e-ISSN:2602-2079

Volume 5
Issue 6
2021

JOURNAL of Surgery and Medicine

International Medical Journal

JOSAM

Journal of Surgery and Medicine

Editor-in-Chief

Editors & Editorial Board

Fatih Sap, Assoc. Prof., MD

Necmettin Erbakan University, Meram Medical Faculty, Konya, Turkey

Subjects: Pediatric, Cardiology, Medical science

Yıldız Atadag, MD

Sahinbey Baglarbasi Family Health Centre, Gaziantep, Turkey

Subjects: Medical sciences, Internal medicine, Family medicine

Abdulkadir Aydin, MD

Family Medicine

Sakarya University, Education and Research Hospital, Sakarya, Turkey

Subjects: Medical sciences, Internal medicine, Family medicine

Didem Kaya, MD

Uskudar Number 23. Family Health Centre, Istanbul, Turkey

Subjects: Medical sciences, Internal medicine, Family medicine

Ilyas Kudas, MD

University of Health Sciences, Sarıyer Hamidiye Etfal Education and Research Hospital, Istanbul, Turkey

Subjects: Hepatobiliary – Renal transplantation, General Surgery

Burak Turan, MD

University of Health Sciences, Kocaeli Derince Education and Research Hospital, Kocaeli, Turkey

Subjects: Cardiology, Medical science

Burak Guler, MD

Buyukcekmece Mimarsinan State Hospital, Istanbul, Turkey

Subjects: Otolaryngology - Head and neck surgery

Suleyman Kalcan, Assis. Prof., MD

Recep Tayyip Erdogan University, Department of Surgery, Rize, Turkey

Subjects: Surgical science

Selman Uranues, Prof., MD, FACS, FEBS

Sektion für Chirurgische Forschung

Medical University of Graz

Graz, Austria

Kafil Akhtar, Prof., MD

Department of Pathology

JNMC, AMU, Aligarh-India

Eren Berber, Prof., MD

Department of Center for Endocrine Surgery

Cleveland Clinic

Cleveland, OH 44195, USA

Eric Revue, MD

Clinical Practice Committee

IFEM International Federation of Emergency Medicine

West Melbourne, Victoria, Australia

Boris Sakakushev, Prof., MD

Division of General and Operative Surgery with Coloproctology

Medical University of Plovdiv

Plovdiv, Bulgaria

Dimitrios Giakoustidis, Assoc. Prof., MD

First Department of Surgery, General Hospital Papageorgiou

Aristotle University of Thessaloniki

Thessaloníki, Greece

Nancy Berenice Guzmán Martínez, MD

Department of Radiology and Molecular Imaging

Centro Médico ABC (The American British Cowdray Medical Center)

Mexico City, Mexico

Sapana Verma, MD, PhD

Center for Liver and Biliary Sciences

New Delhi, India

Wandong Hong, Assist. Prof., MD, PhD

Department of Gastroenterology and Hepatology

The First Affiliated Hospital of Wenzhou Medical University

Wenzhou, Zhejiang, China

Mingyu Sun, Prof., MD, PhD

Institute of Liver Diseases

ShuGuang Hospital, Shanghai University of TCM.

Shanghai, China

Moshiur Rahman, Assist. Prof., MD

Neurosurgery Department

Holy Family Red Crescent, Medical College,

Dhaka, Bangladesh

Mauro Zago, MD

Policlinico San Pietro, Ponte San Pietro

BG, Italy

Language Editor

Advisory Board

Layout Editor

Melanie O. Attia

Support team (Process management - Secretary - Lay-out)

SelSistem ®

www.selsistem.com.tr (http://www.selsistem.com.tr/)

To use the submission system properly, please use one of the following browsers, Chrome or Firefox, with the latest updates.
If you experience problems, it may be necessary to clear the browser cache and history.
Mobile phones are not recommended, please use personal computer.
Fatih BAŞAK © Contact (http://jsurgmed.com/en/pub/contacts)
ULAKBİM Dergi Sistemleri (//dergipark.org.tr/en/)

Fatih BAŞAK © Contact (http://jsurgmed.com/en/pub/contacts)
ULAKBİM Dergi Sistemleri (//dergipark.org.tr/en/)

Volume: 5 - Issue: 6

Contents

Case report

Fatih BAŞAK © Contact (http://jsurgmed.com/en/pub/contacts)
ULAKBİM Dergi Sistemleri (//dergipark.org.tr/en/)

J Surg Med. 2021;5(6):578-582.
DOI: 10.28982/josam.784335

Journal of Surgery and Medicine
e-ISSN=2602-2079

Investigating the relationship between health-promoting lifestyle behaviors and hopelessness among medical and non-medical students

Pelin Özgür-Polat [1], Mustafa Çelik [2]

[1] Department of Psychology, Faculty of Science and Literature, Kirsehir Ahi Evran University, Kirsehir, Turkey
[2] Department of Cardiology, Faculty of Medicine, Kirsehir Ahi Evran University, Kirsehir, Turkey

ORCID ID of the author(s)

PÖP: 0000-0001-6109-4942
MÇ: 0000-0003-4102-1564

Corresponding Author
Pelin Özgür-Polat
Department of Psychology, Faculty of Science and Literature, Kirsehir Ahi Evran University, Turkey
E-mail: pelin.ozgur@ahievran.edu.tr

Ethics Committee Approval
Kirsehir Ahi Evran University, Faculty of Medicine Clinical Research Ethics Committee, 07/01/2020, 2020-01/06.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 May 15

Abstract

Background/Aim: Investigating the correlates of healthy lifestyle habits is essential to promote healthy behaviors in university students to be able to prevent developing non-communicable diseases in the long-term. The primary aim of this research was to investigate whether hopelessness is associated with health-promoting lifestyle behaviors among university students. Also, healthy lifestyle habits of medical students were compared with those of students from different fields of study.
Methods: Four hundred and thirty-five undergraduate students from the Faculties of Medicine and Science and Literature participated in a paper-based cross-sectional study. The data were collected with the demographic information sheet, Health-Promoting Lifestyle Profile II (HPLP II), and Beck Hopelessness Scale (BHS), and analyzed using SPSS 22 statistics software.
Results: There were significant negative correlations between BHS scores and HPLP II total (r=-0.39) and all subscale scores, including health responsibility (r=-0.22), physical activity (r=-0.18), nutrition (r=-0.17), spiritual growth (r=-0.53), interpersonal relations (r=-0.30), and stress management (r=-0.25; $P<0.001$ for all). In addition, medical students had higher physical activity (95% CI [0.64, 2.50], $t(406.03)=3.33$, $P<0.001$) and lower interpersonal relations (95% CI [-1.73, -0.10], $t(429.74)=-2.22$, $P=0.027$) scores than their non-medical counterparts.
Conclusion: This study investigating the relationship between hopelessness and health-promoting lifestyle behaviors among medical and non-medical students revealed that negative expectations about the possible consequences of potential behaviors are associated with retention of activities that can improve health in the long-term. Considering their reported weakness in interpersonal relationships, medical education should provide support to the students in improving their social support network to enhance their health and well-being.

