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Online article not yet published in an issue

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Book

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Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. I n: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93113.

Journal article on the Internet

Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]; 102. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

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

An organization as an author

The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

Acknowledgements

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

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Tables should be complementary, but not duplicate information contained in the text. Tables should be numbered consecutively in Arabic numbers, with a descriptive, self-explanatory title above the table. All abbreviations should be explained in a footnote. Footnotes should be designated by symbols in the following order: *,†, ‡, §, ¶.

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Editorial Correspondence

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JOURNAL OF
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Original Article / Orijinal Araştırma

Comparison of the Predictive Role of First Trimester APRI Score and De-Ritis Ratio in Intrahepatic Cholestasis of Pregnancy

Gebeliğin İntrahepatik Kolestazında Birinci Trimester APRI Skoru ve De-Ritis Oranının Prediktif Rolünün Karşılaştırılması

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Abstract

Aim: The APRI score and De Ritis ratio is associated with liver diseases. There is limited data in the literature on the predictive role of these markers in intrahepatic cholestasis of pregnancy. This study aimed to evaluate and compare the predictive role of first trimester APRI and De Ritis scores for intrahepatic cholestasis of pregnancy.

Material and Method: A total of 60 intrahepatic cholestasis of pregnancy and 60 healthy pregnant were included in this retrospective study. Demographic features, first trimester aminotransferases, complete blood count levels, fasting bile acid levels, coagulation tests, birth outcomes were recorded and compared between groups. Receiver operating curve was used to determine the predictive role of APRI and De-Ritis score for intrahepatic cholestasis of pregnancy.

Results: APRI score was significantly higher (p=0.017) whereas De-Ritis ratio was lower (p=0.002) in intrahepatic cholestasis group. Fasting bile acid was found to be positively correlated with APRI score (r=0.868, p<0.001). There was a weak positive correlation between APRI score and De Ritis ratio (r=0.219, p=0.016). APRI score >0.42 predicted intrahepatic cholestasis with 36.67% sensitivity and 98.33% specificity (AUC=0.626, p=0.016). De Ritis ratio ≤1.3 predicted intrahepatic cholestasis with 83.33% sensitivity and 51.67% specificity (AUC=0.664, p=0.001). No significant difference was found between two index for predicting intrahepatic cholestasis (p=0.065).

Conclusion: The first trimester APRI and De Ritis scores, which are cheap and easily available, can be used to predict intrahepatic cholestasis of pregnancy. Considering that there is no superiority between two markers, we suggest that both can be used for prediction.

Keywords: APRI score, De Ritis ratio, intrahepatic cholestasis of pregnancy

Öz

Amaç: APRI skoru ve De Ritis oranı karaciğer hastalıklarıyla ilişkilidir. Literatürde bu belirteçlerin gebeliğin intrahepatik kolestazındaki öngörücü rolü hakkında sınırlı veri bulunmaktadır. Bu çalışmada, gebeliğin intrahepatik kolestazındaki birinci trimester APRI ve De Ritis skorlarının öngörücü rolünü değerlendirmeyi ve karşılaştırmayı amaçladık.

Gereç ve Yöntem: Retrospektif çalışmamıza toplam 60 intrahepatik gebelik kolestazı ve 60 sağlıklı gebe dahil edildi. Demografik özellikler, ilk trimester aminotransferazları, tam kan sayımı düzeyleri, açlık safra asidi düzeyleri, pıhtılaşma testleri, doğum sonuçları kaydedildi ve gruplar arasında karşılaştırıldı. Receiver operating curve analizi, APRI ve De-Ritis skorunun intrahepatik gebelik kolestazı için öngörücü rolünü belirlemek için kullanıldı.

Bulgular: APRI skoru intrahepatik kolestaz grubunda anlamlı olarak daha yüksek (p=0,017) iken De-Ritis oranı daha düşüktü (p=0,002). Açlık safra asidinin APRI skoru ile pozitif korelasyon gösterdiği bulundu (r=0,868, p<0,001). APRI skoru ile De Ritis oranı arasında zayıf pozitif korelasyon vardı (r=0,219, p=0,016). APRI skoru >0,42, %36,67 duyarlılık ve %98,33 özgüllükle intrahepatik kolestazı öngördü (AUC=0,626, p=0,016). De Ritis oranı ≤1,3, %83,33 duyarlılık ve %51,67 özgüllükle intrahepatik kolestazı öngördü (AUC=0,664, p=0,001). İntrahepatik kolestazı öngörmede iki indeks arasında anlamlı fark bulunmadı (p=0,065).

Sonuç: Ucuz ve kolay hesaplanabilen ilk trimester APRI ve De Ritis skorları, gebeliğin intrahepatik kolestazını tahmin etmek için kullanılabilir. İki belirteç arasında bir üstünlük olmadığı düşünüldüğünde, her ikisinin de tahmin için kullanılabileceğini düşünmekteyiz.

Anahtar Kelimeler: APRI skoru, De Ritis oranı, gebeliğin intrahepatik kolestazı

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy complication characterized by itching localized especially in the hands and feet, worsening at night, and elevations in fasting bile acids and serum transaminases. It especially occurs in late second or third trimester.[1] The prevalence of ICP is between 0.5% and 1%, with variations among ethnicities and geographic regions due to differences in genetic susceptibility and environmental factors.[2] Since the etiology of ICP has not been sufficiently elucidated, management decisions are quite difficult due to insufficient data regarding diagnosis, treatment and adverse perinatal outcomes.[3] It is claimed that the mechanism of occurrence is due to increased circulating steroid levels in the maternal serum due to pregnancy, which leads to liver enzyme dysfunction and disorders in the transportation of the bile acids. Although pruritus disappears and liver function tests return to normal values after birth, patients with ICP may experience hepatobiliary and cardiovascular complications in later life. Moreover it is related to neonatal complications.[4,5] Considering these adverse outcomes, the early prediction of ICP is crucial.

Aspartate aminotransferase to platelet ratio index (APRI) and aspartate to alanine aminotransferase (De Ritis) ratio have been studied in various conditions. Aspartate aminotransferase to platelet ratio index was found to be a predictor for complicated dengue fever, cardiovascular risk for metabolic subject, cholestatic liver diseases in children and HELLP syndrome.[3,6-8] Aspartate to alanine aminotransferase ratio was first described in 1957 by Fernando De Ritis and used in the diagnosis of viral hepatitis, infectious mononucleosis, cirrhosis, Wilson disease and insulin resistance.[9-11]

There is limited data in the literature on the predictive role of these markers in intrahepatic cholestasis of pregnancy, and there are no studies comparing their predictive properties. Here, we aimed to evaluate and compare the predictive role of first trimester APRI and De Ritis scores for intrahepatic cholestasis of pregnancy.

MATERIAL AND METHOD

This is a retrospective case-control study performed at a university affiliated research and training hospital between January 2022 and December 2023. The local ethics committee approved the study with a decision number of 2024-TBEK 2024/08-13. It was in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients for the use of data from medical records.

Study Population

The study was conducted with 120 pregnant women grouped as ICP (n=60) and healthy pregnant women (n=60). The inclusion criteria of the study were as follows: being 16 to 45 years old, having singleton pregnancy, having available regular antenatal follow-up and delivery data. Exclusion criteria were composed of multiple pregnancy, having prepregnancy systemic disease including dermatologic and hematologic disorders, known presence of coagulopathy, infectious diseases, gestational diabetes mellitus, hypertensive disorders of pregnancy, intrauterine growth restriction, placental pathologies, liver or biliary disease, drug and alchool use, patients who have acute viral hepatitis and unavailable medical records.

Demographic features such as age, gravida, parity, body mass index (BMI), first trimester aspartate aminotransferase (AST), alanine aminotransferase (ALT), complete blood count levels such as hemoglobin, white blood cell, platelet, third trimester serum bile acid levels, coagulation blood tests, birth week, birth weight and delivery mode, Apgar scores were obtained from medical records.

In our clinic, intrahepatic cholestasis is routinely diagnosed based on clinical findings of pruritus which is especially located on feet and hands, elevated serum AST, ALT and serum bile acids, negative viral hepatic serology normal hepatobiliary ultrasonography findings. The upper limit of normal was accepted as 34 IU/L for AST, 55 IU/L for ALT and 10µmol/L for fasting bile acids.

The aspartate aminotransferase to platelet ratio index was calculated by using the formula ([AST/upper limit of the normal values] x 100/ number of platelets (10^3/µL) while first trimester AST/ALT ratios was calculated using the following formula [AST(IU/L)] / ALT (IU/L).

Statistical Analysis

The normality of distribution were tested by Shapiro Wilk test. Variable were expressed as mean ± standart deviation for normally distributed variables, median (minimum-maximum) for nonnormally distributed variables and frequency (percentage) for categorical variables. Normally distributed variables were compared between two groups with Student t test and nonnormally distributed ones were compared with Mann-Whitney U test. Chi-square and Fisher's Exact test were performed for group comparison of categorical variables.

Receiver operating curve analysis was used to determine the predictive role of APRI and De-Ritis score for intrahepatic cholestasis of pregnancy. The sensitivity, specificity, Youden index and the cut-off values were analyzed for each index. Also, the predictive role of these indexes were compared with receiver operating curve analysis. Statistical analysis were carried out with SPSS version 22.0 and MedCalc 18 softwares. A p value ≤0.05 was accepted as statistically significant.

RESULTS

The demographic and obstetric characteristics of patients were demonstrated in **Table 1**. There was no statistically significant difference between ICP and control groups in terms of age, BMI, gravida, parity, first and fifth minutes scores. Birth week and weight were lower and cesarean section rate was higher in ICP group.

Table 1. The demographic and obstetric characteristics of patients

	Intrahepatic cholestasis of pregnancy (n=60)	Control (n=60)	p
Age (years)	32 (19-43)	29.5 (17-40)	0.151
Body mass index (kg/m^2)	27.89 (22.43-37.88)	28.93 (23.44-38.29)	0.213
Gravida (n)	2 (1-9)	2 (1-8)	0.909
Parity (n)	1 (0-4)	1 (0-7)	0.143
Birth week (week)	37 (28-38)	38 (31-41)	<0.001
Birth weight (gram)	2735 (945-4220)	3260 (1985-4300)	<0.001
Birth mode (n,%) Vaginal Cesarean section	 13 (21.7%) 47 (83.3%)	 30 (50%) 30 (50%)	0.001
First minute Apgar score	9 (4-9)	9 (5-9)	0.242
Fifth minute Apgar score	10 (5-10)	10 (8-10)	0.140

The laboratory parameters of patients were shown in **Table 2**. No significant difference was found between two groups according to hemoglobin, WBC, platelet, activated partial thromboplastin time and INR levels. Prothrombin time was significantly longer, AST and ALT levels were higher in ICP group. The median fasting bile acid levels was 26.6 (11.2-76.2) µmol/L in ICP group. APRI score was 0.33 (0.10-1.72) in ICP group and 0.23 (0.10-0.99) in control group which was statistically significant (p=0.017). De Ritis ratio was lower in ICP group as compared to control group (0.85 (0.50-4.05) vs 1.32 (0.5-2.4), p=0.002).

Table 2. The laboratory parameters of patients

	Intrahepatic cholestasis of pregnancy (n=60)	Control (n=60)	p
Hemoglobin (g/dL)	10.89±1.69	11.1±1.54	0.494
WBC (x10^3/mm^3)	12.9 (7-24)	12.3 (6.2-27.1)	0.125
Platelet (x10^3/µL)	198 (125-380)	225 (139-373)	0.092
Prothrombin time (sn)	13.3 (11.5-65.2)	12.8 (10.3-23.2)	0.001
Activated partial thromboplastin time (sn)	27.8 (22.4-33.8)	28.3 (19.9-37.6)	0.640
INR	0.98 (0.9-1.1)	0.95 (0.8-1.2)	0.109
Aspartate aminotransferase (IU/L)	21.5 (10-85)	18 (8-64)	0.038
Alanine aminotransferase (IU/L)	23 (6-87)	15 (8-34)	<0.001
APRI score	0.33 (0.10-1.72)	0.23 (0.10-0.99)	0.017
AST to ALT ratio	0.85 (0.50-4.05)	1.32 (0.5-2.4)	0.002

APRI: aspartate aminotranferase to platelet ratio index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, AST to ALT ratio: aspartate aminotransferase to alanine aminotransferase ratio, WBC: white blood cell

The correlations between fasting bile acid, APRI score and De Ritis ratio was shown in **Table 3**. Fasting bile acid was found to be positively correlated with APRI score (r=0.868, p<0.001) while no correlation was detected between fasting bile acid and De Ritis ratio. There was a weak positive correlation between APRI score and De Ritis ratio (r=0.219, p=0.016).

Table 3. The correlations between fasting bile acid, APRI score and De Ritis ratio

Correlations

	Fasting bile acid	APRI score	De Ritis ratio
Spearman's rho			
Fasting bile acid			
Correlation Coefficient	1.000	.868**	.066
Sig. (2-tailed)	.	.000	.616
N	60	60	60
APRI score			
Correlation Coefficient	.868**	1.000	.219*
Sig. (2-tailed)	.000	.	.016
N	60	120	120
De Ritis ratio			
Correlation Coefficient	.066	.219*	1.000
Sig. (2-tailed)	.616	.016	.
N	60	120	120

**. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

The receiver operating curve evaluating the predictive role of APRI for ICP was presented in **Figure 1**. APRI score >0.42 was found to predict ICP with 36.67% sensitivity and 98.33% specificity (AUC=0.626, p=0.016).

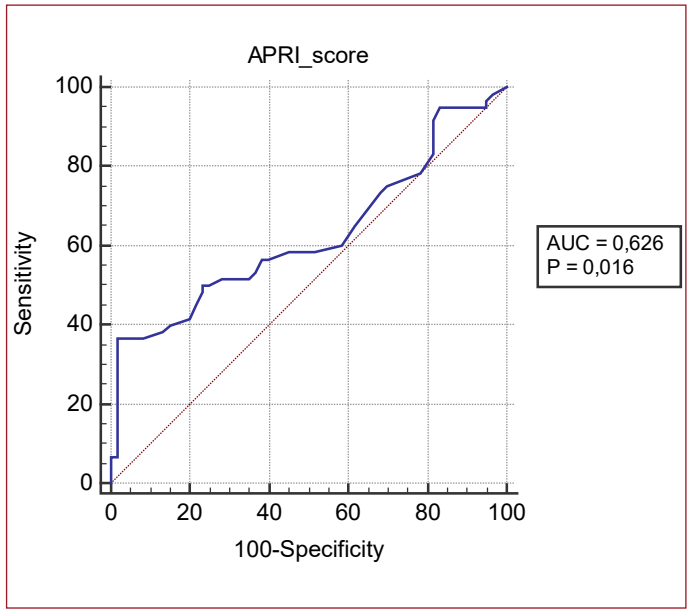

Figure 1. The receiver operating curve evaluating the predictive role of APRI for intrahepatic cholestasis of pregnancy

The receiver operating curve evaluating the predictive role of AST to ALT ratio for ICP was demonstrated in **Figure 2**. AST to ALT ratio ≤ 1.3 was found to predict ICP with 83.33% sensitivity and 51.67% specificity (AUC=0.664, p=0.001).

The receiver operating curve comparing the predictive role of APRI and AST to ALT ratio for ICP were shown in **Figure 3**. No significant difference was found between two index for predicting ICP (p=0.065).

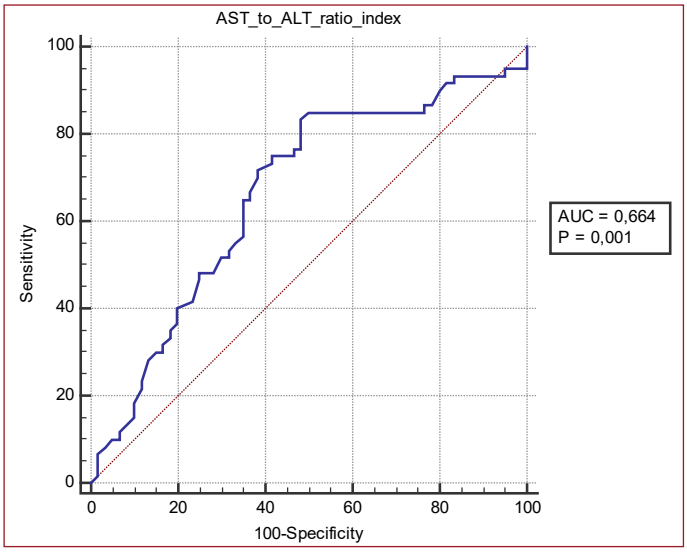

Figure 2. The receiver operating curve evaluating the predictive role of AST to ALT ratio for intrahepatic cholestasis of pregnancy

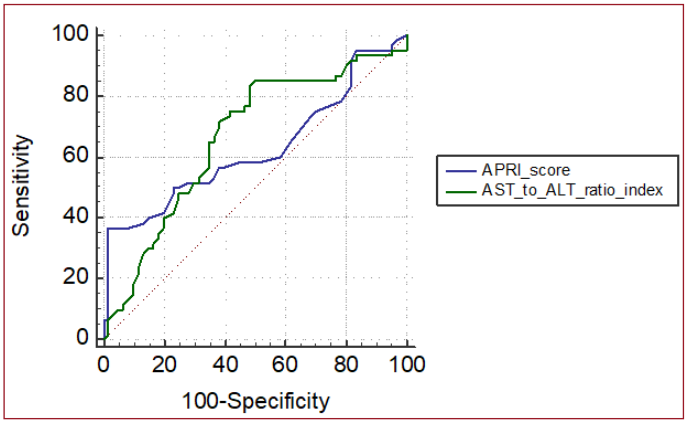

Figure 3. The receiver operating curve comparing the predictive role of APRI and AST to ALT ratio for intrahepatic cholestasis of pregnancy

DISCUSSION

Intrahepatic cholestasis of pregnancy has claimed to be related to the serious neonatal complications such as fetal demise, fetal distress, preterm birth and low birth weight. [12,13] Due to the increased perinatal mortality and morbidity, researchers have focused on finding predictive markers for intrahepatic cholestasis of pregnancy. Aneuploidy screening markers, lipid profile parameters such as total cholesterol and LDL cholesterol levels and sulfated metabolites were found to be a predictor in previous studies.[14-16] Besides these, scoring systems based on laboratory tests were used for the diagnosis and prediction of ICP.[17,18]

The APRI score presents hepatic fibrosis and cirrhosis. When cell damage to the liver fibrosis occurs, AST tends to increase. Then platelet count begin to decrease due to the portal hypertension. As a result, increased APRI scores appear. [19,20] Recently, an APRI score above 3 has been accepted as a noninvasive marker of liver damage.[17] In a meta-analysis including 40 studies, APRI score above 1 predicted cirrhosis with 76% sensitivity and 72% specificity while APRI score above 0.7 predicted liver fibrosis with 77% sensitivity and 72% specificity.[21] In intrahepatic cholestasis of pregnancy, morphologic changes of liver fibrosis is not an expected situation whereas molecular changes of fibrosis are present. This raises the question of whether the APRI score has a place in the prediction of intrahepatic cholestasis.

In the literature, the first study evaluating the association between APRI score and ICP was performed by Tolunay et al. Tolunay et al reported higher first trimester APRI scores in ICP and claimed that APRI score 0.57 predicted ICP with 86.5 % sensitivity and 77.3 % specificity.[17] Then, in a study of Gok et al searching the predictive value of APRI score in 49 ICP cases and 62 healthy control claimed that first trimester APRI score above 0.15 predicted ICP with 79.6% sensitivity and 56.5% specificity.[18] In 2024, Cemortan et al reported higher APRI scores in ICP cases. Also, APRI score above 0.55 was reported to be a predictor with 66.2% sensitivity and 92.9% specificity. [22] Not only first trimester APRI scores were associated with intrahepatic cholestasis of pregnancy, but also second and third trimester APRI scores predicted intrahepatic cholestasis of pregnancy. Sakcak et al claimed that second trimester APRI score above 0.09 predicted ICP with 78% sensitivity and 79% specificity.[23] In a study of Saadi et al, third-trimester APRI score above 0.42 predicted ICP with 65.3% sensitivity and 73.2% specificity.[24] Peker et al evaluated the optimal cut-off values of APRI scores to predict ICP for the first, second, and third trimesters and found that APRI score above 0.101 predicted ICP with 79.7% sensitivity and 79.6% specificity in first, above 0.103 predicted ICP with 78.4% sensitivity and 76.3% specificity in second, and above 0.098 with 72.5% sensitivity and 72% specificity in third trimester.[25] In our study, first trimester APRI score was evaluated. We found APRI score as 0.33 (0.10-1.72) in ICP group and 0.23 (0.10-0.99) in control group which was statistically higher in ICP group. APRI score above 0.42 was found to predict ICP with 36.67% sensitivity and 98.33% specificity. Our study results were consistent with the literature. We suggest that different cut-off levels and sensitivity could be due to the severity of the disease or diagnostic criteria used in the studies. All of these studies, including our study, were far from investigating the severity of intrahepatic cholestasis of pregnancy. Only one study investigated the role of APRI score according to the severity of intrahepatic cholestasis. That study reported higher APRI scores in severe cases. Moreover, APRI score above 1.06 was found to predict severe ICP with 82% sensitivity and 72% specificity.[26]

Although the APRI score is associated with parenchymal damage, fasting bile acid levels circulating in extrahepatic biliary system were found to be correlated with APRI scores in some previous studies. Tolunay et al reported significant positive correlation between first trimester APRI scores and third trimester fasting bile acid levels in ICP (17). Similarly, Eyisoy et al and Cemortan et al reported positive association between APRI scores and fasting bile acid levels.[22,26] Likewise,

in the present study, we found positive correlation between third trimester fasting bile acids and APRI score. The mechanism to explain this correlation is not fully understood.

Another noninvasive marker investigated in liver diseases is De Ritis ratio. In a study of Parmar et al, decreased De Ritis ratio was reported in viral hepatitis while increased De Ritis ratio was present in alcholic liver diseases. No significant difference was reported in cholestasis. De Ritis ratio 1.5 and above claimed to be associated with intrahepatic cholestasis while levels below 1.5 was associated with extrahepatic conditions.[10] There is only one study searching De Ritis ratio in intrahepatic cholestasis of pregnancy. In this study, lower first trimester De Ritis ratio was detected in ICP as compared to healthy pregnants. De Ritis ratio below 1.07 predicted ICP with 64% sensitivity and 62% specificity. Furthermore, the study evaluated the predictive roles of both APRI and De Ritis ratios similar to our study. As previous studies, first trimester APRI scores were higher and APRI score above 0.191 predicted ICP with 66% sensitivity and 66% specificity.[3] In addition to this study, we compared the predictive role of these markers and found no difference between these markers. Also, we found that De Ritis ratio 1.3 and below predicted ICP with 83.33% sensitivity and 51.67% specificity.

The current study has several limitations. First, it was conducted in a single centre and has a retrospective design. Second, liver biopsy results were not available to assess liver fibrosis. Finally, the severity of ICP, which could have affected the results, was not assessed.

CONCLUSION

The first trimester APRI and De Ritis scores, which are cheap and easily available, can be used to predict ICP. Considering that there is no superiority between two markers, we suggest that both can be used for prediction. Early prediction, appropriate monitoring and treatment can reduce the maternal and fetal mortality and morbidity.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bursa Yuksek Ihtisas Research and Training Hospital Ethics Committee (2024-TBEK 2024/08-13).

Informed Consent: Although the study design is retrospective, written informed consent is routinely obtained from all patients at admission for using their data from medical records.

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.

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Original Article / Orijinal Araştırma

Validity and Reliability of the Timed 360° Turn Test in Children with Cerebral Palsy

Serebral Palsili Çocuklarda Süreli 360° Dönme Testinin Geçerliliği ve Güvenirliği

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Abstract

Aim: The purpose of this study was to evaluate the timed 360° turn test (360DTT) in children with cerebral palsy (CP) for validity and reliability.

Material and Method: Children with spastic CP (n=91) with lower extremity spasticity ≤ 3 according to the Modified Ashworth Scale (MAS) and Expanded and Revised Gross Motor Functional Classification System (GMFCS-E&R) Level ≤ 2 were included. 360DTT, Pediatric Berg Balance Scale (PBBS), Timed Up and Go Test (TUG), Pediatric Functional Reaching Test (PFRT) and Four Square Stepping Test (FSST) were performed. 360DTT was repeated by two different physiotherapists on consecutive days. The test-retest reliability of 360DTT was assessed using intraclass correlation coefficients (ICC).

Results: The correlation between PBBS, TUG, PFRT and FSST tests were used for validity. Inter-rater reliability of 360DTT (right) and 360DTT (left) (Inter-rater ICC=0.849-0.918, ICC=0.859-0.924) were found to be excellent. Significiant correlation was found between 360DTT (right) (1st measurement) and PBBS (r=-0.520 p≤0.001), TUG (r=0.304 p=0.003), PFRT front (r=-0.283 p=0.007) PFRT right (r=-0.295, p=0.005), PFRT left (r=-0.228 p=0.03) and FSST (r=0.381 p≤0.001). Also there was correlation between 360DTT (left) (1st measurement) and PBBS (r=-0.517 p≤0.001), PFRT front (r=-0.213 p=0.042), PFRT right (r=-0.253 p=0.016) and FSST (r=0.280, p=0.007). Significiant correlation was found between the 360DTT (right) (2nd measurement) and PBBS (r=-0.542 p≤0.001), TUG (r=0.217 p=0.039), PFRT front (r=-0.272 p=0.009) PFRT right (r=-0.304 p=0.003) and FSST (r=0.312 p=0.003) tests. There was significiant correlation between 360DTT (left) (2nd measurement), PBBS (r=-0.479 p≤0.001), and FSST (r=0.232 p=0.027).

Conclusion: 360DTT was found to be valid and reliable in children with CP.

Keywords: Validity, reliability, timed 360° turn test, cerebral palsy

Öz

Amaç: Bu çalışmada, Serebral Palsi (SP)'li bireylerde Zamanlı 360° Dönme Testi'nin (360DTT) geçerlilik ve güvenilirliğinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Modifiye Ashworth Skalası'na (MAS) göre alt ekstremite spastisitesi ≤ 3 düzeyindeki Genişletilmiş ve Revize Edilmiş Kaba Motor Fonksiyon Sınıflandırma Sistemi (GMFCS-E&R) ≤ 2 olan spastik SP'li (n=91) çocuklar dahil edildi. 360DTT, Pediatrik Berg Denge Skalası (PBBS), Zamanlı Kalk ve Yürü Testi (TUG), Pediatrik Fonksiyonel Uzanma Testi (PFRT) ve Dört Kare Adımlama Testi (FSST) yapıldı. 360DTT farklı günlerde iki ayrı fizyoterapist tarafından tekrarlandı. 360DTT'nin test-tekrar test güvenirliği sınıf içi korelasyon katsayıları (ICC) kullanıldı.

Bulgular: Geçerlilik için PBBS, TUG, PFRT ve FSST testleri arasındaki korelasyon kullanıldı. 360DTT (sağ) ve 360DTT (sol)'in derecelendiriciler arası güvenilirliği (interrater ICC=0.849-0.918, ICC=0.859-0.924) mükemmel bulundu. 360DTT (sağ) (1. ölçüm) ile PBBS (r=-0.520 p≤0.001), TUG (r=0.304 p=0.003), ön PFRT (r=-0.283 p=0.007) sağ PFRT (r=-0.295) (p=0.005) testleriyle, sol PFRT (r=-0.228 p=0.03) ve FSST (r=0.381 p≤0.001) arasında anlamlı korelasyon bulundu. 360DTT (sol) (1. ölçüm) ile PBBS (r=-0.517 p≤0.001), ön PFRT (r=-0.213 p=0.042), sağ PFRT (r=-0.253 p=0.016) ve FSST (r=0.280 p=0,007) arasında anlamlı korelasyon bulundu. 360DTT (sağ) (2. ölçüm) ile PBBS (r=-0,542 p≤0,001), TUG (r=0,217 p=0,039), PFRT ön (r=-0,272 p=0,009) PFRT sağ (r=-0,304 p=0,003) ve FSST (r=0,312 p=0,003) testleri arasında anlamlı korelasyon bulunurken, 360DTT (sol) (2. ölçüm) ile PBBS (r=-0,479 p≤0,001) ve FSST (r=0,232 p=0,027) testleri arasında anlamlı korelasyon bulundu.

Sonuç: 360DTT'nin SP'li çocuklarda geçerli ve güvenilir olduğu bulundu.

