistical Package for Social Sciences (SPSS) program was used for the statistical evaluation of the data. Continuous variables are expressed as the mean±standard deviation and frequency data are expressed as number (%). A P value <0.05 was regarded as statistically significant.

RESULTS

Among 19 patients who were followed up in our clinic with a diagnosis of epileptic encephalopathy and were indicated for ACTH treatment, 16 children who met the inclusion criteria were included in the study. Seven (43.75%) were girls and 9 (56.25%) were boys. One of the patients died of unknown cause during the study.

The mean age of the patients was 2.86±1.86 (range 0.7–7 years) years. Twelve children (75%) were being followed up due to West syndrome. Two thirds of the patients diagnosed with West syndrome were in the symptomatic group (8 cases), and one third (4 cases) were in the cryptogenic group. Distribution by age, evaluation of the cause, degree of sun exposure and mobilization status in the sick children in the study group are summarized in **Table 1**.

Fourteen of the patients (87.5%) received vitamin D supplements in their infancy; none received calcium or phosphorus supplements. Eight (50%) of the patients were exposed to enough sun every day. It was observed that 13 (81.25%) patients preferred the closed clothing style of their mothers and 3 (18.75%) preferred the open clothing style of their mothers. Eight (50%) of the patients were bedridden; 5 (31.25%) could walk without assistance.

In the examinations performed to evaluate bone metabolism before ACTH treatment in the patient group, the Ca, P, ALP, PTH levels of all patients were within normal limits. Serum CTx, osteocalcin and bone-specific ALP could be measured in

only 3 patients before ACTH treatment. Serum CTx in one of these patients, bone-specific ALP in 2, and osteocalcin in one patient were above normal limits for age. The relationship between serum CTx, bone-specific ALP or osteocalcin levels of the patients with a history of vitamin D supplementation during pregnancy, a history of vitamin D supplementation, the mother's dressing style, degree of mobility or sun exposure were not found to be statistically significant. The tests performed to evaluate the bone metabolism and adrenal pathway before and after ACTH treatment are shown in **Table 2**.

Table 1. Classification of the patient group in terms of distribution by age, cause, duration of sun exposure and mobility

Diagnosis	Number of patients	Percentage
Distribution by age		
Age range of the patients		
0–1 years	6	37.50
1–2 years	3	18.75
2–3 years	2	12.50
3–4 years	2	12.50
4–5 years	2	12.50
6–7 years	1	6.25
Total	16	100.00
Distribution by cause		
Preparatory cause		
West syndrome	12	75.00
Cryptogenic	4	25.00
Symptomatic	8	50.00
Periventricular leukomalacia	2	
Genetic	1	
Hypoglycemic sequela	1	
Pseudo-TORCH syndrome/hydrocephalus	1	
Traumatic brain injury	1	
Structural brain anomaly	1	
Sturge-Weber syndrome	1	
Congenital metabolic disease: mitochondrial disease	1	6.25
ESES: Rolandic epilepsy	1	6.25
Focal ESES: Herpes simplex encephalitis sequela	1	6.25
Myoclonic astatic epilepsy	1	6.25
Total	16	100.00
Patients' exposure to the sun		
Every day	8	50.00
>3 days a week	3	18.75
<3 days a week	2	12.50
Rarely	3	18.75
Total	16	100.00
Degree of mobility		
Bedridden	8	50.00
Unable to walk without help, but not confined to bed	3	18.75
Able to walk without help	5	31.25
Total	16	100.00

Abbreviation: ESES, electrical status epilepticus in sleep.

Table 2. Comparison of biochemical markers related to bone metabolism and the adrenal pathway in patients with epileptic encephalopathy before and after ACTH treatment

	Before ACTH treatment	After ACTH treatment	P value
Markers of bone metabolism			
Serum Ca (mg/dl)	9.52±0.29	9.85±0.46	0.03
Serum P (mg/dl)	5.10±0.78	5.90±0.73	0.004
Serum ALP (u/L)	197±104	217±60	0.20
Serum PTH (pm/L)	22.80±2.58	29.88±2.82	0.003
Serum CTx (ng/ml)	1.65±0.43	2.47±0.74	0.16*
Serum osteocalcin (ng/ml)	91.16±13.09	93.80±8.70	0.60*
Urinary Ca/creatinine	0.24±0.17	0.17±0.13	0.12
Biochemical markers related to the adrenal pathway			
Serum glucose (mg/dl)	82.6±9.7	88.8±27.3	0.43
Serum Na (mEq/L)	138.5±2.6	138.6±1.9	0.92
Serum K (mEq/L)	4.57±0.56	4.67±0.42	0.59
Serum cortisol (µg/dl)	12.9±5	11.0±4.0	0.12
Serum ACTH (pg/ml)	24.2±11.2	24.4±8.5	0.99

P values <0.05 are statistically significant. Abbreviations: ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; PTH, parathyroid hormone; CTx, C-terminal collagen. *Evaluation was possible in 3 patients before treatment.

In the pre-treatment renal ultrasonography, 11 (78.6%) patients were found to be normal, 2 had (14.3%) nephrolithiasis and 1 (7.1%) was suspicious for nephrolithiasis. No statistically significant correlation was found between ultrasonographic findings and serum Ca, P, ALP, PTH levels or urinary Ca/creatinine ratio. There was no significant difference between the evaluations made by renal ultrasonography in terms of nephrolithiasis before and after treatment (P> 0.05).

The serum 25-OH vitamin D level was below 20 ng/ml in 4 patients in the pre-treatment patient group. No statistically significant correlation was found between the 25-OH vitamin D level of the patients and variables such as whether they received vitamin D supplementation, the degree of mobility, whether the mother took vitamin D during pregnancy, the mother's dressing style or sun exposure (P> 0.05).

When the characteristics of bone metabolism of the patients who received ACTH treatment were compared before and after the treatment, a significant increase was observed in serum Ca, P and PTH levels (P< 0.05), but no significant difference was found in the serum ALP level and urinary Ca/creatinine ratio (**Table 2**). The values for serum CTx, bone-specific ALP and osteocalcin levels were measured in only 3 patients in the pre-treatment period, therefore statistical evaluation could not be done. After ACTH treatment, CTx, bone-specific ALP and osteocalcin levels were observed to be above normal limits in 6 patients.

When the characteristics of the adrenal pathway of the patients who received ACTH treatment were compared before and after the treatment, no significant difference was found in the fasting glucose, Na, K, cortisol, ACTH tests (P> 0.05). A low-dose ACTH stimulation test was performed because basal cortisol values in 2 patients before treatment and 3 patients after treatment were below 10 µg/dl. In these cases, adrenal insufficiency was excluded by finding adequate cortisol responses after the ACTH stimulation test.

The biochemical markers related to bone metabolism and the adrenal pathway of the patient group with epileptic encephalopathy before and after ACTH treatment are compared with the control group in **Table 3**.

Tablo 3. Biochemical markers related to bone metabolism and the adrenal pathway in patients with epileptic encephalopathy before and after ACTH treatment compared with the control group

Biochemical marker	Patient group	Control group	P value
Before treatment			
Bone metabolism			
Serum P (mg/dl)	5.03±0.75	5.2±0.51	0.09
Serum ALP (u/L)	190.4±98.0	227±72	0.25
Serum PTH (pm/L)	25.0±11.9	29±11	0.73
Serum 25-OH-Vit D	29.8±15.6	26.7±9.9	0.26
Urinary Ca/creatinine	0.23±0.16	0.06±0.70	0.02
Serum CTx (ng/ml)	1.65±0.43	2.17±0.54	0.59
Serum bone-specific ALP (µg/dl)	87.20±4.77	70.4±12.7	0.16
Serum osteocalcin (ng/ml)	91.1±13.9	72.2±20.8	0.32
Adrenal pathway			
Serum glucose (mg/dl)	82.0±9.5	78.8±12.3	0.98
Serum Na (mEq/L)	138.4±2.6	137.0±2.3	0.84
Serum K (mEq/L)	4.5±0.5	4.7±0.52	0.15
Serum cortisol (µg/dl)	13.0±4.8	12.0±2.7	0.08
Serum ACTH (pg/ml)	23.0±10.9	28.6±12.7	0.79
After treatment			
Bone metabolism			
Serum Ca (mg/dl)	9.85±0.46	9.85±0.49	1.00
Serum P (mg/dl)	5.90±0.73	5.24±0.51	0.01
Serum ALP (u/L)	217.0±60.4	227.0±72.3	0.68
Serum PTH (pm/L)	29.8±10.5	29.3±11.2	0.90
Urinary Ca/creatinine	0.15±0.12	0.06±0.07	0.04
Serum CTx (ng/ml)	2.09±0.59	2.17±0.54	0.69
Serum bone-specific ALP (µg/dl)	82.7±11.8	70.4±12.7	0.03
Serum osteocalcin (ng/ml)	62.2±24.1	72.2±20.8	0.24
Adrenal pathway			
Serum glucose (mg/dl)	88.8±28.3	78.8±12.3	0.21
Serum Na (mEq/L)	138.60±1.99	137.25±2.35	0.10
Serum K (mEq/L)	4.67±0.42	4.70±0.52	0.90
Serum cortisol (µg/dl)	11.04±4.87	12.33±2.56	0.36
Serum ACTH (pg/ml)	24.26±8.55	28.6±12.7	0.28