Keywords: Hopelessness, Healthy lifestyle behaviors, University students

How to cite: Özgür-Polat P, Çelik M. Investigating the relationship between health-promoting lifestyle behaviors and hopelessness among medical and non-medical students. J Surg Med. 2021;5(6):578-582.

Introduction

A healthy lifestyle is conceptualized as the way individuals control every behavior that may affect their health and choose the behaviors that increase health through their day-to-day activities [1]. Therefore, behaviors that serve individuals to maintain and improve their own well-being are considered as healthy lifestyle behaviors. These include, but are not limited to, regular physical activity, a healthy diet, good quality sleep, stress management, and taking responsibility for protecting and improving one's health [2].

To be able to prevent the long-term effects of modifiable risk factors for developing non-communicable diseases (e.g. physical inactivity, unhealthy diet, and smoking), promoting healthy lifestyle habits in early years, especially during the university period, is essential [3, 4]. The constant stress leading to exhaustion among medical doctors, for example, can be determined by their health habits during medical education years [5]. Researchers [6] suggested that medical students are more likely to adopt a healthy lifestyle since they gain a significant level of knowledge on the importance of performing health behaviors compared to non-medical students. However, a growing body of literature also provides evidence against this argument [6-9], referring to the knowledge-behavior gap issue in behavior change area [10]. For instance, a study [8] performed with 2118 students from seven medical schools across Turkey has found that first-year students had higher scores in various domains of health-promoting behaviors compared to last year students. Studies revealed that during college years, experiencing difficulties in living conditions, lack of access to healthy food, lack of motivation, poor time management skills, low self-efficacy, and negative mood can make it difficult for students to acquire healthy living habits even if they are well-informed on the possible consequences of those behaviors [11].

In addition to these factors, researchers [12] suggested that hopelessness can inhibit an individual from engaging in healthy habits. Although there is no consensus about its definition, hopelessness mainly refers to having negative expectations and beliefs about the future [10]. Concerning the behavioral domain, being hopeless for the future can lead to being reluctant to obtain knowledge on the possible consequences of risky behaviors [13], determining goals to protect health in the long-term, and making plans to achieve these goals [10]. Given the important role it plays in encouraging people to develop and maintain health habits [14], hopeful thinking could predict health promotion habits for the students.

In the literature, few studies have attempted to investigate the links of hopelessness with physical activity [15] as well as physical health issues, such as metabolic syndrome [15], cardiovascular health [10, 16], and hypertension [17], among diverse samples. However, the research to date has not examined the relationship between hopelessness and acquiring healthy lifestyle habits among medical and non-medical students.

The primary aim of this research was to investigate whether hopelessness is associated with health-promoting lifestyle behaviors among college students. Also, healthy lifestyle habits of medical students were compared with those of students from different fields of study.

Materials and methods

Instruments

Demographic Information Sheet (DIS): DIS was used to obtain participants' sociodemographic information including their age, gender, year of study, faculty and department, perceived socioeconomic status, living conditions, weight and height to calculate the Body Mass Index (BMI), smoking status, and existing physical and psychological health issues.

Health Promoting Lifestyle Profile II Scale (HPLP II): The 52-item scale was developed by Walker, Sechrist, and Pender [18] and adapted into Turkish by Bahar et al. [19]. The scale consists of 5 subscales, which include health responsibility (HR; 9 items), physical activity (PA; 8 items), nutrition (N; 9 items), spiritual growth (SG; 9 items), interpersonal relations (IR; 9 items), and stress management (SM; 8 items). Each item is rated on a 4-point Likert scale ranged from 1 (never) to 4 (routinely), and higher scores show higher levels of having a healthy lifestyle. The scale's Cronbach's alpha reliability was found .90 in this study.

Beck Hopelessness Scale (BHS): The scale was developed by Beck, Weissman, Lester, and Trexler [20] to measure the magnitude of negative expectations about the future. The Turkish adaptation of BHS was performed by Durak and Palabiyikoglu [21]. The 20 items are rated on a binary Likert scale as Yes or No, and some items are reverse scored. Higher total scores obtained from BHS show higher levels of hopelessness. The Cronbach's alpha reliability of the scale was found .88 in the present study.

Study design and participants

The present research adopted a cross-sectional design. In this study, participants were selected by convenience sampling, which is a nonprobability sampling technique [22]. The 435 undergraduate students from the two faculties, Faculty of Medicine (FoM) and Faculty of Science and Literature (FoSL), of Kirsehir Ahi Evran University participated in the study. The data were anonymously collected through distributing the paper-based questionnaires in classes. An informed consent form was signed by each participant prior to data collection.

This study was conducted in accordance with the Declaration of Helsinki. The ethical board approval was obtained from Kirsehir Ahi Evran University, Social Science and Humanities Scientific Research and Publication Ethics Committee (Number: 2020-01/06).

Statistical analysis

The data were analyzed using IBM SPSS 22 statistical analysis software and expressed as mean (standard deviation). A *P*-value of less than 0.05 was considered statistically significant. To handle the missing data in the scales HPLP II and BHS, missing values were replaced with series means. Pearson correlation coefficients were calculated to check for the association between all studied parameters. Differences were tested by independent samples t-test and multivariate analysis of variance. Nonparametric tests were used when the normality of data was violated.

Results

In total, 435 university students from Kirsehir Ahi Evran University participated in study. Majority of participants

were women (68.8%) and the mean age was 20.59 (SD=1.43) years (range: 18-27 years). The sociodemographic profile of the participants is given in Table 1.