Anahtar Kelimeler: Geçerlilik, güvenirlik, 360 derece dönme testi, serebral palsi

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INTRODUCTION

Cerebral Palsy (CP) is a group of disorders with with sensorimotor problems that start in early childhood and have a lifelong impact on posture and muscle coordination.[1] Damage in the developing brain cause the problems of regulating movements, maintaining posture and balance. Motor function disorders are the core symptoms of CP, but other dysfunctions accompanied like sensory, perceptual, cognitive, communication..etc.[1,2] Children with CP display a diverse array of motor skills and difficulties. About 58% of people with CP can walk on their own, but the remaining individuals have a wide range of movement abilities. CP is often thought of as a disorder affecting both posture and mobility, as it impairs a child's gait and balance.[1,3]

Static reflexes and dynamic sensory systems work together to provide the complex skill of postural control. It comprises two fundamental components: postural balance and postural orientation.[4,5] Somatosensory problems, as well as impairment to any underlying systems, can cause postural control abnormalities in people with CP. Because of inadequate adaptive responses, extended activation durations, and co-contraction in antagonist muscles, children with CP have loss of postural control compared to healthy peers.[6,7] Functional skills, balance control, and walking ability are all hampered by poor postural control. Thus, children with CP have negative effects on their everyday activities and quality of life.[8-10] A precise and timely assessment of the underlying cause of balance disorders (vestibular, somatosensorial, visual, etc..) is crucial for developing a therapy plan, following the prognosis, thoroughly describing symptoms, and maximizing treatment efficacy.[10] Therefore, a good performance test should be simple to use, assess the issue, have a high degree of reliability and validity in the population being studied, and be adaptable to changes. It should also assess how an individual's traits relate to the environment and task performance.[11] The Pediatric Berg Balance Scale (PBBS),[12] the Pediatric Functional Reach Test (PFRT),[13] The Timed Up Go (TUG) test,[14] and the Timed Up Down Stairs (TUDS) test,[15] the Kids-Balance Evaluation Systems Test (Kids-BESTest),[16] and Fullerton Advanced Balance Scale (FAB),[17] are just a few of the several objective tests that assess balance in people with CP. Each has a number of drawbacks even though they are both trustworthy and effective tests for determining static and functional balance. The TUG and TUDS tests do not evaluate static balance; instead, they measure dynamic balance.[14,15] FRT measures the forward-reaching control.[13] Although it takes longer and requires different equipment, the Kids-BESTest has been used to differentiate between the effects of sensory integration disorder and the sensory systems on postural control in children with CP.[16] According to studies, the PBBS can identify balance abnormalities in children with varying degrees of neurological involvement, but it is insufficient for children who are functional but just slightly affected.[12] Similarly, the PBBS lacks items to evaluate damage in the multisensory systems that interpret sensory inputs during function.[4,8]

It has recently been proposed that children with CP require balance-related aids designed for those with greater functional abilities.[17,18] A quick, simple, and accurate way to assess an individual's rotation capacity is to use the Timed 360° Turn Test (360DTT).[19] It measures the time it takes for a person to turn from a standing position. This test has demonstrated strong test-retest, intraobserver, and interobserver reliability in the studies.[19] A crucial element of many clinical mobility and balance evaluations is turning ability. Turning, for instance, is a fundamental component of the TUG.[20] and BBS,[8] two of the most widely used evaluation instruments for determining balance and mobility. Nevertheless, TUG does not evaluate 180° rotation twice in particular. Of the 14 items, only timed 360° turn test is scored by BBS. The rotation's score ranges from 0 to 4, depending on whether it is standing or below 4seconds. When evaluating rotation capacity, 360DTT is a more accurate and efficient testing method than TUG and BBS. It is accessible to senior citizens who live in communities through functional partnerships.[21] For these reasons, this study aimed to examine the validity and reliability of 360DTT in children with CP.

MATERIAL AND METHOD

Participants

Children with CP between the ages of 7 and 18 who applied to Kahramanmaraş Sütçü Imam University, Faculty of Medicine, Pediatric Neurology Clinic were included in the study. Parents of the children signed written informed consent. The study was obtained from Kahramanmaras Sutcu Imam University Medical Research Ethics Committee (Date: 12.02.2022, Decision No: 2022/07). And the study performed according to the principles of the Declaration of Helsinki. The clinical trial number is NCT05213039.

Children with spastic CP were diagnosed according to SCPE criteria, children whose lower extremity spasticity was ≤2 according to Modified Ashworth Scale (MAS), The Gross Motor Function Classification System - Expanded & Revised (GMFCS-E&R) level of ≤2, Communication Function Classification System (CFCS) level ≤3 and the children who were able to follow verbal commands were included. Who had received Botox (Botulinum toxin) or surgery in the last 6 months, and had contractures in the ankle or knee joints were excluded from the study.

Measurements

The assesments were performed at the deparment of Physiotherapy and Rehabilitation. Demographic information was recorded. The tests were experienced by the children at first. All of the tests started with 360DTT. The measurements were performed by two separate physiotherapists (Physiotherapist A and B) with 10 years of experience of pediatrics. The completion times of the tests were recorded. The assesments were made in two separate sessions in seperate days. On the first day, in the first session, the first physiotherapist (A Physiotherapist) performed the 360DTT three times. Data collection procedure is shown in Figure 1. Then, the PBBS, TUG, PFRT and Four Square

Step Test (FSST) were performed. The second physiotherapist (B Physiotherapist) performed the 360DTT three times in the other session consecutive day. The average of the three recorded times was noted by two Physiotherapists. All of the children were evaluated in the same environment with their shoes on a hard surface without any orthosis.

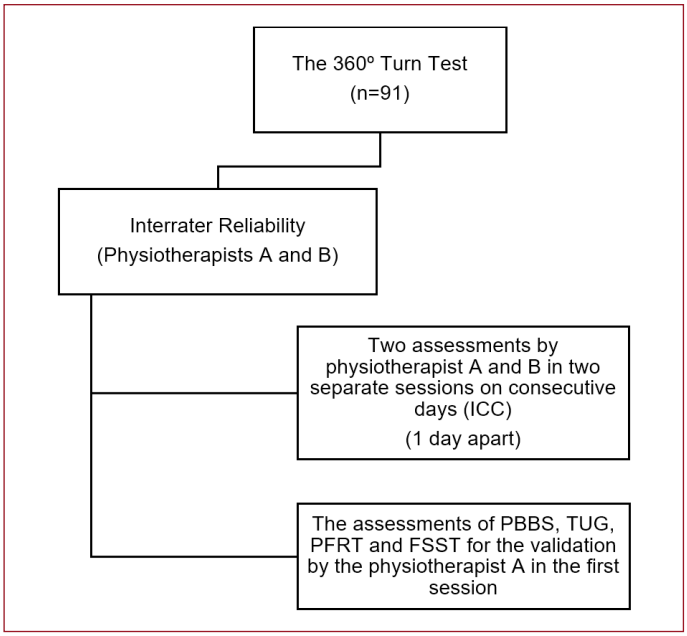

Figure 1. Data collection procedure. ICC: intraclass correlation coefficient, PBBS: Pediatric Berg Balance Scale, TUG: Timed Up and Go Test, PFRT: Pediatric Functional Reach Test, FSST: Four Square Step Test

Modified ashworth scale (MAS): It classifies resistance to passive movement in the direction of the antagonist of the spastic muscle. The bilateral hip flexors, hip adductors, knee flexors, plantar flexors were measured in supine position. The tone felt in these muscles were classified as; 0: No increase in tone- 4: The affected part is rigid.[22]

The gross motor function classification system - expanded & revised (GMFCS-E&R): Children with CP are categorized using a standard classification system for their gross motor functions. GMFCS classifies the children from level 1 to 5: Level 1 represents the best and 5 represents the worst motor function.[23]

The timed 360° turn test (360DTT): A stopwatch is used to measure the time, and a marker is used to indicate the starting point. Each participant stands comfortably at the starting point and turns 360° on each side. Timing begins with the word "start" and ends when the participant's shoulder looks forward again. Three trials on each side and the average of these trials is recorded. The average score for the timed 360DTT performance is recorded.[19]

Pediatric Berg Balance Scale (PBBS): It consists of 14 problems that get harder as you go, testing functional skills linked to daily life activities including sitting and standing on one leg. Every item is given a score on an ordinal five-point scale from 0 to 4, with a maximum score of 56. Better postural balance is indicated by a higher score. The test-retest and inter-rater reliability in children with CP is high.[8] PBBS is used in this validation study. Because this scale measures the dinamic and static balance of children which is similar to 360DTT.

Timed up and go test (TUG): It measures functional mobility, gait speed, postural control, and balance with high reliability. Children were seated in chairs appropriate to their height. A distance of 3 meters was marked. The children was asked to get up and walk to the marked area with the command, then return and sit on the chair. The stopwatch was started with the command and stopped with the child's sitting. The average of the three measures was collected after the test was conducted three times.[15] TUG measures the dinamic parameters of the balance as if 360DTT. So it is used for the validation in this study.

Pediatric functional reach test (PFRT): The test was explained to the children verbally and visually. The child was asked to stand sideways against a wall, extending their elbows without contacting the wall and bending their shoulders to a 90-degree angle. In this position, the initial measurement was taken. Then, without taking a step, they were instructed to reach forward. The youngsters' final point of reach was noted. These two lengths were separated by a reported distance expressed in meters. When the child stepped off the ground, the test was repeated.[24] PFRT was preferred for the validation of 360DTT, because it measures the balance reactions.

Four square step test (FSST): Four 90-cm-long walking sticks and a timer are required pieces of equipment for this test. The sticks are laid flat on the ground, forming a square with 4. The child stands in square on a marked area divided into 4 squares. The child steps into each square as quickly as possible in these order: forward, backward, right and left in a sequence of 2, 3, 4, 1, 4, 3, 2 and 1. One of the two FSST measurement time is been recorded in seconds (sec). Stop watch begins with the first foot touching the floor in frame 1 and ends in frame 4.[25] FSST was prefeered for the validation of 360DTT, as it is similar to use the dinamic balance reastions in standing position.

Sample Size Calculation

The sample size was calculated using the G*Power 3.1.9.7 package program. For the reliability part of the study; when the null hypothesis was intraclass correlation coefficient (ICC)=0.70, the alternative hypothesis was ICC=0.90, alpha coefficient=0.05 and power=0.95, 57 children were calculated.[34] For the validity part; When effect size=0.62, alpha coefficient=0.05 and power=0.90, 57 children were calculated.[34]

Data Analysis

IBM SPSS 24 package program (SPSS Inc., Chicago, IL, USA) was used. Descriptivites were given as mean, standard deviation (X±SD) and percentage. Intraclass correlation coefficient (ICC) was used to assess the interrater reliability of the 360DTT, and Cronbach's alpha was used for internal consistency.

Two-way mixed effects models were used on mean measurements with the agreement definition form of ICC. Concurrent validity of 360DTT; correlation with PBBS, TUG, PFRT and FSST tests was evaluated with Pearson correlation

analysis. Coefficient value is defined as if: >0.75 good reliability, between 0.51 and 0.75 moderate reliability, and <0.5 poor reliability. Pearson correlation coefficient was evaluated as unacceptable between 0-0.49, moderate between 0.50-0.69, high between 0.70-0.79 and excellent between 0.80-1.00. Significance level of p≤0.05 was evaulated.

The Standard Error Measure (SEM) was utilized to assess the variations in individual scores across multiple assessments. The MDC value was used to evaluate the data and decide whether a change observed between testing was due to chance or actual performance changes.[26] Practically, MDC values help researchers and doctors identify whether an individual's physiological gait performance genuinely varies under various circumstances, including experimental settings, aging-related changes in the body, and surgical or rehabilitation procedures.[27] The SEM was computed using formula and the 95% confidence interval's minimal detectable change (MDC) was then computed as if below.[28]:

- (1) SEM = [SD at first assessment] x sqrt (1- intra-class correlation coefficient)
- (2) MDC = [SEM] x 1.96x sqrt

RESULTS

The children's (n=91) (11.40±2.84 years) sociodemographic information is shown in **Table 1**.

Table 1. Sociodemographic information of the children in the study

	(n=91) X±SD (Min-max)
Age (year)	11.40±2.84 (7-11)
Weight (kg)	41.21±12.64 (21-72)
Height (cm)	140.98±15.26 (106-165)
Sex (n) %	
Male	37 (40.7)
Female	54 (59.3)
Clinical Type of CP (n) %	
Spastic Hemiparetic	54 (59.3)
Spastic Diparetic	37 (40.7)
Dominant side (n) %	
Right	58 (63.7)
Left	33 (36.3)
Education (n) %	
None	14 (15.4)
Primary	28 (30.8)
Secondary	41 (45.1)
High School	8 (8.8)
GMFCS Level (n)%	
Level 1	48 (52.7)
Level 2	13 (47.3)
Orthosis (n)%	
Yes	37 (40.7)
No	54 (59.3)

n:number, %: Percent, X:mean; SD: Standard Deviation; min: minimum; max: maximum; CP: Cerebral Palsy, kg: Kilogram, cm: centimeter

The averages of the 360DTT, PBBS, TUG, PFRT and FSST tests used in the study are given in **Table 2**.

Table 2. Averages of tests 360DTT, PBBS, TUG, PFRT and FSTT used in the study

	Test X±SD (min-max)
360DTT right (First Physiotherapist)	7.24± 2.74 (3.12-20.4)
360DTT left (First Physiotherapist)	6.13± 2.8 (2.84-20.01)
360DTT right (Second Physiotherapist)	6.37±2.75 (2.95-19.5)
360DTT left (Second Physiotherapist)	5.92±3.35 (2.27-30)
PBBS	49.13±7.05 (30-56)
TUG	12.75±7.69 (4.43-35.6)
PFRT (front)	17.65±7.47 (0-34)
PFRT (right)	13.93±6.18 (0-29)
PFRT (left)	15.01±6.01 (3-36)
FSST	1.87±11.71 (5.43-50.05)

360DTT: The Timed 360° Turn Test, PBBS: Pediatric Berg Balance Scale, TUG: Timed Up and Go Test, PFRT: Pediatric Functional Reach Test, FSST: Four Square Step Test

The inter-rater reliability of 360DTT (right) and 360DTT (left) was found to be excellent (Inter-rater ICC=0.849-0.918, ICC=0.859-0.924) For the right and left sides, the SEM values were 1,06 sec. and 1,27 respectively. And the MDC values were 1.44 and 1.57 sec. respectively (**Table 3**).

Significant correlation was found between the tests of 360DTT (right) (1st measurement) and PBBS (r=-0.520 p≤0.001), TUG (r=0.304 p=0.003), PFRT front (r=-0.283 p=0.007), PFRT right (r=-0.295 p=0.005), PFRT left (r=-0.228 p=0.03) and FSST (r=0.381 p≤0.001) (**Table 4**).

Significant correlation was found between the tests of 360DTT (left) (1st measurement) and PBBS (r=-0.517 p≤0.001), PFRT front (r=-0.213 p=0.042), PFRT right (r=-0.253 p=0.016) and FSST (r=0.280 p=0.007) (**Table 4**).

Significant correlation was found between PBBS (r=-0.542 p≤0.001), TUG (r=0.217 p=0.039), PFRT front (r=-0.272 p=0.009), PFRT right (r=-0.304 p=0.003) and FSST (r=0.312 p=0.003) tests of 360DTT (right) (2nd measurement). Significant correlation was found between PBBS (r=-0.479 p≤0.001) and FSST (r=0.232 p=0.027) tests of 360DTT (left) (2nd measurement) (**Table 4**).

DISCUSSION

This study revealed that 360DTT has a high test-retest reliability and a good validity for using as a performance test of the assessment of functional mobility and balance in children with CP who is at GMFCS (E&R) levels I and II. It is thought that the use of a performance test such as 360DTT, which evaluates turning skills in children with CP, may be beneficial in terms of functional skills.

Table 3. Test-retest reliability of 360DTT

n=91	Two assessments by different physiotherapists in 2 separate sessions on consecutive days	Cronbach's Alpha	ICC*	95% CI	SEM (sec)	MDC (sec)
Test-Retest Reliability	360DTT (right)	0.918	0.849-0.918	0.780-0.946	1,06	1,44
	360DTT (left)	0.924	0.859-0.924	0.794-0.950	1,27	1,57

*Two-way mixed-effect model on average measures with absolute agreement definition. CI: Confidence Interval; ICC: intraclass correlation coefficient, MDC: Minimal detectable change; SEM: standard error of measurement, sec: second

Table 4. The correlation between 360DTT and PFRT, PBBS, FSST and TUG

		PFUT (front)	PFUT (right)	PFUT (left)	PBBS	FSST	TUG
360DTT right (First Physiotherapist)	r	-0.283	-0.295	-0.228	-0.520	0.381	0.304
	p	0.007*	0.005*	0.03*	≤0.001**	≤0.001**	0.003*
360DTT left (First Physiotherapist)	r	-0.213	-0.253	-0.154	-0.517	0.280	0.162
	p	0.042*	0.016*	0.144	≤0.001**	0.007*	0.124
360DTT right (Second Physiotherapist)	r	-0.272	-0.304	-0.176	-0.542	0.312	0.217
	p	0.009*	0.003*	0.095	≤0.001**	0.003**	0.039*
360DTT left (Second Physiotherapist)	r	-0.199	-0.192	-0.116	-0.479	0.232	0.126
	p	0.058	0.068	0.276	≤0.001**	0.027*	0.234

Pearson correlation, *p<0.05, **≤0.001, 360DTT: The Timed 360° Turn Test, PFRT: Pediatric Functional Reach Test, PFUT: Pediatrik Fonksiyonel Uzanma Testi, PBBS: Pediatric Berg Balance Scale, TUG: Timed Up and Go Test, FSST: Four Square Step Test

Studies on the validity and reliability of 360DTT have been carried out in various patients except CP in recent studies.[29,30] This study was performed with CP children by the interrater assessments of two physiotherapists who have high mobility levels but also can have loss of postural control and balance problems in daily life. CP is classified in different clinical types. The functional mobility and balance disorders of children with CP varies over time according to clinical types and functional classification.[15] 360DTT is a performance test that may be utilized in the clinics to categorize these children into several functional group. Therefore, the 360DTT can be an alternative method in the clinics as an objective performance test for classifying these children's mobility and balance problems into different functional groups.

The 360DTT, which can be easily applied in clinical measurements, may be important in terms of functionality in daily life in the assessment of dynamic balance by interacting with the somatosensory system and postural control mechanisms. In this respect, we believe that determining that the 360DTT is valid and reliable in children with high mobility levels of CP will contribute to the literature.

There are many studies of the validity and reliability of 360DTT that were carried out in various disease populations like Parkinson's Disease (PD), Multiple Sclerosis (MS), Stroke, ankle sprain, adults with cognitive impairment and knee osteoarthritis.[19,29-33] In the current study the inter-rater reliability The 360DTT's ICC value was determined to be consistent with values reported in other populations.[29-33] The studies of 360DTT showed that it has a good test-retest, intrarater, and interrater reliability people with Parkinson's Disease (PwPD), MS, Stroke, ankle sprain, cognitive impairment, and knee osteoarthritis (KO).[19,29-33] 360DTT was also found to be connected with motor symptoms, dynamic balance, functional mobility, and the severity of PD.[29] ICCs range was found high for dominant side (ICC=829-0.971) and non-dominant side (ICC=0.827-0.972) with PD.[29] In the MS population ICC range was found 0.898 to 0.980 (dominant side) and 0.893 to 979 (non-dominant side).[30] Also the ICC values were excellent and similar to the current study (ICC=0.849-0.924) with the individuals of cognitive impairment (ICC=0.96–0.98), ankle sprain (ICC=0.87), and stroke ICC=0.824-0.993), and KO (ICC=0.933-0.937).[19,30-33] Consequently, it can be seen that the 360DTT intra- and inter-rater reliability (ICC) values for the children with CP were found to be consistent with other studies.[29-32] Similarly, both GMFCS (E&R) levels had outstanding ICC values. These results showed that this test can be used for postural control, dynamic mobility and balance in different populations.

The measurement error that could occur is represented by the SEM value of clinical assessment tests. The SEM values of 360DTT in children with CP were 1,06 sec. and 1,27 respectively for the right and left sides. Yildiz et. al. found the SEM value 0.101 in ankle sprain patients.[33] This value might suggest that a low SEM value can give a sense of whether any change is genuine and can also provide high confidence with other outcomes. These findings provide as baseline information for future research with children with CP.

The MDC for both the 360DTT times on the dominant and non-dominant sides in MS patients were 1.49 sec. and 1.53 sec, respectively.[30] The minimum difference that would accurately reflect the differences in finishing the 360DTT is represented by such MDC values. From a clinical perspective, the MDC may prove beneficial in upcoming CP clinical trials when assessing whether the intervention protocol has indeed improved turning ability.

The minimal difference that would indicate a real change in the patient's state of health might be shown by the MDC. Also the MDC values of 360DTT were found 1.44 and 1.57 sec. respectively in children with CP. When Soke et al. identified the intra-rater MDC values of 1.98 s for dominant side and 1.48 sec. for nondominant side in PS patients,[29] Shiu et al. revealed that MDC values were 1.22 seconds for participants turning toward the unaffected side and 0.76 seconds for subjects turning toward the damaged side in stroke patients.[19] With terms of clinical trials, the MDC may prove beneficial for assessing whether the turning ability of participants with CP has indeed changed as a result of the intervention program.

Research investigating the 360DTT's concurrent validity in evaluating dynamic balance across various populations has revealed the test's strong validity. In these research, the Berg Balance Scale (BBS), TUG, and FSST were primarily utilized for concurrent validity.[19,30-33] These tests are similar to the 360DTT in that they require functional independence, coordination, stability in postural control, and both static and dynamic balance. We used PBBS, PFRT, TUG and FSST for validation.

Correlations were detected between 360DTT (right-left) and PBBS, PFRT, FSST, and TUG in all children with CP. The examination of dynamic balance by changing the center of gravity by turning and increasing the functional mobility of the 360DTT is considered to upload more postural control mechanisms like activating balance reactions or increasing muscle activity with using somatosensory and vestibular systems.

Deficits in balance are common in children with neurological (central and peripheral), orthopedic, and/or vestibular problems. Strong evidence for the use of one or more functional balance tests in children with CP cannot be offered due to a dearth of high-quality methodological studies. Furthermore, the establishment of a criterion standard for measuring balance is necessary in children with CP.[34] The PFRT, PBBS, 3meter walk test (3mBWT), FSST and TUG tests have all undergone extensive testing and demonstrate strong reliability in children with CP.[14,24,25,34-37] But the review studies shows that there is an absence of a criteria standard to gauge balance control raises questions about validity.[34] Technical tests are difficult to apply in clinical practice, and developmental scales are not expressly developed to evaluate balance control. So 360DTT can be useful for measurement of the dynamic balance as a good and practical performance test for CP children the GMFCS (E&R) level I and II.

The 360DTT is a simple, quick, and accurate assessment method for determining a person's ability to turn after a stroke.[19] It measures how long it takes an individual to rotate from a standing position. A crucial element of many clinical mobility and balance evaluations is turning ability. Turning, for instance, is a fundamental feature of the TUG and PBBS, two of the most widely used evaluation instruments for determining balance and mobility.[12,36,38]

Despite turning 180° twice, TUG does not expressly evaluate rotation.[38] The 360° turn is the only one of the 14 tasks that the PBBS measures. It receives a score ranging from 0 to 4 based on whether it takes less than or more than 4 seconds to complete. When evaluating turning abilities, the timed 360DTT is a more accurate and efficient assessment method than the TUG and PBBS.[29] It is associated to functional dependence among elderly people who live in communities.[29,30]

Functional mobility tests typically assess the capacity to move forward and turn and are performance-based. Understanding the many mechanisms underlying postural control in children with CP is necessary for conducting effective balance measurements. We think that the 360DTT dynamic balance test will be a valuable tool for all clinicians to employ in order to objectively observe the advanced functional skills that children with CP possess.

One of our limitations was that children with varying clinical types of CP and GMFCS (E&R) III were not assessed for the 360DTT. Because of this, it is not possible to apply the results to all children with CP. However, investigations involving children with CP of all different clinical types and functional levels can compute minimal detectable change (MDC) values of 360DTT in future studies. Additional research can also be conducted to identify the cut-off value of 360DTT for assessing the risk of falls in these children. For future studies, it could be beneficial to include qualitative feedback from the physiotherapists' experiences with the 360DTT.

CONCLUSION

This study revealed that 360DTT has a good test–retest reliability in children with CP in the level of GMFCS I and II. Also 360DTT is a good performance test to evaluate functional mobility and dynamic balance in children with CP. The advantages of 360DTT are that it specifically evaluates rotations in standing position. It may be better in this regard than other functional mobility tests since it incorporates additional parameters that are difficult for current evaluations to fully capture. As a result, we believe that this test should be used often for assessing dynamic balance, functional mobility, and gait in clinical settings.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was obtained from Kahramanmaras Sutcu Imam University Medical Research Ethics Committee (Date: 12.02.2022, Decision No: 2022/07).

Informed Consent: Parents of the children signed written informed consent.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article / Orijinal Araştırma

Investigation of the Public Knowledge Level about Rational Antibiotic Use

Akılcı Antibiyotik Kullanımı Hakkındaki Halkın Bilgi Düzeyinin Araştırılması

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Abstract

Aim: Antimicrobial agents are among the most commonly used medications in the community. They are also the drug group with the highest rate of misuse. The purpose of this study was to investigate the level of public knowledge regarding antibiotic drug use.

Material and Method: This study was conducted from November 6, 2022, to November 26, 2022, with the participation of 459 individuals aged 18 years and older. Participants completed an 11-question questionnaire that was distributed via the internet.

Results: The proportion of females was 75.8%, and 64.7% of participants were between the ages of 18-24. 17.9% of participants reported using leftover antibiotics from a previous prescription when they became ill again, while 19.4% of participants visited a hospital and requested antibiotic prescription from a doctor. The analysis revealed no statistically significant relationship between the use of antibiotics left in the box and the status of applying to the hospital for antibiotic prescription, gender, the way of accessing health-related information, and studying or graduated from medicine (p>0.05).

Conclusion: The fact that there is no positive difference between those who have received health education and others in terms of antibiotic use shows that educational activities on this issue should be carried out for everyone, including all levels of society. In addition, it would be beneficial to expand all these activities in the Internet-based environment, considering the high rate of people accessing health-related information through the Internet.

Keywords: Public health, antibiotic resistance, information

Öz

Amaç: Toplumda en çok kullanılan ilaçlar arasında antimikrobik ajanlar bulunmaktadır. Bu ilaçların aynı zamanda yanlış kullanım oranı en fazla olan ilaç grubu olduğu da bilinmektedir. Bu çalışmadaki amacımız, halkın antibiyotik ilaç kullanımı hakkında bilgi düzeyini araştırmaktır.

Gereç ve Yöntem: Bu çalışma 06.11.2022-26.11.2022 tarihleri arasında 18 yaş ve üzeri 459 kişinin katılımı ile gerçekleştirildi. Katılımcılar internet üzerinden gönderdiğimiz 11 soruluk anketi cevapladılar.

Bulgular: %75,8'inin kadınların oluşturduğu katılımcı popülasyonunun %64.7'si 18-24 yaş aralığındadır. Katılımcıların %17,9'u bir sonraki hatalıklarında kutuda arta kalan antibiyotikleri kullandıklarını ifade ederken %19,4'ü hastaneye müracaat ederek doktordan antibiyotik reçete etmesini istemiştir. Kutuda arta kalan antibiyotiklerin kullanımı ve antibiyotik reçete etmek için hastaneye müracaat etme durumunun cinsiyet, sağlık ile ilgili bilgilere ulaşma şekli ve sağlık bölümlerinde okuma veya mezun olma arasında anlamlı düzeyde ilişki bulunmamıştır (p>0.05).

Sonuç: Sağlık alanında eğitim alanlar ile diğerleri arasında antibiyotik kullanımı açısından olumlu yönde bir farkın olmaması bu konudaki eğitici faaliyetlerin toplumun tüm katmanlarını içerecek şekilde herkese yönelik yapılması gerektiğini ortaya koymaktadır. Ayrıca, sağlık ile alakalı bilgileri internet üzerinden ulaşan kişilerin oranının yüksekliği göz önünde bulundurulduğunda tüm bu faaliyetlerin sanal ortamda da yaygınlaştırılmasının faydalı olacağı değerlendirilmiştir.