P values <0.05 are statistically significant. Abbreviations: ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; PTH, parathyroid hormone; CTx, C-terminal collagen.

When the bone metabolism tests of the children in the patient group before ACTH treatment were compared with the basal tests of the children in the control group, no significant differences were found between the 2 groups except for the urinary Ca/creatinine ratio. The urinary Ca/creatinine ratio was found to be significantly higher in patients with epileptic encephalopathy compared with the control group. When the results of bone metabolism tests for the patients after ACTH treatment were compared with the results for the control group, serum P and bone-specific ALP values and the urinary Ca/creatinine ratio were found to be significantly higher in the patients who received ACTH treatment (P< 0.05).

In the comparison of the basal test results performed for the adrenal pathway in the control group and the results related to the adrenal pathway both before and after treatment in the patient group (**Table 3**), no significant differences were found between the 2 groups (P> 0.05).

DISCUSSION

ACTH is generally the first treatment option for epileptic encephalopathy. Although some studies have reported that ACTH treatment can be applied safely, there is not enough information in the literature about the effect of ACTH on the short-term adrenal pathway and bone metabolism. In our study, 16 patients with a diagnosis of epileptic encephalopathy who received an indication for ACTH treatment were followed prospectively. The aim was to investigate the short-term effect of ACTH treatment by comparing bone metabolism and adrenal pathway functions in the patient group before and early after treatment.

Considering the age characteristics of the patient group, most of the children were between 0 and 3 years of age (11; 68.75%). More than half of these patients (6; 37.5%) were in infancy. The concentration of patients in the first 3 years was associated with the fact that most cases (12; 75%) were diagnosed with West syndrome and this syndrome is observed more frequently in the first 2 years of life. Two thirds of the patients diagnosed with West syndrome were in the symptomatic group,[8] and one third[4] were in the cryptogenic group. The higher number of patients in the symptomatic group was attributed to the advances in diagnostic laboratory examinations in recent years and was consistent with the literature.[6]

The source of vitamin D in infancy is transplacental transmission from the mother, breast milk and sunlight. The serum 25-OH vitamin D level of the patients in the study group was below 20 ng/ml in 4 patients participating in the study. Contrary to what was expected, no statistically significant relationship was found between the 25-OH vitamin D level of these patients and patient-dependent factors such as whether they received vitamin D prophylaxis, degree of mobility or sun exposure, as well as maternal variables such as whether the mother took vitamin D during pregnancy or the mother's dressing style. In a study investigating the vitamin D level in infants and the factors affecting this level, Özdemir et al.[7] found that the vitamin D level was associated with the mother's dressing style, the baby given vitamin D prophylaxis at the recommended dose and duration, and adequate exposure to sunlight. In our study, no statistically significant relationship was found between vitamin D and these variables. The reason why this relationship could not be determined may be related to the small number of cases and the small number of mothers [3] who prefer an open dressing style.

The importance of physical activity and immobilization in bone metabolism and its relationship with secondary osteopenia is known.[8] Eight (50%) of the patients in the study group were bedridden, 5 (31.25%) could walk unaided and 3 (18.75%) could walk with assistance. There was no difference between the 3 groups in terms of the degree of immobility and serum Ca, P, ALP, PTH or serum vitamin D levels. Taşdemir et al.[9] reported immobilization as an important variable on bone mineral density and bone metabolism markers in their study on 24 patients with mobile and immobile cerebral palsy and a control group. In our study, no significant relationship was found between immobilization and bone metabolism markers. This may be due to the shorter immobilization times than the studies in the literature and the small number of patients and their young age.

Epidemiological studies show that the risk of osteoporotic fractures increases depending on the glucocorticoid dose.[10] It has been shown that glucocorticoids used in congenital adrenal hyperplasia and primary adrenal insufficiency at physiological doses have no effect on bone mineral density.[11] However, the effect of standard ACTH treatment on glucocorticoids and bone metabolism is controversial. In our study group, the serum Ca, P and PTH values, which were measured to evaluate bone metabolism, increased statistically significantly after treatment compared with before treatment. Although the P and PTH values remained within normal limits, the Ca value was found to be above the normal limit in 4 patients. In addition to the increase in mean serum Ca levels after treatment, hypercalcemia was observed in 1 of every 4 patients, suggesting that ACTH treatment has an effect on Ca metabolism in the short term. Although ACTH treatment causes an increase in cortisol, there may be adrenal suppression and temporary cortisol insufficiency as a result of prolonged negative feedback during the treatment process. In the case of cortisol insufficiency, Ca absorption from the intestines increases and hypercalcemia may develop. As observed in our patients, the short-term effects of ACTH treatment on Ca and P mineral metabolism and on bone health in the long term should be evaluated clinically. Consistent with our results, Riikonen et al.[12] showed a statistically significant increase in mean serum Ca and P levels after ACTH treatment. However, they showed that these biochemical changes are reversible and therefore reported that short-term ACTH treatment may not lead to permanent changes in bone metabolism.

It is known that glucocorticoids cause hypercalciuria and urinary Ca excretion returns to normal after treatment. Düzen et al.[13] showed that there was no significant change in serum Ca, P, ALP, PTH levels in 42 patients who received low-dose glucocorticoids before and after treatment; urinary Ca excretion increased during treatment, but returned to normal after treatment cessation. In a study evaluating the development of hypercalciuria with ACTH treatment, it was shown that urinary calcium excretion increased statistically significantly after ACTH treatment and this returned to normal at the end of the first month. In their studies evaluating bone metabolism in children with nephrotic syndrome who received glucocorticoid treatment, Koşan et al.[14] showed that the urinary Ca/creatinine ratio measured before treatment was increased significantly at the 4th and 12th weeks of the treatment. Our results do not support this finding and the decrease in urinary Ca excretion after ACTH treatment, although noteworthy, was not statistically significant in our cases. Our findings suggest that hypercalciuria is not an important complication of ACTH treatment.

There are results showing that hypercalciuria due to increased cortisol caused by ACTH may result in renal calcification. Secondary hyperparathyroidism, hypercalcemia, hyperphosphatemia and metabolic alkalosis are thought to predispose to this situation. ACTH or glucocorticoids are known to increase glomerular filtration, disrupt tubular function, and cause hypercalciuria and nephrolithiasis.[15] In our study, nephrolithiasis was detected in 2 of the patients in the period before treatment with ACTH was initiated, and both patients had significant hypercalciuria. It was thought that calcium imbalance disorder in the baseline evaluation of these patients might be due to metabolic processes related to the underlying primary diseases. When all cases were evaluated, no significant difference was found in terms of hypercalciuria and nephrolithiasis in the period after ACTH treatment. Although Riikonnen et al.[12] reported an increase in the rate of nephrolithiasis in a postmortem study of children who received ACTH treatment, it is not possible to establish a direct relationship between ACTH treatment and nephrolithiasis, because various risk factors such as immobilization and malnutrition may accompany the risk of stone formation in children receiving ACTH treatment. In our study, a statistically significant increase in nephrolithiasis before and after treatment in patients who received ACTH and in hypercalciuria could not be demonstrated in the patients who developed suspicious nephrolithiasis after treatment. Nevertheless, due to the small size of our patient group, it would be appropriate to follow up patients who received ACTH therapy in terms of nephrolithiasis until more comprehensive study results are available.