Table 1: The sociodemographic profile of participants

		n	%
Gender	Female	300	68.8
	Male	136	31.2
Faculty	Medicine	209	47.9
	Science and Literature	227	52.1
Class	1st year	117	26.8
	2nd year	106	24.3
	3rd year	136	31.2
	4th year	77	17.7
Socioeconomic status	High	8	1.8
	Upper-middle	127	29.1
	Middle	280	64.2
	Lower-middle	15	3.4
	Low	4	0.9
	Missing	2	0.5
Smoking	Yes	85	19.5
	No	350	80.3
	Missing	1	2.0
Total		436	100

Multiple comparisons were performed based on participants' demographic characteristics. The results are presented in Table 2. The normality of distribution was violated for BHS scores as assessed by Shapiro-Wilk's test (P<0.001). A Mann-Whitney U test was run to determine if there were differences in hopelessness scores between categorical groups. Hopelessness score was not statistically significantly different between males (Mdn=4.00) and females (Mdn=4.00; U = 19,408, z=0.914, P=0.361), and FoM (Mdn=3.00) and FoSL (Mdn=4.00; U=23,360.50, z=1.634, P=0.102). Distribution of hopelessness scores for smokers (Mdn=5.00) and non-smokers (Mdn=4.00) was significantly different (U=11,665.50, z=-2.216, P=0.027).

Table 2: Distribution of Health-Promoting Lifestyle Profile II, Beck Hopelessness Inventory, scores according to faculty, gender, year of study, socioeconomic status, living conditions, and smoking status (n=435)

Descriptive feature	Health responsibility	Physical activity	Nutrition	Spiritual growth	Interpersonal relations	Stress management	HPLP II Total
Faculty							
Medicine	19.48 (4.40)	17.14 (5.33)	19.12 (3.72)	22.98 (4.38)	24.89 (4.35)	18.88 (3.70)	122.49 (18.75)
Sci. and Lit.	19.23 (4.23)	15.57 (4.44)	19.28 (3.72)	23.31 (4.43)	25.80 (4.27)	18.88 (3.84)	122.08 (18.10)
t	0.60	3.33	-0.47	-0.78	-2.22	0.13	0.23
P-value	0.552	0.001*	0.640	0.436	0.027*	0.990	0.817
Gender							
Female	19.59 (4.35)	15.28 (4.36)	19.06 (3.72)	23.08 (4.38)	25.58 (4.38)	18.88 (3.76)	121.46 (18.05)
Male	18.83 (4.18)	18.61 (5.37)	19.53 (3.70)	23.32 (4.46)	24.89 (4.19)	18.90 (4.19)	124.08 (19.07)
t	1.73	-6.34	-1.24	-0.52	1.56	-0.06	-1.35
P-value	0.085	<0.001*	0.216	0.605	0.120	0.955	0.178
Year of study							
1st year	19.95 (4.62)	16.81 (4.70)	19.65 (3.81)	23.08 (4.80)	25.49 (4.31)	19.20 (3.93)	124.19 (19.66)
2nd year	19.04 (4.63)	16.33 (5.18)	18.32 (3.80)	23.20 (4.40)	25.38 (4.52)	19.06 (3.95)	121.34 (19.96)
3rd year	19.36 (3.73)	16.21 (4.96)	19.82 (3.47)	23.40 (4.12)	25.53 (4.16)	18.80 (3.66)	123.11 (15.77)
4th year	18.24 (3.76)	15.01 (4.63)	18.34 (3.72)	22.60 (4.36)	24.70 (4.39)	18.12 (3.49)	117.00 (17.53)
F	2.53	2.05	4.95	0.53	0.66	1.38	2.59
P-value	0.057	0.106	0.002*	0.660	0.575	0.249	0.053
Socioeconomic status							
Low	15.00 (2.10)	21.00 (2.44)	18.50 (1.86)	19.38 (2.20)	24.25 (2.15)	18.25 (1.89)	116.38 (9.13)
Lower-middle	17.57 (1.12)	14.63 (1.30)	16.87 (1.00)	22.57 (1.18)	25.81 (1.15)	18.21 (1.01)	115.66 (4.88)
Middle	19.06 (0.26)	15.91 (0.30)	19.22 (0.23)	22.97 (0.27)	25.00 (0.26)	18.61 (0.23)	120.76 (1.12)
Upper-middle	19.87 (0.38)	16.58 (0.45)	19.28 (0.34)	23.64 (0.40)	26.02 (0.40)	19.32 (0.35)	124.71 (1.67)
High	20.75 (1.49)	19.50 (1.72)	19.75 (1.32)	23.25 (1.56)	25.50 (1.52)	20.75 (1.34)	129.50 (6.45)
F	2.62	2.66	1.45	1.27	1.28	1.37	1.82
P-value	0.035*	0.032*	0.216	0.280	0.278	0.242	0.126
Smoking status							
Smoker	18.57 (4.39)	16.83 (5.15)	18.98 (3.81)	22.23 (5.20)	25.81 (4.89)	18.25 (4.08)	120.66 (20.39)
Non-smoker	19.54 (4.28)	16.21 (4.89)	19.26 (3.70)	23.36 (4.16)	25.24 (4.28)	19.02 (3.67)	122.64 (17.90)
t	-1.84	1.00	-0.61	-1.87	1.05	-1.61	-0.82
P-value	0.068	0.317	0.541	0.065	0.297	0.110	0.413

*P-value is significant at 0.05. Sci. and Lit.: Science and Literature, HPLP II: Health-Promoting Lifestyle Behaviour Scale II.

A Kruskal-Wallis test was performed to determine if there were differences in Hopelessness scores between four groups of participants in different years of study and with different SES. Distributions of BHS scores were similar for all groups, as assessed by visual inspection of a boxplot. Median BHS scores were not statistically significantly different between classes (H(3)=2.004, P=0.572) and SES groups (H(4)=7.364, P=0.118).

The correlation analyses were performed to investigate the associations between BHS and HPLP II total and subscale scores. Preliminary analyses showed the relationship to be linear with all variables except BHS, as assessed by Shapiro-Wilk's test (P>0.05). A Spearman's rank-order correlation was performed to assess the relationships between BHS scores and HPLP II total and subscale scores, and a Pearson's correlation coefficient was calculated to determine the associations between all other variables.

All results were in the expected direction (see Table 3). There were significant negative correlations among BHS scores and HPLP II total and subscale scores. In addition, HPLP II total and subscale scores were positively intercorrelated (P<0.001).