Anahtar Kelimeler: Halk sağlığı, antibiyotik direnci, bilgi

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INTRODUCTION

Antibiotics are a diverse group of structural and molecular entities unified by their capacity to inhibit microbial growth at high concentrations, rather than a distinct class of molecules viewed from an anthropocentric perspective. The original usage of the term 'antibiotic' was merely a generic term reflecting the outcome of a laboratory test.[1] In modern usage, antibiotic refers to a low molecular weight molecule categorized as narrow-spectrum or broad-spectrum according to its natural, semi-synthetic, and synthetically produced spectrum of activity, utilized to inhibit bacterial growth (bacteriostatic) or kill them (bactericidal), and encompasses a wide range of chemical substances.[2] The intensive use and misuse of antibiotics are undoubtedly the primary factors linked to the high prevalence of resistant pathogenic and commensal bacteria worldwide. Both the amount and manner in which antibiotics are administered contribute to the selection of resistant strains. However, other social, environmental, and genetic factors influence the direct relationship between use and the frequency of resistance.[3] The overuse of antibiotics has been reported in both community and hospital settings globally, particularly in developing countries.[4] It is reported that antibiotics are the most commonly used drugs in Turkey, accounting for approximately 20% of the market value of drugs.[5] Antimicrobial use is the most critical determinant of resistance development. Many essential parameters for rational antimicrobial therapy have been defined. Maximum treatment efficacy should be combined with minimum toxicity at the lowest cost. The quality of antimicrobial use depends on knowledge of various aspects of infectious diseases. In terms of efficacy, many of our indications for antimicrobial use need to be critically evaluated. Irrational use should be discouraged. Preventing the development of resistance is a quality parameter that requires more attention.[6] High levels of antibiotic consumption increase the levels of bacterial resistance that threaten public health. However, antibiotics still provide highly effective treatments for common diseases with a significant impact on human health. The challenge for public education is to achieve a significant reduction in unnecessary antibiotic use without compromising the treatment of bacterial infections.[7] Antimicrobial agents are among the most widely used drugs. At the same time, they are the most misused group of drugs. Our aim in this study was to investigate the level of public knowledge about the use of antibiotics.

MATERIAL AND METHOD

This study was conducted online from November 6th to November 26th, 2022, with participation from 459 individuals over 18 years old who completed questionnaires. The online data collection form consisted of two sections related to basic sociodemographic data and antibiotic use characteristics. In the initial section, sociodemographic characteristics, including age, gender, academic status (i.e., whether the individual was currently studying or had previously graduated from a medical programme), and smoking status, were investigated with regard to their association with demographic characteristics. The second section of the questionnaire inquired about the sources of health-related information, the individuals who recommended the use of antibiotics, and general knowledge about antibiotics and their mechanism of action. This study was evaluated by the ethics committee of Health Sciences University Hamidiye Medical Faculty at its meeting dated October 14th, 2022, and found ethically appropriate.

RESULTS:

Of the 459 participants, 75.8% were female and 48.6% were between the ages of 18-24 years. Other sociodemographic and general information about antibiotic use of the participants are shown in **Table 1**.

Table 1. Demographic distribution and general information about antibiotics

	N	%
Gender		
Women	348	75.8
Men	111	24.2
Age		
18-24 y	223	48.6
25-34 y	81	17.6
35-44 y	98	21.4
45 y and older	57	12.4
Studying or graduated from medicine		
Yes	162	35.3
No	297	64.7
Current smoking		
Yes	95	20.7
No	348	75.8
Quit smoking	16	3.5
How to access health-related information		
Internet	113	24.6
By applying to health institutions	344	74.9
Who recommends your antibiotics?		
Medical doctor	450	98.0
Pharmacist	5	1.1
Others	4	0.9
What is the mechanism of action of antibiotics?		
Reduce fever	9	2.0
Protect from disease	18	3.9
Reduce pain	13	2.8
Reducing inflammation by killing microbes	400	87.1
No idea	19	4.1
What is the duration of antibiotic use?		
Until the box ends	117	25.5
As prescribed by the doctor	307	66.9
Until the complaints are gone	32	7.0
Until fever reduces	3	0.7
Antibiotics are effective against viruses		
Yes	136	29.6
No	246	53.6
No idea	77	16.8
Do you use leftover antibiotics from the medicine box without consulting a doctor?		
Yes	82	17.9
No	377	82.1
Did you admit the hospital and ask the doctor to prescribe antibiotics?		
Yes	89	19.4
No	370	80.6

The analysis revealed no significant relationship was found between gender, access to health-related information, studying or graduated from medicine and the use of leftover antibiotics in the medicine box without consulting a doctor (p>0.05) (**Table 2**).

Table 2: Comparison of the increased use of antibiotics without consulting a doctor with gender, access to health-related information and studying or graduated from medicine

		Gender		P value
		Women	Men	
Do you use the remaining antibiotics without consulting the doctor?	Yes	57 (16.4)	25 (22.5)	0.141
	No	291 (83.6)	86 (77.5)	
		Access to health information		P value
		Internet	By applying to health institutions	
	Yes	25 (22.1)	55 (16)	0.136
	No	88 (79.9)	289 (84)	
		Studying or graduated from medicine		P value
		Yes	No	
	Yes	26 (16)	56 (18.9)	0.453
	No	136 (84)	241(81.1)	

Table 3 also illustrates the comparison of gender, access to health-related information, studying or graduated from medicine with the status of applying to the hospital and prescribing antibiotics to the doctor.

Table 3: Comparison of gender, the way of accessing health-related information and the status of studying or graduated from medicine on the status of going to the hospital and prescribing antibiotics to the doctor

		Gender		P value
		Women	Men	
Did you admit to the hospital and ask the doctor to prescribe antibiotics?	Yes	67 (18.3)	22 (19.8)	0.895
	No	281 (80.7)	89 (80.2)	
		Access to health information		P value
		Internet	Applying to health institutions	
	Yes	22 (19.5)	65 (18.9)	0.893
	No	91 (80.5)	279 (81.1)	
		Studying or graduated from medicine		P value
		Yes	No	
	Yes	27 (16.7)	62 (20.9)	0.276
	No	135 (83.1)	235 (79.1)	

DISCUSSION

In this study, we examined the level of knowledge about antibiotic use in a population of 459 individuals. The discovery of antibiotics is considered one of the most significant medical advancements of the last century.[8] Antibiotics are substances that kill or inhibit the growth of microorganisms causing infectious diseases, either found in nature or synthesized partially or entirely in a factory,[9] and save millions of lives annually by preventing many infectious complications when used appropriately.[10] Their development has been the most critical advance in preventing, controlling, and curing serious infections.[11] However, the widespread and indiscriminate use of these drugs,[12] along with poor practices related to disease prevention and control, has led to the development of resistance in many microorganism strains worldwide, resulting in antibiotic resistance, which is defined as the ability of microorganisms to resist the action of antimicrobial agents and occurs when an antibiotic loses its effectiveness in inhibiting bacterial growth.[13] The relationship between antibiotic consumption and resistance is well-documented at spatial and temporal scales in hospitals, nursing homes, primary healthcare facilities, and communities, as well as across countries.[14] In the absence of next-generation antibiotic development, appropriate use of existing antibiotics is essential to ensure long-term availability of effective treatment for bacterial infections.[15] Rational drug use involves prescribing the appropriate drug at the right time.[16] Irrational antibiotic use is a persistent global public health issue that warrants increased attention. The World Health Organization (WHO) estimates that more than 50% of all medicines globally are inappropriately prescribed, dispensed, or sold.[17] If antibiotics become ineffective, established and emerging infectious diseases can lead to increased morbidity, healthcare utilization, and premature mortality.[18] A study conducted by Botan et al. in 2015 on 154 adults aged 18 and above who applied to a family health center in Van's city center found that 24.5% of women and 33.3% of men requested antibiotic prescription when consulting a doctor for any reason, but there was no statistically significant difference between genders.[19] Similarly, a study by Baydar Artantaş et al. involving 257 adults who applied to hospital family medicine outpatient clinics found that 55.8% of those using antibiotics without examination for conditions like influenza, colds, and flu were women and 44% were men; additionally, 55.6% of those prescribing antibiotics without patient consent or buying antibiotics without prescription were female and 44.4% were male.[20] A study by Napolitano F et al. in 2013 involving 419 individuals investigating Italian population knowledge, attitudes, and behaviors regarding antibiotics found no significant relationship between gender and antibiotic use without prescription.[21] In our study, when evaluating participants based on gender variables, 16.4% of female participants and 22.5% of male participants stated they used increased antibiotics without consulting doctors. Additionally, 18.3% of female participants and 19.8% of male participants stated they went to the hospital and requested antibiotic prescription from doctors. Similar to previous studies,[20,21] it was concluded that inappropriate antibiotic use behaviors were more common among male participants than female participants. In a study by İlhan et al. conducted in February 2006 among 2696 individuals aged 18 and above who applied to five primary healthcare centers where Gazi University's Faculty of Medicine conducted education and research activities, it was found that 17% of women, 8% of men, and 21.2% of men self-administered antibiotics; a significant relationship was observed between

male gender, being single, having secondary school or higher education, being employed, and not having social security.[22] In our study, 16.7% of participants who studied in medicine or graduated from medicine stated they used increased antibiotics without consulting doctors and 16.7% stated they requested antibiotic prescription from doctors by going to the hospital; while 18.9% of participants who did not study in medicine or graduate from medicine stated they used increased antibiotics without consulting doctors and 20.9% stated they requested antibiotic prescription from doctors by going to the hospital. Today, individuals are expected to have skills to access health-related information, use health services correctly, and take responsibility for their own health to protect and improve health. To achieve this expectation, individuals need sufficient health literacy to access and understand health information and communicate with healthcare providers during diagnosis, treatment, rehabilitation, and health protection processes. [23] With the development and integration of mobile Internet and mobile phones, tablet computers, and other mobile terminals, people can now search for health information online regardless of time or place, allowing them to solve unexpected health problems. Therefore, the Internet and its various applications have become increasingly integrated into daily life.[24] In our study, 22.1% of participants who accessed health information via the internet stated they used their antibiotics without consulting their doctors; 19.5% stated they requested antibiotic prescription from doctors by going to the hospital; while 16% of those who accessed health information by applying to healthcare institutions stated they used their antibiotics without consulting their doctors; and 18.9% stated they requested antibiotic prescription from doctors by going to the hospital. When examined in percentage terms, we can comment that access to health information via the internet increases inappropriate antibiotic use behavior. As health-related information becomes increasingly accessible to the public, it is essential to evaluate the quality of accessible resources such as the internet in disseminating information about antibiotics and their appropriate use.[25] Antibiotics have been one of the most important discoveries that have transformed human health quality by preventing life-threatening bacterial infections; however, as resistance to existing antibiotics continues to increase, it will be necessary to develop new agents with new targets or mechanisms of action. The combination of currently available antibiotics may continue to be useful in treating resistant pathogens; however, it is likely that physicians will run out of options in the future. Several experimental molecules exist in the literature and are being considered for clinical development. There is no doubt that as antibiotic resistance increases worldwide, physicians and industry alike will face great challenges in finding new products to continue the antibiotic miracle long into the future. Every effort must be made today to preserve and optimize the agents in our treatment arsenal.

CONCLUSION

Upon evaluating the participants in our study based on gender, we found that 16.4% of female participants and 22.5% of male participants reported using antibiotics without consulting a physician. Additionally, 18.3% of female participants and 19.8% of male participants stated that they visited the hospital and requested antibiotic prescription from healthcare providers. Upon examination of gender variables, we found that inappropriate antibiotic use behaviors were more prevalent among male participants compared to female participants, although no significant correlation was observed between these parameters. In our study, no significant association was identified between having studied in medicine or graduated from medicine and inappropriate antibiotic consumption or requesting antibiotic prescription. However, when examined as a percentage, we noted that the awareness levels of participants who had studied in medicine or graduated from medicine were higher than those of other participants. Furthermore, when analyzed as a percentage, we observed that access to health information via the internet is associated with increased inappropriate antibiotic use behavior. Given the increasing accessibility of health-related information to the public, it is essential to evaluate the role of variable quality accessible sources, including the internet, in disseminating information about antibiotics and their appropriate use.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was evaluated by the ethics committee of Health Sciences University Hamidiye Faculty of Medicine at its meeting dated 14.10.2022 and was found ethically appropriate.

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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Original Article / Orijinal Araştırma

Comparison of Inflammation Scores of Patients Diagnosed with Hyperemesis Gravidarum who Applied to the Emergency Clinic and Were Hospitalized with Pregnant Women with a Normal Course

Acil Polikliniğine Başvuran ve Hospitalize Edilen Hiperemezis Gravidarum Tanılı Hastaların İnflamasyon Skorlarının Normal Seyirli Gebelerle Karşılaştırılması

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Abstract

Aim: We aimed to compare systemic inflammatory markers ((NLR (neutrophil/lymphocyte ratio), PLR (platelet/lymphocyte ratio), MLR (monocyte/lymphocyte ratio), SII (systemic immune-inflammation index) and SIRI (systemic inflammation response index)) in patients diagnosed with HEG with normal pregnant women in the first trimester.

Material and Method: Our research is a retrospective diagnostic study. The study included 52 pregnant women who applied to the emergency gynecology clinic between the 7th and 12th weeks of pregnancy and were hospitalized due to 2+ ketonuria. The control group consisted of healthy pregnant women at the same gestational age who applied to the gynecology clinic. Statistical analysis was performed with the SPSS (Statistical package for Social Sciences-SPSS Inc., version 20.0; Chicago, IL) program.

Results: There was no statistically significant difference between the groups in terms of maternal age, parity, body mass index (BMI) and elective curettage numbers (p>0.05). When platelet, monocyte, leukocyte and lymphocyte values were compared between the two groups, no difference was found (p>0.05). However, when neutrophil count, NLR and PLR results were evaluated, we observed a statistically significant difference (p<0.05). We also found that combined inflammatory indices, including SII and SIRI, were significantly higher in Group HEG (p=0.000 and p=0.0011, respectively).

Conclusion: The results of our study showed that neutrophil and combined systemic inflammatory indices (NLR, PLR, SII, SIRI) were associated with the presence of HEG. According to our results, NLR was determined to have the strongest diagnostic efficacy in detecting the presence of HEG.

Keywords: Combined systemic inflammatory indexes, hyperemesis gravidarum, pregnancy

Öz

Amaç: HEG tanılı hastalarda sistemik inflamatuar belirteçlerin (NLR(nötrofil/lenfosit oranı) , PLR (platelet/lenfosit oranı), MLR (monosit/lenfosit oranı), SII(sistemik immun-inflamasyon indeksi), ve SIRI (sistemik inflamasyon cevap indeksi), normal gebelerle, ilk trimesterde karşılaştırılması amaçlandı.

Gereç ve Yöntem: Araştırmamız retrospektif tanısal değerlilik çalışmasıdır. Çalışmaya, 7-12. gebelik haftaları arasında acil kadın doğum kliniğine başvuran ve 2+ ketonüri nedeniyle hospitalize edilen 52 gebe kadın dahil edildi. Kontrol grubu ise aynı gebelik haftasında olan, kadın doğum polikliniğine başvuran sağlıklı gebelerden oluşturuldu. İstatistiksel analiz SPSS (Statistical package for Social Sciences-SPSS Inc., version 20.0;Chicago, IL) programı ile yapıldı.

Bulgular: Maternal yaş, parite, vücut kitle indeksi (BMI) ve elektif küretaj sayıları açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu (p>0,05). İki grup arasında trombosit, monosit, lökosit ve lenfosit değerleri karşılaştırıldığında fark bulunmadı(p>0,05). Ancak, nötrofil sayısı, NLR ve PLR sonuçları değerlendirildiğinde istatistiksel olarak anlamlı bir fark gözlemledik (p<0,05). Ayrıca, SII ve SIRI'yı içeren kombine inflamatuar indekslerin de HEG grubunda anlamlı derecede yüksek olduğunu tespit ettik (sırasıyla, p=0,000 ve p=0,0011).

Sonuç: Çalışmamızın sonuçları, nötrofil ve kombine sistemik inflamatuar indekslerinin (NLR, PLR, SII, SIRI) HEG varlığı ile ilişkili olduğunu gösterdi. Sonuçlarımıza göre, NLR'nin HEG varlığını tespit etmede en güçlü tanısal etkinliğe sahip olduğu belirlendi.

Anahtar Kelimeler: Kombine sistemik inflamatuar indeksler, hiperemezis gravidarum, gebelik

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INTRODUCTION

Nausea and vomiting are complaints that are seen in approximately 80% of pregnant women in the first trimester of pregnancy, usually end before the 20th week of pregnancy, and can sometimes continue until birth.[1,2] Hyperemesis Gravidarum (HEG) is a very severe form of these symptoms which can cause dehydration, ketonemia, ketonuria, electrolyte imbalance and loss of more than 5% of pre-pregnancy weight.[3,4]

The incidence of HEG has been reported as 0.5-2% in many studies, but it has been emphasized that this rate may vary depending on ethnicity.[5] While HEG is usually seen between the 8th and 12th weeks of pregnancy, it can last throughout pregnancy in 5% of cases.[6] The etiology of HEG has been examined in many studies, but no clear conclusion has been reached due to the heterogeneity of the results. Hormonal changes, immunological and psychological factors, abnormal gastric motility, Helicobacter pylori infection, genetic predisposition and liver dysfunction, inflammation are effective in the pathophysiology of HEG.[7-9] In the presence of chronic inflammation, relative thrombocytosis develops secondary to proliferation in megakaryocytes. As a result of increased apoptosis, lymphocyte numbers decrease. Because platelets modulate inflammatory reactions, they can also affect the monocyte/lymphocyte ratio (MLR), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR).[10,11] It has been shown that these indicators are associated with gestational diabetes accompanied by increased inflammation, preeclampsia, preterm birth and acute appendicitis.[12,13] Studies have reported that other inflammation indicators such as C-reactive protein (CRP), vaspin, and acute phase reactants also increase in HEG cases.[14,15] Considering the detection of inflammation, the high cost of these tests directs the clinician to less costly and easily accessible routine hemogram tests. In addition to MLR, NLR and PLR, inflammation has been evaluated with combined inflammatory indices in recent studies. Systemic immune-inflammation index (SII) and Systemic inflammatory response index (SIRI) are newly defined combined indices that evaluate the inflammatory process and response. The negative consequences of these indices in pregnant women with coronavirus disease and their relationship with cancer patients have been evaluated.[16-18]

However, there is not enough data regarding the relationship of these indices with the presence of HEG.

We aimed to compare systemic inflammatory markers ((NLR (neutrophil/lymphocyte ratio), PLR (platelet/lymphocyte ratio), MLR(monocyte/lymphocyte ratio), SII (systemic immune-inflammation index) and SIRI (systemic inflammation response index)) in patients diagnosed with HEG with normal pregnant women in the first trimester.

MATERIAL AND METHOD

The study was carried out with the permission of University Karamanoğlu Mehmet Bey, Faculty of Medicine Clinical Researches Ethics Committee (Date: 04.03.2024, Decision No: E-11095095-050.04-181579).

Patients who applied to Karaman Training and Research Hospital Emergency Gynecology and Obstetrics Outpatient Clinic with complaints of extreme nausea, vomiting and inability to feed, were diagnosed with HEG and were hospitalized between 01.06.2023 and 01.12.2023 were included in our study. The control group consisted of healthy pregnant women who had routine outpatient clinic follow-ups and who were not diagnosed with HEG. The inclusion criteria of our study are; singleton pregnancy,7-12. weeks of pregnancy, presence of >+2 ketonuria in complete urine analysis, absence of chronic disease and vaginal bleeding. Multiple pregnancies, pregnant women <18 years of age, pregnant women with inflammatory diseases, or using anti-inflammatory or corticosteroid-containing drugs were not included in the study. Demographic and obstetric data of pregnant women diagnosed with HEG who applied to the emergency clinic, TIT (complete urinalysis) result taken at the time of admission, hemogram parameters (Sysmex xn-1000 device) and SII (platelet x neutrophil /lymphocyte), SIRI (neutrophil x monocyte/lymphocyte), NLR (neutrophil/total lymphocyte), MLR (monocyte/ total lymphocyte), PLR (platelet/total lymphocyte) results were recorded.

Statistical Analysis

G-Power analysis was applied to determine the number of groups. According to these results, the groups were planned to include a minimum of 52 pregnant women with a power of 0.85 and a margin of error of 10%. Statistical Package for Social Sciences (SPSS Inc., version 20.0; Chicago, IL) was used in statistical analyses. All statistical data were made with SPSS 20.0 version program for Windows. The normal distribution of the data was evaluated with histogram, one of the graphical methods. Skewness-kurtosis method and Kolmogorov Smirnov test and method were used to evaluate the normal distribution of variables. Descriptive statistics were used in the demographic analysis of the patients. Numerical values are expressed as mean ± standard deviation and minimum-maximum values. In evaluating the data, the t-test, the significance test of the difference between two means in independent groups, was applied. Statistical significance level was accepted as $p<0.05$. Cut-off evaluation of statistically significant results was made with the ROC (Receiver-Operating Characteristics) curve.

RESULTS

Our study started with the evaluation of 60 patients, five of our patients were due to abortion; three of our patients due to loss of follow-up were not included in our sample. The average age of 52 pregnant women in each HEG and contol

pregnant group were 27.2±4.6/year in the HEG group and 29.1±4.5/year in the control pregnant group and there was no statistically significant difference between HEG patients and the control group in terms of age (p>0.05).

Accordingly, when the gravida numbers of the HEG patient and control pregnant groups were compared, there was a significant difference (p<0.05), while BMI (body mass index), parity and abortion numbers did not create a significant difference between the groups (p>0.05). When the gestational weeks of the HEG patients and other groups were evaluated, the data of 10.5±2.9/week in the HEG patient group and 8.6±1.3/week in the control pregnant group were found to be statistically significant (p<0.05) (**Table 1**).

Table 1. Demographic data distribution of patients

Demographic features Independent variables (IVs)	Group 1 (HEG)	Group 2 (Control)	p value
Age (Mean±SD)	27.2±4.6/years	29.1±4.5/years	0.93
BMI (Mean±SD)	24.6±3.6	26.7±5.8	0.72
Gravida (Mean±SD)	1.8±0.8	2.1±1.2	0.03*
Parite (Mean±SD)	0.9±1.03	0.5±0.7	0.06
Abort (n,%)	10(19.2%)	10 (20%)	<0.81
Week of pregnancy	10.5±2.9	8.6±1.3	<0.05*

HEG:hyperemesis gravidarum, BMI: body mass index, SD: Standard Deviation Chi-square test and t-test were used in statistical analysis. *p<0.05 was considered significant

Laboratory data of hyperemesis gravidarum patients and differences between groups:

The neutrophil values of the HEG patients were found to be statistically significantly higher (p < 0.05), and the difference in WBC (white blood cell), lymphocyte, monocyte and platelet values between the 2 groups was not statistically significant (p > 0.05). While there was no significant difference between the groups when the monocyte/lymphocyte ratio was evaluated (p>0.05), a statistical difference was observed in the neutrophil/lymphocyte, platelet/lymphocyte ratios (p<0.05). However, when the SII and SIRI indices were compared, the higher results of HEG group compared to control group were statistically significant (p <0.05) (**Table 2**).

Table 2 Laboratory results of patients

Laboratory parameters	Group 1 (HEG) (Mean±SD)	Group 2 (Control) (Mean±SD)	p value
WBC (4.0-10.0 × 10^9/L)	9.5±2.9	8.9±1.9	0.053
Neutrophil (2.0-6.0× 10^9/L)	7.4±2.7	6.2±1.4	0.004*
Lymphocyte (1.1-3.2 ×10^9/L)	1.6±1.5	2.0±0.6	0.111
Monocyte (%)	0.46±0.15	0.64±0.9	0.190
Platelet/ml	246.9±61.5	253±56.4	0.297
SII	1721.5±753.8	753.9±252.6	0.000*
SIRI	3.4±4.3	1.9±2.8	0.011*
NLR	8±11.3	3±0.9	0.000*
MLR	0.44±0.4	0.31±0.43	0.082
PLR	231±23,5	123±35.2	0.001*

HEG:hyperemesis gravidarum, SD: Standard Deviation, WBC:white blood cell, SII: systemic immune-inflammation index, SIRI: systemic inflammation response index, NLR: Neutrophil/lymphocyte ratio, MLR: Monocyte/lymphocyte ratio, PLR: Platelet/lymphocyte ratio
T-test were used in statistical analysis, *p<0.05 was considered significant.

ROC analysis evaluation of Leukocyte, Neutrophil and SII:

SII and SIRI parameters, neutrophil, NLR, PLR of HEG patients were analyzed with ROC curve and area under the curve (AUC), cut-off, sensitivity and specificity in order to guide the clinician about the patient's condition during patient follow-up. Parameters with AUC <0.6 and (P>0.05) not found to be statistically significant were excluded. For SII, AUC, cut-off, sensitivity, and specificity were 0.780, 860, 71%, and 76%, respectively. For SIRI, AUC, cut-off, sensitivity and specificity were 0.680, 1.9, 56% and 78%, respectively. AUC, cut-off, sensitivity, specificity for neutrophil were 0.645, 5.7, 78% and 62%, respectively. AUC, cut-off, sensitivity, specificity for Neutrophil/Lymphocyte ratio were 0.785, 3.17, 79% and 68%, respectively. AUC, cut-off, sensitivity, specificity for Platelet/Lymphocyte ratio were 0.776, 126.5, 77% and 62%, respectively (**Figure 1**).

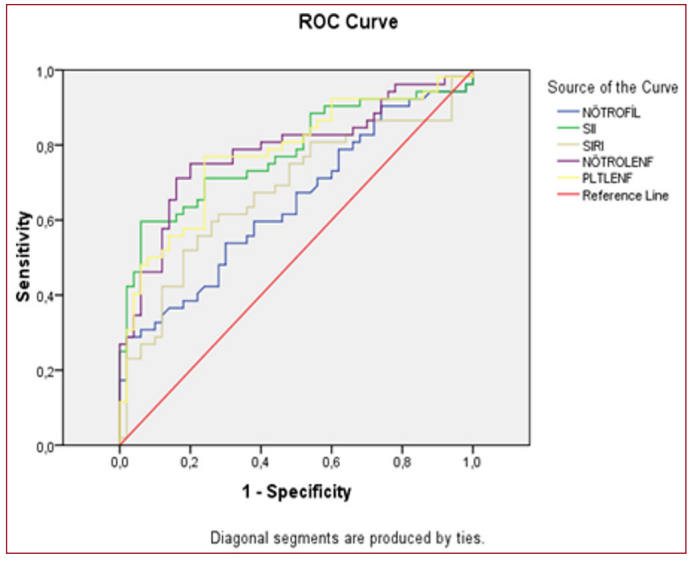

Figure 1. Receiver operating characteristic analysis of Neutrophil, SII, SIRI, Neutrophil/lymphocyte ratio, Platelet/lymphocyte ratio for the prediction of hyperemesis gravidarum

DISCUSSION

In the current study, the diagnostic value of NLR, PLR, SII, SIRI was evaluated in patients with HEG. According to the results of the current study, NLR, PLR, SII, SIRI values were increased in patients with HEG compared to those without HEG, and the sensitivity of the specified parameters was found to be low, and the selectivity was relatively high. This shows that biomarkers can be a diagnostic aid but cannot be used as an exclusion test. In our study, neutrophils, NLR, PLR, SI and SIRI stand out as clinical markers in HEG patients. HEG may progress in a severe form that may require hospitalization, and Wernicke encephalopathy may also be present.[19] The NLR is a marker of systemic inflammation and stress.[1-3] In HEG, studies have shown elevated NLR levels, indicating an increased neutrophil count relative to lymphocytes. This elevation suggests a heightened inflammatory response.[20-22] Similar to NLR, the PLR is another marker of systemic inflammation. Elevated PLR levels in HEG patients reflect increased platelet counts,

which are involved in inflammatory processes and immune responses.[23-25] The SII is a composite marker that incorporates neutrophil, platelet, and lymphocyte counts. It provides a more comprehensive assessment of the inflammatory response.[26,27] Elevated SII levels in HEG patients suggest a robust inflammatory state involving multiple immune cell types. In the literature, there are three plausible pathogenesis explanations for the results of the study, including hormonal changes,[28,29] immune system modulation,[30] and possibly infections. Pregnancy induces significant hormonal changes, particularly elevated levels of human chorionic gonadotropin (hCG) and estrogen, which are believed to contribute to HEG.