There is no study in the literature investigating the effect of ACTH treatment on bone mineral metabolism with bone turnover markers. It is thought that the effects of ACTH on bone are due to the increase in glucocorticoid. Glucocorticoids suppress osteoblastic activity in bone and increase bone resorption. Kruse et al.[16] evaluated bone metabolism in 11 patients who previously received dexamethasone, prednisolone or ACTH, and showed that serum ALP, osteocalcin and urine hydroxyproline levels decreased, and glucocorticoids decreased osteoblastic

activity and increased osteoclastic activity. We planned to evaluate serum CTx, bone-specific alkaline phosphatase and osteocalcin levels, parameters of bone turnover before the treatment, but these markers could be measured in only 3 patients for technical reasons at the time of the study. Although the CTx level was normal before treatment in 1 of the patients, it was above the normal limit after treatment. After the treatment, the osteocalcin level was normal. In our study group, in contrast to Kruse et al.[16] ACTH treatment significantly increased the level of bone-specific alkaline phosphatase in children whose bone turnover parameters were measured in the post-treatment period compared with children in the control group. It is known that the effects of glucocorticoids on ALP may be different in vivo and in vitro, decreasing ALP in in vivo conditions and increasing the production of ALP in in vitro conditions.[17] Although an increase in bone-specific ALP, increase in CTx and decrease in osteocalcin could not be shown in our study group, it suggests that bone formation was stimulated. Whether this increase in bone formation is temporary or permanent would require further follow-up of the patients.

ACTH treatment may cause adrenal insufficiency by suppressing CRH and ACTH production in children. The risk of adrenal insufficiency may vary according to the daily dose and duration of plasma ACTH suppression.[18] In our study, we aimed to investigate whether standard ACTH therapy exerts pressure on the adrenal gland in the short term. In our patient group, there were no significant differences between the adrenal pathway evaluations before and after ACTH treatment. Similarly, the adrenal pathway evaluations in our control group did not differ significantly with both the pre-treatment and post-treatment evaluations in our patient group. These findings show that standard ACTH therapy does not cause adrenal suppression in the early period. It is known that suppression of the adrenal pathway caused by glucocorticoid therapy may vary from person to person, and the pathway can spontaneously return to normal between 3 weeks and 6 months after cessation of treatment. Perheentupa et al.[19] evaluated the adrenal pathway in the first days after the treatment, and we deemed it appropriate to perform the adrenal pathway evaluation 1 month after the treatment. The results of the 2 evaluations were different in terms of adrenal pathway suppression, which may be related to the time after treatment. Assessment of the adrenal pathway is difficult due to the diurnal release of cortisol and the possibility of changes in this release due to ACTH treatment. In our study, obtaining a sufficient adrenal response to the low-dose ACTH stimulation test in patients with low cortisol 1 month after the ACTH treatment suggested that possible short-term adrenal suppression disappeared at the end of 1 month at the latest, even during the treatment process. In conclusion, we believe that there is no need for routine adrenal pathway evaluation in children receiving standard ACTH therapy.

CONCLUSION

Although ACTH treatment is often used as the first option in the treatment of epileptic encephalopathy, there is not enough information about its short-term effects on the adrenal pathway and bone metabolism. Our study was planned to investigate the short-term effects of ACTH on the adrenal pathway and bone metabolism, and according to our results, ACTH treatment does not have an early negative effect on the adrenal pathway. The effects of ACTH treatment on bone metabolism are controversial. According to the results of our study, ACTH treatment might have an effect on Ca, P mineral metabolism in the short term. Although our results suggest that bone metabolism markers may be useful in showing possible instantaneous changes in the bone formation resorption cycle during ACTH treatment, their net effects on bone health in the long term should be monitored.

In conclusion, although ACTH therapy is a reliable treatment method in terms of suppression of the adrenal pathway, its effects on bone metabolism have not been adequately clarified. New comparative studies in which patients are followed up for a long time are needed to better evaluate bone metabolism.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kocaeli University Clinical Research Ethics Committee (Date: 09.04.2013, Decision No: 8/16).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Scheffer IE, Liao J. Deciphering the concepts behind "Epileptic encephalopathy" and "Developmental and epileptic encephalopathy". Eur J Paediatr Neurol 2020; 24:11–14.
2. Wright SK, Wood AG. Neurodevelopmental outcomes in paediatric immune-mediated and autoimmune epileptic encephalopathy. Eur J Paediatr Neurol 2020; 24:53–57.
3. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. Cochrane Database Syst Rev 2013;(6):CD001770.
4. Shumiloff NA, Lam WM, Manasco KB. Adrenocorticotropic hormone for the treatment of West Syndrome in children. Ann Pharmacother 2013; 47:744–754.
5. Riikonen R, Donner M. ACTH therapy in infantile spasms: side effects. Arch Dis Child1980; 55:664–672.
6. Pavone P, Polizzi A, Marino SD, et al. West syndrome: a comprehensive review. Neurol Sci 2020; 41:3547-3562.

7. Özdemir AA, Ercan Gündemir Y, Küçük M, et al. Vitamin D deficiency in pregnant women and their infants. J Clin Res Pediatr Endocrinol 2018; 10:44–50.
8. Landry BW, Driscoll SW. Physical activity in children and adolescents. PM&R 2012; 4:826–832.
9. Tasdemir HA, Buyukavci M, Akcay F, Polat P, Yildiran A, Karakelleoglu C. Bone mineral density in children with cerebral palsy. Pediatr Int 2001; 43:157–160.
10. Cooper MS. Glucocorticoids in bone and joint disease: the good, the bad and the uncertain. Clin Med 2012; 12:261–265.
11. Falhammar H, Nyström HF, Wedell A, Brismar K, Thorén M. Bone mineral density, bone markers, and fractures in adult males with congenital adrenal hyperplasia. Eur J Endocrinol 2013; 168:331–341.
12. Riikonen R, Simell O, Jääskeläinen J, Rapola J, Perheentupa J. Disturbed calcium and phosphate homeostasis during treatment with ACTH of infantile spasms. Arch Dis Child1986; 61:671–676.
13. Duzen O, Erkoc R, Begenik H, Soyoral YU, Aldemir MN. The course of hypercalciuria and related markers of bone metabolism parameters associated with corticosteroid treatment. Ren Fail 2012; 34:338–342.
14. Koşan C, Ayar G, Orbak Z. Effects of steroid treatment on bone mineral metabolism in children with glucocorticoid-sensitive nephrotic syndrome. West Indian Med J 2012; 61:627–630.
15. Miyahara H, Akiyama T, Hasegawa K, et al. Laboratory changes during adrenocorticotropic hormone therapy associated with renal calcified lesions. Pediatr Int 2020; 62:587–592.
16. Kruse K, Büsse M, Kracht U, Kruse U, Wohlfart K. Disorders of calcium and bone metabolism in glucocorticoid treatment. Monatsschrift Kinderheilkd Organ Dtsch Ges Kinderheilkd1988; 136:237-242.
17. Cooper MS, Hewison M, Stewart PM. Glucocorticoid activity, inactivity and the osteoblast. J Endocrinol1999; 163:159–164.
18. Yamamoto T. Latent adrenal insufficiency: concept, clues to detection, and diagnosis. Endocr Pract 2018; 24:746–755.
19. Perheentupa J, Riikonen R, Dunkel L, Simell O. Adrenocortical hyporesponsiveness after treatment with ACTH of infantile spasms. Arch Dis Child1986; 61:750–753.

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Original Article / Orijinal Araştırma

Evaluation of the Correlation between Spousal Support, Postpartum Depression, and Breastfeeding Self-Efficacy in the Postpartum Period

Doğum Sonu Dönemde Eş Desteği, Postpartum Depresyon ve Emzirme Öz Yeterliliği Arasındaki İlişkinin Değerlendirilmesi

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Abstract

Aim: This study aimed to determine the correlation between spousal support, postpartum depression and breastfeeding self-efficacy (BSES) in the postpartum period.