Table 3: The correlations among and descriptive statistics for variables

Var.	n	M	SD	1	2	3	4	5	6	7	8
1. Age	432	20.59	1.43								
2. BHS*	414	5.41	4.71	-.04							
3. HPLP	436	122.28	18.39	-.11	-.39						
4. HR	436	19.35	4.31	-.07	-.22	.74					
5. PA	436	16.32	4.94	-.04	-.18	.70	.40				
6. N	436	19.20	3.72	-.05	-.17	.66	.49	.44			
7. SG	436	23.16	4.40	-.01	-.53	.78	.41	.41	.36		
8. IR	436	25.36	4.33	-.06	-.30	.70	.47	.25	.26	.59	
9. SM	436	18.88	3.76	-.07	-.25	.76	.44	.44	.39	.61	.44

*Spearman's rank order correlation was run. Significant correlations in bold have P<0.001. BHS: Beck Hopelessness Inventory, HPLP: Health-Promoting Lifestyle Profile II Scale, HR: Health responsibility, PA: Physical activity, N: Nutrition, SG: Spiritual growth, IR: Interpersonal relations, SM: Stress management

Discussion

Unhealthy behavioral habits adopted in the early years are among the significant risk factors for developing non-communicable diseases. Therefore, barriers to and facilitators of making healthy lifestyle choices should be determined to promote health behaviors in younger populations. The transition from high school to university period and college years are suggested as critical periods in health behaviors to become habitual [11]. Since medical doctors are more likely to be under constant stress in their professional life compared to other professions, acquiring a healthy lifestyle as early as possible is vital for protecting their health and well-being [5]. Hopelessness has been shown as one of the significant factors of performing healthy behaviors; however, research has yet to systematically investigate its link with health-promoting lifestyle behaviors in the university student population. This study examined the relationship between hopelessness and adopting a health-promoting lifestyle among university students. Besides, medical students were compared with their peers from the Science and Literature faculty in terms of hopelessness and health-related behaviors.

The data from 435 university students showed that hopelessness was negatively associated with all domains of healthy lifestyle and smoking. Participants who were less active in their lives, smoking, and had less healthy food choices reported higher levels of hopelessness. These findings provide evidence on the direct relationship between hopelessness and

modifiable risk factors for developing diseases although the magnitudes of these links were relatively small.

The most substantial relationship of hopelessness was with spiritual growth. Participants who had more positive expectations about the future consistently reported higher feelings of having a meaningful life and being more motivated to work towards their long-term objectives. Researchers claim that if a person feels hopeful for the possible outcomes, they are more likely to continue to perform a behavior [23]. Therefore, as a significant domain of a healthy lifestyle, the negative relationship of spiritual growth with hopelessness is compatible with the literature.

Hopelessness was also negatively correlated with interpersonal relations and stress management skills, while these two lifestyle domains were positively intercorrelated. Research showed that individuals with high social hopelessness carry more negative beliefs and expectations about their interpersonal relationships. Also, social hopelessness was associated with daily stress [24]. Although the BHS does not differentiate social and achievement hopelessness from general hopelessness, the findings of the present study support the literature.

This study also sought to investigate how medical students were distinguished from other university students studying different subjects in terms of behaviors that promote healthy lifestyle, and hopelessness. The findings showed that these two groups were significantly different regarding only two domains of health-promoting lifestyle: Physical activity and interpersonal relations.

Considering the range of scores obtained from physical activity subscale of HPLP II, both groups were moderately active with average scores of 17.14 (5.33) among medical and 15.57 (4.44) among non-medical students. However, medical students were found physically more active than their non-medical counterparts. This finding is consistent with the previous studies comparing these two student groups [25].

Interpersonal relations domain of healthy lifestyle is about building strong relationships with others through expressing thoughts and emotions, and related to communication skills and opportunities of individuals. In this study, medical students reported lower levels of a social life than students from other areas of study. The intensity of medical education and excessive workload requires adopting a socially isolated lifestyle compared to the other fields of education [5, 26]. Although IR scores were strongly associated with a healthy lifestyle in general, similar to the findings regarding physical activity, IR does not appear to be the sole determinant of lifestyle as medical and non-medical students had similar health-promoting lifestyle profiles.

When the domains of health-promoting lifestyle were examined in terms of other demographic variables, a few differences were detected in health responsibility, physical activity, and nutrition.

Health responsibility (HR) is the individual's active sense of responsibility for their own well-being. Taking care of one's own health includes being informed on health and seeking professional help when necessary [19]. Therefore, HR can be expected to be linked with the field of education since students reading health sciences should be well-informed on how to protect and improve health and well-being [9]. However, in the current study, there was no significant difference between medical and non-medical students in terms of HR. This finding can be explained by students' perceived SES levels considering our findings showing that HR scores tended to increase with SES levels, and most students reported being from middle SES.

Compatible with the literature [27-29], male students reported adopting a more active lifestyle compared to female students. An active lifestyle also seemed to be related to perceived socioeconomic status as students who perceived themselves as having very high and low SES tended to report being physically more active than those from the other SES groups. This finding could be related to the measurement method of physical activity. The PA subscale of HPLP II fails to differentiate mild, moderate, and vigorous exercise: Walking, for example, can be equally scored with regular gym sessions. Therefore, the similarity between very high and low SES groups' activity levels could be misleading.

Having a healthy diet was linked with the years of study. The students seem to be making healthier food choices as they continue their educational path. This result may be related to better adaptation to regular life conditions in time —the insignificant differences between SES groups in terms of the nutrition and hopelessness support this argument.

In terms of spiritual growth and stress management skills, none of the groups were significantly different. This finding is in the anticipated direction since there are more significant factors related to these two domains, rather than gender, smoking status, or field of education. It is well-documented that dispositional factors, such as personality traits, temperament, and genetic influences, can also determine one's ability to cope with stressful situations [30].

Limitations

This study suffers from some limitations. Since the present study adopted a cross-sectional design, establishing a causal relationship between hopelessness and healthy lifestyle behaviors is beyond its scope. Therefore, the findings can only have correlational implications. In addition, this study was not multicenter, which prevents the generalization of the findings.