Studies evaluating the relationship between inflammatory parameters and HEG were available in the literature.[31-33] However, HEG; Although it is a clinical condition that develops during pregnancy, its cause is still not fully known. Whether hemogram parameters and their relationship with markers such as SI and SIRI are related to diagnosis and their use in treatment follow-up may reduce the duration of hospital stay. Apart from clinical conditions affecting the mother such as dehydration, tachycardia, and confusion, intrauterine growth retardation may also occur in severe HEG cases. Protection of maternal and fatal health is very decisive in the development level of countries. Clinical guidance of inflammatory processes will positively affect the length of hospital stay and hospital cost analysis. It has been discussed in the literature whether acute phase reactants can be effective along with clinical laboratory parameters that occur with pregnancy. Yoneyama et al. reported that TNF-α values were high in HEG patients.[34] Kaplan et al. They also emphasized that TNF-α, which plays a role in immune disorders, is effective in the pathogenesis and progression of HEG.[35] IL-6, another inflammation marker, was found to be higher in hyperemesis cases than in low-risk pregnant women.[36] In a different study, vaspin level was evaluated and it was emphasized that this inflammation marker increased as the gestational week progressed in HEG patients.[14] In a study involving 194 patients using routine complete blood count parameters, Çintesun et al. found the PLR and NLR results to be statistically significantly higher in HEG patients.[37] The same results were obtained in terms of PLR, NLR and CRP values in a different series of 154 patients (38). In our study, we found PLR and NLR results, which coincide with literature data, to be significantly higher in the HEG group.

Although an increase in leukocyte, hemoglobin and hematocrit levels based on hemoconcentration is expected in the presence of HEG due to nausea, vomiting and dehydration, no significant difference was observed with the control group in the studies conducted. In our study, we only compared leukocyte values and determined that the increase in the HEG group was not significant. When the lymphocyte count was evaluated, while in some studies the lymphocyte count of HEG patients was found to be high,[33] this difference was not observed in different studies.[40] We observed that this parameter is also lower in HEG group than in the control group, but there is no significant difference.

Minagawa et al. In their study, they found the neutrophil level to be statistically significantly higher in HEG cases, but when they compared the lymphocyte numbers, lymphopenia did not show a significant difference.[41] Similar to Minagawa's results, in our study, we found that the neutrophil level was significantly higher in the HEG group. In a study including 100 HEG patients, Yıldırım et al. found that the severity of HEG was associated with NLR and PLR values.[42]

The inflammation cascade is a complex process that does not operate through a single cell or mediator, but where cells and mechanisms activate and inhibit each other. Considering that evaluating single cell activity will not be sufficient, combined indices have been defined for this purpose.[18,42,43] In the study of Yıldırım et al., it was emphasized that SII and SIRI results were positively correlated with the presence and severity of HEG. When all parameters were evaluated in the same study, according to ROC analysis, the highest correlation was observed in SIRI and NLR indices.[42] Our study was a study in which NLR, PLR, SII and SIRI were evaluated together. We think that we will contribute to the literature by comparing these values with ROC analysis. The predictive value of neutrophil and SIRI (AUC values 0.680, AUC: 0.645 respectively) values in HEG patients was moderate. When we evaluated the ROC analyses, we found the strongest relationship in the NLR, PLR and SII parameters.

CONCLUSION

According to the results of the current study, NLR, PLR, SII, SIRI values were increased in patients with HEG compared to those without HEG, and the sensitivity of the specified parameters was found to be low and the selectivity was relatively high. NLR was determined to have the strongest diagnostic efficacy in detecting the presence of HEG. This shows that biomarkers can be a helpful test for diagnosis, but cannot be used as an exclusion test.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Karamanoğlu Mehmet Bey, Faculty of Medicine Clinical Researches Ethics Committee (Date: 04.03.2024, Decision No: E-11095095-050.04-181579).

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.

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Original Article / Orijinal Araştırma

Retrospective Evaluation of Pediatric Patients Hospitalized with Brucellosis: Single Center Study in Istanbul

İstanbul'da Hastaneye Yatırılan Pediatrik Brusellozlu Hastaların Retrospektif Değerlendirmesi: Tek Merkezli Bir Çalışma

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Abstract

Aim: Brucellosis is a zoonotic disease and mainly develops as a result of consuming products of infected animals such as cattle, sheep and pigs.

Material and Method: Pediatric patients under the age of 18 who were hospitalized with a diagnosis of brucellosis in a third-level city hospital were included in the study. Serology titer ≥1:160 and/or Brucella spp. in blood culture growth was determined as the diagnostic criterion for the diagnosis of brucellosis.

Results: Of the 35 pediatric patients diagnosed with brucellosis, 22 were boys and 13 were girls, and the average age was determined as 154.2±53.1 months (25-214). Hospital admission complaints were determined in order of frequency as follows; joint pain (51.4%), fever (31.4%), headache (17.1%) and abdominal pain (5.2%). Eleven of the patients (31.4%) had polyarthralgia and 7 (20%) had monoarthralgia. The most common physical examination findings were hepatomegaly (48.6%) and splenomegaly (40%), respectively. Joint involvement was detected in 17.1% of the patients. Sacroiliac joint involvement was reported in 3 (8.6%) patients, ankle joint involvement in 2 (5.7%) patients, and knee joint involvement in 1 (2.9%) patient. Anemia (60%) was the most common hematological finding. The average hemoglobin value was determined as 12.5±1.44 (10.2-15.9) g/dl. When patients are compared in terms of joint involvement; neutrophil count and treatment duration were found to be statistically higher in patients with joint involvement ($p<0.05$).

Conclusion: Brucellosis is a zoonotic disease that is endemic in our country, affects all age groups, and can cause complications and relapses, and continues to be a serious public health problem for our country.

Keywords: Brucella, child, zoonotic disease

Öz

Amaç: Bruselloz, zoonotik bir hastalık olup, başlıca enfekte sığır, koyun ve domuz gibi hayvanların ürünlerinin tüketilmesi sonucu gelişir.

Gereç ve Yöntem: Üçüncü düzey bir şehir hastanesinde bruselloz tanısıyla hastaneye yatan 18 yaş altı çocuk hastalar çalışmaya dahil edildi. Seroloji titresinin ≥1:160 olması ve/veya kan kültüründe Brucella spp. üremesi bruselloz tanısı için tanı kriteri olarak belirlendi.

Bulgular: 35 bruselloz tanılı çocuk hastanın 22'si erkek, 13'ü kız idi ve ortalama yaş 154.2±53.1ay (25-214) olarak belirlendi. Hastane başvuru şikayetleri sıklık sırasında göre şöyle belirlendi; eklem ağrısı (%51.4), ateş (%31.4), baş ağrısı (%17.1) ve karın ağrısı (%5.2). Hastaların 11'inde (%31.4) poliartralji, 7'sinde (%20) ise monoartralji şikayeti mevcut idi. En sık saptanan fizik muayene bulguları sırasıyla hepatomegali (%48.6) ve splenomegali (%40) olarak belirlendi. Hastaların %17.1'inde eklem tutulumu saptandı. 3 (%8.6) hastada sakroiliak eklem, 2 (%5.7) hastada ayak bileği eklemi, 1(%2.9) hastada ise diz eklem tutulumu raporlandı. Anemi (%60) en sık saptanan hematolojik bulgu idi. Hemoglobin değeri ortalama 12,5±1,44 (10,2-15,9) g/dl olarak saptandı. Hastalar eklem tutulumu açısından karşılaştırıldığında; eklem tutulumu olan hastalarda nötrofil sayısı ve tedavi süresi istatistiksel olarak daha yüksek bulundu ($p<0,05$).

Sonuç: Bruselloz ülkemizde endemik olan, tüm yaş gruplarını etkileyen, komplikasyon ve nükslere neden olabilen zoonotik bir hastalıktır ve ülkemiz için ciddi bir halk sağlığı sorunu olmaya devam etmektedir.

Anahtar Kelimeler: Brusella, çocuk, zoonotik hastalık

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INTRODUCTION

Brucellosis, also known as "Mediterranean fever" or "Malta fever", is a most common zoonotic infection transmitted to humans by consuming the products of infected cattle, sheep, pigs and some other animals.[1] Several species of the Brucella genus cause this disease, four Brucella types known as *Brucella abortus* (*B. abortus*), *B. melitensis*, *B. suis* and *B. canis* cause disease in humans, and *B. melitensis* and *B. suis* are known to be more virulent subspecies.[2] In this infectious disease, which usually has an incubation period of two to four weeks, clinical findings can vary in a wide range, but it can be said that the characteristic findings are fever, fatigue and arthralgia.[3] One of the most important and frightening features of Brucella disease is that it can affect all organs. The osteoarticular system is the most frequently involved system in brucellosis, followed by genitourinary system involvement.[4,5] Although less frequently, neurological involvement, hematological involvement, ocular involvement, skin involvement, cardiovascular involvement and pulmonary involvement can also be observed. Although brucellosis is a disease that can be seen at any age, 20-30% of cases are diagnosed in childhood.[6,7]

Brusellosis is endemic in Mediterranean basin countries, China, the Middle East, the Indian subcontinent, sub-Saharan Africa and parts of South America and 500,000 cases are reported worldwide every year.[1,8] Our country, Turkey, is an endemic country for brucellosis. According to the statistics of the General Directorate of Public Health of our country, the number of cases, which was 4173 in 2015, was reported as 6457 in 2017.[9] Although it is more common in the eastern provinces of our country, where the animal husbandry profession is more common, cases are encountered in every province throughout the country due to the habit of eating village cheese. In this study, we aimed to present the general characteristics and treatment regimen of patients hospitalized with the diagnosis of brucellosis.

MATERIAL AND METHOD

The study was performed in a tertiary city hospital in Istanbul which has a capacity of 100-bed pediatric unit. Electronic medical records from May 2015 to May 2023 were retrospectively reviewed to identify patients aged between 1 month and 18 years who were diagnosed with brucellosis.

All patients were questioned in terms of suspicious food consumption. Clinical and physical examination findings consistent with the disease and positive serology titer of ≥1:160 or patients with a positive blood culture for Brucella spp. was diagnosed with brucellosis. A positive blood culture in an asymptomatic patient was also accepted as diagnostic.[10,11] Some patients also underwent related serological tests such as ELISA.

Although fever, night sweats, fatigue, and arthralgia were considered the main clinical findings, symptoms such as weight loss, headache, abdominal pain, back pain, and depression were accepted as clinical findings consistent with the disease. Findings such as hepatomegaly, splenomegaly, lymphadenopathy, and pallor were also accepted as physical examination findings compatible with the disease.

Patients were identified through the department's archived patient files, and patients' information including age, sex, clinical findings, laboratory findings [(white blood cell; WBC), hemoglobin count, platelet count, C-reactive protein (CRP), erytrocyte sedimantation rate (ESR), liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT)], microbiological findings (blood culture), radiological findings (ultrasonography), treatment strategies and duration of hospital stay were collected. Echocardiography was performed in all patients with the diagnosis of brucellosis.

This study was approved by the Medical Research Ethics Committee of our institution (Date: 28.08.2023 Report Number:2023/514/256/4).

Normally distributed quantitative variables were expressed as mean±standard deviation, whereas non-normally distributed quantitative variables were expressed as median with interquartile ranges (IQR). Chi square test was used for comparing categorical variables. Mann–Whitney U test was used to compare two groups of non-normally distributed data. Student t-test was used to compare two groups of normally distributed data. All analyses were conducted using SPSS 25 software (IBM SPSS Statistics, New York), and $p< 0.05$ indicated a statistically significant difference.

RESULTS

Thirty-five children diagnosed with brucellosis were included in the study. 22 of the patients were male and 13 were female (male/female: 1.7) and the average age was 154.2±53.1 months (25-214). 94.2% of the patients had a history of consumption of raw milk and its products. All the patients were live in Istanbul, and there was no history of travel to other provinces from an epidemiological perspective.

The most common presenting symptom was arthralgia (51.4%), followed by fever (31.4%), headache (17.1%) and abdominal pain (5.2%). 11 (31.4%) of the patients with joint pain presented with polyarthralgia and 7 (20%) presented with monoarthralgia. When physical examination findings are examined; the most common finding was hepatomegaly (48.6%), while splenomegaly (40%) was the second most common finding. Joint involvement was detected in 17.1% of the patients, and when evaluated in terms of the sites of involvement, it was determined that the sacroiliac joint was involved in 3 (8.6%) patients, the ankle joint was involved in 2 (5.7%) patients, and the knee joint was involved in 1 (2.9%) patient.

Blood cultures of all patients were taken and *Brucella* spp. was detected in the blood cultures of 3 (8.6%) patients. While 28

(80%) patients aged over 8 years were given doxycycline and rifampicin oral treatments, 7 (20%) patients under 8 years of age were given trimethoprim-sulfometaxazole and rifampicin oral treatment combinations. Additionally, 10 (28.5%) patients received triple combination therapy with aminoglycosides. Although the treatment duration was determined as a minimum of six weeks, the treatment duration of patients with joint involvement was planned to be at least 3 months and was decided on a patient-by-patient basis.

The mean WBC count was 7440.29±2068.2/mm³ (min-max (3000-12300), the mean ANC was 3705.4±1676.1/mm³ (min-max: 1000-8320), the mean platelet count was 274834±111932.4/mm³ (min–max: 2000-504000), and the median CRP was 2.5 mg/dL (IQR: 0.66-4.6, min–max: 0.1-50). The median erythrocyte sedimentation rate (ESR) was 11mm/h (IQR: 4-20, min–max: 0-121). Anemia was detected in 60% of the patients and the average hemoglobin value was determined as 12.5±1.44 (10.2-15.9) g/dl.

The median alanine aminotransferase (ALT) was 19 (IQR: 10-31, min–max: 6-174) and the median aspartate aminotransferase (AST) was 28 (IQR: 19-39, min–max: 12-142). Demographic and clinical characteristics of patients are shown in **Table 1**.

Table 1. Demographic and clinical characteristics of patients (n, %)

Sex	Male		22 (62.9)
	Female		13(37.1)
Age (month) mean±SD (min-max)			154.2 ± 53.1 (25-214)
Age distribution	<8 years		7 (20)
	≥8 years		28 (80)
Symptoms	Arthralgia	Monoarthralgia	7 (20)
		Polyarthralgia	11 (31.4)
	Fever		11(31.4)
	Headache		6 (17.1)
	Abdominal pain		2 (5.7)
Hepatomegaly			17 (48.6)
Splenomegaly			14 (40)
Joint involvement		Sacroiliac	3 (8.6)
		Ankle	2 (5.7)
		Knee	1 (2.9)
Lymphadenopathy			1 (2.9)

Echocardiography was performed in all patients and no cardiac involvement was detected in any patient. The mean hospitalization duration was 57.71 ±28.6 days (min–max: 42–180 days). None of the patients died, and clinical cure was achieved in all patients.

We also compared patients with joint involvement and patients without joint involvement. The neutrophil count and treatment duration were found to be higher in patients with joint involvement than in those without joint involvement ($p<0.05$). AST and ALT values were found to be higher in patients without joint involvement ($p<0.05$). **Table 2** shows the comparison of patients with and without joint involvement.

The prognoses of the patients were generally favorable, with all patients achieving clinical cure and no deaths reported. Additionally, no patients experienced any drug side effects.

DISCUSSION

Brucellosis is a zoonotic disease that is endemic in our country, affects all age groups, and can cause complications and relapses, and continues to be a serious public health problem for our country. The main routes of transmission are the consumption of raw milk or dairy products of the infected animal, but it can also occur as a result of contact with the secretions of the infected animal, such as blood or urine.[3] In our study, the main transmission route was found to be consumption of unpasteurized milk and dairy products such as yoghurt and cheese. In the study conducted by Tanır et al. with 90 pediatric patients with a diagnosis of brucellosis in our country, the most common mode of transmission was found to be the consumption of contaminated milk and dairy products, similar to our study.[12] However, in a meta-analysis of 68 studies in China, it was reported that 79.4% of brucellosis was transmitted as a result of contact with sick animals.[13] In a study conducted with pediatric patients diagnosed with brucellosis in Chicago, USA, where brucellosis is partially less problematic, consumption of raw milk and unpasteurized dairy products was found to be the cause of transmission at a rate of 76%.[14]

Table 2. Comparison of patients with and without joint involvement

	Patients with joint involvement (n=6)	Patients without joint involvement (n=29)	p
Age (month) (median) (IQR)	185.5 (145-196.5)	169,00 (105.5-198.0)	0.431
Hb (g/dl) (Median) (IQR)	11.4 (11.0-13.5)	12.5 (11.6-13.4)	0.324
WBC (/mm³) (Median) (IQR)	8555 (7080-9917)	7400 (5750-8490)	0.149
Lymphocyte (/mm³) (Median) (IQR)	2245 (2005-3807)	2880 (2025-3835)	0.555
Neutrophil (/mm³) (Median) (IQR)	5885 (3415-6420)	3300 (2375-4040)	0.026
Platelet (/mm³) (Median) (IQR)	324000 (239750-374250)	273000 (201000-333000)	0.229
CRP (Median) (IQR)	1.34 (0.24-28.32)	2.98 (0.68-4.63)	0.710
ALT (U/L) (Median) (IQR)	9.5 (4.5-11.5)	21 (15-37)	0.003
AST (U/L) (Median) (IQR)	16.5 (13.5-23.5)	30 (20.5-41.5)	0.010
ESR (mm/h) (Median) (IQR)	23 (3,5-54,2)	10 (3.5-18)	0.188
Treatment duration (days) (Median) (IQR)	77 (60.7-112.2)	42 (42-52.5)	0.001

Hb:Hemoglobin; WBC:White Blood Cell; CRP:C-reactive protein; ALT:Alanine transaminase; AST:Aspartate transaminase; ESR:Erythrocyte sedimentation rate

In our study, although the disease was seen in both genders, it was observed that it was more common in male sex. The male/female ratio was determined as 1.7. In accordance with our study, in one of the most comprehensive studies conducted in our country, 189 pediatric patients with brucellosis were examined over a 16-year period and it was observed that 61.4% of the cases were male patients.[15] Similarly, in another comprehensive study conducted with 212 pediatric patients diagnosed with brucellosis between 2005 and 2018 in our country, Kaman et al. reported that 59.9% of the cases were male.[7] In a study conducted in Europe examining both children and adults diagnosed with brucellosis, it was shown that both genders were affected by the disease at almost equal rates (51% male).[16]

In the study conducted by Özdem et al. in our country and published in 2022, the most common symptoms in 189 pediatric patients with brucellosis were determined as arthralgia (71.4%), fever (59.2%), weight loss (23%), and night sweats (14.3%). In the same study, fever (23%), hepatomegaly (19%), arthritis (17%), splenomegaly (14%) and lymphadenopathy (6%) were reported as the most common clinical findings, respectively.[15] When we examine different geographical regions, it is seen that there are similar findings. In a study conducted in 246 pediatric patients diagnosed with brucellosis in Europe (Bosnia and Herzegovina) between 2000 and 2013, the most common clinical findings were reported as fever (78.86%) and joint pain (64.22%).[16] In a study by Logan et al. in the United States, the most common findings in pediatric patients with brucellosis were fever (95%), anorexia (48%), fatigue (33%), chills (24%), arthralgia (24%), and weight. loss (24%) was reported.[14] Similarly, in a study conducted by Madut et al. in Africa examining pediatric and adult patients with brucellosis, fever and headache were determined as the most common findings, and shivering, fatigue, joint pains and night sweats were reported as other observed findings. [17] Similarly, in our study, the most common presenting symptom was joint pain (51.4%), followed by fever (31.4%), headache (17.1%) and abdominal pain (5.2%). When physical examination findings are examined; the most common finding was hepatomegaly (48.6%), while splenomegaly (40%) was the second most common finding.

In a study examining 408 patients with brucellosis in Germany between 2006 and 2018, *B. melitensis* was the most commonly isolated species (91%), followed by *B. abortus* (8.1%) and *B. suis* (0.5%).[18] In the articles published by Alshaalan et al., it was reported that the most common species causing brucellosis in Saudi Arabia and surrounding countries was *B. melitensis*, and the second most common species was *B. abortus*.[19] In our study, we had patients with growth in blood culture, but we could not type them.

In our study, anemia was found to be the most common hematological finding. The most comprehensive study on pediatric patients diagnosed with brucellosis was conducted in the city of Van, located in the east of our country, and Parlak et al. shared the data of 496 patients and anemia (20.4%), thrombocytopenia (15.5%), and leukopenia (12.1%) were reported as the most common hematological findings, respectively. In the same study, elevation of lactate dehydrogenase was found in 63.1% of the patients, and the acute phase values of C-reactive protein and erythrocyte sedimentation rate were found to be high by 58.7% and 55.2%, respectively.[20] In a study conducted in Iran, the data of 100 patients with a definitive diagnosis of brucellosis were examined, and it was determined that neutrophil counts were higher in patients diagnosed with brucellosis than in the control group.[21] In the study which Balın et al. examined the importance of hematological parameters in the diagnosis of osteoarticular brucellosis, they showed that neutrophil numbers were higher in brucellosis cases with osteoarticular involvement than in the control group.[22] In our study, elevated CRP was detected in 22.9% of our patients and the neutrophil count was found to be higher in patients with joint involvement than in those without joint involvement. We think that these results can be considered normal since joint involvement is considered to be a more complicated condition of the disease. On the other hand, although liver enzymes such as AST and ALT were within the normal range, they were found to be higher in patients without joint involvement. Since liver enzymes were within the normal range, although there was a statistically significant difference between the two groups, we did not consider this as liver involvement.

In a study conducted in our country and investigating the complications of 283 patients including both pediatric and adult patients with brucellosis, the most common complication was found to be osteoarticular system involvement with a rate of 69%, and the most frequently involved joint was reported as the sacroiliac joint.[23] On the other hand, in the study of Akkoç and Tekerek in which they examined 185 pediatric patients with brucellosis, hip joint involvement was determined as the most common joint involvement.[24] In the study of Fanni et al. with Iranian children diagnosed with brucellosis, the most frequently affected joints were hip and knee, followed by elbow, wrist, ankle, and sacroiliac joints, respectively.[25] In our study, joint involvement was detected in 17.1% of the patients, and when evaluated in terms of the sites of involvement, it was determined that the sacroiliac joint was involved in 3 (8.6%) patients, the ankle joint was involved in 2 (5.7%) patients, and the knee joint was involved in 1 (2.9%) patient.

In uncomplicated brucellosis cases, the treatment duration is generally 6 weeks. The main treatment regimen used in children under eight years of age includes the combined oral use of trimethoprim-sulfometaxazole and rifampin drugs. In children older than eight years of age, combined oral use of doxycycline and rifampin drugs is the main treatment method, but combined treatment regimens with doxycycline and aminoglycosides (amikacin or streptomycin) can also be applied instead of rifampin.[4,10,26] The optimal

treatment protocol in cases of brucellosis with osteoarticular involvement is not clear, but in general, triple combination therapy of doxycycline (TMP-SMX instead of doxycycline in children younger than 8 years of age), rifampin and aminoglycoside (amikacin or streptomycin) is recommended for pediatric patients.[27,28] The treatment duration is recommended as a minimum of 12 weeks.[29] Although we treat all our patients with joint involvement for a minimum of 12 weeks, we have also had cases where treatment times have been extended for up to 6 months on a case-by-case basis. In our study, we showed that statistically the treatment duration was longer in our patients with joint involvement.

Although the limitation here is that the study was absence of of long-term follow-up data to provide data on possible relapses, strength of our study is that clinical and laboratory findings were comprehensively evaluated in pediatric brucellosis cases with detailed data obtained from a single center.

CONCLUSION

Brucellosis is a zoonotic disease that we see in our country due to the continued consumption of raw milk and its products. It continues to be an important public health problem because it causes osteoarticular involvement and requires long-term treatment. It should be kept in mind that the disease can be prevented by simple methods such as health inspection of animals and pasteurization.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Medical Research Ethics Committee of our institution (Ethic Committee Name: University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital Medical Research Ethics Committee Date: 28.08.2023 Report Number: 2023/514/256/4).

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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Original Article / Orijinal Araştırma

Knowledge, Attitudes and Behaviors of Parents of Healthcare Workers Towards Rotavirus Vaccination in Turkey

Türkiye'de Sağlık Çalışanı Ebeveynlerin Rotavirüs Aşılamasına Yönelik Bilgi, Tutum ve Davranışları

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Abstract

Aim: This study aims to reveal what parents with children under the age of five working in health services in Turkey know, what they think, and what their attitudes and behaviors are about the rotavirus (RV) vaccine, RV infection, and RV vaccination rates.

Material and Method: The 'Demographic Characteristics Questionnaire' and the 'RV Information/Vaccination Status Survey' both online surveys, were the two main tools used in this descriptive study, which involved 1317 willing participants who were parents of healthcare workers and was conducted between December 1, 2021, and May 1, 2022. The first focused on gathering crucial demographic information, while the second examined participant knowledge, attitudes, and behaviors related to rotavirus and its vaccination.

Results: The mean age of participants was 33.76±5.28 years. Of the participants, 70.3% were women, 47.3% were doctors, and 90.9% had a university or higher education level. 91.% stated that their children do not have any chronic disease and it was determined that 94.2% of them had their children regularly vaccinated with childhood vaccines. The RV vaccination rate was 55.6%, and 60.9% stated that their children had no previous RV infection. Of those who were infected with RV, 38.3% were hospitalized and treated. 85.2% of those with RV-infected children had no RV vaccine, and the reason why they did not have the vaccine was its high cost.

Conclusions: This finding emphasizes how crucial it is to remove financial obstacles and improve accessibility to guarantee broader access to necessary vaccines, including the RV vaccine, to protect public health.

Keywords: Rotavirus, child, vaccine, parents, awareness, attitude and behavior

Öz

Amaç: Bu çalışmanın amacı, Türkiye'de sağlık hizmetlerinde çalışan beş yaş altı çocuğu olan ebeveynlerin rotavirüs (RV) aşısı, RV enfeksiyonu ve RV aşılama oranları hakkında ne bildiklerini, ne düşündüklerin ve nasıl bir tutum ve davranış içerisinde olduklarını ortaya çıkarmaktır.

Gereç ve Yöntem: Her ikisi de çevrimiçi anket olan 'Demografik Özellikler Anketi' ve 'RV Bilgi/Aşı Durum Anketi', sağlık çalışanlarının ebeveynleri olan 1317 gönüllü katılımcının dahil edildiği bu tanımlayıcı çalışmada iki ana veri toplama aracı olarak kullanıldı. Çalışma 1 Aralık 2021 ile 1 Mayıs 2022 arasında yürütüldü. İlki önemli demografik bilgilerin toplanmasına odaklanırken, ikincisi katılımcıların rotavirüs ve aşısına ilişkin bilgi, tutum ve davranışlarını inceledi.

Bulgular: Katılımcıların yaş ortalaması 33,76±5,28 yıl idi. Katılımcıların %70,3'si kadın, %47,3'u doktor ve %90,9'u üniversite ve üzeri eğitim seviyesine sahipti. Katılımcıların %91,1'i çocuklarında herhangi bir kronik hastalığın bulunmadığını belirtirken, %94,2'sinin çocuklarına düzenli olarak çocukluk çağı aşılarını yaptırdıkları belirlendi. RV aşılama oranı %55,6 olup, %60,9'ı çocuklarının daha önce RV enfeksiyonu geçirmediğini belirtmiştir. RV enfeksiyonuna yakalananların %38,3'si hastaneye kaldırılarak tedavi altına alındı. RV enfeksiyonu olan çocukların %85,2'unun RV aşısı olmadığı, aşı yaptırmamalarının nedeni ise maliyetinin yüksek olduğu görüldü.

Sonuç: Bu bulgular, halk sağlığını korumak için RV aşısı da dahil olmak üzere gerekli aşılara daha geniş erişimi garanti altına almak için finansal engelleri kaldırmanın ve erişilebilirliği arttırmanın ne kadar önemli olduğunu vurgulamaktadır.