Material and Method: This descriptive study was performed on 300 postpartum women. Data collected with using The Perceived Spousal Support among Women in Early Postpartum Period Scale (PSSAWEPP), The Edinburgh Postpartum Depression Scale (EPDS) and Postpartum Breastfeeding Self-Efficacy Scale-Short Form (BSES-SF).

Results: There was a negative correlation between women's perceived level of spousal support and their postpartum depression status (p<.001). A negative correlation was found between the postpartum depression status of women and the level of breastfeeding self-efficacy (p<.05). MANOVA analysis showed that spousal support did not affect breastfeeding self-efficacy (p>0.05). And satisfaction with the relationship with their spouse (p=0.000 η2=0.055) and the employment status of the spouse (p=0.040 η2=0.014) have a statistically significant effect on the PPD scores of women; also the breastfeeding self-efficacy of women with a single child is lower than others (p=0.000 η2=0.051).

Conclusion: Our study findings are important for to realize that spousal support perceived by women in the early postpartum period may be a predictor of PPD and breastfeeding self-efficacy, and they should evaluate women in terms of spousal support. Health care professionals working in obstetrics should assess all women in early postpartum period as a part of routine care for symptoms of postpartum depression by using objective screening tools and plan supporting initiatives in cooperation with psychiatric consultation for the women at risk.

Keywords: Postpartum depression, spousal support, breastfeeding, nursing, midwifery

Öz

Giriş: Bu çalışmada doğum sonu dönemde dönemde eş desteği, postpartum depresyon ve emzirme öz-yeterliliği arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Tanımlayıcı tipte planlanan bu çalışma postpartum dönemdeki 300 kadın ile gerçekleştirilmiştir. Veriler "Doğum Sonu Erken Dönemde Eş Destek Ölçeği (PSSAWEPP)", "Edinburgh Postpartum Depresyon Ölçeği (EPDS)" ve "Postpartum Emzirme Öz-Yeterlilik Ölçeği-Kısa Formu (BSES-SF)" kullanılarak toplanmıştır.

Bulgular: Kadınların algıladıkları eş desteği düzeyi ile doğum sonrası depresyon durumları arasında negatif bir ilişki vardır (p<.001). Kadınların doğum sonrası depresyon durumu ile emzirme öz-yeterlik düzeyleri arasında negatif ilişki bulunmuştur (p<.05). MANOVA analizi, eş desteğinin emzirme öz yeterliliğini etkilemediğini göstermiştir (p>0.05). Eşiyle ilişkisinden duyduğu memnuniyet (p=0,000 η2=0,055) ve eşinin çalışma durumu (p=0,040 η2=0,014) kadınların postpartum depresyon puanları üzerinde istatistiksel olarak anlamlı bir etkiye sahiptir; ayrıca tek çocuğu olan kadınların emzirme öz yeterliliği diğerlerine göre daha düşüktür (p=0,000 η2=0,051).

Sonuç: Çalışma bulgularımız, kadınların erken postpartum dönemde algıladıkları eş desteğinin doğum sonrası depresyon ve emzirme öz yeterliliğinin belirleyicisi olabileceğini ve kadınları eş desteği açısından değerlendirmeleri gerektiğinin vurgulanması açısından önemlidir. Obstetri alanında çalışan sağlık profesyonelleri, erken postpartum dönemdeki tüm kadınları rutin bakımın bir parçası olarak postpartum depresyon semptomları açısından objektif tarama araçlarını kullanarak değerlendirmeli ve risk altındaki kadınlar için psikiyatri konsültasyonu ile iş birliği içinde destekleyici girişimler planlamalıdır.

Anahtar Kelimeler: Postpartum depresyon, eş desteği, emzirme, hemşirelik, ebelik

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INTRODUCTION

The early postpartum period, which covers the first week after childbirth, is a complicated process in which the mother tries to adapt to physical and psychological changes.[1,2] While the new mother tries to cope with the problems caused by the physical changes, she also tries to adapt to changing situations such as maintaining her daily activities, along with caring for a newborn baby, insomnia, fatigue, and motherhood. Therefore, mothers need more support within the first weeks after delivery.[3,4] The physical, social, and emotional support the spouse would provide would be important for the physical and mental well-being of the mother, her adaptation to the role of motherhood, and the breastfeeding process.[4]

The changeover to motherhood and the adaptation process may increase the risk of developing various emotional and anxiety disorders in some women.[5] Postpartum depression (PPD) is the most common mental disorder during postpartum period. PPD is a significant public health problem negatively affecting the health of the mother and the infant.[6] Although PPD is usually experienced around the 4th to 6th weeks after delivery, it can develop right after the delivery or following the pregnancy depression.[7] Studies report that factors such as low socioeconomic status, unplanned pregnancy, low social support, insufficient spousal support, a history of depression, unemployment of the spouse, and stressful life events are the predictors of PPD.[8-10] Studies also indicate higher PPD rates in women not receiving adequate support from their spouses.[5,11] On the other hand, women supported by their spouses in the early postpartum period are more socially active, feel better psychologically, easily cope with the stressful situations they encounter, and easily and quickly achieve the changeover process to motherhood.[4]

One of the crucial components of the transition to motherhood in the postpartum period is breastfeeding. Women need self-confidence and support in the successful initiation and maintenance of breastfeeding, the benefits of which are indisputable for maternal and infant health. Breastfeeding self-efficacy appears to be a factor affecting women's breastfeeding success. Studies have shown a high level of breastfeeding self-efficacy to be associated with the success of starting and maintaining breastfeeding,[12,13] and breastfeeding self-efficacy to be influenced by the support of the spouses, among other factors.[14] Additionally, studies in the literature report a positive correlation between the level of spousal support and breastfeeding self-efficacy.[4,14]

Considering that women with low spousal support are at risk for PPD, it is probable that the mental well-being of women who do not receive enough support from their suppose would deteriorate, thus breastfeeding would be negatively affected, causing a decrease in breastfeeding self-efficacy.

Zubaran and Foresti[15] report a negative correlation between breastfeeding self-efficacy and PPD. Several studies in the literature examine the relationship between spousal support, breastfeeding self-efficacy, and depression in the postpartum period. However, there were no studies where these three variables were evaluated together in the same sample group of women in the early postpartum period to the best of our knowledge. This study examined the relationship between the perceived spousal support, postpartum depression, and breastfeeding self-efficacy of women in the early postpartum period and the factors affecting them.

MATERIAL AND METHOD

This cross-sectional and descriptive study was conducted in Ankara, Turkey, between May 1st and November 30th, 2019. The study sample consisted of 300 women in the early postpartum period (first 72 hours) who gave birth in a public tertiary training and research hospital. This hospital has the title of a baby-friendly hospital, and breastfeeding education is provided to all women by midwives and nurses during the postpartum period. The study sample included 300 women in the postpartum period volunteering to participate in the study and satisfying the inclusion criteria.

Inclusion criteria

The sample of the study included volunteering women over 18 years old who delivered at term (37 – 42 weeks), who were in the first 72 hours of postpartum, breastfeeding their baby, who could speak and understand Turkish, and who had no history of psychiatric diseases, and who had no complications in the mother or the baby during postpartum period.

Measures

Four separate forms were used to collect the data. In order to determine the socio-demographic and obstetric characteristics of women, a personal information form prepared by the researchers was used. "The Perceived Spousal Support among Women in early Postpartum Period Scale (PSSAWEPP)" and "The Edinburgh Postpartum Depression Scale (EPDS)" were used to determine the level of spousal support and to determine the risk of postpartum depression in women, respectively. The "Postpartum Breastfeeding Self-Efficacy Scale-Short Form (BSES-SF)" was used to determine the state of breastfeeding self-efficacy.

Perceived spousal support among women in early postpartum period scale (PSSAWEPP)

The scale was developed by Hotun Şahin et al.[2] to determine the perceived spousal support of women during the early postpartum period. The scale, consisting of 16 items, is a 5 points Likert-type scale. Positive and negative statements are intricately listed on the scale. While items 1, 2, 3, 4, 5, 6, 7, 11, 13, 16 are scored positively, the items 8, 9, 10, 12, 14, 15 are scored negatively. The total score obtained from the scale is between 16 and 80. A high score indicates that support during the early postpartum period is at a sufficient level, and a low score indicates that it is insufficient. The Cronbach alpha value of the scale was calculated by Hotun Şahin et al.[2] as 0.87, and it was calculated in our study as 0.90.