Conclusion

This study set out to examine the relationship of hopelessness and health-promoting lifestyle domains among medical and non-medical university students. Negative expectations about the possible consequences of future behaviors appear to be associated with retention of activities that can improve health in the long-term. However, a systematic understanding of how despair contributes to health behaviors is still lacking. Further research testing the mediational models to discover the possible mechanisms is needed. As a final remark, considering the workload of medical students and the significant association found between hopelessness and poor interpersonal relationships, providing support to medical students to build stronger social connections is essential to improve their health-related behaviors and well-being.

Acknowledgements

We gratefully acknowledge Aybüke Gizem Çakın for her tremendous effort in distributing questionnaires and collecting data. We are also thankful to Berkan Tülek, Burak

Buz, Mehmet Özkan, Nuray Albar, Oğulcan Sorhan, Ravza Göleç, Oğuz Tetik, Hamit Yılmaz, and Üzlifet Kurnaz for their contribution in data collection.

References

1. Ertop NG, Yılmaz A, Erdem Y. Üniversite öğrencilerinin sağlıklı yaşam biçimleri. Kırıkkale Üniversitesi Tıp Fakültesi Dergisi. 2012;14(2):1-7.
2. Sonmezer H, Cetinkaya F, Nacar M. Healthy life-style promoting behaviour in Turkish women aged 18-64. Asian Pac J Cancer Prev. 2012;13(4):1241-5.
3. Wei CN, Harada K, Ueda K, Fukumoto K, Minamoto K, Ueda A. Assessment of health-promoting lifestyle profile in Japanese university students. Environ Health Prev Med. 2012;17(3):222-7. Epub 2011/10/12. doi: 10.1007/s12199-011-0244-8. PubMed PMID: 21987366; PubMed Central PMCID: PMCPMC3348247.
4. Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJ, Martin BW, et al. Correlates of physical activity: why are some people physically active and others not? The lancet. 2012;380(9838):258-71.
5. Kotter T, Tautphaus Y, Obst KU, Voltmer E, Scherer M. Health-promoting factors in the freshman year of medical school: a longitudinal study. Med Educ. 2016;50(6):646-56. Epub 2016/05/14. doi: 10.1111/medu.12987. PubMed PMID: 27170083.
6. Sajwani RA, Shoukat S, Raza R, Shiekh MM, Rashid Q, Siddique MS, et al. Knowledge and practice of healthy lifestyle and dietary habits in medical and non-medical students of Karachi, Pakistan. J Pak Med Assoc. 2009;59(9):650-5. Epub 2009/09/16. PubMed PMID: 19750870.
7. Kanikowska D, Sikorska D, Kuczynska B, Grzymislawski M, Breborowicz A, Witowski J. Do medical students adhere to advice regarding a healthy lifestyle? A pilot study of BMI and some aspects of lifestyle in medical students in Poland. Adv Clin Exp Med. 2017;26(9):1391-8. Epub 2018/02/15. doi: 10.17219/acem/65783. PubMed PMID: 29442460.
8. Nacar M, Baykan Z, Cetinkaya F, Arslantas D, Ozer A, Coskun O, et al. Health promoting lifestyle behaviour in medical students: a multicentre study from Turkey. Asian Pac J Cancer Prev. 2014;15(20):8969-74. Epub 2014/11/07. doi: 10.7314/apjcp.2014.15.20.8969. PubMed PMID: 25374238.
9. Can G, Ozdilli K, Erol O, Unsar S, Tulek Z, Savaser S, et al. Comparison of the health-promoting lifestyles of nursing and non-nursing students in Istanbul, Turkey. Nurs Health Sci. 2008;10(4):273-80. Epub 2009/01/09. doi: 10.1111/j.1442-2018.2008.00405.x. PubMed PMID: 19128303.
10. Feldman DB, Sills JR. Hope and cardiovascular health-promoting behaviour: education alone is not enough. Psychol Health. 2013;28(7):727-45. Epub 2013/01/08. doi: 10.1080/08870446.2012.754025. PubMed PMID: 23289597.
11. Yüksel H. Üniversite Öğrencilerinin Sağlığı Geliştirici Yaşam Biçimi Davranışlarına Etki Eden Sosyal Faktörler. Dumlupinar University Journal of Social Science/Dumlupinar Üniversitesi Soysyal Bilimler Dergisi. 2012(34).
12. Salovey P, Rothman AJ, Detweiler JB, Steward WT. Emotional states and physical health. American psychologist. 2000;55(1):110.
13. Irving LM, Seidner AL, Burling TA, Pagliarini R, Robbins-Sisco D. Hope and recovery from substance dependence in homeless veterans. Journal of Social and Clinical Psychology. 1998;17(4):389-406.
14. Snyder CR, Harris C, Anderson JR, Holleran SA, Irving LM, Sigmon ST, et al. The will and the ways: development and validation of an individual-differences measure of hope. Journal of personality and social psychology. 1991;60(4):570.
15. Valtonen M, Laaksonen DE, Laukkanen J, Tolmunen T, Rauramaa R, Viinamäki H, et al. Leisure-time physical activity, cardiorespiratory fitness and feelings of hopelessness in men. BMC Public Health. 2009;9:204. Epub 2009/06/27. doi: 10.1186/1471-2458-9-204. PubMed PMID: 19555509; PubMed Central PMCID: PMCPMC2717082.
16. Mathews L, Ogunmoroti O, Nasir K, Blumenthal RS, Utuama OA, Rouseff M, et al. Psychological Factors and Their Association with Ideal Cardiovascular Health Among Women and Men. J Womens Health (Larchmt). 2018;27(5):709-15. Epub 2018/01/30. doi: 10.1089/jwh.2017.6563. PubMed PMID: 29377738; PubMed Central PMCID: PMCPMC5962331.
17. Joyner J, Moore AR, Mount DL, Simmons DR, Ferrario CM, Cline DM. Emergency department patients self-report higher patient inertia, hopelessness, and harmful lifestyle choices than community counterparts. J Clin Hypertens (Greenwich). 2012;14(12):828-35. Epub 2012/12/05. doi: 10.1111/jch.12001. PubMed PMID: 23205749.
18. Walker SN, Sechrist KR, Pender NJ. The Health Promoting Lifestyle Profile development and psychometric characteristics. Nursing Research. 1987;36(2):76-80.
19. Bahar Z, Beşer A, Gördes N, Ersin F, Kissal A. Sağlıklı yaşam biçimi davranışları ölçeği II'nin geçerlik ve güvenirlik çalışması. Cumhuriyet Üniversitesi Hemşirelik Yüksekokulu Dergisi.12(1):1-13.
20. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: the hopelessness scale. Journal of consulting and clinical psychology. 1974;42(6):861.
21. Durak A, Palabıyıkoğlu R. Beck umutsuzluk ölçeği geçerlilik çalışması. Kriz Dergisi. 1994;2(2):311-9.
22. Sedgwick P. Convenience sampling. BMJ. 2013;347:f6304.
23. Bruininks P, Malle BF. Distinguishing Hope from Optimism and Related Affective States. Motivation and Emotion. 2005;29(4):324-52. doi: 10.1007/s11031-006-9010-4.
24. Heisel MJ, Flett GL, Hewitt PL. Social hopelessness and college student suicide ideation. Archives of Suicide Research. 2003;7(3):221-35.
25. Naim Z, Anwar K, Rahman A, Zuliani N. Physical Inactivity Among Medical and Non-medical students: A cross sectional study. International Journal of Public Health and Clinical Sciences. 2016;3(5):48-58.
26. Yiu V. Supporting the well-being of medical students. CMAJ. 2005;172(7):889-90. doi: 10.1503/cmaj.050126. PubMed PMID: 15795410.
27. Alzahrani SH, Malik AA, Bashawri J, Shaheen SA, Shaheen MM, Alsaib AA, et al. Health-promoting lifestyle profile and associated factors among medical students in a Saudi university. SAGE Open Med. 2019;7:2050312119838426. Epub 2019/04/03. doi: 10.1177/2050312119838426. PubMed PMID: 30937167; PubMed Central PMCID: PMCPMC6434441.
28. El Ansari W, Stock C, John J, Deeny P, Phillips C, Snelgrove S, et al. Health promoting behaviours and lifestyle characteristics of students at seven universities in the UK. Central European journal of public health. 2011;19(4):197-204.
29. Trost SG, Owen N, Bauman AE, Sallis JF, Brown W. Correlates of adults' participation in physical activity: review and update. Medicine & science in sports & exercise. 2002;34(12):1996-2001.
30. Howell JL, Sweeny K. Health behavior during periods of stressful uncertainty: associations with emotions, cognitions, and expectation management. Psychol Health. 2020:1-21. Epub 2020/01/28. doi: 10.1080/08870446.2020.1713323. PubMed PMID: 31983235.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):583-587.
DOI: 10.28982/josam.915654