Anahtar Kelimeler: Rotavirus, çocuk, aşı, ebeveynler, farkındalık, tutum ve davranış

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INTRODUCTION

Childhood vaccination programs are the most effective practices carried out to protect and improve health in children, reduce child mortality and maintain public health for older ages.[1,2] The Rotavirus (RV) is one of the leading causes of gastroenteritis in children aged up to 5 years.[3] Globally, the RV infection incidence rate was reported as 5-25% in the United States of America (USA), 20-40% in Europe, 30-50% in Asia, and 10-65% in Africa. In studies from Turkey, The RV infection incidence has been reported as 9.8-39.8%.[4-6] In times when the RV vaccine was not mandatory or inadequate, RV disease and death rates were around 453.000.[7] With increasing RV vaccination coverage rates and awareness, this rate has fallen to 128.500-146.000.[6,7] In terms of global rates, in its 2016 report the World Health Organization (WHO) stated that 528.000 mortality due to RV in 2000 declined to 215.000 in 2013.[8,9] WHO has recommended vaccination against RV in all national immunization programs since 2009 and reported that RV vaccination is an indication of a country's level of development.[7,11-13] RV vaccine has been placed in the routine vaccination schedule in the USA, South Africa, Australia, Finland, 5 countries from the Middle East, and 4 countries from Europe. One other point is that children going to communal living spaces like kindergartens or nursing homes and hospitalized children are at risk of the disease.[7,8,10-13]

Turkey has low vaccination rates because it is a non-mandatory vaccine. As an important healthcare problem, the reasons for these low vaccination rates against RV disease were parents' doubt about the vaccine, its being non-mandatory, lack of accurate information and practice and most important of all the fact that it is not free. In the literature, there have been many regional studies in Turkey, but there has not been a study performed across Turkey.[5,6] This study aims to reveal what parents with children under the age of five working in health services in Turkey know, what they think, and what their attitudes and behaviors are about the rotavirus (RV) vaccine, RV infection, and RV vaccination rates.

MATERIAL AND METHOD

Study Design and Objectives

This study was performed in a cross-sectional descriptive type.

Study Universe and Sampling

The population of the study consisted of parents who had children under the age of five and were healthcare professionals. Individuals who met these criteria and voluntarily agreed to participate verbally and in writing were included in the study. The study was conducted with a total of 1317 parents with children under 5 years old.

Data Collection

The study's data was obtained from an online survey performed between December 1, 2021, and April 30, 2022, online on social media (WhatsApp, Telegram, Facebook, and Twitter). The Demographic Characteristics Questionnaire and The RV Information/Vaccination Status Survey were used to collect data. Surveys were prepared through Google Forms and submitted to participants online.

Data Collecting Tools

Demographic Characteristics Questionnaire: It was formed by examiners in parallel to the literature.[13,14] Eight questions about participants' demographic characteristics (age, sex, education, marital status, monthly income, study year) and the number of children up to 5 years of age were included.

The RV Information/Vaccination Status Survey: This survey includes 19 questions. Number of children, the presence of chronic disease in children, the number and causes of hospital admission, and their information and attitudes about the RV disease and its vaccine.[6,15-18]

Ethics Committee Approval: Our study was approved by Ethics Committee with 21/13-1 and E.1342 decision and document numbers, respectively. The students who agreed to participate in the study were informed that the purpose of the study and personal information will be kept confidential, participation is in line with the principle of volunteering, and their permission was obtained. In the study, the principles of the Helsinki Declaration were followed.

Statistical Analysis

Data were analyzed with the SPSS 22 package program (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The age analysis of 1317 people was presented as means and standard deviation; answers to questions about sex, marital status, occupation, working time, educational status, monthly income, and other demographic characteristics and information and attitudes about the RV infection and vaccine were presented as percent and frequency distribution. The Chi-square test was used to detect a statistical relationship between occupation, educational status, monthly income, the status of children's RV vaccination and vaccine dose, and history of the RV infection. The Chi-square test was used to analyze any statistical relationship between whether a vaccine was implemented and the need for outpatient and inpatient treatment after contracting the RV. A p-value of <0.05 is considered statistically significant.

RESULTS

The study's participants had an average age of 33.76±5.28 years. In this study, 70.3% of the participants were women, 47.3% were doctors, and 97.1% were married. In addition, 49.9% of the participants stated that they had worked for more than ten years. A high percentage of the participants (90.9%) had a university degree or higher. About forty-one percent of participants reported having a monthly income of at least 10,000 Turkish Lira (TL). Additionally, 77.5% of individuals had one child, while 22.2% had two children under the age of five. **Table 1** provides a thorough description of these demographic factors.

Table 1. Distribution of demographic characteristics		
Age		
Mean±Standard deviation (years)	33,76±5,28	
	Number	**Percent**
Sex (n=1314)		
Women	924	70.3%
Men	390	29.7%
Occupation (n=1373) (more than one option can be selected)		
Doctor	620	47.3%
Academician	103	7.9%
Nurse/midwife/EMT	588	44.9%
Lab tech/rad tech	23	1.8%
Dietitian/physiotherapist	12	0.9%
Medical Secretary	27	2.1%
Marital status (n=1317)		
Married	1276	97.1%
Other	38	2.9%
Working Year (n=1317)		
<1 year	13	0.9%
1-5 years	189	14.4%
6-9 years	457	34.7%
>10 years	658	49.9%
Educational status (n=1317)		
High school and/or under	120	9.1%
University and/or over	1197	90.9%
Monthly income (n=1310)		
≤5000TL	49	3.7%
5001-7500TL	497	37.9%
7501-10000TL	223	17.0%
≥10001TL	541	41.3%
No children aged <5 years (n=1317)		
1	1021	77.5%
2	292	22.2%
4	4	0.3%
Owning children aged <1 year (n= 1313)		
Absent	1040	79.2%
Present	273	20.8%

A total of 91.1% of participants stated that their children do not have a chronic disease, and 94.2% said they had their children regularly vaccinated with childhood vaccines. In the current, 83.1% of mothers made vaccine follow-ups, 92.3% did not give frequent hospital admissions and 96.9% knew about the RV. About forty-three of the participants did not get any education on RV infection, 60.1% had enough information about RV infection and 60.9% said that their children did not get RV infection. In addition, 61.7% of RV-infected children took outpatient treatment, 38.3% were hospitalized, and 85.2% of the RV-infected children were not vaccinated against the RV. However, %95.8 knew about the RV vaccine, 48.4% were not educated about the RV vaccine and 55.6% had their children vaccinated against RV. Furthermore, 45.4% of participants had 2 doses of vaccine, 44.3% stated that they followed instructions of the RT Ministery of Health about the RV vaccine and 43.6% followed instructions of the World Health Organization. In this study, 75.9% knew that the RV vaccine is not mandatory in Turkey; 66.9% thought that the RV infection might cause life-threatening complications in children and 64.5% of the reasons for not getting the vaccine was its high cost. The distribution of answers to the rest of the survey questions given by participants are presented in **Table 2**.

Table 2. Distribution of Responses to Survey Questions		
	Number	**Percent**
Child/children's chronic disease (n=1307)		
No	1190	91.1%
Yes	117	8.9%
Children regularly vaccinated with childhood vaccines (n=1314)		
No	35	2.7%
Yes	1238	94.2%
Not remember	41	3.1%
The child's history of frequent hospitalizations (n=1314)		
No	1213	92.3%
Yes	101	7.7%
The person who follows vaccination (n=1314)		
Mother	1092	83.1%
Mother and father	27	2.1%
Father	161	12.3%
Family physician/nurse/midwife	29	2.2%
Nursemaid	5	0.4%
Information about RV (n=1317)		
No	40	3.1%
Yes	1277	96.9%
Status of RV infection (n=1317)		
No	802	60.9%
Yes	162	12.3%
Not remember	353	26.8%
Mode of RV infection treatment (n=162)		
Outpatient	100	61.7%
Inpatient	62	38.3%
Intensive care		0%
The RV vaccination status of child/children with RV infection (n=162)		
No	138	%85,2
Yes	24	%14,8
Thinking that information about RV infection is enough (n=1317)		
No	314	23.8%
Yes	792	60.1%
Uncertain	211	16.1%
Education on RV infection (n=1317)		
No	572	43.4%
Yes	581	44.1%
Not know/not remember	164	12.5%
Awareness about the RV vaccine (n=1317)		
Yes	1262	95.8%
Not know/not remember	55	4.2%
Education on RV vaccine (n=1317)		
No	638	48.4%
Yes	516	39.2%
Not know/not remember	163	12.4%
Child/Children vaccinated against RV (n=1317)		
No	525	39.9%
Yes	732	55.6%
Not know/not remember	60	4.5%

Table 2. Distribution of Responses to Survey Questions (Cont...)

	Number	Percent
No of RV vaccine doses (n=1317)		
0 dose	525	39.9%
1 dose	96	7.3%
2 doses	598	45.4%
3 doses	38	2.9%
not remember	60	4.5%
Following RT Ministry of Health data/ recommendations on RV vaccine (n=1317)		
Not follow	734	55.7%
Follow	583	44.3%
Following World Health Organization data/recommendations on RV vaccine (n=1317)		
Not follow	743	56.4%
Follow	574	43.6%
Knowing that RV vaccine is not mandatory in Turkey (n=1307)		
No	41	3.1%
Yes	999	75.9%
Indecisive	277	21.0%
Thinking that RV infection causes life-threatening/severe complications in children (n=1317)		
No	123	9.3%
Yes	881	66.9%
Indecisive	313	23.8%
Reason for not getting the vaccine (n=569)		
Vaccine not free	367	64.5%
Hesitancy about vaccine's efficacy	124	21.8%
Fear of vaccine's side effects	63	11.1%
Not have time for a vaccine	15	2.6%

There was a statistically significant relationship between occupation (p=0.002), monthly income (p=0.017), vaccine doses received by children (p=0.032), and whether children were infected with the RV. On the other hand, no statistically significant relationship was found between participants' educational status (p=0.115) whether parents had their children vaccinated against RV (p=0.365), and whether children were infected with the RV. There was a statistically significant relationship between whether participants had their children inoculated with the vaccine and the type of treatment ($p < 0.001$). Evaluation of the relationship between having a RV infection and occupation, educational status, monthly income, status of vaccination, and vaccine dose are presented. Parents' employment status, income status and associated rotavirus vaccination status, and number of doses administered are presented in **Table 3**.

DISCUSSION

The study participants' demographic profile offers important context for comprehending the variables influencing parental RV vaccine coverage among Turkish healthcare workers' children. These demographic characteristics shed light on the profile of the healthcare worker parents participating in the study and show that they are well-educated, mostly married and wealthy.

The findings of our study revealed that a sizable majority of participants (94.2%) adhered to routine immunization protocols for their children, including receiving their typical childhood vaccines. Unexpectedly, since the vaccine is not in our country's routine vaccination program and is a paid vaccine, these findings are consistent with recent scientific studies on related subjects. The study carried out by Odabaş and Kuzlu Ayyıldız in 2020[19] reported a nearly identical vaccination rate of 95.5% among parents, covering both routine and required vaccines. Similar to what was stated above, Üzüm et al.'s study on relatives of patients who applied to the pediatric outpatient clinic reported a high compliance rate, with 94% of parents ensuring regular and routine vaccinations for their children.[20] The general homogeneity of our study's findings with the literature, despite some reported rates having varied, highlights the strength of the trend toward widespread routine child immunization.[19,20]

According to the findings from this study, 12.3% of children had RV infection. This rate is within the range of 14–62% recorded worldwide, highlighting the significant variation in RV incidence rates between various countries.[21-24] Regarding RV prevalence in children, our study's findings are consistent with those found in the literature.[25,26] These reported variations in RV infection rates can be related to several variables, including regional, climatic, and socioeconomic changes as well as differences in healthcare practices and vaccine coverage among communities.[21,22]

When the findings of the study were evaluated, it was determined that 96.9% of the parents had high awareness about RV infection and vaccines. This level of awareness is higher than previous academic articles on the subject. For example, in the research conducted by Odabaş and Kuzlu Ayyıldız[19] in 2020, 57.6% of parents showed that they were knowledgeable about Caravans. Additionally, in Çoklar and Güner's study[25] on childhood vaccinations, 24.6% of the participants were aware of the RV vaccine and its cost. It is thought that this high rate is due to the fact that the parents included in the study are healthcare professionals.

The RV vaccination rate in our study was 55.6%. This rate indicates that the vaccination rate is at a moderate level. However, in other studies vaccination rate has been lower. In their study among parents in 2020, Barutçu et al reported that only 27.7% of parents had their children vaccinated against RV.[6] In a similar study by Kaçmaz Ersu et al. in 2016, it was reported that 29% of participants were aware of the RV vaccine, however, due to a lack of confidence in the vaccine and its non-mandatory nature only 7% had the RV vaccine.[15] In a study conducted with parents from Italy; 40.7% reported that they heard about RV infection however, only 15.3% had their children vaccinated.[18] In this study, the higher RV vaccination rate compared to the literature is considered a positive development. This positive situation obtained in the study can be explained by the fact that the participating parents are healthcare professionals and vaccination awareness has increased in recent years.

Table 3. Parent's employment status, income status, and associated rotavirus vaccination status and number of doses administered and evaluation of the relationship between having a RV infection and occupation, educational status, monthly income, status of vaccination, and vaccine dose

	Test statistics	Degree of freedom (df)	P value
Occupation	17.844 (Fisher's Exact)		0.002
Educational status	2.482 (Yates Chi-square)	1	0.115
Monthly income	10.251 (Pearson Chi-square)	3	0.017
Vaccine status	0.820 (Pearson Chi-square)	1	0.365
Vaccine dose	6.906 (Pearson Chi-square)	2	0.032

			The RV Infection		Total
			No RV infection	History of RV infection	
Occupation	Doctor	No	444	85	529
		Percent	83.9%	16.1%	100.0%
	Academician	No	81	16	97
		Percent	83.5%	16.5%	100.0%
	Nurse/midwife/EMT	No	243	45	288
		Percent	84.4%	15.6%	100.0%
	Lab tech/rad tech	No	0	4	4
		Percent	0.0%	100.0%	100.0%
	Dietitian/physiotherapist	No	8	0	8
		Percent	100.0%	0.0%	100.0%
	Medical Secretary	No	12	6	18
		Percent	66.7%	33.3%	100.0%
	Total	No	788	156	944
		Percent	83.5%	16.5%	100.0%
Monthly income and RV infection					
Monthly income					
	≤5000TL	No	29	11	40
		Percent	72.5%	27.5%	100.0%
	5001-7500TL	No	208	43	251
		Percent	82.9%	17.1%	100.0%
	7501-10000TL	No	178	20	198
		Percent	89.9%	10.1%	100.0%
	>10001 TL	No	372	82	454
		Percent	81.9%	18.1%	100.0%
		No	787	156	943
		Percent	83.5%	16.5%	100.0%
The RV vaccine dose and RV infection					
The RV vaccine dose					
	1.00	No	73	15	88
		Percent	83.0%	17.0%	100.0%
		% Total	10.7%	2.2%	12.9%
	2.00	No	465	92	557
		Percent	83.5%	16.5%	100.0%
		% Total	68.4%	13.5%	81.9%
	3.00	No	35	0	35
		Percent	100.0%	0.0%	100.0%
		% Total	5.1%	0.0%	5.1%
	Total	Count	573	107	680
		% within the RV vaccine dose	84.3%	15.7%	100.0%
		% Total	84.3%	15.7%	100.0%
The RV Treatment Mode			**Outpatient**	**Inpatient**	**Total**
The RV vaccine					
	No Vaccine	No	17	32	49
		Percent	34.7%	65.3%	100.0%
	Vaccinated	No	77	30	107
		Percent	72.0%	28.0%	100.0%
	Total	No	94	62	156
		Percent	60.3%	39.7%	100.0%

*TL: Turkish liras

In our study, it was detected that 85.2% of children had RV infection history, who had not been vaccinated against RV. This finding indicated the vaccine's efficacy. When the study findings were compared with the literature, some similar studies were found. In the Kaçmaz Ersu et al. study, it was reported that 93% of those who had RV were not vaccinated against RV.[15] When the literature was reviewed, the reasons for parents not having the RV vaccine were lack of information, the cost, the side effects, and the non-mandatory nature of the vaccine. In Odabaş and Kuzlu Ayyıldız,[19] it was reported that the first three reasons why parents did not have the RV vaccine were lack of information about the vaccine, mistrust in the vaccine, and side effects. When parents of unvaccinated children were asked "the reasons for not getting the RV vaccine", 80.3% said they did not hear and know about the vaccine. In many studies, the important reason has been the cost of the vaccine.[14,21] In a similar study (Hasar et al. 2023), 59% of the participants stated the reason for parents' refusal of vaccination as "Vaccines are safe" "I do not think there are side effects/I am worried" (96.7%), while 53 parents stated "Negative information about vaccines" "There is," he said. "From the media" (86.9%). Approximately 64% of the participants stated that the reason for not getting vaccinated was the high cost. One of the most important findings of the same research was that approximately 64 percent of the participants stated the high cost as the reason for not getting vaccinated.[27] In the current study, a comprehensive analysis was conducted to see if there was a link between the respondents' level of education and history of RV infection in children. In the statistical study, no statistically significant relationship was found between the education level of the participants and whether their children had rotavirus infection or not. There are contrary studies in the literature. The results of the study conducted by Apa et al. revealed a positive relationship between socioeconomic status in terms of educational status and level and vaccination uptake.[26] According to the results of the study, there was no statistically significant relationship between the participants' education level and whether their children had rotavirus infection. In the literature, there are studies that show similarities with the findings of the study, as well as studies that report contrary results. The degree of education a mother had was also found to be significantly correlated with her children's vaccination rates in earlier studies that evaluated maternal educational status and vaccine knowledge.[27,28] Additionally, numerous studies have repeatedly shown that parental education is a strong predictor of vaccine compliance.[19,20,28-30] This is especially true for parents with less education. These cumulative research findings highlight the important role that socioeconomic and educational factors play in vaccine compliance and uptake. Higher levels of education are thought to be favorable to improved vaccine acceptability, which is further supported by the positive association between educational status and vaccination rates that Apa et al.'s study[26] found. Similar to this, the findings that are consistent across numerous studies evaluating the impact of maternal education on vaccination rates emphasize the significance of health literacy and awareness in influencing immunization decisions.[19,20, 28,30]

According to the study findings, there was a statistically significant relationship between the monthly income of the participants and whether the children had RV infection. There are parallel and controversial studies in the literature. In a similar study by Çıklar and Döner Güler, it was reported that age and monthly income do not affect the paid vaccination rate.[25] In a similar study by Kaçmaz Ersu et al., any significant relationship between participants' income and infection rate was not reported.[15] However, in a study Gencer et al. performed with parents in 2015, it was reported that household income and non-routine and paid vaccination rates are parallel.[28] In many international studies, it was reported that misinformation of families about vaccines, resistance to vaccines, household income, and distrust of the vaccine negatively affect the vaccination rate. Therefore, it is emphasized that, from time to time, eradicated disease might cause epidemics.[31-35]

An important finding of the study was that there was a statistically significant relationship between the occupation of the participants and whether their children had rotavirus infection. The literature is similar to this finding. When the studies are examined, educational status and occupation with occupation positively affect the vaccination rate. This finding can be explained by the fact that the participant parents are health professionals.[19,20,26,28,29]]

The kid vaccination rate in this comprehensive epidemiological study conducted throughout Turkey was determined to be 94.2%, indicating a reassuringly high level of immunization coverage. The percentage was significantly lower at 55.6% for the RV vaccine, though. It was determined that the RV vaccine's expensive price, which posed a significant barrier for many families, was a major contributing factor in children's inadequate uptake of the vaccination.

Rotavirus incidence rate and age of incidence vary from time to time. In the study conducted by Taşkın Dalgıç et al. age and incidence before and after the Covid 19 pandemic were found to be different. This situation shows that the disease and vaccination should be kept up-to-date in children under 5 years of age.[37]

In the study limitations: The study has two important limitations. First, the data obtained from the study are based only on the opinions of individuals who voluntarily participated in the study, and the results cannot be generalized to the population.

CONCLUSION

Implementing targeted educational campaigns, improving vaccine accessibility, and addressing potential immunization barriers will help maintain high vaccination rates and

build public health defenses against preventable diseases. Further investigation into the factors influencing vaccination behaviors in different communities can also aid in better understanding the complexities involved and direct evidence-based solutions to increase vaccine acceptance and compliance among parents and caregivers. To sum up, we may work to close the immunization gap and increase the RV vaccination rate in our nation by creating and enacting health policies that include the RV vaccine in routine pediatric vaccination practices or provide it free of charge. A population that is healthier and more resistant to the burden of RV-related diseases will be created as a result of such proactive actions, which will not only protect the health of particular children but also strengthen herd immunity.

ETHICAL DECLARATIONS

Ethics Committee Approval: The current study was approved by Ethics Committee of Bitlis Eren University (date: 10.11.2021, session no: 21/13-1, decision no: E.1342).

Informed Consent: Informed consent was obtained from all individual participants in present study.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article / Orijinal Araştırma

Carotis Intima-Media Thickness, Lipid Accumulation Product Index, Cardiovascular Risk Calculation Score and Their Relationship with Monocyte to HDL Ratio in Middle-Aged Women with Polycystic Ovary Syndrome

Perimenopozal Polikistik Over Sendromlu Kadınlarda Monosit/HDL Oranının, Lipid Birikim Ürünleri, Karotis İntima Media Kalınlığı ve SCORE2 Kardiyovasküler Risk Hesaplama Sistemi Skoru ile Karşılaştırılması

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Abstract

Aim: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women in the reproductive age and also associated with many comorbidities that increase the risk of cardiovascular disease in later ages. This study explores the potential correlation between the monocyte to HDL ratio (MHR) and established cardiovascular risk factors in women with PCOS.

Material and Method: This cross-sectional analysis includes PCOS-diagnosed women (n=40) in menopausal transition over 40 years old, and a control group of non-PCOS healthy women (n=40) matched for age and body-mass index (BMI). Various parameters, including demographic and anthropometric measurements, lipid profiles, carotis intima-media thickness (CIMT), free androgen index (FAI), lipid accumulation product (LAP) index, homeostasis model assessment-insulin resistance (HOMA-IR), MHR, and SCORE2 risk scores were compared between the groups.

Results: Results indicate no significant differences in age, BMI, smoking, lipid profiles, fasting glucose, insulin levels, MHR, LAP index, HOMA-IR, and SCORE2 scores. However, sex-hormone binding globulin and total testosterone were higher in the PCOS group (p<0.001). Metabolic syndrome rates, FAI, and average CIMT were notably higher in the PCOS group (p=0.045, p=0.003, p=0.022). MHR was positively correlated with LAP index, HOMA-IR, FAI, and left CIMT (r=0.235; r=0.297; r=0.28; r=0.215; respectively).

Conclusion: In conclusion, PCOS women exhibit higher metabolic syndrome rates and average CIMT measurements compared to healthy age and BMI matched counterparts. Positive correlations of the MHR with various risk factors emphasize the importance of assessing cardiovascular risk in this population and shows that MHR can be used as a much cheaper predictor of cardiovascular risk compared to other predictors in perimenopausal PCOS patients.

Keywords: Polycystic ovary syndrome, monocyte to hdl ratio, lipid accumulation product index, homa-ir, carotid intima-media thickness

Öz

Amaç: Polikistik over sendromu (PCOS), reprodüktif çağdaki kadınların en sık görülen endokrin hastalığıdır ve ilerleyen yaşlarda kardiyovasküler hastalık riskinde artış ile ilişkilendirilmiş bir çok komorbiditeye yol açmaktadır. Bu çalışma, kardiyovasküler risk faktörleri ile daha önceden ilişkilendirilmiş belirteçlerle monosit/HDL oranı (MHR) arasındaki potansiyel ilişkiyi belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: Kesitsel olarak tasarlanan bu çalışma, 40 tane menopozal geçiş dönemindeki PCOS tanısı almış hasta ile yaş ve beden kitle indeksi (BMI) açısından eşleşmiş 40 PCOS olmayan hasta üzerinde yürütülmüştür. Demografik ve antropometrik ölçümler, lipid profilleri, karotis intima-media kalınlığı (CIMT), serbest androjen indeksi (FAI), lipid birikim ürünleri (LAP) indeksi, homeostasis model assessment-insulin resistance (HOMA-IR), MHR ve SCORE2 risk skorları iki grup arasında karşılaştırılmıştır.

Bulgular: Yapılan istatistik analizde; yaş, BMI, sigara içiciliği, lipid profilleri, açlık glukozu ve insülin seviyeleri, MHR, LAP indeksi, HOMA-IR değerleri ve SCORE2 skorları açısından anlamlı fark bulunamamıştır. Ancak, seks hormon bağlayıcı globulin ve total testosteron seviyeleri PCOS grubunda istatistiki anlamlı yüksek bulunmuştur (p<0,001). Metabolik sendrom oranları, FAI ve CIMT ölçümleri PCOS grubunda istatistiki anlamlı olacak şekilde yüksek bulunmuştur (sırasıyla p= 0,045; 0,003; 0,022). MHR; LAP indeksi, HOMA-IR, FAI değerleri ve CIMT ölçümleri ile pozitif korele bulunmuştur (sırasıyla r= 0,235; 0,297; 0,28; 0,215).

Sonuç: PCOS hastası kadınlar, BMI açısından eşleştirilmiş PCOS olmayan yaşıtlarına göre artmış metabolik sendrom ve ortalama CIMT ölçümlerine sahiptir. Kardiyovasküler riskle ilişkisi daha önceden bilinen parametrelerle MHR arasındaki pozitif korelasyon değerleri, bu popülasyondaki kardiyovasküler risk faktörlerini değerlendirme konusunda dikkat çekmektedir ve perimenopozal PCOS hastalarında MHR'nin diğer kardiyovasküler risk prediktörlerine oranla çok daha ucuz bir prediktör olarak kullanılabilirliğini göstermektedir.

Anahtar Kelimeler: Polikistik over sendromu, monosit/HDL oranı, lipid birikim ürünleri indeksi, HOMA-IR, karotis intima-media kalınlığı

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women in reproductive ages, with reported prevalence rates ranging from 6% to 20% depending on which diagnostic criteria used.[1,2] PCOS presents as a complex interplay of neuroendocrine, metabolic and ovarian dysfunctions, contributing to its perpetuating cycle.

In reproductive years, PCOS shows up with ovulatory and cosmetic issues, such as infertility, oligomenorrheae and increased body hair. In PCOS women, prevalance and numbers of cardiovascular risk factors increases over the years.[3] However, it remains uncertain to what extent PCOS itself, or its common comorbidities, mediates the increased risk for severe adverse outcomes, like cardiovascular disease (CVD).

In women with PCOS, the prevalence of insulin resistance, a comorbidity that accompanies PCOS and increases the risk of cardiovascular disease (CVD), ranges from 60-80%, while the prevalence of type 2 diabetes mellitus is around 10%.[4] Additionally, PCOS has been associated with metabolic syndrome (MS).[5] Due to the complexity of diagnostic criteria for MS, the simpler metabolic status assessment tool, the LAP index, has been introduced.[6] It was found to predict the presence of MS with 85% sensitivity when the threshold value was set at 28.4 cm.mmol/L.[7] The SCORE, a cardiovascular risk calculation system, was revised by the European Society of Cardiology in 2021 and reintroduced as SCORE2.[8,9] Beyond predicting CVD risk, direct visualization is possible. CIMT measurement provides valuable predictive insights into asymptomatic early atherosclerosis in women with PCOS.[10,11] Instead of separately evaluating the increase in monocyte count, a source of proinflammatory cytokines, and the decrease in HDL cholesterol (HDL-C), MHR has been proposed. MHR was found to be elevated in women with PCOS, emphasizing its utility in predicting cardiovascular risk in the chronic inflammatory nature of PCOS.[12]

This study aims to assess the presence of multiple cardiovascular risk factors in PCOS and evaluate the value of MHR as a simpler marker compared to multiple cardiovascular risk factor determination systems. The findings may provide valuable insights into better risk assessment and management strategies for women with PCOS, ultimately leading to improved cardiovascular outcomes in this vulnerable population.

MATERIAL AND METHOD

Women aged ≥40 years who were previously diagnosed with PCOS and 40 non-PCOS healthy women, who were in similar age and body mass index (BMI) range and applied to Evliya Çelebi Education and Research Hospital between June 2021-April 2022 were included in this study. Approval of Kütahya Health Science University Ethics Committee was provided in 10.06.2021 with decision number: 2021/10-23. Informed consent was obtained from all patients participating in the study. The study was conducted in accordance with the ethical rules of the WMA Declaration of Helsinki. Inclusion criterias for the study were:

For the PCOS Group:

- Women aged 40 years and older with menstrual bleeding.
- Women in menopausal transition without vasomotor symptoms
- Women with history of PCOS based on Rotterdam ESHRE/ASRM criteria and under follow-up.

For the Control Group:

- Similar age and BMI
- No history of oligomenorrhea/amenorrhea, hirsutism complaints, and/or infertility.

Exclusion Criterias for the study were:

- Menstrual period absence for at least one year.
- For the women with history of oligomenorrhea/secondary amenorrhea; FSH levels >45 IU/L.
- Presence of vasomotor symptoms, pregnancy, lactation, cardiovascular disease (CVD) history, family CVD history, thyroid, adrenal, pituitary diseases, diabetes (fasting blood glucose >126 mg/dl), chronic kidney or lung disease.
- Use of non-steroidal anti-inflammatory drugs in the last ten days, hormonal contraception, antihypertensive drugs, steroids, oral antidiabetic drugs, anticoagulant drugs in the last three months.
- Immun-suppressive therapy use for any diagnosis.
- Heavy smoking (>20 cigarettes per day).