Edinburgh Postpartum Depression Scale (EPDS)

The scale was developed by Cox et al.[16] in 1987 to determine the risk of depression in the postpartum period. The Turkish validity and reliability study of the scale was conducted by Engindeniz et al.[17] The scale, consisting of 10 items, is a 4-points Likert-type scale. The total score obtained from the scale varies between 0 and 30. The cut-off score of the scale is 13, and women who receive this score and above are considered at risk for postpartum depression. The scale is widely used in studies. Cronbach's alpha value for EPDS was determined by Cox et al. as 0.87, Engindeniz et al. determined this value as 0.79, and it was determined as 0.84 in our study.

Postnatal Self-Efficacy Scale Short Form (BSES-SF)

This scale was first developed by Dennis and Faux[18] as 33 items to assess the level of breastfeeding self-efficacy of the mothers. Later, the scale was revised and converted into a short form of 14 items. The total score obtained from the scale, a 5-points Likert-type scale, ranges from 14 to 70. A high score obtained from the scale indicates that breastfeeding self-efficacy is high. The Turkish validity and reliability study of the scale was conducted by Aluş Tokat et al.,[19] and the Cronbach alpha value was calculated as 0.87. In our study, the Cronbach alpha value of the scale was calculated as 0.88.

Data collection

The study data were collected by the researchers using the face-to-face interview method. Before the study, the women were informed about the study, and their consent was taken. Filling out the data collection forms took 10-15 minutes.

Ethical considerations

The study was conducted following the principles of the Helsinki Declaration. The permission of the ethics committee was obtained (June 11th, 2019, 19 /231) before starting the study. After the participants were informed about the study, women's verbal consent who agreed to participate was obtained.

Data analyses

The data were transferred to a computer environment and evaluated in the research. The quantitative variables were summarized as mean, standard deviation, minimum, and maximum values, and the qualitative variables were summarized as numbers and percentages. The Kolmogorov-Smirnov test was used to test the suitability of the data for normal distribution. In the study, the scores obtained by women from postpartum depression, breastfeeding self-efficacy, and perceived spousal support scales are dependent variables. The relationship between the scale scores was examined by Pearson's correlation analysis. MANOVA (Multivariate ANOVA) was used in analyzing the independent variables affecting the scores obtained from the scales used in the study. The significance level was taken as $p<0.05$ in all analyses.

RESULTS

In the study, the average age of the women was found to be 29.02±5.92, and the duration of marriage was 6.44±5.64. Most women were high school graduates (40%), do not work in an income-generating job (74.3%), have a nuclear family (88.3%), and report that their family income is equivalent to their expenses (69.7%) (**Table 1**).

Table 1. Socio-demographic and obstetric characteristics of women

Specifications (n=300)		
Age (Mean ± SD)	29.02±5.92	
Duration of marriage (Mean ±SD)	6.44 ± 5.64	
Educational status	**n**	**%**
Primary school	34	11.3
Secondary school	57	19.0
High school	120	40.0
University and above	89	29.7
Educational status of the spouse		
Primary school	14	4.7
Secondary school	64	21.3
High school	120	40.0
University and above	102	34.0
Employment status		
Unemployed	223	74.3
Employed	77	25.7
Employment status of the spouse		
Unemployed	4	1.3
Employed	296	98.7
Perception of income level		
My income is less than my expense	57	19.0
My income is equal to my expense	209	69.7
My income is more than my expense	34	11.3
Family type		
The nuclear family	265	88.3
Extended family	35	11.7
Being dissatisfied with the relationship with a spouse		
Satisfied	276	92.0
Partially satisfied	22	7.3
Not satisfied	2	0.7
Gravida		
Primipara	124	41.7
Multipara	176	58.3
Number of children		
One	125	41.7
Two	105	35.0
Three and more	70	23.3
Type of birth		
Vaginal delivery	140	46.7
Cesarean delivery	160	53.3
The weight of the newborn		
SGA (≤2500 grams)	15	5.0
Normal	268	89.3
LGA (≥4000 grams)	17	5.7
	300	100

40% of women's spouses were high school graduates, and only 1.3% were unemployed. Of the participant women, 92% reported being satisfied with their spouse, and 82% reported that their spouse spent enough time at home. Among the participants, 41.7% of women had their first baby, 46.7% had normal spontaneous births, 5% of newborns were underweight, and 5.7% were large for gestational age babies (**Table 1**).

When the mean and standard deviations of the scores of the women who participated in the research were examined, it was found that "the Edinburgh postpartum depression scale", "the Postnatal Breastfeeding self-efficacy Scale-short form", and "the Perceived Spousal Support of Women in the Early Postpartum Process scale" scores were 5.50±4.88, 57.94±8.09, and 67.39±10.69 respectively (**Table 2**).

Table 2. The scores obtained by women from the scales used in the study

Scales (n=300)	$\bar{X}$ ± SD (min-max)
EPDS	5.50 ± 4.88 (0-23)
BSES-SF	57.94 ± 8.09 (30-70)
PSSAWEPP	67.39 ± 10.69 (24-80)

Abbreviations: EPDS, Edinburgh postpartum depression scale; PSSAWEPP, Perceived spousal support among women in early postpartum period scale; BSES-SF, Postnatal Self-Efficacy Scale Short Form.

According to the Edinburgh Postpartum Depression Scale scores, 8% of women had a risk of depression (**Figure 1**).

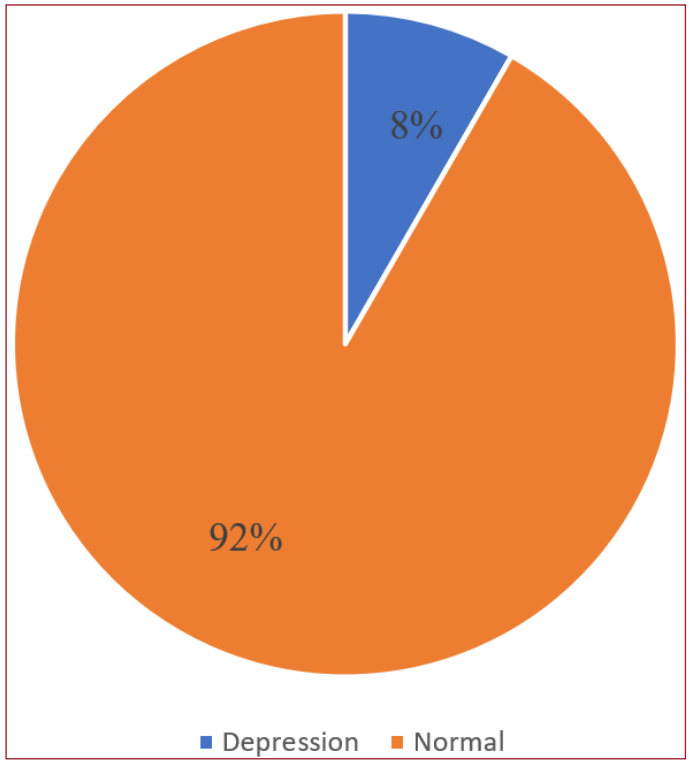

Figure 1. Prevelance of postpartum depression

There is a statistically significant inverse relationship between the scores of women on the Edinburgh Postpartum Depression Scale and the Perceived Spousal Support Spouse During Early Postpartum Process Scale (r= -.425, p < .001). As the perceived spousal support of women decreases, depression scores increase. Similarly, there is a statistically significant inverse relationship between the Edinburgh Postpartum Depression Scale scores and the Postnatal Breastfeeding Self-Efficacy Scale, implying that as the depression score increases, breastfeeding self-efficacy decreases (r= -.125, p = .031). There was no relationship between breastfeeding self-efficacy and perceived spousal support of women (r= .086, p= .139) (**Table 3**).

Table 3. Correlation of scale scores (n=300)

	R	p
EPDS PSSAWEPP	-.425	.000**
EPDS BSES-SF	-.125	.031*
BSES-SF PSSAWEPP	.083	.150

**Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed). Abbreviations: EPDS, Edinburgh postpartum depression scale; PSSAWEPP, Perceived spousal support among women in early postpartum period scale; BSES-SF, Postnatal Self-Efficacy Scale Short Form.