Journal of Surgery and Medicine
e-ISSN=2602-2079

The effects of exposure to endocrine-disrupting chemicals in intrauterine life on thyroid function tests during the neonatal period

Serkan Özsoylu [1], Tamer Gunes [2], Leyla Akin [3], Mustafa Kendirci [4]

[1] Erciyes University Medical Faculty, Department of Pediatrics, Kayseri, Turkey
[2] Erciyes University Medical Faculty, Department of Pediatrics, Division of Neonatalogy, Kayseri, Turkey
[3] Erciyes University Medical Faculty, Department of Pediatrics, Division of Pediatric Endocrinology, Kayseri, Turkey
[4] Erciyes University Medical Faculty, Department of Pediatrics, Division of Pediatric Metabolism and Endocrinology, Kayseri, Turkey

ORCID ID of the author(s)
SÖ: 0000-0002-2315-5027
TG: 0000-0002-2286-9319
LA: 0000-0002-8071-426X
MK: 0000-0002-2100-3628

Corresponding Author
Serkan Özsoylu
Erciyes University Medical School, Department of Neonatalogy, Talas Kayseri, Turkey
E-mail: sozsoylu@hotmail.com

Ethics Committee Approval
The study protocol was approved by the Medical Ethics Research Committee at Erciyes University with a number of 2014/176.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
This study was supported by the BAP Committee of Erciyes University (TTU-2014-5044).

Published
2021 May 15

Abstract

Background/Aim: Animal studies have shown that endocrine-disrupting chemicals can cause transient hypothyroidism. The aim of this study is to investigate the effects of exposure to endocrine disrupting chemicals (polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), bisphenol A (BPA) in plastics) in intrauterine life on thyroid function tests during the neonatal period.
Methods: In this observational cohort study, cord blood samples were obtained from all infants at birth to measure endocrine disruptors. Serum bisphenol A, di-(2-ethylhexyl) phthalate, and mono-ethylhexyl phthalate levels were measured by high performance liquid chromatography (HPLC). We excluded newborns whose mothers had thyroid function disorders.
Results: The male newborns' cord bisphenol A concentrations were significantly higher than those of female newborns (1.14 (0.26) ng/ml vs 0.85 (0.25) ng/ml, respectively; P=0.007). When we examined the correlation between the cord blood phthalate values and the maternal and newborn's thyroid function tests, a negative relationship between mono-ethylhexyl phthalate and newborn thyroid stimulating hormone was detected (r= -0.284, P=0.003).
Conclusion: A negative correlation was detected between cord blood mono-ethylhexyl phthalate levels and neonatal thyroid stimulating hormone levels suggesting that phthalate exposure may affect the thyroid function of babies in the prenatal period.

Keywords: Bisphenol A, di-(2-ethylhexyl) phthalate, Mono-ethylhexyl phthalate, Cord blood, Thyroid function

How to cite: Ozsoylu S, Gunes T, Akin L, Kendirci M. The effects of exposure to endocrine-disrupting chemicals in intrauterine life on thyroid function tests during the neonatal period. J Surg Med. 2021;5(6):583-587.

Introduction

Endocrine disruptors affect the development and functions of the endocrine system. They are exogenous substances or their mixtures. These substances act on the production of hormone secretion, attachment, transport, activity, destruction, and excretion from the body. As they can be found in nature, they are also included in various industrial and synthetic products [1, 2].

Bisphenol-A (BPA) has been used as a synthetic estrogen in cattle and poultry since 1930 to achieve industrial gain. We are easily exposed to BPA due to the large numbers of plastic in various products, such as food containers, plastic bottles, canisters, thermal receipts, medical equipment, tableware, and water supply pipes [3]. Bisphenol-A may interfere with thyroid hormone (TH) action by interacting directly with the TH receptor. It was revealed that BPA acts a thyroid hormone receptor antagonist and suppresses the receptor's transcriptional activity, which is stimulated by the thyroid hormone (T3) [4].