In the statistical analysis, the sample size of the study with 0.05 α-error probability, 0.5 effect size and 85% power were calculated 40 for the PCOS group and 40 for the control group.

Age, BMI, arterial blood pressure in a resting position, waist circumference (WC) measurement, menstrual cycle features, smoking habit, presence of clinic features for hyperandrogenism (modified Ferriman- Gallwey score were higher than 8) and detailed medical/ obstetric/ gynecologic histories were recorded.

The ovaries of all women were evaluated by transvaginal ultrasonography using a Voluson 730 Professional Edition (General Electric Company, USA) device with an endovaginal 5 MHz probe; polycystic ovarian morphology in the ovaries was recorded for phenotypic evaluation.

Following an overnight fasting; complete blood count, fasting glucose, fasting insulin, total cholesterol, HDL-C, LDL-C, triglyceride, total testosterone and SHBG values were evaluated and the results were recorded. Menopause status was excluded by evaluating the FSH levels of women in the PCOS group who described amenorrhea or oligomenorrhea. Biochemical and hormonal parameters were acquired by enzyme-linked immuno assays in UniCel DxI 600 Access Immunoassay System biochemistry device (Beckman Coulter Life Sciences Headquarters, Indianapolis, IN).

BMI of the cases were calculated by dividing body weight by the square of their heights in meters (kg/m^2). WHR were calculated by dividing waist circumference by hip circumference in centimeters. The normal value for WHR was accepted as less than 0,83.[13] Free androgen index (FAI) was calculated by dividing the total testosterone value (nmol/L) by the SHBG value (nmol/L) and multiplying the obtained value by 100. Values greater than 5% were considered abnormal.[14] The HOMA-IR value was calculated by multiplying the fasting glucose values (mg/dL) with the simultaneous fasting insulin values (IU/L) and dividing the obtained value by 405. IR values of 2.5 and above were considered abnormal.[15] LAP index was calculated with the formula "[Waist circumference(cm)-58] x Triglyceride(mg/dL) x 0.0113". Values of 39.82 cm.mmol/L and above were considered abnormal.[16]

SCORE cardiovascular risk scores were calculated by entering age, gender, systolic blood pressure, total cholesterol, HDL-cholesterol, LDL-cholesterol and smoking information of the cases on the calculator of the website "https:// heartscore.escardio.org/Calculate/quickcalculator.aspx?". The obtained values were compared with the SCORE2 European High-Risk Region cards. For cases under 50 years of age, <2.5% was considered low risk, 2.5-7.5% moderate risk and ≥7.5% high risk.

CIMT measurements were performed on the Acuson S3000 ultrasonography device (Siemens Medical Solutions, Mountain View, CA) by the same trained ultrasonographer, following the methods specified in the literature.[10] The recorded values included left CIMT, right CIMT and their mean CIMT. Abnormal values were defined as those exceeding the 75th percentile or 0.634 mm in population-based studies.[17]

MHR was calculated by dividing monocyte counts per mililiter by HDL-C levels in mg/dl. A cut-off value of 9,9 and above was considered abnormal.[18]

Patients meeting three or more of the ATP-III criteria (waist circumference >88 cm; triglyceride ≥150 mg/dL; HDL-C <50 mg/dL; blood pressure ≥130/85 mmHg; fasting glucose ≥110 mg/dL) was diagnosed and recorded as present or no metabolic syndrome.

Coding and analysing of datas were made with The Statistical Package for the Social Sciences version 26.0 (SPSS Inc. Chicago, IL). Normality tests of the variables were obtained by Kolmogorov-Smirnov and Shapiro-Wilk tests. Continous variables were compared with Student's t test or Mann-Whitney U test, depending on normal distribution. The results were presented as "mean- standart deviation" or "median-interquartile range". Categorical variables were evaluated with Chi-Square test and the results were reported as "number-percentage". The relationship between MHR, LAP index, WHR, CIMT measurements (left, right and mean), FAI and HOMA-IR were evaluated with Spearman correlation analysis. Parameters with p value of <0.05 were considered statistically significant.

RESULTS

Mean age of 80 women included in the study was 42.69±2.72. Mean BMI was 27.89± 4.91 kg/m^2. Two groups were similar in terms of age and BMI. Due to cluster in phenotype C and D (35 cases) and only five cases were in phenotype A, phenotype based subgroup analysis couldn't be done in PCOS group. Among PCOS cases, modified Ferriman-Gallwey score was calculated 8 and above for 11 cases. Free androgen index was calculated above 5 for only one case.

In comparison analysis, total testosterone levelwas significantly higher in PCOS group (p<0.001) but other biochemical and anthropometric values were similar. Demographic features, lipid profiles, laboratory values and metabolic parameters was shown in **Table 1**.

Table 1. Comparison of demographic features, lipid profiles, laboratory values and methabolic parameters between PCOS and control groups

Variable	PCOS(n=40)	Control (n=40)	p-value
Age	41.00 (40.75-44.00)	42.00 (41.00-43.00)	0.182[a]
BMI	28.42±5.48	27.38±4.27	0.352[b]
WC (cm)	92.58±13.46	95.35±9.03	0.283[b]
WHR	0.87±0.07	0.89±0.05	0.219[b]
Smoking Status			
Yes	25 (62.5 %)	21 (52.5 %)	0.497[c]
No	15 (37.5 %)	19 (47.5 %)	
Fasting Glucose (mg/dL)	98.00 (88.75-105.25)	95.00 (87.00-101.25)	0.326[a]
Fasting Insulin (IU/L)	7.21 (5.44-11.22)	6.10 (3.88-8.27)	0.082[a]
T.testosteron (nmol/L)	0.44 (0.31-0.66)	0.25 (0.15-0.40)	<0.001[a]
SHBG (nmol/L)	43.65 (30.08-60.12)	45.55 (38.60-56.73)	0.548[a]
T.Cholesterol (mg/dL)	200.50 (179.00-230.00)	186.50 (170.00-212.25)	0.133[a]
HDL-C (mg/dL)	46.00 (43.75-58.50)	50.50 (45.00-57.00)	0.512[a]
LDL-C (mg/dL)	125.53±36.96	117.33±25.58	0.253[b]
Triglyceride (mg/dL)	120.00 (88.00-185.00)	108.50 (89.25-152.00)	0.430[a]
Monocyte (count/mL)	0.48 (0.36-0.51)	0.42 (0.35-0.52)	0.438[a]
SBP (mmHg)	125.00 (120.00-130.00)	120.00 (120.00-130.00)	0.247[b]

BMI: Body Mass Index; WHR: Waist-to Hip Ratio; SHBG:Sex Hormone Binding Globulin; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein SPB: Systolic Blood Pressure
a: Mann-Whitney U test; datas are shown as median (interquartile range).
b: Student's t test; datas are shown as mean±standart deviation.

HOMA-IR values, FAI values, LAP indices and MHR were similar between two groups. Mean CIMT and left CIMT measurements were significantly higher in PCOS group (p=0.022; p=0.01; respectively) (**Table 2**).

In Chi-Square analysis, presence of metabolic syndrome was statistically significantly higher in PCOS group (p=0,045). The distribution of cases between PCOS and control group depending on SCORE2 risk group was similar (**Table 2**).

Table 2. Comparison of cardiovascular risk parameters between PCOS and control groups

Variable	PCOS(n=40)	Control(n=40)	p-value
Right CIMT(mm)	0.70 (0.60-0.90)	0.70 (0.60-0.80)	0.086[a]
Left CIMT(mm)	0.70 (0.60-0.90)	0.60 (0.60-0.72)	0.010[a]
Mean CIMT(mm)	0.70 (0.64-0.88)	0.65 (0.60-0.76)	0.022[a]
HOMA-IR	1.64 (1.17-2.89)	1.36 (0.88-2.09)	0.156[a]
FAI	0.85 (0.57-2.02)	0.52 (0.31-0.90)	0.003[a]
LAP index(cm.mmol/L)	42.10 (28.10-86.04)	50.18 (30.79-67.00)	0.942[a]
MHR	9.29±3.47	8.90±3.12	0.595[b]
Metabolic syndrome			
Present	19 (47.5%)	11 (27.5%)	0.045[c]
No	21 (52.5%)	29 (72.5%)	
SCORE2 risk category			
Low risk	24 (60%)	21 (52.5%)	0.499
Moderate risk	16 (40%)	19(47.5%)	

CIMT: Carotid Intima-Media Thickness; HOMA-IR:Homeostasis Model Assessment-Insulin Resistance; FAI:Free Androgen Index; LAP: Lipid Accumulation Product; MHR: Monocyte to HDL Ratio.
a: Mann-Whitney U test; datas are shown as median (interquartile range).
b: Student's t test; datas are shown as mean±standart deviation.
c:Pearson Chi-Square test, datas are shown as count (column- percent)
p<0,05 is considered statistically significant.

In Spearman correlation analysis, MHR was found correlated with HOMA-IR (r=0.297; p=0.007), LAP index (r=0.235; p=0.035), left CIMT measurement (r=0.215; p=0.049) and FAI (r=0.280; p=0.012). MHR was also positively correlated with WHR, right CIMT and mean CIMT measurements but no significance was found. Correlation table is presented in **Table 3**.

Table 3. Correlation table of cardiovascular risk parameters

n=80	MHR correlation r value	p-value
HOMA-IR	0.297	0.007
LAP Index	0.235	0.035
WHR	0.108	0.341
Right CIMT	0.081	0.477
Left CIMT	0.215	0.049
Mean CIMT	0.143	0.205
FAI	0.280	0.012
SCORE risk point	-0.044	0.697
HOMA-IR correlation r value		
LAP Index	0.301	0.007
FAI	0.238	0.033

MHR: Monosit/ HDL Ratio; LAP: LipidAccumulation Product); WHR: WaisttoHipRatio; CIMT: CarotisIntima- Media Thickness;
FAI: FreeAndrogen Index; SCORE: SystemicCoronor Risk Evalution; HOMA-IR: Homeostasis Model Assessment-InsulinResistance
p<0,05 is considered statistically significant.
Spearman correlation analysis is used for all correlation analyzes.

Among smoker cases, median values for MHR were 11.36 for PCOS group (9.35-11.90; interquartile range) and 8.0 for control group (6.36-9.60; interquartile range) and the difference was statistically significant (p=0.001). Also, among SCORE2 moderate risk cases, median values for MHR were 10.69 for PCOS group (8.20-13.10; interquartile range) and 7.81 for control group (5.71- 9.60; interquartile range) and the difference was statistically significant (p=0.017)

DISCUSSION

It's known that cardiovascular risk count and severity was increased with advancing age in PCOS women.[19-21] In this study, metabolic parameters and scoring systems which may present cardiovascular risk such as MHR, SCORE2 risk point, LAP index, HOMA-IR, WHR, CIMT measurements and FAI were compared and correlation was investigated between MHR and the other parameters among 40 middle-aged PCOS women and 40 non-PCOS healthy women, matched in terms of age and BMI. In results, we found that MHR was positively correlated with LAP index, HOMA-IR, left CIMT measurement and FAI (r=0.235; r=0.297; r=0.215; r=0.280; respectively). In comparison analysis, metabolic syndrome presence was more frequent in PCOS group than control group.

In a large-sampled study, rates of diabetes mellitus, hypertension and dyslipidemia were found higher in PCOS group than non-PCOS group; however coronary heart disease, cerebrovascular disease and peripheral vascular disease frequencies were found similar.[22] In another long-term follow up study, PCOS women's prevalance of DM, hypertension, hypercholesterolemia, hypertriglyceridemia and WHR values were found higher than non-PCOS group. However coronary heart disease dependent morbidity and mortality were similar between two groups.[21] Many studies on perimenopasual and postmenopausal PCOS women's cardiovascular risk were retrospective and the results were controversial. Our study is a rare prospective study that evaluating many cardiovascular parameters together in middle-aged PCOS women.

MHR was correlated with mortality rate among patients who underwent percutan coronary intervention in follow-up.[23] In a study, higher MHR values were found in cases of young PCOS women compared to age matched non-PCOS women.[12] All studies in literature that investigating MHR and PCOS correlation were conducted among reproductive ages.[12,18,24-28] Our study has the feature to be the first study to evaluate cardiovascular risk in perimenopausal PCOS women via MHR. The studies that resulted with remarkably higher MHR values had also lower HDL-C levels in PCOS group while our study was conducted between two groups matched in terms of WC, WHR, smoking status, BMI, age and blood lipid profiles. Although, in our study, analysis conducted among only smoker cases showed that MHR values were significantly higher in PCOS group than control group. It can be concluded that in PCOS women, smoking habit was triggering inflammatory processes more than non-PCOS women.

Soysal et al. have reported that phenotype A PCOS women had higher MHR values than other phenotypes.[27] In our study, there was a cluster on phenotype D due to improved hyperandrogenic and menstrual cycle features of PCOS in menopausal transition age, so phenotype based statistical analysis could not be done. MHR values could differ in a study with a larger sample size and including also phenotype A cases.

In a meta-analysis evaluating 19 studies, it was stated that measurement of the carotid intima media thickness was higher in PCOS group than in the control group.[29] It was reported that thickening in the left carotid begins approximately 10 years earlier than right carotid and while right CIMT measurements were more affected by hemodynamic parameters, left CIMT measurements were more related to inflammatory processes.[30] Since the right carotid originates from the brachiocephalic trunk and the left carotid exits directly from the thoracic aorta, left carotid does not have to share inflammatory substances with the subclavian artery unlike right carotid so that may be more affected more by inflammatory accumulations than right carotid artery.[31] While in our study, left and mean CIMT measurements were found to be significantly higher in the PCOS group, and a positive correlation was reported between left CIMT measurements and MHR; we can conclude that MHR could be used instead of CIMT measurement which was requiring special equipment and specialized health worker.

The positive correlation between HOMA-IR and FAI in our study draws attention to the activator role of insulin in IGF-1 and IGF-2 mediated androgen biosynthesis in ovarian tissue. Considering the studies in which HOMA-IR values were higher in women with PCOS than in the control group,[32] the importance of the hyperandrogenic pathophysiology of PCOS in insulin resistance can be emphasized.

In a study conducted in the age group similar to our study, it was shown that women with oligomenorrhea and hyperandrogenism were diagnosed with metabolic syndrome more than other groups, and the prevalence was 41%.[33] In our study, the frequency of metabolic syndrome in the PCOS group was 47.5%, similar to aforementioned study.

The LAP index's relation with cardiovascular risk, metabolic syndrome and insulin resistance in PCOS has been found in various studies.[16,34,35] In a study investigating 1720 genes focusing on the transcriptional and epigenetic changes of adipose tissue, PCOS women have multiple transcriptional and epigenetic changes in the adipose tissue associated with the development of the disease.[36] In an animal experiment conducted on rats, it was found that mesenteric fat tissues of mice fed with a high-fat diet exhibited a greater chemotactic response to MCP-1 in cell cultures compared to those obtained from mice fed a normal diet. Additionally, higher levels of nitric oxide and TNF-alpha were detected in mice fed with a high-fat diet.[37] This highlights the importance of inflammatory processes in adipose tissue. This study can be seen as the first study to reveal a positive correlation between MHR and LAP index, emphasizing the importance of lipid accumulation and its inflammatory activity.

There are many scoring systems to prevent mortality and morbidity by revealing the existing risks before CVD occurs. Framingham and SCORE2 are well-known and widely used CVD risk calculator systems.[9,38] In a multicenter study, comparing patients' SYNTAX scores with Framingham and SCORE values, it was reported that SCORE risk scores matched moderately better with SYNTAX scores.[39] Therefore, we preferred the SCORE2 calculation system, since the risk regions including our country are defined in the SCORE2 calculation system and it provides gender-specific assessment. In our study, there was no significant difference in SCORE2 risk between the groups and it may be attributed to the similarity between the SCORE2 variables of the groups.

The weakness of this study is the lack of assessment of lifestyles (exercise, alcohol use, eating habits, etc.) that have been habituated over the years and may affect the parameters studied. In addition, women who were diagnosed and followed up with PCOS during the reproductive period were included in our study. The fact that hyperandrogenic and reproductive problems can improve with age, and metabolic problems increase with age may be a factor may be the cause of cluster on phenotype D. For this reason, the change in CVD risk according to PCOS phenotypes was not mentioned in our study.

The strengths of this study are that it is the first study to investigate the relationship with PCOS and CVD with parameters that have been shown to be associated with CVD risk in different population and to evaluate the correlation of these parameters with the simple and inexpensive MHR test, especially in women approaching or in the menopausal transition period. Our study is also the first to evaluate MHR in PCOS patients over the age of 40. The similarity of anthropometric measurements and laboratory values between PCOS and control groups emphasizes the importance of increased cardiovascular risk markers in the PCOS group, as revealed by the study.

CONCLUSION

In summary, it was shown that cardiovascular risk factors in PCOS women worsens over years in our study. MHR was found correlated with HOMA-IR, LAP index and CIMT measurement. These findings offer that MHR could be a substitute for multiple cardiovascular risk predictor systems such as CIMT, LAP index, HOMA-IR, metabolic syndrome and SCORE2 risk points to reveal the cardiovascular risk in perimenopausal PCOS women. MHR can be used as a cardiovascular risk screening test, especially in women in the menopausal transition who smoke and have a moderate risk SCORE2 risk, compared to other expensive and specialized tests.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was obtained from Kutahya Health Science University Ethics Committee (Date: 10.06.2021, Decision No: 2021/10-23).

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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Original Article / Orijinal Araştırma

An Investigation into Sleep Habits in Obese Children

Obez Çocuklarda Uyku Alışkanlıklarının İncelenmesi

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Abstract

Aim: This study aims to reveal the extent to which sleep habits differ between obese children and healthy children.

Materıal and Method: This comprehensive study involved 236 obese children and adolescents aged 8-17 who were closely monitored in our clinic. Additionally, 114 children and adolescents who visited the child health and diseases outpatient clinic for various reasons participated. All participants underwent a meticulous assessment of their sleep habits, which included 33 detailed questions about bedtimes, sleep behavior, waking up during the night, getting up in the morning, and daytime sleepiness.

Results: No statistically significant difference in age and gender characteristics between the patient and control groups. The sleep duration for obese children was 6.44±1.3 hours, compared to 6.31±1.29 hours in the control group (P=0.426). No statistical difference was observed in the components assessing sleep habits between the patient and control groups. There is no statistical difference between obese girls and boys considering sleep duration, respectively: 6.41±1.41, 6.5±1.07) (P=0.603). In addition, there is no significant difference between obese and healthy girls and boys according to all sleep parameters.

Conclusion: Our findings indicate that there are no significant differences in sleep habits between obese children and healthy children. However, some studies in the literature reported that different parameters, such as age, pubertal status, timing of sleep and eating behaviors, and sleep duration (or restriction), can affect the relationship between sleep and obesity. Therefore, longitudinal and experimental studies with children are needed to determine the nature of the relationships between sleep and obesity in children.

Keywords: Sleep duration, childhood, obesity, adolescent

Öz

Amaç: Bu çalışma, obez çocuklar ile sağlıklı çocuklar arasındaki uyku alışkanlıklarının ne ölçüde farklılık gösterdiğini ortaya koymayı amaçlamaktadır.

Gereç ve Yöntem: Bu çalışmaya kliniğimizde takip edilen 8-17 yaş arası 236 obez çocuk ve ergen ile çeşitli nedenlerle çocuk sağlık ve hastalıkları polikliniğine başvuran 114 çocuk ve ergen katılmıştır. Mevcut çalışmadaki tüm katılımcılar, yüz yüze görüşmelerle çocuklarda uyku alışkanlıklarının değerlendirilmesinden geçirilmiştir. Değerlendirme, yatma saatleri, uyku davranışı, gece uyanma, sabah kalkma ve gündüz uykululuk ile ilgili 33 soruyu içermektedir.

Bulgular: Hasta ve kontrol grupları arasında yaş ve cinsiyet özellikleri açısından istatistiksel olarak anlamlı bir fark bulunmamıştır. Obez çocukların uyku süresi, kontrol grubunda 6,31±1,29 saat iken 6,44±1,3 saat olarak tespit edilmiştir (P=0,426). Hasta ve kontrol grupları arasındaki uyku alışkanlıklarını değerlendiren bileşenlerde istatistiksel bir fark gözlemlenmemiştir. Obez kız ve erkek çocuklar arasında uyku süreleri açısından da istatistiksel bir fark bulunmamaktadır (sırasıyla: 6,41±1,41, 6,5±1,07) (P=0,603). Ayrıca, obez ve sağlıklı kız ve erkek çocuklar arasında tüm uyku parametreleri açısından anlamlı bir fark yoktur.

Sonuç: Bulgularımız, obez çocuklar ile sağlıklı çocuklar arasında uyku alışkanlıkları açısından önemli farklılıklar olmadığını göstermektedir. Ancak literatürde, yaş, ergenlik durumu, uyku ve yeme davranışlarının zamanlaması, uyku süresi (veya kısıtlaması) gibi farklı parametrelerin uyku ile obezite arasındaki ilişkiyi etkileyebileceğini bildiren bazı çalışmalar bulunmaktadır. Bu nedenle, çocuklar arasında uyku ile obezite arasındaki ilişkilerin doğasını belirlemek için uzunlamasına ve deneysel çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Uyku süresi, çocukluk çağı, obezite, ergenler

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INTRODUCTION

Childhood obesity has become an increasingly significant health issue worldwide and in our country, Türkiye, especially in recent years.[1] Obesity is primarily a significant problem and also may be a cause of many health issues. The prevalence of metabolic syndrome, which includes insulin resistance, hypertension, and disturbances in glucose regulation, has increased in children alongside obesity.[2] In addition, it has been observed that obesity is associated with many factors that negatively affect quality of life. Sleep disorders, eating behavior problems, and social withdrawal are some of the significant health issues seen in these patients. Moreover, dyslipidemia, cardiometabolic risk factors, hypertension, and insulin resistance are health problems that can be observed in both childhood and adulthood related to obesity.[3] Many studies have been conducted in the literature regarding the sleep habits of obese children and adolescents.[4,5] Some researchers have identified an independent relationship between obesity and sleep disorders, while some have found such a relationship specifically in obese girls but not in boys. Others have reported no relationship between obesity and sleep, regardless of gender differences.[4] Sleep duration is suggested to be a risk factor for childhood obesity. Short sleep duration is associated with weight gain and increased body mass index values.[5] In this study, we aimed to evaluate the sleep habits of obese patients being monitored in our clinic. A sleep habits questionnaire assessing bedtime, sleep behavior, waking during the night, and morning wakefulness/daytime sleepiness was administered using face-to-face interview techniques across the entire study group.

MATERIAL AND METHOD

This study was conducted at the Pediatric Health and Diseases Department of Gaziosmanpaşa University School of Medicine between September 2014 and January 2015. In the present study, 236 obese children and adolescents monitored in our clinic, along with 150 non-obese patients who presented for various reasons to the pediatric health and diseases outpatient clinic, were included. This study was initiated after obtaining ethical approval from the Gaziosmanpaşa University Ethics Committee (file no: 14-KAEK-056). Surveys were administered to all participants through face-to-face interviews. To maintain consistency, the same researcher administered all surveys and scales. Following the explanation of this study's scope and purpose, written consent was obtained from all participants and their parents. The height and weight of the patients were measured using a digital scale and height meter (Seca Corp., Chino, CA, USA). Based on age and gender, participants with a body mass index above the 95th percentile were classified into the obese group; in contrast, the healthy control group included those below the 85th percentile. Patients with any syndrome, Cushing syndrome, hypothyroidism, or chronic illness that causes obesity were not included in the study. The questionnaire administered to the study group evaluated sleep habits in preschool and school-aged children. The Turkish validity and reliability were established by Fiş et al.[6] The scale included eight subscales that could be categorized as resistance to bedtime (items 1, 3, 4, 5, 6, 8), delayed sleep onset (item 2), sleep duration (items 9, 10, 11), sleep anxiety (items 5, 7, 8, 21), nighttime awakenings (items 16, 24, 25), parasomnias (items 12, 13, 14, 15, 17, 22, 23), sleep-related breathing disturbances (items 18, 19, 20), and daytime sleepiness (items 26, 27, 28, 29, 30, 31, 32, 33). A total of 33 questions were posed to participants, divided into four sections. These questions assessed bedtime, sleep behavior, nighttime awakenings, and morning wakefulness/daytime sleepiness. Parents were asked to consider the sleep habits of their children and answer these questions based on a week prior. If, for any reason, there were circumstances one week ago that differed from their usual routine—such as the child having a feverish infection and experiencing sleep difficulties or disruptions in home life due to moving or renovations—they were instructed to reflect on the last week their child had a regular routine to answer the questions. Respondents were asked to consider how often these situations occurred: if it happened 5-7 times a week, it should be answered as "usually;" if it occurred 2-4 times, "sometimes;" and if it happened once or not at all, "rarely."

Statistical Analysis

A significance test was assessed using the independent sample t-test to compare continuous variables between groups. Pearson correlation analysis was used to determine the relationships. Continuous variables were expressed as mean (M) and standard deviation (SD). P-values calculated to be below 0.05 were considered statistically significant. The calculations were performed using commercial statistical software (IBM SPSS Statistics 19, SPSS Inc., an IBM Company, Somers, NY).)

RESULTS

This study included 136 patients, of which 82 (62.3%) were female and 82 (37.6%) were male; the control group consisted of 66 (57.8%) females and 48 (42.1%) males. The average age of the patients was 11.86±3.03 years, and the BMI of all obese participants was between the 95th and 99th percentiles, while the average age of the control group was 11.38±3.13 years, with no statistically significant difference between the two groups (**Table 1**). The average BMI of the patients was 28.21± 4.91, while the average BMI of the control group was 24.13± 4.5 (P<0.001). There was no significant correlation between BMI and sleep duration in obese children (r = -0.123, P=0.093). Going to bed reluctantly title in this study questioned and there is no significantly difference found between obese and healthy children (P:0,604). Difficulty in falling asleep is evaluated by questionare and found no difference between two groups and genders (P: 0,712). Anxiety of falling asleep is guestiond to two groups and the answers were found similar and we found no statistically difference between two groups (P: 0,768). Breathing problems and daytime somnolence evaluated in two groups and no statistically differences were found, respectively P:0,584 and P:0,236. The sleep duration for

obese children was 6.44±1.3 hours, compared to 6.31±1.29 hours in the control group (P=0.426). When comparing sleep duration between female and male obese children, no significant difference was found 6.41±1.41 hours for females and 6.5±1.07 hours for males (P=0.603) (**Table 2**).

Table1. Comparison of obese children and healthy controls in terms of sleep habits

	Control (n=114)	Patients (n=218)	P
Going to bed reluctantly	10.85±2.30	10.71±2.37	0.604
Difficulty in falling asleep	2.51±0.72	2.48±0.75	0.712
Sleep latency	6.31±1.29	6.44±1.3	0.426
Falling asleep anxiety	6.19±2.32	6.27±2.41	0.768
Night awakenings	4.42±1.35	4.62±1.66	0.297
Nightmares	10.23±3.36	9.87±3.37	0.410
Breathing problems	4.16±1.68	4.29±1.93	0.584
Daytime somnolence	15.72±3.37	15.25±3.24	0.236

Table2. Sleep habits in terms of gender in obese children

	Female N:136	Male N:82	P
Going to bed reluctantly	10.79±2.39	10.55±2.34	0.482
Difficulty in falling asleep	2.42±0.78	2.59±0.71	0.105
Sleep latency	6.41±1.41	6.5±1.07	0.603
Falling asleep anxiety	6.45±2.51	5.97±2.23	0.162
Night awakenings	4.65±1.77	4.58±1.47	0.769
Nightmares	9.91±3.42	9.8±3.3	0.844
Breathing problems	4.09±1.87	4.61±2	0.070
Daytime somnolence	15.44±3.14	14.92±3.4	0.270

DISCUSSION

This study is an important research to evaluate the sleep habits of obese children in our region and to compare them with healthy children. In this study, there is no significant difference between obese and healthy children according to children's sleep habits questionnaire. Childhood obesity is increasingly widespread in Türkiye and worldwide. Although the prevalence of obesity is still lower than in North America and Western Europe, it is increasing in Türkiye, which is parallel to the trend in many countries.[7,8] The increasing prevalence of obesity in children has a considerable impact on the development of many comorbidities that will disrupt sleep comfort, such as obstructive sleep apnea and obesity-related hypoventilation syndrome.[9] The relationship between sleep and obesity is not fully understood.