In the study, MANOVA was applied to examine the effect of independent variables on scale scores. According to the results of MANOVA, perceived spousal support scale scores of women in the early postpartum process indicate statistically significant differences according to the variables, respectively being satisfied with their relationship with their spouses (p=0.000), thinking that their spouses are spending enough time at home (p=0.022), their spouses' employment status (p=0.002), family type (p=0.027) and the number of children (p=0.000).

Eta square values are a statistical measure used to sort the effect of independent variables on dependent variables. If this value is close to 1, this indicates that the effect of the variable is excessive. When Eta square values were considered, the factors affecting the perceived spousal support the most were: Being satisfied with the relationship with their spouses (η2=0.091), the number of children (η2=0.044), the spouses' employment status (η2=0,031), thinking that their spouses are spending enough time at home (η2=0.018) and family type (η2=0.017). The results of the post hoc analysis revealed that women: Who are dissatisfied or partially satisfied with their relationship with their spouse, have children aged 2 and over, whose spouse is unemployed, who do not think that her spouse spends enough time at home and women with extended families receive lower spousal support (**Table 4**).

The results of MANOVA respectively show that satisfaction with the relationship with their spouse (p=0.000 η2=0.055) and the employment status of the spouse (p=0.040 η2=0.014) have a statistically significant effect on the depression scale scores of women. Women who are dissatisfied and partially satisfied with their relationship with their spouse and women whose spouse is unemployed have higher depression scores (**Table 4**).

When the variables affecting the breastfeeding self-efficacy scores of women were evaluated according to the results

of MANOVA, it was determined that the breastfeeding self-efficacy of women with a single child is lower than others (p=0.000 η2=0.051), and their relationship with the spouse and their family type did not show a statistical difference (**Table 4**).

Table 4. Multivariate ANOVA results

	Type III Sum of Squares	df	Mean Square	F	Sig.	Eta Squared
The Correlation Model						
PSSAWEPP	9726.106	5	1945.221	23.347	.000	.284
BSES-SF	1054.095	5	210.819	3.349	.006	.054
EPDS	889.463	5	177.893	8.393	.000	.125
Intercept						
PSSAWEPP	35064.813	1	35064.813	420.855	.000	.589
BSES-SF	9516.205	1	9516.205	151.191	.000	.340
EPDS	102.054	1	102.054	4.815	.029	.016
Employment status of the spouse						
PSSAWEPP	788.835	1	788.835	9.468	.002	.031
BSES-SF	5.220	1	5.220	.083	.774	.000
EPDS	89.919	1	89.919	4.242	.040	.014
Being dissatisfied with the relationship with a spouse						
PSSAWEPP	2441.151	1	2441.151	29.299	.000	.091
BSES-SF	9.834	1	9.834	.156	.693	.001
EPDS	360.854	1	360.854	17.025	.000	.055
Do not think that the spouse spends enough time at home						
PSSAWEPP	443.273	1	443.273	5.320	.022	.018
BSES-SF	42.656	1	42.656	.678	.411	.002
EPDS	36.107	1	36.107	1.704	.193	.006
Number of children						
PSSAWEPP	1127.203	1	1127.203	13.529	.000	.044
BSES-SF	1003.991	1	1003.991	15.951	.000	.051
EPDS	51.213	1	51.213	2.416	.121	.008
Family type						
PSSAWEPP	414.267	1	414.267	4.972	.027	.017
BSES-SF	17.541	1	17.541	.279	.598	.001
EPDS	7.772	1	7.772	.367	.545	.001

Abbreviations: EPDS, Edinburgh postpartum depression scale; PSSAWEPP, Perceived spousal support among women in early postpartum period scale; BSES-SF, Postnatal Self-Efficacy Scale Short Form.

DISCUSSION

In our study assessing the relationship between the perceived spousal support in the early postpartum period, PPD, and breastfeeding self-efficacy, we found that "as the perceived spousal support of mothers decreased, their postpartum depression scores increased" and "as their postpartum depression scores increased their breastfeeding self-efficacy scores decreased" and the perceived spousal support scores did not show a statistically significant correlation with breastfeeding self-efficacy (p = .000).

The early postpartum period is a difficult transition process for women, and during this period, mothers need the support of their spouses more than ever. Possibly, the psychological well-being of women who do not receive enough support from their spouses may deteriorate, and related problems may arise. We found the PPD scale scores of women with low perceived spousal support in the early postpartum period to be higher (p = .000). Spousal support affects depression, which may develop during or after childbirth.[5,20] Decreased spousal support is associated with postpartum depression.[3,7,21,22] In a meta-analysis examining the risk factors affecting PPD, the spouse/father support was the risk factor with the greatest impact.[5] Results in our study revealed that women who are dissatisfied/partially satisfied with their relationship with their spouses and whose spouse is unemployed have higher depression scores, in accordance with the literature. This confirms that poor marital relationships or dissatisfaction with marriage are important predisposing factors for PPD.[6-9,11] Although PPD is associated with various financial, psychological, and lifestyle variables, it may be possible to prevent or reduce PPD by providing adequate spousal support.[21]

Our results, about the variables affecting women's perceived spousal support, show that women who live in an extended family, who are "dissatisfied/ partially satisfied" with their relationship with their partner, whose spouse is unemployed, and who do not think that their spouse spends enough time at home, receive lower spousal support.

Another study in Turkey, showed that "the spousal support scores of women" stating to be happy in their marriage, got along well with their spouse, and thought that their spouses spent enough time at home were significantly higher than the others.[1] Our results point out that women who live in an extended family and do not have an excellent marital relationship are in the risk group for PPD since they do not receive adequate spousal support, and should be evaluated more carefully at the early postpartum period. Therefore, it is important for midwives and nurses to evaluate especially spouse/partner support and spouse-related characteristics in the care of women in the early postpartum period and to plan interventions to increase the spouse and/or social support of women who are at risk in this respect.

Postpartum depression can be mentioned as "a dangerous thief" stealing women's dreams about their precious time to spend with their babies during their pregnancies.,and may have many negative effects on newborn's health.[23] We found that breastfeeding self-efficacy decreased as women's risk of postpartum depression increased (p = .000). Similarly, in the literature, there are many studies showing that postpartum depression negatively affects breastfeeding.[15,20,24-26] The risk of PPD was found in the vast majority of mothers who do not want to breastfeed their babies.[24] A decrease in breastfeeding self-efficacy is expected in women with impaired mental well-being and a high risk of postpartum depression. Therefore, it would be an important preventive service for midwives and nurses working in obstetrics to screen the risk of PPD in women using objective tools as part of routine care in the early postpartum period and not to miss mothers in the risk group.

PPD is the most common mental disorder in the postpartum period.[9] The prevalence of PPD was 23.8% in a meta-analysis conducted in Turkey.[11] PPD in the CDC's 2018 report was 13.2%, and its incidence was reported to be increasing in the later weeks postpartum, rather than the first week.[20] We found the risk of PPD in women in the early postpartum period to be 8%. Closely, another study made in the early postpartum period reported the incidence of PPD as 9.1%.[7] Our study findings indicate that PPD symptoms occur earlier in women who lack spousal support and it negatively affect breastfeeding self-efficacy. Considering breastfeeding problems are often experienced during the first days of postpartum and that the first days are crucial for the successful initiation and continuation of breastfeeding, the risk assessment and planning of appropriate interventions for early symptoms of PPD in women will be important initiatives for breastfeeding.