Di-(2-ethylhexyl) phthalate (DEHP) is the most frequently used form of phthalate. The main area of use (95%) is PVC production. Di-(2-ethylhexyl) phthalate is considered an estrogen agonist and testosterone antagonist, but its mechanisms of toxicity are still not well understood [5].

Thyroid hormones (TH) play an essential role in pre- and postnatal growth and brain development in humans. Prenatal THs are essential for normal brain development. A number of studies have shown that variations in maternal T4 or TSH levels during gestation are associated with reduced cognitive abilities and increased risk of behavioral problems in childhood [6].

We evaluated whether BPA or phthalates (DEHP and MEHP) can affect thyroid functions and cause transient neonatal hypothyroidism. Experimental evidence supports this hypothesis. In an animal study, oral exposure to BPA resulted in a temporary decrease in free thyroxine (T4) in pregnant rats, but it had no effect on total thyroxine [7]. On the other hand, in another study, prenatal exposure to BPA was related to a temporary dose-related elevation in total T4 among both male and female pups (8) and increase in free T4 (at postnatal day 7) followed by a decrease (at postnatal day 21) among male pups only [7].

Few studies have examined the relationship between BPA and thyroid function and have yielded conflicting results. Meeker et al. [9] found no association among serum free T4, total T3 and TSH and BPA concentrations in urine samples collected from 167 men at an infertility clinic in Boston, Massachusetts.

There is very little information about the association between thyroid functions and DEHP and the results from previous studies are not consistent. This prompted us to undertake a study about this issue.

Materials and methods

Participants

After obtaining informed parental consent, we included 100 newborns to the study who were born with caesarian section or normal vaginal birth between May 2015-June 2015 in Erciyes University Maternity unit. Before delivery, thyroid function tests were obtained from mothers so that we could exclude newborns from the study whose mothers had thyroid function disorders.

The study protocol was approved by the Medical Ethics Research Committee at Erciyes University with the decision number 2014/176. All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We obtained informed consent from the parents.

Sample analysis

Thyroid function tests were performed in newborns at postnatal 3 to 7 days. Cord blood samples were obtained from all infants at birth to measure BPA, DEHP and MEHP levels.

In the delivery room, the cord was immediately clamped by the nurse from the mother's side and from the baby's side after birth, then 3 cc of cord blood was stored in a glass tube with a metal injector to avoid contact with plastic. Cord blood was centrifuged for 5 minutes at 4000 g, after which the plasma layer was transferred to plasma tubes. The plasma was stored at -80^{o}C. Serum levels of BPA, DEHP and MEHP were studied using HPLC method.

BPA measurement

Bisphenol-A measurements were made by using an Agillent 1100 series brand HPLC chromatographic system and C-18 column. (250mm X 4.6 mm) A fluorescence detector with a 227-nanometer wavelength extraction and 313-nanometer wavelength emission was used as a detector. Mobile phase A (70%) included acetonitrile and mobile phase B (30%) included water. The procedure was performed using a double pump. Chromatographic analysis was studied at 25 ° C, using a 1 ml/minute flow rate and a 20 ml injection volume.

Extraction of the serum samples was performed as the first step of the analysis. For this, 100 µl 0.01 mol/L ammonium acetate buffer and 4 ml n-hexane and a 70:30 mixture of a diethylether were added to 500 µl samples. Once the samples were centrifuged, the organic phase was evaporated under a stream of nitrogen. Subsequently, the sample was completed to 100 µl with HPLC compatible acetonitrile and analyzed.

Stock standard solutions of 0:50 mg/ml of BPA were prepared in methanol. The standard working solutions were obtained by using the stock standard solution diluted to varying concentrations of methanol again**.**

At the end of the study, the retention time was set at 3.7 min for BPA. According to the peak areas obtained from standard work, the linear calibration curve was calculated from the peak area of the sample. This way, we could calculate the BPA value.

Phthalate measurement

Di-(2-ethylhexyl) phthalate and MEHP concentration measurements were made by using an analytical ODS2 C-18 column (250 mm X 4.6 mm, Waters, Milford, MA) in the HPLC device (Hewlett Packard Agilent 1100 Series, Vienna, Austria). Separation was performed at room temperature. The mobile phase consisted of a 90:10 (v/v) mixture of acetonitrile and the 0.1% orthophosphoric acid. The mobile phase was prepared daily, and the flow rate was 1 ml/min. The peaks were detected by a UV detector at a 230 nm wavelength. Stock standard

solutions were prepared in acetonitrile containing 2000 ppm DEHP and MEHP. The standard working solutions of varying concentrations were prepared by diluting the stock solution with the mobile phase. Standard solutions at +4 degrees can remain stable for about 1 month. Extraction was carried out prior to analysis.

First, 400 ul 1 N NaOH and 100 uL of 50% H3PO4 and 600 µl of acetonitrile were added to the 200 µl sample. The supernatant was removed after each sample was centrifugated for 10 minutes at 3500 rpm and it was extracted with 600 µl of acetonitrile residue. After a second centrifugation under the same conditions, the supernatant was evaporated. In the last step, after the addition of the 400 µl mobile phase, 100 µl was injected into the chromatography system. The calibration curves were obtained according to the peak area of standards and sample concentrations were calculated.

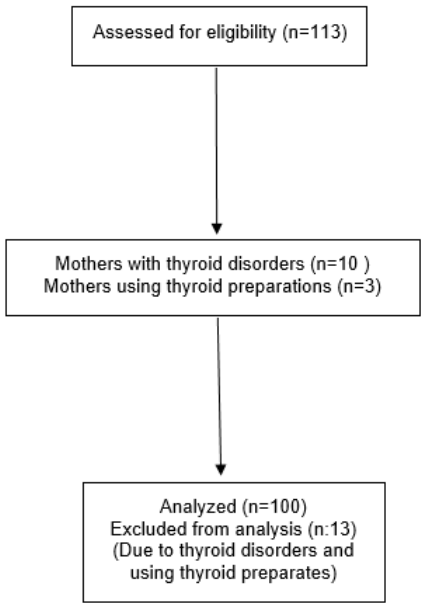
Statistical analysis

In G-power 3.1.9.2 program, power analysis was conducted at 0.25 effect size, 5% type 1 error, and 80% power. Accordingly, the number of samples required was calculated as 90. The study was planned with 100 patients considering 10% data loss. Data were evaluated in the IBM SPSS Statistics 22.0 statistical packages program (IBM Corp., Armonk, New York, USA). Normal distribution of the data was assessed by the Shapiro-Wilk normality test and Q-Q graphs. Descriptive statistic values were presented as mean (standard deviation) and median (25^{th}-75^{th}. percentile). Comparisons between groups were analyzed by t-test and Mann-Whitney U-test for independent samples. The relationship between the numerical variables were analyzed with Pearson and Spearman correlation analysis. The relationship between categorical variables was analyzed with the exact method of the chi-square test. $P<0.05$ was considered statistically significant.