Members of the American Academy of Sleep Medicine developed consensus recommendations for the amount of sleep needed to promote optimal health in children and adolescents. In these recommendations, Children 6 to 12 years of age should sleep 9 to 12 hours and teenagers 13 to 18 years of age should sleep 8 to 10 hours per 24 hours on a regular basis to promote optimal health.[10] Sleeping for the recommended number of hours regularly is associated with better health outcomes, such as attention, behavior, learning, memory, emotional regulation, quality of life, and mental and physical health.

Chronic short sleep duration was associated with increased adiposity and obesity from infancy to school age.[4] Additionally, researchers have suggested that short sleep duration is a risk factor for the development of obesity and overweight.[5] Pileggi et al.[11] conducted a study from a cross-sectional perspective, considering various factors that affect body weight, and showed that chronic sleep deprivation is associated with a higher BMI in children around the age of 10. In their study, 39% of children were classified as short sleepers, and the mean sleep duration was 9.4 (SD±60.6), and the mean age was 9.9 years. In our study, the mean sleep duration was 6.31(±1.29) in obese children, and the mean age was 11.8 years. The age range in our study affected the result.

Sleep requirements change throughout childhood, so definitions of short sleep duration vary across different age groups. In a pediatric study of 8,274 Japanese children ages 6 to 7, those who slept fewer than eight hours were almost three times more likely to be overweight than those who slept more than 10 hours.[12] Also, previous studies have reported that longer nighttime sleep reduces the risk of developing overweight.[13,14]

While some researchers have stated that obesity development associated with short sleep duration is only seen in boys, and the same is not true for girls, others have suggested that short sleep duration is associated with obesity in both genders.[11,15] In our study, it was observed that there was no difference in sleep duration according to gender. A larger study may be needed to highlight the difference.

In the literature, it has been found that late bedtime in children is predicted as an independent parameter in the relationship between short sleep duration and obesity. It has been suggested that these children consume more calories and spend more time in front of the screen before bedtime and have shorter sleep times due to this late bedtime. However, the researchers who conducted this study emphasized that the number of cases in their study was insufficient.[16,17] In our study, there was no statistically significant difference between the groups in terms of bedtime resistance and delay in falling asleep. Another study indicated that insufficient sleep at age 14 was a predictor of weight gain between the ages of 14 and 18, with the strongest correlations observed among adolescents.[18] It also found a consistent association between short sleep in early childhood (ages 3–7) and concurrent or later obesity.[19] A study conducted on Danish children aged 8-11 found that varying sleep schedules over a specific week were associated with increased energy intake, independent of total sleep duration, screen time, and demographic confounders.[20] Going to bed reluctantly is evaluated in this study. Especially obese children are mostly using internet more than the others and watching television up to late hours. Internet addiction is related to poor sleep quality.[21] In this study we did not evaluate the internet addiction but we found no difference between obese and healthy children considering with going tobe reluctantly title. Eliacık et al.[21] investigated the sleep habits in obese children

and found that there is no significant difference between obese and healthy children, considering sleep disturbances and daytime dysfunction. On the other hand, obese children may have some breathing problems. In this questionnaire, participants were asked about breathing problems. Data showed that there was no difference between obese and healthy volunteers. Yang et al. described some breathing problems in obese children, as many studies investigated sleep disorders in obese children.[22] Our results were not compatible with the literature. In many studies, investigators use polysomnography to detect breathing problems. However, this study is based on observation.

Limitations

Consistent with most similar studies in the literature,[11,23] in our study, sleep duration was obtained from parents' self-reports, and there is no existing resource to verify or validate this information. However, parent reports of sleep behaviors have been found in the literature to have significant validity and reliability when compared with objective actigraphic measures.[24] The wide age range of our study group constituted another limitation. The definition of the sleep requirement during childhood varies by age, so the criteria for short sleep duration also differ across various age groups. Another limitation of the study is that physical examination findings environmental or personal factors and laboratory results that may affect sleep duration could not be evaluated statistically.

CONCLUSION

In this study we evaluate sleep habits of obese children and we compare them to healthy children. We found no differeence between two group. Therefore, longitudinal and experimental studies with children are needed to determine the nature of the relationships between sleep and obesity in children.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was initiated after obtaining ethical approval from the Gaziosmanpaşa University Ethics Committee (Decision no: 14-KAEK-056).

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.

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Letter to the Editor/ Editöre Mektup

A Case of Pediatric Tuberculosis Presenting with Pleurisy and Pyrazinamide Resistance

Plörezi İle Başvuran Pirazinamid Direnci Saptanan Pediatrik Tüberküloz Olgusu

Yalçın Kara

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Dear Editor,

Tuberculosis is an infectious disease caused by the Mycobacterium tuberculosis bacteria with high mortality and morbidity. Especially, delay in diagnosis and treatment of childhood tuberculosis causes an increase in adult tuberculosis. According to the World Health Organization, 11% of all tuberculosis cases in 2018 and 12% in 2019 were children under the age of 15. And in 1991, 450,000 out of 1.3 million children with tuberculosis (TB) aged <15 years in developing countries were lost.[1] TB eradication can be achieved not only via the development and widespread use of anti-tuberculosis agents but also by determining the source individual, early diagnosis, and appropriate treatment.

A 15-year-old female patient had a fever, cough, and chest pain for about 1 week. On physical examination, breathing sounds were weak in the left lower lobe, and on chest radiography, there was consolidation and effusion in the left lobe. A Thorax CT scan demonstrated an enlarged mediastinal lymph node and a 4 cm pleural effusion in the left lobe of the lung (**Figure 1**). Approximately 200 ml of yellow pleural fluid was drained from the thoracostomy tube. Remarkable pleural fluid parameters:glucose: 5 mmol, pH: 6.9, LDH: 1200 U/L. When the patient's history was questioned again, it was learned that his father was treated for pulmonary tuberculosis approximately 1 year ago, and isoniazid prophylaxis was recommended to all family members at that time, but she did not use it. Pleural fluid was analyzed acid-resistant staining (ARB) was positive and mycobacter tuberculosis PCR was positive. Tuberculin skin test: 18 mm, quantiferon was positive. Isoniazid, rifampicin, pyrazinamide, and ethambutol treatments were started for the patient. During the follow-up of the patient, the amount of pleural effusion gradually decreased and the thorax tube was removed. In the 2nd week of treatment, the patient's effusion disappeared completely, and respiratory distress subsided and discharged with the recommendation to continue taking anti-tuberculosis medications and close polyclinic control. All family members were directed to the tuberculosis dispensary.

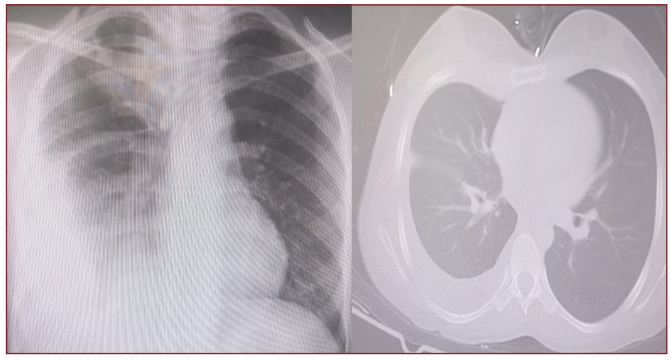

Figure 1. X-Ray and Tomography Image of the Case

Minimal effusion was detected on the chest x-ray of the patient, who presented with chest pain again in the 3rd month of treatment. The family was questioned again and it was learned that she did not use medications regularly. Directly supervised treatment was planned by contacting the tuberculosis dispensary. Drug resistance was studied

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and pyrazinamide resistance was detected by BACTEC MGIT 960 kit from the mycobacterial culture isolates taken from the patient's pleural fluid at the time of diagnosis. According to the Ministry of Health's tuberculosis diagnosis and treatment guide, maintenance treatment was planned to be extended to 7 months.

Tuberculosis disease (TB) continues to be an important public health problem in the world and our country due to its high mortality and morbidity rate, despite advances in its treatment. Early recognition and treatment of childhood tuberculosis have an important place in the fight against adult tuberculosis.[1] Screening close contact with a tuberculosis patient and including them in a prophylactic treatment program is one of the most important steps in the fight against tuberculosis.[2] Drug resistance is an increasing problem in tuberculosis treatment. In patients who do not respond to treatment or who do not use treatment regularly, drug resistance should be kept in mind and the appropriate treatment regimen should be designed by working on drug resistance.[2,3]

Keywords: Tuberculosis, pyrazinamide resistance, pediatric

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Letter to the Editor/ Editöre Mektup

Necrotizing Pneumonia due to Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infection

Toplum Kökenli Metisiline Dirençli *Staphylococcus aureus* Enfeksiyonuna Bağlı Nekrotizan Pnömoni

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Dear Editor,

Necrotizing pneumonia is a severe and potentially life-threatening serious complication of pneumonia characterized by the necrosis and liquefaction of lung parenchyma. It accounts for approximately 4% of community-acquired pneumonia.[1]

A 10-month-old male patient was admitted with a five-day history of fever and difficulty breathing. He had used oral amoxicillin clavulanic acid for five days before admission. The patient had a history of cesarean delivery at 38 weeks gestation with a birth weight of 3500 grams, and had no history of chronic disease or previous hospitalization. Vaccines were administered following the National Vaccination Schedule. Physical examination revealed a fever, decreased breath sounds in the right lung, and bilateral crackles. The patient also exhibited tachypnea.

In laboratory tests, hemoglobin 9.4 g/dl, leucocyte counts 15010/mm³, absolute neutrophil count 10380/mm³. Acute phase reactants were elevated as C-reactive protein (CRP) was 263 mg/l (normal value 0-5 mg/l). Chest X-rays showed one small cavity within areas of pulmonary consolidation (**Figure 1a**). Cefotaxime treatment was initiated. As the fever persisted on the third day of hospitalization, vancomycin was added to the treatment regimen, and the CRP level was 170 mg/L.

On the sixth day of hospitalization, cefotaxime treatment was discontinued, and meropenem treatment was initiated. The CRP level was 122 mg/L. Chest X-ray and chest tomography revealed cystic and nodular lesions with cavitation containing air and fluid levels, consistent with necrotizing pneumonia (**Figure 1b**).

Thoracentesis was performed but no sample was obtained. On the 10th day of treatment, a lung tissue sample was obtained by the interventional radiology department and methicillin-resistant *Staphylococcus aureus* (MIC value was 0.5 mg/L for vancomycin, 0.25 mg/L for clindamycin) growth was detected in this specimen.

The patient remained afebrile from the eleventh day of treatment onwards. He completed a 25-day course of vancomycin and a 19-day course of clindamycin. Following the discontinuation of intravenous treatment, oral clindamycin was initiated, with the total duration of treatment extending to six weeks.

The Tuberculin skin test was 0 mm while the Interferon-gamma release assay test resulted as indeterminate twice. Acid-resistant bacteria were not detected in the gastric aspirates taken over three consecutive days, and the Mycobacterium tuberculosis complex did not grow. Immunologic examination of the patient revealed normal levels of immunoglobulins, lymphocyte subsets, and a normal dihydrorhodamine test. HIV testing was negative. An echocardiographic examination revealed no abnormalities. The patient's chest X-ray showed progressive improvement, and no problems were encountered during the six-month follow-up after discharge (**Figure 1c**).

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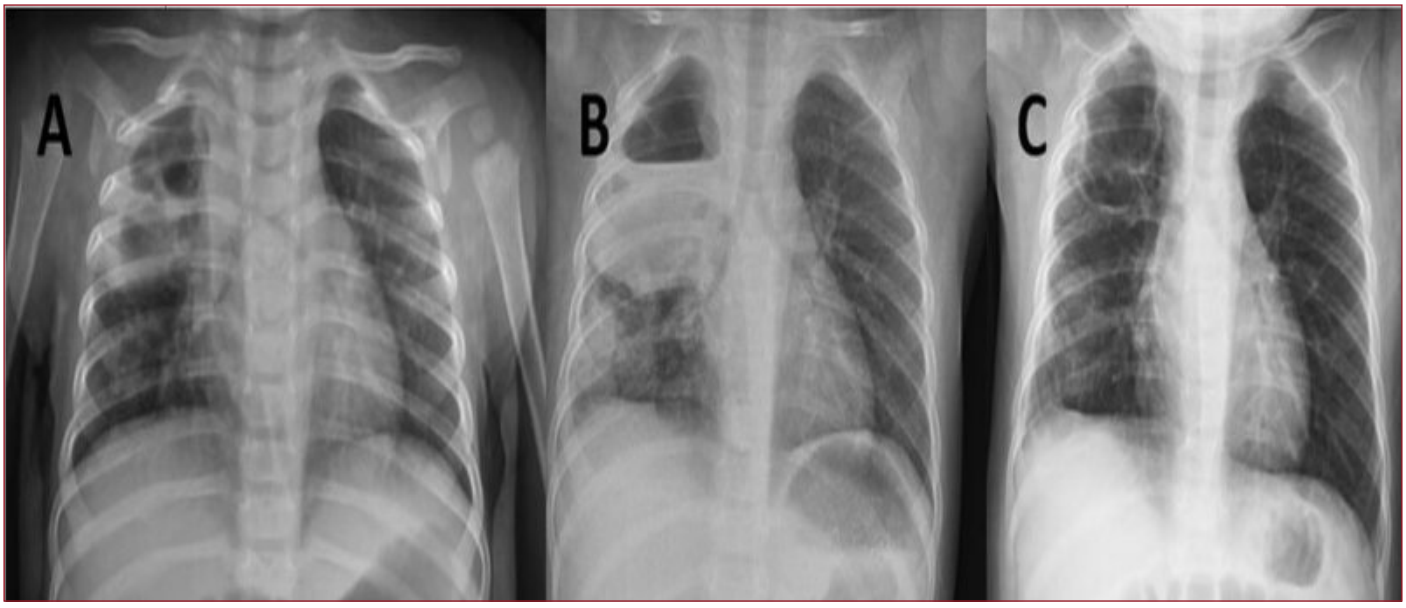

Figure 1. Chest X-ray of patient (A: At admission, B: The 6th day of treatment, C: The 30th day of treatment)

Necrotizing pneumonia is a severe infection that usually affects immunocompetent children, timely and effective treatment is life-saving. Although identifying the causative agent and determining antibiotic susceptibility is the most important step in guiding treatment, the causative agent can be demonstrated in less than half of the cases.[1,2] The lack of an effective vaccine against *S. aureus* increases the importance of early diagnosis and treatment.[3]

Keywords: Child, necrotizing pneumonia, *Staphylococcus aureus*

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Review / Derleme

Improving Performance Through Nutrition: Muscle Recovery Strategies

Beslenme Yoluyla Performansı Artırma: Kas İyileştirme Stratejileri

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Abstract

Muscle recovery and nutrition play a crucial role in enhancing an athlete's performance, maintaining a healthy body and accelerating recovery. Proper nutrition ensures that the body receives essential nutrients such as protein, carbohydrates, fats and other nutrients required for muscle repair and growth, which are critical for muscle recovery and strengthening. A sound nutritional strategy not only enhances an athlete's performance and reduces the risk of injury, but also promotes overall health and well-being. The use of performance-enhancing products is current, but not new to mankind. Substances that enhance performance, reduce fatigue, aid recovery and potentially influence decisiveness has been utilized since ancient times in the form of stimulants, depressants or anabolic agents. In addition, maintaining fluid balance and preventing dehydration are critical not only to an athlete's performance, but also to their overall health. In some sports, in addition to fluid and electrolyte intake, carbohydrate intake is also important, as carbohydrates consumed with fluid are easier to transport and metabolise in the body. In recent years, the effect of coenzyme Q10 supplementation, known for its important role in cellular bioenergetics and redox reactions as well as its antioxidant properties, on post-exercise muscle tissue recovery has attracted attention. While the potential benefits of supplementation in this area are intriguing, further research is necessary to illuminate its effects.

Keywords: Muscle recovery, nutrition, protein, carbohydrate, coenzymeQ10

Öz

Kas iyileşmesi ve beslenme, sporcuların performansını artırmada, sağlıklı bir vücut yapısına sahip olmada ve iyileşme sürecini hızlandırmada önemli bir rol oynar. Doğru beslenme alışkanlıkları, vücudun kas onarımı ve büyümesi için gerekli olan protein, karbonhidrat, yağ gibi temel besin maddelerini almasını sağlar; bu da kasların iyileşmesi ve güçlenmesi için kritik öneme sahiptir. Etkili bir beslenme stratejisi, sporcuların performansını artırırken yaralanma riskini azaltabilir ve genel sağlığı iyileştirebilir. Performans artırıcı ürünlerin kullanımı günceldir, ancak insanlık için yeni değildir. Performansı artıran, yorgunluğu azaltan, iyileşmeye yardımcı olan ve potansiyel olarak kararlılığı etkileyen maddeler, eski zamanlardan beri uyarıcılar, depresanlar veya anabolik ajanlar şeklinde kullanılmaktadır. Buna ek olarak, sıvı dengesini korumak ve dehidrasyonu önlemek sadece bir sporcunun performansı için değil, aynı zamanda genel sağlığı için de kritik öneme sahiptir. Özellikle bazı spor branşlarında sıvı ve elektrolit alımı ile birlikte karbonhidrat tüketimi, besinlerin vücutta taşınması ve metabolize olmasını kolaylaştırır. Son yıllarda, hücre bioenerjetiği ve redoks reaksiyonlarında önemli bir rol oynayan ve aynı zamanda güçlü bir antioksidan olan Koenzim Q10 takviyesinin, spor sonrası kas dokusundaki iyileşme üzerine etkisi giderek daha fazla ilgi çekmektedir. Bu alanda takviye kullanımının potansiyel faydaları öenmli olmakla birlikte, daha fazla araştırmaya ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Kas iyileşmesi, beslenme, protein, karbonhidrat, koenzimQ10

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INTRODUCTION

Recovery strategies should address the primary causes of fatigue, both within the general population and among athletes community. Physical activity stimulates the metabolism and improves the functioning of the body's systems.[1,2]

Numerous studies have underscored the significance and effectiveness of proteins, amino acids, emergency intervention principles and metabolic regulators (such as vitamins and minerals) in promoting muscle recovery.[1-3]

Exercise-induced muscle damage (EIMD) is defined by histopathological alterations in muscle tissue due to skeletal muscle injury, leading to an inflammatory response that reduces the athlete's physical performance and athletic capacity. As a result, muscle regeneration has become a top priority for elite athletes in various sports.[4]

The implementation of a recovery process through nutritional intervention can be crucial both for the general population and particularly for athletes. Muscle damage can take days to recover.[5] Faster and more efficient recovery allows athletes to train harder and respond more positively to exercise, which requires adequate nutrient intake.[6]

Nutrition has a significant impact on stimulating muscle recovery. However, it's important to improve the intake of sufficient energy, nutrients and fluids and to time them appropriately in relation to training and competition schedules.[7]

These recovery strategies emphasise not only the role of specific nutrients, but also the timing and quantity of intake, which are critical to maximising the benefits of nutritional interventions. A holistic approach that integrates both macro- and micronutrients is essential for effective recovery. It is also important to take into account the psychological aspects of recovery, as mental well-being has a significant impact on physical recovery processes. Addressing psychological resilience and stress management can improve overall recovery and performance.[8]

In addition, personalised nutrition plans that take into account individual differences in metabolism, nutritional needs and recovery rates can optimise the effectiveness of recovery strategies for athletes.[9] Such tailored approaches ensure that interventions are not only scientifically sound, but also practically applicable to the individual's unique physiological and psychological profile (**Table 1**).[8,9]

Table 1. Comprehensive Recovery Strategies for Muscle Recovery and Fatigue Management in Athletes

Title	Description
Causes and Mitigation of Fatigue	Fatigue causes should be addressed both in the general population and among athletes. Physical activity stimulates metabolism and improves the functioning of body systems.
Role of Nutrients in Muscle Recovery	Proteins, amino acids, emergency intervention principles, and metabolic regulators (such as vitamins and minerals) promote muscle recovery.
Exercise-Induced Muscle Damage (EIMD)	EIMD is defined by histopathological changes in muscle tissue due to skeletal muscle injury, leading to an inflammatory response that reduces physical performance.
Nutritional Intervention and Recovery	Nutritional intervention can be crucial for both the general population and athletes. Muscle damage can take days to recover. Faster and more efficient recovery allows athletes to train harder and respond more positively to exercise, which requires adequate nutrient intake.
Impact of Nutrition on Muscle Recovery	Nutrition significantly impacts muscle recovery. It's important to ensure sufficient energy, nutrients, and fluids intake and to time them appropriately in relation to training and competition schedules.
Holistic Recovery Strategies	Recovery strategies emphasize not only the role of specific nutrients but also the timing and quantity of intake, which are critical to maximizing the benefits of nutritional interventions.
Psychological Aspects of Recovery	Addressing psychological resilience and stress management can improve overall recovery and performance, as mental well-being significantly impacts physical recovery processes.
Personalized Nutrition Plans	Personalized nutrition plans that consider individual differences in metabolism, nutritional needs, and recovery rates can optimize the effectiveness of recovery strategies for athletes.

Key Components of Athletic Nutrition and Recovery

Adequate Protein Intake

During any training or performance session, a decline in muscle function can reduce both the quality and intensity of the activity, putting athletes at risk of injury. It's thought that consuming protein around the time of exercise may improve muscle recovery, however, existing research on this topic has yielded inconsistent results. Whey protein (WP) stands out as a high-quality protein source, abundant in essential amino acids that stimulate muscle protein synthesis (MPS)[10-13] after exercise, a benefit that exceeds that of other lower quality protein sources.[14]

One study[15] investigated the effects of a mixture of WP and casein in an 80:20 ratio, based on the ratio of rapidly and slowly absorbed proteins, reflecting the benchmark for protein quality and nutrient content comparable to what is found in human breast milk (HBM).[16] Although no beneficial effects on protein metabolism markers were observed, amino acid kinetics indicated that WP was the most effective supplement for increasing plasma leucine concentration. The combination of WP and casein (CAS) did not offer any advantage in amino acid persistence at peak levels compared to WP alone; nevertheless, it was determined that the blend of WP and CAS minimised muscle soreness compared to CAS and placebo groups.[15]

Two trials investigated the relative efficacy of WP versus vegetable protein on EIMD.[16,17] They reported that three doses of 0,3 g/kg WP isolate per day for five days after exercise reduced muscle damage in the group studied. Alternatively, pea protein supplementation had a small effect on reducing EIMD.[16] Collectively, these data endorse the utilization of three doses of 0.3 g/kg WP isolate daily.

The potential of WP to enhance muscle recovery is particularly significant given its high quality protein content, abundant in essential amino acids that are critical for stimulating MPS.[17] While the existing literature shows mixed results, it is clear that the timing of protein consumption concerning exercise is pivotal for its efficacy.[18] This underscores the necessity for additional research to optimise protein supplementation strategies, particularly in the context of athletic training and recovery.

Another study[19] suggests that adequate daily protein intake (1.2-1.6 g/kg or 1.4-2.0 g/kg) and protein intake around the time of exercise promotes muscle recovery. In conclusion, protein supplementation contributes to the enhancement of lean mass, increased strength and improved recovery if the guidelines identified in their research are followed.[16,19]

Glutamine, along with other amino acids, facilitates a muscle-building state by increasing protein synthesis.[20,21] Glutamine supplementation has been observed to attenuate "The inflammatory reaction subsequent to eccentric exercise[22] and to reduce muscle soreness, suggesting a possible association with reduced muscle damage.[21] Data presented suggest that glutamine supplementation reduces circulating markers of muscle damage, while balancing catabolic and anabolic hormonal responses and stabilising leukocyte counts (**Table 2**).[23]

Table 2. Effects of Different Types of Protein Supplementation on Muscle Recovery

Protein Type	Effects and Findings
Whey Protein (WP)	Effective in increasing MPS, supports recovery after exercise.
WP and Casein Mix (80:20)	Most effective in increasing plasma leucine concentration, reduces muscle soreness better than casein and placebo groups.
WP and Plant Protein	Three doses of 0.3 g/kg WP isolate per day reduce muscle damage post-exercise; pea protein has a small effect on reducing EIMD.
General Protein Intake	Adequate protein intake around exercise (1.2-1.6 g/kg or 1.4-2.0 g/kg) promotes muscle recovery, increases lean mass and strength.
Glutamine	Increases muscle protein synthesis, reduces inflammatory reactions, lessens muscle soreness, and stabilizes leukocyte counts.

Carbohydrate Consumption

Carbohydrate (CHO) ingestion during endurance exercise, it has been demonstrated to postpone neuromuscular fatigue and, in particular, improve exercise capacity, depending on the dose administered. In addition, carbohydrate (CHO) supplements can improve exercise performance in specific physical activities of different intensity and duration and adjust biomarkers of exercise-induced muscle damage (EIMD). Numerous studies have examined the impact of carbohydrate (CHO) intake on physical performance, covering different aspects such as repeated sprint performance,[24] neuromuscular function[25] and markers linked to exercise-induced muscle damage.[26,27]

A randomized, double-blind, placebo-controlled, crossover trial in 15 recreational athletes concluded that carbohydrate (CHO) intake just piroir to and during short, maximal and repeated sprint exercise did not affect performance or improve training quality.[22] These findings challenge the previously observed ergogenic effects of CHO on prolonged anaerobic performance. The study provides valuable information for prescribing CHO intake to optimise practical performance-enhancing training. It appears that this form of carbohydrate intake does not improve adenosine triphosphate (ATP) turnover and therefore does not improve anaerobic cycling performance compared to the effects observed with placebo. Therefore, this form of carbohydrate intake does not seem to offer any ergogenic advantage.[24]

Two studies have shown that a higher carbohydrate intake during an endurance test (up to 120 g/hour) than currently recommended effectively promotes prolonged neuromuscular recovery and mitigates the decline in exercise capacity 24 hours after a mountain marathon, providing an appropriate strategy to modulate EIMD.[26,27]

Evidence suggests that while carbohydrate (CHO) supplementation may not significantly improve short-term, high-intensity anaerobic performance, it has a pronounced benefit in prolonging endurance and facilitating recovery in longer-duration events.[28] This difference in efficacy highlights the importance of context-specific nutritional strategies tailored to the nature and duration of exercise. Therefore, practitioners should consider the type of exercise when advising on carbohydrate intake, as the benefits are more apparent in endurance activities than in short bursts of high-intensity effort (**Table 3**).[29]

Table 3. Effects of Carbohydrate Intake on Exercise Performance and Recovery

Effect	Description
Enhancing Endurance	Carbohydrate (CHO) intake delays neuromuscular fatigue and increases exercise capacity in endurance exercises.
Ineffective on Short-Term, High-Intensity Performance	CHO intake does not improve performance or training quality in short-term, high-intensity anaerobic exercises.
Supporting Recovery After Exercise	High doses of CHO intake reduce exercise-induced muscle damage (EIMD) and accelerate neuromuscular recovery after prolonged exercises.
Application as a Nutritional Strategy	The benefits of CHO intake vary depending on the type and duration of exercise. Benefits are more pronounced in endurance activities and less so in short, high-intensity efforts.

Fluid Balance

The body's water balance depends on daily fluid intake and fluid loss.[30] The majority of water (72% by weight) is stored in the muscles.[31] Because of the extra demands placed on the body by exercise, maintaining the body's water balance is very important for these mechanisms to work effectively.[30]

The consequences of dehydration include reduced physical and cognitive performance, confusion, impaired gastrointestinal function, impaired renal function, impaired cardiac and haemodynamic function, headaches and deterioration of skin structure. In athletes, in special circumstances or in the presence of chronic diseases, the consequences of dehydration are even more severe.[32]

Ensuring hydration allows athletes to reduce fluid losses, maintain performance, reduce submaximal heart rate, maintain plasma volume and be less affected by heat stress.[33] To ensure fluid balance, a fluid and electrolyte intake plan should be established for each athlete before, during and after training, and based on the duration and intensity of training, adjustments should be made as necessary considering factors such as environmental conditions (altitude, temperature, etc.) or competition period (changes in training frequency, competition stress, etc.).[30,34]

It is of utmost importance to calculate the timing and amount of fluid and electrolytes to be ingested specifically for the athlete; carbohydrates may need to be supplemented to the fluid to be ingested depending on the athlete's training programme and discipline.[30]

To replace fluid lost through sweating during training and exercise, it's advisable to drink 150-200 ml of water or sports drink every 15-20 minutes throughout the activity.[35]

The consumption of beverages containing 4-8% carbohydrate is extremely important to maintain hydration and performance, especially during exercise lasting more than an hour.[30] It is recommended that athletes consume 600-1200 ml/hour of beverages containing carbohydrate (30-60 g/L) and Na (0.5-0.7 g/L) during exercise.[33]

The strategic approaches to hydration outlined above are essential to optimise performance and maintain physiological function during exercise.[34] This tailored hydration strategy is essential not only for performance but also for preventing the adverse effects of dehydration, which can severely impact an athlete's health and ability to perform optimally. The inclusion of carbohydrates and electrolytes in fluids, as specified, further enhances the absorption and retention of water, providing the dual benefit of maintaining energy levels and supporting electrolyte balance (**Table 4**).[35] Thus, proper hydration management is a crucial element of athletic training, particularly in endurance events where sweat loss is significant.