Contrary to what we expected, there was no relationship between perceived spousal support and breastfeeding self-efficacy in the early postpartum period, and our MANOVA analysis also showed that spousal support did not affect breastfeeding self-efficacy. Previous studies reported a positive correlation between breastfeeding self-efficacy and spousal support.[4,27,28] Women who received more support from their spouse, mother, father, and nurse/midwife in the early postpartum period had higher breastfeeding self-efficacy scores.[14] Our MANOVA results to determine the variables affecting spousal support and breastfeeding self-efficacy showed that women with a single child had lower breastfeeding self-efficacy, but their perceived spousal support was higher than women with two or more children. It is a fact that previous breastfeeding experience affects breastfeeding self-efficacy.[14] Similar to our results, studies conducted in China and America in the early postpartum period showed that breastfeeding self-efficacy was higher in multiparas than in primiparous women.[14,28,29]

Determination of perceived spousal support to be lower in women with two or more children in our study could be related to the traditional Turkish family structure. Our results showed that the majority of the women in our sample did not work in a paying job. This suggests that their husbands, took responsibility for supporting the family, while women were responsible for household chores and baby care. Therefore, especially with the increasing number of children in this patriarchal family structure, women's domestic workload and support expectations- are increasing. Another study in Turkey determined that the perceived spousal support of women decreased as the number of children increased, as in our results.[1]

Our findings showed higher spousal support for women with single child. We found no correlation between spousal support and breastfeeding self-efficacy, and since the previous breastfeeding experience was the most effective variable in breastfeeding self-efficacy, this finding suggested that the first time mothers could not take particular support from their spouses about breastfeeding. We believe expecting couples should participate in antenatal breastfeeding trainings together and prospective fathers should be thought how to support mothers during breastfeeding, this practice should be supported by all health professionals as a part of antenatal care.

CONCLUSION

Our study results show that women who live in an extended family and do not have a good marital relationship are in the group at risk for PPD because they do not receive adequate spousal support, and that the breastfeeding self-efficacy of women who have high risk of PPD, is impaired. We found that as the level of spousal support perceived by women at early postpartum period decreased, their PPD scores increased, and also their breastfeeding self-efficacy scores decreased. However, contrary to what was expected, there was no relationship between the level of perceived spousal support by women and their breastfeeding self-efficacy. Perceived spousal support levels of women are affected mainly by their satisfaction with their relationship with their spouse, the number of children, the employment status of the spouse, the thought that the spouse spends enough time at home, and the family type. Women's PPD scores were most affected by satisfaction with the relationship with their spouse and the partner's employment status. Breastfeeding self-efficacy levels were affected by the number of children.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee permission was obtained from the University of Health Sciences Non-Interventional Researches Ethical Committee with the code 19 /231 and the date June 11th, 2019,

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Akbay AS, Tascı Duran E. How does spousal support affect women's quality of life in the postpartum period in Turkish culture? Asian Women 2018;4(3):29–45.
2. Hotun Sahin N, Dissiz M, Dinc H, Soypak F. Erken lohusalık sürecinde kadınların algıladıkları eş desteği: ölçek geliştirme çalışması. J Anatolia Nurs Health Sciences 2014;17(2):73–79.

3. Kızılırmak A, Calpbinici P, Tabakan G, Bahtışen K. Correlation between postpartum depression and spousal support and factors affecting postpartum depression. Health Care Women Int 2021;42(12):1325–39.
4. Uludag E, Ozturk S. The effect of partner support on self-efficiency in breastfeeding in the early postpartum period. Am J Fam Ther 2020;48(2):211–19.
5. Edwards LM, Le HN, Garnier-Villarreal M. A systematic review and meta-analysis of risk factors for postpartum depression among Latinas. Matern Child Health J.2021;25(4):554–64.
6. Nurbaeti I, Deoisres W, Hengudomsub P. Association between psychosocial factors and postpartum depression in South Jakarta, Indonesia. Sex Reprod Healthc 2019;20:72–76.
7. Serhan N, Ege E, Ayranci U, Kosgeroglu N. Prevalence of postpartum depression in mothers and fathers and ıts correlates. J Clin Nurs 2013;22(1–2):279–84.
8. Çankaya S. The effect of psychosocial risk factors on postpartum depression in antenatal period: a prospective study. Arch Psychiatr Nurs 2020;34(3):176–83.
9. Desta M, Memiah P, Kassie B, Ketema DB, Amha H, Getaneh T, Sintayehu M. Postpartum depression and ıts association with ıntimate partner violence and ınadequate social support in Ethiopia: a systematic review and meta-analysis. J Affect Disord 2021;279:737–48.
10. Yoruk, S, Acıkgoz, A, Turkmen H, Karlıdere T. The prevalence of postpartum depression and the correlation of perceived social support and quality of life with postpartum depression: a longitudinal study. P R Health Sci J 2020;39(4):327-335.
11. Ozcan Keser N, Boyacıoglu NE, Dinc H. Postpartum depression prevalence and risk factors in Turkey: a systematic review and meta-analysis. Arch Psychiatr Nurs 2017;31(4):420–28.
12. Chipojola R, Chiu HY, Huda MH, Lin YM, Kuo SY. Effectiveness of theory-based educational interventions on breastfeeding self-efficacy and exclusive breastfeeding: a systematic review and meta-analysis. Int J Nurs Stud 2020;109, 1-8.
13. Kılcı H, Çoban A. The correlation between breastfeeding success in the early postpartum period and the perception of self-efficacy in breastfeeding and breast problems in the late postpartum. Breastfeed Med 2016;11(4):188-95.
14. Yang X, Gao LL, Ip WY, Chan WCS. Predictors of breast feeding self-efficacy in the ımmediate postpartum period: a cross-sectional study. Midwifery 2016;41:1–8.
15. Zubaran C, Foresti K. The correlation between breastfeeding self-efficacy and maternal postpartum depression in Southern Brazil. Sex Reprod Healthc 2013;4(1):9–15.
16. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-ıtem edinburgh postnatal depression scale. Br J Psychiatry 1987;150:782–86.
17. Engindeniz AN, Kuey L, Kultur S. Edinburgh Doğum Sonrası Depresyon Ölçeği Türkçe formu geçerlilik ve güvenilirlik çalışması. Bahar Sempozyumları 1996;1:51-52.
18. Dennis CL, Faux S. Development and psychometric testing of the Breastfeeding Self-Efficacy Scale. Res Nurs Health 1999;22(5):399-409.
19. Alus Tokat M, Okumus H, Dennis CL. Translation and psychometric assessment of the Breast-Feeding Self-Efficacy Scale-Short form among pregnant and postnatal women in Turkey. Midwifery 2010;26(1):101–8.
20. Al Nasr, RS, Altharwi K, Derbah MS, Gharibo SO, Fallatah SA, Alotaibi SG, Almutairi KA, Asdaq SMB. Prevalence and predictors of postpartum depression in Riyadh, Saudi Arabia: a cross sectional study. PLoS One 2020;15(2):1-13.
21. Almutairi AF, Salam M, Alanazi S, Alweldawi M, Alsomali N, Alotaibi N. Impact of help-seeking behavior and partner support on postpartum depression among Saudi women. Neuropsychiatr Dis Treat 2017;13:1929–36.
22. Bolak Boratav H, Toker O, Kuey L. Postpartum depression and ıts psychosocial correlates: a longitudinal study among a group of women in Turkey. Women and Health 2016;56(5):502–21.
23. Beck CT. Postpartum depression stopping the thief that steals motherhood. AWHONN Lifelines 1999;3(4):41–4.
24. Ayhan Baser D. The evaluation of the relationship between postpartum depression and breastfeeding. Ankara Medical Journal 2018;18(3):276-85.
25. Ngo LTH, Chou HF, Gau ML, Liu CY. Breastfeeding self-efficacy and related factors in postpartum Vietnamese women. Midwifery 2019;70:84–91.
26. Webber E, Benedict J. Postpartum Depression: A multi-disciplinary approach to screening, management and breastfeeding support. Arch Psychiatr Nurs 2019;33(3):284–9.
27. Dennis CL, Janssen PA, Singer, J. Identifying women at-risk for postpartum depression in the immediate postpartum period. Acta Psychiatr Scand 2004;110(5): 338-46.
28. Hinic K. Predictors of breastfeeding confidence in the early postpartum period. J Obstet Gynecol Neonatal Nurs 2016 Sep-Oct;45(5):649-60.
29. Dennis CL. The Breastfeeding Self-Efficacy Scale: psychometric assessment of the short form. J Obstet Gynecol Neonatal Nurs 2003;32(6):734–44.

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Case Report / Olgu sunumu

Association of Iron Deficiency Anemia and Eating Clove in an 8-Year-Old Girl: A Rare Case Report

8 Yaşında Bir Kız Çocuğunda Demir Eksikliği Anemisi ve Karanfil Yeme Birlikteliği: Nadir Bir Olgu Sunumu

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Abstract

Iron-deficiency anemia is the most common nutrient disorder worldwide. It is defined pica as eating non-nutritive, non-food substances over a period of at least one month. Different types of pica have been reported in the literature. Although the exact etiology of pica is unknown, pica has been related to iron and other mineral/nutritional deficiencies. Although a relationship between iron-deficiency anemia and pica has been reported in the literature, no such association has been reported with eating clove so far. Therefore, I present the case of an 8-year-old girl diagnosed with iron-deficiency anemia with clove pica.

Keywords: Anemia, child, clove, iron deficiency, pica

Öz

Demir eksikliği anemisi dünya çapında en yaygın beslenme bozukluğudur. Pika, besleyici olmayan, gıda dışı maddelerin en az bir aylık bir süre boyunca tüketilmesi olarak tanımlanır. Literatürde farklı pika türleri bildirilmiştir. Pika'nın kesin etiyolojisi bilinmemekle birlikte, pika demir ve diğer mineral/besin eksiklikleri ile ilişkilendirilmiştir. Literatürde demir eksikliği anemisi ile pika arasında bir ilişki bildirilmiş olmasına rağmen, şimdiye kadar karanfil yemek ile böyle bir ilişki bildirilmemiştir. Bu nedenle, karanfil pikası ile demir eksikliği anemisi tanısı konulan 8 yaşında bir kız olgusunu sunmaktayım.

Anahtar Kelimeler: Anemi, çocuk, karanfil, demir eksikliği, pika

INTRODUCTION

It is defined pica as eating non-nutritive, non-food substances over a period of at least one month. Additionally, the behavior must not be in keeping with the child's developmental stage and must not be socially normative or culturally acceptable behavior.[1] Although the exact etiology of pica is unknown, pica has been related to iron and other mineral/nutritional deficiencies dysfunctional eating patterns obsessive–compulsive disorder and psychosocial stressors.[2]

Iron-deficiency anemia (IDA) is the most common nutrient disorder worldwide. Early identification and treatment is important because the damage attributed to periods of IDA in children is irreversible despite treatment.[3] Clove has been used for centuries as an analgesic for toothache.[4] Although a relationship between IDA and pica has been reported in the literature, no such association has been reported with eating clove so far. Therefore, I present the case of an 8-year-old girl diagnosed with IDA with clove pica.

CASE

An previously healthy 8-year-old girl was sent to general pediatric outpatient clinic before the multiple dental filling procedure under general anestesia from the dentistry department. Medical history revealed chronic toothache due multiple tooth decay for the last 3 months. Since anemia was found in routine hemogram, pica was asked in the anamnesis. Personal history revealed that the patient had eaten more than 30 cloves per day after chewing them thoroughly for the last two months. In

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her anamnesis, it was learned that she initially put clove on her teeth to relieve toothache, and then she began to eat them. Neurodevelopmental steps were normal. The socioeconomic status of her family was lower. There was no family history of hereditary hemoglobinopathies. Since the patient had a history of eating clove, further investigations were performed. On physical examination, the skin and mucous membranes were pale. On admission, weight: 25 kg (50 percentile), height: 125 cm (25-50 percentile) and vital signs were normal. Cardiac, abdominal, and neurologic exams were normal. The patient underwent biochemical and hematological testing to screen for possible nutritional deficiencies which could have explained her pica. Hemoglobin was found to be 7.4 g/dl (normal:12-16), hematocrit – 24.8% (normal:35-49), White Blood Cells – 8.73 cells/µl (normal:4-12), platelets – 374,000/µl (normal:150-350,000), MCV – 59.1 fl (normal:80-100), MCH-17.6 pg (normal:27-34), MCHC-29.8 g/dl (normal:31-37), RDW-17.9% (normal:11-16), RBC 4.19×10^6/µl (normal:3.5-5.2×10^6). Iron studies revealed an iron level of 9 µg/dl (normal:37-145), serum iron binding capacity - 478 µg/dl (normal:110-370), serum ferritin level – 1.7 µg/l (normal:14.5-290). Examination of her blood smear revealed anisocytosis and hypochromia Serum B12 level was 703 ng/l (normal:195-961). The renal functions and liver enzymes were all within normal limits. After hemogram and iron tests, the patient was diagnosed with IDA. Oral iron(II)-glycine-sulphate-complex treatment was started at a dose of 5 mg/kg/day. On follow up two weeks later, she reported her pica resolved. Control hemogram was as follows. Hemoglobin was found to be 10.5 g/dl, hematocrit – 33.9%, White Blood Cells– 8.73 cells/µl, platelets – 285,000/µl, MCV – 69.5 fl, MCH-21.6 pg, MCHC-31.1 g/dl and RBC 4.88 ×10^6/µl. A significant increase in hemoglobin value was observed with treatment for IDA. Iron treatment was planned to continue for 3 months. The patient's dental treatment was carried out by the dentistry. The general pediatric outpatient follow-up of the patient continues.

DISCUSSION

The meta-analysis examining micronutrient status and pica noted a strong association between pica and anaemia.[5] In the literature, it is recommended to make full-blood picture and iron studies in all children with pica and treat any nutritional deficiencies identified.[1] In the present case, due to the detection of anemia during routine hemogram, it was asked whether there was pica and detailed iron studies were performed. Thus, it was learned that there was a clove pica, which has never been reported before in the literature. In the present case, a diagnosis of clove pica and IDA was made by anamnesis, physical examination and laboratory examinations. Two weeks after iron treatment, signs of pica disappeared. The present case has shown that all children should be questioned in terms of pica when taking anamnesis.

In literature, it was stated that the physical examination was mostly normal in children with pica.[6] Some children with pica may appear undernourished, exhibit developmental delay, or experience abdominal distress or pain if large quantities of indigestible constituents are consumed. Pallor, if present, suggests anemia which may result from iron deficiency.[7] In the present case, physical examination was normal, except for pallor of the skin and mucous membranes.

Considering the possible complications of the substance taken in the anamnesis and examination, it should be acted upon.[1] In the present case, there was no adverse event or complication detected other than IDA accompanying pica.

There has been clay, raw starch, ice, raw, raw potatoes, hair, fibrous plant roots, paint chips, sand, pebbles/stones, sharp objects, glass, uncooked rice, paper, soap, burned matches, feces, vomitus, wooden materials, sponge, polyurethane foam, grass, leaves, paper, chalk, baby talcum powder, crayons, pencil erasers, cigarette butts, ashes, charcoal, coins, buttons, cloth, eggshells and insects among the different types of pica.[7]

The efficacy of iron supplementation in eliminating pica associated with iron deficiency states is well-recognised.[8] In the present case, the patient who was diagnosed with IDA with a similar approach was successfully treated.

CONCLUSION

I believe this is the first case of a pediatric patient with IDA accounting for her clove eating pica in the literature so far. Pediatricians should inquire about pica in every pediatric patient's anamnesis during follow-up of healthy children.

ETHICAL CONSIDERATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Status of Peer-review: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. McNaughten B, Bourke T, Thompson A. Fifteen-minute consultation: the child with pica. Arch Dis Child Educ Pract Ed 2017;102(5):226-29.
2. Hackworth SR, Williams LL. Pica for foam rubber in patients with sickle cell disease. South Med J 2003;96(1):81-3.
3. Paoletti G, Bogen DL, Ritchey AK. Severe iron-deficiency anemia still an issue in toddlers. Clin Pediatr (Phila) 2014;53(14):1352-8.
4. Kumar R, Mirza MA, Naseef PP, Kuruniyan MS, Zakir F, Aggarwal G. Exploring the Potential of Natural Product-Based Nanomedicine for Maintaining Oral Health. Molecules 2022;27(5):1725.

5. Miao D, Young SL, Golden CD. A meta-analysis of pica and micronutrient status. Am J Hum Biol 2015;27:84–93.
6. Al Nasser Y, Muco E, Alsaad AJ. Pica. [Updated 2022 Nov 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532242/
7. Leung AKC, Hon KL. Pica: A Common Condition that is Commonly Missed - An Update Review. Curr Pediatr Rev 2019;15(3):164-9
8. Nemeth J, Hwang P. Pica? Check a hemoglobin. Iron deficiency anemia? Ask about pica. CJEM 2021;23(4):556-7.