Table 4. Hydration strategies and their impact on athletic performance

Aspect	Description
Importance of Hydration	Maintaining the body's water balance is crucial for effective functioning during exercise.
Consequences of Dehydration	Reduced physical and cognitive performance, confusion, impaired gastrointestinal, renal, and cardiac functions, headaches, deterioration of skin structure.
Hydration Benefits for Athletes	Reduces fluid losses, maintains performance, lowers submaximal heart rate, maintains plasma volume, and reduces heat stress impact.
Hydration Strategy	Establish a fluid and electrolyte intake plan before, during, and after training, adjusting for environmental conditions and competition periods.
Fluid Intake Recommendations	Drink 150-200 ml of water or sports drink every 15-20 minutes during exercise.
Carbohydrate-Containing Beverages	Consume beverages with 4-8% carbohydrate content, especially during exercise lasting more than an hour.
Specific Intake Guidelines	Consume 600-1200 ml/hour of beverages containing carbohydrates (30-60 g/L) and sodium (0.5-0.7 g/L) during exercise.
Customized Hydration Plan	Calculate the timing and amount of fluid and electrolytes specific to the athlete's needs; may include carbohydrate supplementation based on training program and discipline.
Overall Hydration Strategy	Essential for optimizing performance, maintaining physiological function, preventing dehydration effects, and supporting energy and electrolyte balance.

Coenzyme Q10 Supplementation

The CoQ10 molecule is a fat-soluble, vitamin-like compound found extensively throughout the body, and it serves a critical function in cellular bioenergetics. It acts as a cofactor in the mitochondrial respiratory chain, which provides energy to cells.[36-39]

It (CoQ10) facilitates ATP production by participating in redox reactions.[36] Besides its function in the mitochondria, CoQ10 has other functions. It acts as a lipid-soluble antioxidant, protecting DNA,[40] phospholipids and mitochondrial membrane proteins from lipid peroxidation.[41,42] CoQ10 also supports the regeneration of vitamins C and E and reduces markers of inflammation. By scavenging reactive oxygen species (ROS), CoQ10 functions as an antioxidant in both mitochondria and lipid membranes.[38,43]

Recent research has demonstrated the exercise-induced effects of coenzyme Q10 (CoQ10) on glucose metabolism and bone remodelling.[44,45] Furthermore, the potential benefits of CoQ10 in improving glucose metabolism and bone remodelling suggest its importance not only as a direct energy facilitator, but also in broader physiological adaptations to exercise.[46] Interestingly, because of its ubiquitous presence at the metabolic level, CoQ10 is expected to exert beneficial effects by improving the performance of exercise-related systems. This molecule has many other potential actions or effects related to exercise and sport,[47] such as its influence on the nervous system and muscular disorders,[48] stabilisation of red blood cells (to improve resistance to oxidative stress),[49] improvement of fluidity,[50] optimisation of endothelial dysfunction,[51,52] and possibly even modification of muscle composition.[53]

The multifaceted role of CoQ10 in supporting athletic performance extends beyond its primary functions within cellular bioenergetics. By enhancing ATP production and providing robust antioxidant protection, CoQ10 helps to maintain cellular integrity and function under the stress of

exercise.[46] Its involvement in mitigating oxidative stress and supporting mitochondrial health is critical, particularly in high-intensity exercise environments where rapid energy production and efficient recovery are paramount.[54]

Therefore, the widespread study of CoQ10 and its use as a supplement can be explained by its potential to support energy metabolism and reduce oxidative stress.[55] In the literature, CoQ10 has been associated with several health benefits, such as supporting cardiovascular health, slowing the ageing process and improving exercise performance.[56] In addition, many studies have shown that CoQ10 is a safe supplement with minimal side effects, even with long-term use.[57] For all these reasons, CoQ10 stands out as a supplement of choice, especially in situations where mitochondrial function needs to be supported and oxidative damage needs to be reduced. The potential benefits of this supplement may be particularly important in sports that require high endurance and rapid recovery. CoQ10's role in enhancing exercise performance and speeding up the recovery process makes it a valuable ingredient in sports nutrition. Choosing CoQ10 as a supplement is therefore a logical strategy for optimising energy production and maintaining cellular health (**Table 5**).

Table 5. The Multifaceted Role of CoQ10 in Exercise and Athletic Performance

Aspect	Description
Basic Function	CoQ10 is a fat-soluble, vitamin-like compound that acts as a cofactor in the mitochondrial respiratory chain, facilitating ATP production.
Antioxidant Role	Protects DNA, phospholipids, and mitochondrial membrane proteins from lipid peroxidation; regenerates vitamins C and E; reduces inflammation markers; scavenges reactive oxygen species (ROS).
Exercise-Induced Effects	Improves glucose metabolism and bone remodelling, suggesting its role in broader physiological adaptations to exercise.
Potential Athletic Benefits	Enhances nervous system and muscular health, stabilizes red blood cells, improves resistance to oxidative stress, optimizes endothelial function, and possibly modifies muscle composition.
Importance in High-Intensity Exercise	Supports rapid energy production and efficient recovery by mitigating oxidative stress and supporting mitochondrial health.
Research Implications	Necessitates further research as an adjunct strategy for athletes, particularly in sports requiring high endurance and rapid recovery.

Other Nutritional Supplements and Their Effects

In addition to Coenzyme Q10 (CoQ10), several other nutritional supplements are commonly used to enhance muscle recovery and athletic performance. Branched-chain amino acids (BCAAs) are essential amino acids that play a significant role in muscle protein synthesis and recovery. Supplementation with BCAAs has been shown to reduce muscle soreness and fatigue following intense exercise. However, the effectiveness of BCAAs in significantly enhancing muscle recovery remains debated in some studies, with mixed results reported on their impact on muscle damage markers and performance.[58]

Creatine is another popular supplement known for its ability to enhance strength, power, and muscle mass. It works by increasing the availability of ATP, the primary energy currency of cells, particularly during high-intensity, short-duration exercises. While creatine supplementation is generally considered safe and effective, some individuals may experience gastrointestinal discomfort or muscle cramping.[59]

Omega-3 fatty acids, found in fish oil, have anti-inflammatory properties that can aid in reducing muscle soreness and promoting recovery. Studies suggest that omega-3 supplementation can help mitigate exercise-induced inflammation and support overall cardiovascular health. However, excessive intake of omega-3s can lead to issues such as bleeding disorders and immune system suppression.[60]

The integration of supplements like BCAAs, creatine, and omega-3 fatty acids further underscores the importance of a comprehensive and personalized approach to sports nutrition. Incorporating these nutritional strategies into training programs can help athletes achieve peak performance, maintain cellular integrity, and ensure efficient recovery. Unlike these supplements, CoQ10 also plays a crucial role in improving cellular energy production efficiency and protecting cells from oxidative damage, making it a potentially more holistic option for supporting athletic performance and recovery.[55-57]

CONCLUSION

Optimising muscle recovery through nutrition is essential for athletes seeking to improve performance and overall health. Essential nutrients such as proteins, carbohydrates, fats, and micronutrients are critical for muscle repair, growth, and reducing the risk of injury. Proteins and amino acids, often used as supplements, are important ergogenic aids that support health and performance. Carbohydrates are essential for replenishing muscle glycogen stores to enhance performance, with an optimal intake ratio of glucose to fructose of 2:1 for up to 120g/hr. Vitamins, minerals, and antioxidants play a significant role in supporting cellular metabolism and alleviating oxidative stress. Coenzyme Q10 (CoQ10) has shown positive anti-inflammatory and protective effects in response to exercise, although additional research is necessary to fully comprehend its advantages on muscle recovery and performance.

In addition to its role in cellular bioenergetics, CoQ10 is known to enhance mitochondrial function and reduce oxidative damage, which can be particularly beneficial for athletes undergoing intense training regimens. This makes CoQ10 not only valuable for immediate recovery but also for long-term athletic performance. Incorporating these nutritional strategies, including CoQ10 supplementation, into training programs can help athletes achieve peak performance, maintain cellular integrity, and ensure efficient recovery.

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Review / Derleme

Where is the Human Papillomavirus vaccine heading? A Review

Human Papillomavirus aşısı nereye koşuyor? Derleme

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Abstract

DNA oncogenic viruses include Human papillomavirus that causes epithelial proliferation at cutaneous and mucosal surfaces. Human papillomavirus is the most common sexually transmitted infection. It spreads through contact between the skin or mucosa also enters the body through cutaneous or mucosal damage. Vertical transfer from mother to baby during birthing is a possibility but is uncommon. Human papillomavirus infection can result in cancer even though it is usually asymptomatic and readily treated by the immune system. Cancers of the head and neck mucosal regions, cervical, and anogenital areas are examples of malignant lesions associated with Human papillomavirus. It is also linked to non-cancerous disorders such recurrent respiratory papillomatosis and ano-genital warts. Globally, both men and women have an equal chance of contracting the infection at least once in their lifetime. The most important protection methods against Human papillomavirus are education and immunization. It is estimated that within a few decades, countries with effective national HPV vaccination programs will have eliminated cervical cancer. Cervical cancer remains a leading source of morbidity and mortality in underdeveloped countries without systematic screening and HPV immunization programs. In Turkey, cervical cancer screening is a routine procedure, and research is ongoing by the Ministry of Health to include Human papillomavirus vaccine in the national immunization schedule. In addition to discussing some of the challenges faced in achieving universal Human papillomavirus vaccination coverage and, consequently, the eradication of cervical cancer, this review seeks to increase awareness of efficiency, and safety of the Human papillomavirus vaccine.

Keywords: Human papillomavirus, cervical cancer, HPV vaccines

Öz

DNA onkojenik virüsleri arasında kutanöz ve mukozal yüzeylerde epitel proliferasyona neden olan Human papillomavirus bulunur. Human papillomavirus, cinsel yolla bulaşan en yaygın enfeksiyondur. Cilt veya mukoza arasındaki temas yoluyla yayılır, ayrıca kutanöz veya mukozal hasar yoluyla vücuda girer. Doğum sırasında anneden bebeğe dikey geçiş olasılığı vardır ancak, nadirdir. Genellikle asemptomatik olmasına ve bağışıklık sistemi tarafından kolayca bertaraf edilmesine rağmen kansere neden olabilir. Baş ve boyun mukozal bölgeleri, servikal ve anogenital bölgelerin kanserleri Human papillomavirus ile ilişkili kötü huylu lezyonlara örnektir. Ayrıca rekurren respiratuvar papillomatozis ve ano-genital siğiller gibi benign rahatsızlıklarla da bağlantılıdır. Hem erkekler hem de kadınlar yaşamları boyunca en az bir kez enfeksiyona yakalanma konusunda eşit riske sahiptir. Human papillomavirus'e karşı en önemli korunma yöntemleri eğitim ve aşılamadır. Birkaç on yıl içinde, etkili ulusal aşılama programları olan ülkelerin serviks kanserini ortadan kaldıracağı tahmin ediliyor. Serviks kanseri, sistematik tarama ve bağışıklama programları olmayan az gelişmiş ülkelerde önde gelen bir morbidite ve mortalite kaynağı olmaya devam etmektedir. Türkiye'de serviks kanseri taraması rutin bir işlemdir ve Sağlık Bakanlığı tarafından ulusal aşılama takvimine Human papillomavirus aşısını dahil etmek için çalışmalar sürmektedir. Bu inceleme, evrensel Human papillomavirus aşılama kapsamına ulaşmada karşılaşılan zorluklardan bazılarını ve dolayısıyla serviks kanserinin ortadan kaldırılmasını tartışmanın yanı sıra, Human papillomavirus aşısının etkinliği ve güvenliği konusunda farkındalığı artırmayı amaçlamaktadır.

Anahtar Kelimeler: Human papillomavirus, serviks kanseri, HPV aşıları

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INTRODUCTION

Globally, the most prevalent sexually transmitted infection affecting both sexes is caused by the Human papillomavirus (HPV).[1] According to estimates, the likelihood of contracting the virus during one's lifetime is approximately 90% for men and 80% for women.[1] Humans can readily become infected by skin-to-skin or skin-to-mucosal contact, even though sexual activity is the main way that HPV is spread.[1] Researches have shown that self-inoculation, mouth, fingers, skin contact, and fomites can all be potential routes for HPV infection in children and adults.[2] Warts related to tattoos, for instance, can spread through ink, equipment, etc.[3] An other HPV transmission pathway is vertical transmission from mother to child.[2]

Approximately 311,000 women lose their lives to cervical cancer each year, with 500,000 new cases being diagnosed.[4] Furthermore, in developing nations, 30 children under the age of ten pass away for every 100 moms who pass away from breast and cervical cancer.[5] Every year in our nation, there are 1,245 cervical cancer-related fatalities and 2,532 new cases.[6] About 40% of the general population is thought to be infected with HPV.[1] Compared to men, a significantly higher percentage of women suffer from and pass away from HPV-related illnesses.[1] The group of men with HIV who have intercourse with other men has the greatest frequency of HPV infection among all other groups in terms of males.[7]

Young age at first pregnancy, multiparity, use of hormonal contraceptives, tobacco use, immune system weakened individuals, HIV infection or immunosuppressive therapy, co-infection with other sexually transmitted infections (herpes virus, chlamydia, and gonococcal infections) are among the conditions that increase the risk of cervical cancer.[8]

Human Papillomavirus

HPV is a double-stranded, non-enveloped DNA virus from the Papillomaviridae family.[7] It has major (L1) and minor capsid proteins (L2).[7] There are more than 200 types of HPV.[7] Low-risk forms, such types HPV 6 and 11, are not usually linked to cancer but can cause benign disorders like genital warts.[1] High-risk types, like 16 and 18, are known to be carcinogenic.[1] Up to 92% of cervical cancers are caused by genotypes 16/18/31/33/45/52/58.[9] Viral oncogenesis is caused by the E6 and E7 oncoproteins, which impair the function of the tumor suppressors p53 and pRB after they enter host cells and also APOBEC genes of host contribute to oncogenesis.[10]

Human Papillomavirus Infections

HPV types can be classified into two groups: cutaneous and mucosal.[11] These cutaneous warts are benign and include common skin warts, flat warts, filiform warts, and plantar warts.[2,11,12] (**Figure 1**). The mucosal types are papilloms/warts of mucous membranes, including the upper respiratory tract, oral, anogenital, and conjunctival areas like condylomata acuminata, conjunctival papilloma, recurrent respiratory papillomatosis etc.[2,11,12] The other mucosal types are associated with precancers and cancers of anogenital, cervical, and oropharyngeal regions.[11,12]

It should be mentioned that most infected people are asymptomatic, or they may just have a temporary infection.[14] Mostly infected people are not aware of it.[15] Immunocompromised individuals, such as those infected with HIV, those undergoing chemotherapy, or those undergoing transplants, or with autoimmune diseases have a higher burden of HPV-associated illnesses.[1,11] Human papillomavirus infection can also affect reproductive organs in men, too.[1,15] HPV infection negatively affects sperm parameters, especially spermatozoa motility and number, semen volume, viscosity, so it can cause infertility.[1,15] Furthermore, HPV may have a role in the decreased rates of implantation and pregnancy during assisted reproductive technology operations by adversely affecting the invasiveness of trophoblastic cells.[1,15] Following HPV vaccination, there was an improvement in sperm motility and anti-sperm antibody prevalence, which led to a higher pregnancy rate than in unvaccinated couples recovering from HPV infection.[1]

Human papillomavirus can also cause cancers of the anus, vulva, vagina, penis, oropharynx, and head and neck.[8] HPV is associated with 85% of head and neck cancers, 60-78% of vaginal cancers, 19-48% of vulvar cancers, 80% to 97% of anal cancers, 40-53% of penile cancers, 13–60% of oropharyngeal cancers, and 5-11% of oral cavity.[8,9,16] The typical symptoms of laryngeal papillomas include stridor, poor vocal quality, growing hoarseness, and even severe airway blockage.[17]

Figure 1. A. Penile warts[13], B. Finger wart, C. Face wart.

A rare genetic illness called epidermodysplasia verruciformis is thought to be caused by a lack of cell-mediated immunity, which leads to an aberrant vulnerability to specific kinds of HPV and manifests as skin malignancies and persistent cutaneous lesions.[10]

Cervix Cancer Screening

Every three years, women between the ages of 21 and 29 should get a Papanicolaou (Pap) test. It is advised that women between the ages of 30 and 65 have further HPV/Pap testing every five years.[18] Women with negative HPV DNA are tested again after 5 years.[17] It may be suggested that women over 65 who have undergone repeated testing and received a negative diagnosis should stop getting checked for cervical cancer.[18]

For females thirty years of age or older, cytologic testing should be combined with HPV DNA testing.[18,19] After receiving the HPV vaccine, women should continue to get frequent screenings for cervical cancer.[20] HPV vaccinations can not change the course of infections that already existed prior to vaccination, nor do they offer protection against all HPV strains linked to the development of cervical cancer.[11] Cervical cytologic testing should start at age 21 for all healthy females, regardless of sexual experience, according to recommendations from the American College of Obstetricians and Gynecologists, the American Society for Colposcopy and Cervical Pathology.[11,20] Testing should start at age 25, according to the American Cancer Society.[11] According to the World Health Organisation and Ministry of Health recommendations, cervical cancer can be detected through screening from the age of 30 (from the age of 25 for women living with HIV).[8,19] In sexually active girls, if there is HIV infection, organ transplantation, or long-term corticosteroid treatment, cervical cytological screening should be performed twice at 6-month intervals within the first year and if the results are normal, it should continue to be performed annually thereafter.[11]

HPV vaccination, education, condom use, and male circumcision protect against HPV infections.[21]

Human Papillomavirus Vaccines

The "HeLa cells," an immortalized cancer cell line obtained from Henrietta Lacks's cervical carcinoma in 1951, just before her death, were used to support numerous medical advancements, such as the creation of the vaccination against the human papillomavirus.[22]

The first publicly available HPV vaccine licensed in 2006 for use in preventing illnesses caused by HPV infection in females aged 9 to 45, and and for males 9 to 26 years of age is Gardasil®, a quadrivalent vaccine (4vHPV).[12] Using recombinant DNA technology, the L1 protein is produced in *Saccharomyces cerevisiae* cells.[23] Gardasil® shields against HPV-6 and -11 infections in addition to HPV-16 and 18, which account for 90% of genital warts.[12] An amorphous aluminum hydroxyphosphate sulfate adjuvant is used to adsorber Gardasil®.[22] Approved in our country in 2008.[23]

The European Medicines Agency (EMA) granted a license for Cervarix®, a bivalent vaccine (2vHPV) in 2007.[12] L1 protein was expressed as non-infectious virus-like particles (VLPs) in cells cultured in *Trichoplusia* butterflies through the use of a DNA recombinant Baculovirus production system.[12] It is an inactive vaccine.[12] Cervarix® is formulated in a proprietary AS04 adjuvant containing aluminum hydroxide, 3-O-desacyl-4'-monophosphoryl lipid A (MPL), and is effective in defending against HPV-16 and HPV-18, which are responsible for nearly 70% of cervical cancers.[21] Registered in Turkey in 2007.[24]

With FDA approval in 2014, Gardasil 9® that is a 9-valent vaccine (9vHPV) provides more comprehensive protection against five more HPV strains (HPV-31, 33, 45, 52, and 58), which may be responsible for up to 20% of instances of cervical cancer.[12] Gardasil 9® is recommended for girls between the ages of 9 and 45, and for males 9 to 26 years of age in order to avoid diseases linked to HPV.[23] Gardasil 9® is also recommended for the prevention of dysplastic lesions, warts, anal lesions, oropharyngeal, and neck malignancies.[24] Amorphous aluminum hydroxyphosphate sulfate is used as an adjuvant in the formulation of Gardasil 9®.[12,25] Approved in Turkey on 11/21/2019.[24]

Since the VLP don't contain viral DNA, they can't replicate, infect cells, or cause illness.[25] Information on vaccines are shown in **Table 1**.

Table 1. Comparison of HPV vaccines[21,26]

Vaccine type	Bivalent	Quadrivalent	Nonavalent
Active ingredient	HPV types 16 and 18 L1-capsid virus-like particles	HPV types 6,11,16 and 18 L1-capsid virus-like particles	HPV types 6,11,16,18 31,33,45,52 and 58 L1-capsid virus-like particles
Vaccine type	inactivated recombinant	inactivated recombinant	inactivated recombinant
Production place	cells cultured in Trichoplusia butterflies	*Saccharomyces cerevisiae* cells	*Saccharomyces cerevisiae* cells
Protection	Premalignant lesions and cancers of cervical, vulvar and vaginal, anal	Premalignant lesions and cancers cervix, vulva, vagina, and anus Genital warts (condyloma acuminata)	Premalignant lesions and cancers of cervix, vulva, vagina, and anus Genital warts (condyloma acuminata)
Cross-defence	31, 33	31, 45	Not necessary
Method of administration	Intramuscular injection	Intramuscular injection	Intramuscular injection

For adolescents aged nine to fourteen, it can be administered according to the 2-dose schedule: The second injection should be given between 5 and 13 months after the first injection.[25] If the second dose is administered before 5 months after the first dose, the third dose must be administered.[25] For those aged 15 and over, it can be administered according to the 3-dose schedule: The second injection should be given 2 months after the first injection (not earlier than 1 month after the first dose), the third injection should be given 6 months after the first injection (not earlier than 3 months after the second dose).[11,25] According to current WHO recommendations, girls aged 9 to 20 should receive 1 or 2 doses, after 21 years of age, 2 doses at 6 intervals, and immunosuppressed individuals should receive at least 2 doses, and if possible, 3 doses.[27] A 3-dose HPV vaccination schedule is advised for people with primary or secondary immunocompromising conditions between the ages of 9 and 26, regardless of the age at onset, due to the possibility that immune responses and vaccine efficacy may be lower in immunocompromised people than in immunocompetent people.[11,25] Until the age of 26, the Advisory Committee on Immunization Practices (ACIP) advises males who have sex with men and immunocompromised individuals (including those who are HIV positive) to get vaccinated with 9vHPV or 4vHPV.[28] A series begun with 4vHPV or 2vHPV can be finished with 9vHPV but, for those who have already finished a 4vHPV or 2vHPV vaccination series, there is no suggestion regarding further immunization with 9vHPV.[11,28] The effectiveness of less than three doses of 9vHPV is not well-documented.[28]

The HPV vaccine series should begin at age 9 for children who have had past sexual abuse or assault, as their likelihood of experiencing such behavior again may be increased.[11]

Precautions and Contraindications

Cervarix® should not be administered to individuals who have experienced anaphylactic latex allergy.[28] Prefilled syringe of 2vHPV could contains latex rubber, vial stopper does not latex.[29,30] Those who have experienced acute yeast hypersensitivity in the past should not take 4vHPV or 9vHPV.[28,30] Individuals who have severe allergies to any part of a vaccine should not to get it.[28,30] Those who are suffering from mild to severe acute illnesses shouldn't get vaccinated until their condition has improved.[25,30]

It is also not recommended to administer HPV vaccines to women who are pregnant.[28,30] If a woman becomes pregnant after starting the vaccination series, the remaining three doses should be postponed until the end of her pregnancy.[28] If a vaccine dose has been administered during pregnancy, no action is required.[28,30]

Vaccine Safety

The most often reported adverse events on the Vaccine Adverse Event Reporting System (VAERS) were headache, dizziness, syncope, nausea, and soreness, redness, or swelling in the arm where the vaccine was administered.[31] Of the reports to VAERS, 6% were deemed serious.[31]

A person may, in extremely rare cases, experience a life-threatening allergic reaction (anaphylaxis) to any vaccine, including those for HPV.[30] According to reports, there are three incidences of anaphylaxis in the US for every million doses of vaccine.[31] In November 2015, the European Medicines Agency concluded that there is insufficient evidence to establish a causal relationship between HPV vaccines and either autoimmune disorders, Postural Orthostatic Tachycardia Syndrome (POTS) and Complex Regional Pain Syndrome (CRPS).[25,32]

Vaccine Effectiveness

Clinical trials on females have demonstrated the excellent efficacy of 4vHPV and 2vHPV in preventing cervical precancers associated with HPV strains 16 and 18.[11] Infections with the four HPV varieties that 4vHPV prevents declined 88% among females aged 14–19 and 81% among females aged 20–24 in the United States within 12 years of the vaccine's launch.[31] 4vHPV has been proven in clinical trials to be highly successful in avoiding genital warts associated with HPV types 6 and 11 in both male and female participants aged 16 to 26.[11] Between 2006 and 2014, the prevalence of anogenital warts in females dropped by 61% among those aged 15 to 19 and 44% among those aged 20 to 24.[31] Cervical precancer rates among tested females in 2014–2015 were 36% lower in 21–24-year-olds and 50% lower in 18–20-year-olds compared to 2008–2009.[31] It has also been demonstrated that 4vHPV is very successful in preventing anal precancers in males between the ages of 16 and 26.[11]

Since the introduction of immunization in the United States, Juvenile-onset recurrent respiratory papillomatosis has dramatically decreased.[31] Clinical trials involving female participants aged 16 to 26 have demonstrated that 9vHPV offers 97% protection against the additional 5 HPV types (31, 33, 45, 52, and 58) in the nonavalent product and produces noninferior immunogenicity for the 4 HPV types in the quadrivalent product (6, 11, 16, and 18).[11] Among unvaccinated women, there was a 40.1% reduction in the proportion infected with one or more of the quadrivalent vaccine-type HPV infections alone and a 57.6% reduction in HPV infections with the other five types of the nonavalent vaccine, excluding HPV 6/11/16/18, through herd immunity.[20] Heterosexual men have shown a decline in genital warts of about 82%.[2]

HPV Vaccine Coverage

A total of 144 nations have included HPV vaccines into their national immunization programs, covering girls only in 69 of them and both sexes in 75.[33] Notwithstanding the advantages of HPV vaccination, the global vaccination rate is falling short of what is needed to create herd immunity. Research indicates that a global vaccination rate of 80% is required to eradicate HPV infections.[34] The goal of the WHO's strategy to end cervical cancer as a public health

issue is to achieve 90% in girls, HPV vaccination coverage by 2030.[35] 35 (40%) countries had coverage of 50% or less with the last dose, while just 5 (6%) countries had coverage of 90%.[35] World population coverage is estimated at 15% with the last HPV dose.[36]

One challenge affecting HPV vaccination is vaccine availability and accessibility.[36] Another is vaccine hesitancy due to lack of parental knowledge and education or misinformation about the vaccine.[34] Additionally, noteworthy attitudes and beliefs that support HPV vaccine hesitation include doubt, mistrust of immunization providers, worries about side effects, and worries about vaccine safety.[35]

For the vaccines added to the vaccination schedule, the Expanded Immunization Program is provided with the supply of materials required for its implementation, target strategies are determined, logistic needs are met, work is carried out to train the staff responsible for vaccination services and the community, vaccine and syringe needs are determined, and stock and cold chain monitoring is carried out.[37]

For vaccines that are wanted to be added to the vaccination schedule, vaccine stocks must be kept stable and can be increased to meet rising worldwide demand.[38] Planning specialized trainings for parents and healthcare professionals, battling misinformation, and making responsible and constructive use of the media are all crucial. Transparency must be prioritized in order to establish trust.[39]

CONCLUSION

Increasing HPV vaccination stands out among the precautions that can be used to lower the incidence and death of cancer. Vaccination of all youth, regardless of gender, against HPV has been shown to be effective and safe, and to reduce the incidence of cancer and other diseases associated with HPV. In Turkey, access to the vaccine is difficult for adolescents with low socioeconomic status. It is known that the Ministry of Health is working on adding it to the national immunization schedule. This is is a long-term, highly profitable healthcare undertaking. Maternal and child health, and thus a healthy future, is undoubtedly the goal of all of us. A concentration on expanding the HPV vaccine's coverage and uptake on a worldwide scale will undoubtedly hasten the achievement of this objective.

ETHICAL DECLARATIONS

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