Results

A total of 113 women were included in the study, but 13 had thyroid dysfunction or were using thyroid preparations (Figure 1). Finally, 100 newborns (52 males, 48 females) who were born in Erciyes University maternity unit between May 2015 and June 2015 were enrolled in the study.

Figure 1: Flow chart description of the trial



Infants born before 34 weeks were considered early premature, those born between 34-37 weeks were considered late premature and those born at 37 weeks or later were considered mature. The mean gestational age of newborns in the study was 37.38 (2.3) weeks (male newborns: 37.18 (2.4) weeks, female newborns: 37.53 (2.1) weeks); the mean body weight was 2907.2g (624.3 g) [male newborns: 2891.9 (690.6), female newborns: 2917.2 (557.9)]. The mean length was 48.6 (2.5) cm [male newborns: 48.4 (2.5) cm, female newborns: 48.9 (2.4cm)] (Table 1).

Table 1: Newborn anthropometric measurements and cord bisphenol, mono-ethylhexyl phthalate (MEHP) and Di-(2-ethylhexyl) phthalate (DEHP) values

	All n=100 (100%)	Male n=52 (52%)	Female n=48 (48%)	*P*-value
Gestational age (week) mean (SD)	37.38 (2.3)	37.53 (2.1)	37.18 (2.4)	0.174
Weight (kg) mean (SD)	2907.2 (624.3)	2891.9 (690.6)	2917.2 (557.9)	0.412
Height (cm) mean (SD)	48.6 (2.5)	48.4 (2.5)	48.9 (2.4)	0.321
BISPHENOL-A (ng/ml) mean (SD)	9.97 (2.93)	11.42 (2.60)[a]	8.52 (2.51)	0.007
MEHP (µg/ml) median (min-max)	0.20(0.03-0.78)	0.22 (0.14)	0.21 (0.16)	0.124
DEHP (µg/ml) median (min-max)	2.72(1.16-7.14)	2.72 (0.72)	3.04 (1.19)	0.137

DEHP: Di-(2-ethylhexyl) phthalate, MEHP: mono-ethylhexyl phthalate

The mean cord blood BPA levels of all newborns was 0.99 (0.29) ng/mL. The median DEHP value of all newborns was 2.72 µg/ml (1.16 to 7.14). The median MEHP value of all newborns was 0.20 µg/ml (0.03-0.78).

We found that the male newborns' cord BPA mean value was higher than that of female newborns (1.14 (0.26) ng/ml vs 0.85 (0.25) ng/ml, respectively) (P=0.007).

When the median MEHP value was compared by sex, we found that the male newborns' cord MEHP value was similar to that of female newborns (0.22 (0.14) µg/ml, 0.21 (0.16) µg/ml, respectively) (P=0.124).

The male newborns' cord DEHP mean value was slightly lower than that of female newborns (2.72 (0.72) µg/ml, 3.04 (1.19) µg/ml, respectively) (P=0.137).

There was no significant relationship between the cord blood BPA levels and the maternal and newborns' thyroid function tests; however, a negative relationship was found between MEHP and newborn TSH levels (r= -0.284 p=0.003) (Table 2). There was no significant relationship between MEHP values, maternal T3, newborn T3 and newborn T4 levels (P=0.214).

Table 2: Correlation coefficient between mono-ethylhexyl phthalate (MEHP) and newborn-mother thyroid function tests

MEHP Values (N:100)	MEHP (µg/ml)	Mother TSH (µIU/ml)	Mother fT3 (pg/ml)	Mother fT4 (ng/dl)	Newborn TSH (µIU/ml)	Newborn fT3 (pg/ml)	Newborn fT4 (ng/dl)
MEHP (µg/ml)	1						
Mother TSH (µIU/ml)	-0.23[a]	1					
Mother fT3 (pg/ml)	0.15	-0.10	1				
Mother fT4 (ng/dl)	-0.06	-0.14	0.09	1			
Newborn TSH (µIU/ml)	-0.28[b]	0.09	-0.07	0.11	1		
Newborn fT3 (pg/ml)	0.00	0.12	-0.08	-0.03	0.17	1	
Newborn fT4 (ng/dl)	0.00	0.16	-0.04	0.08	0.07	0.43[b]	1

[a] $P<0.05$, [b] $P<0.01$, MEHP: mono-ethylhexyl phthalate, TSH: Thyroid Stimulating Hormone, fT3: Free triiodothyronine, fT4: Free thyroxine

Discussion

The patient, who is informed about the need for an operation, faces a stressful situation. This anxiety reaches the maximum level especially in the preoperative preparation room. The main reason for this anxiety is pain and fear of not waking up after surgery [10-12]. Detailed information and premedication prior to the operation have an important role in the prevention of this preoperative incapability [9, 13]. This anxiety, pre-operative fasting, and fluid restriction significantly increase the level of stress. It induces various physiological, metabolic, and psychological responses to protect the body from this stress [3, 14]. The body's response is characterized by increased activation of catabolic and immunosuppressive hormones from the pituitary gland with activation of the sympathetic nervous system [15]. The aim of this study is to investigate the effects of stress and fluid restriction before anesthesia induction on patient clinic, endocrine responses, and a new peptide-made hormone, Nesfatin-1 level. The State-Continuity Anxiety Scale (STAI 1-STAI 2) is an easy-to-apply scale that can be answered by the individual as well as the patient's hemodynamic and biochemical data in the measurement of anxiety. Taşdemir et al. [16] showed that preoperative anxiety was significantly higher than postoperative anxiety. Domar et al. [17] found an average score of 45 preoperatively. In our study, according to the results of the statistical analysis for the STAI test, no significant differences were observed between the groups. The preoperative anxiety score in our study was 44 on average. This is similar to the results of other studies.

In our study, systolic and diastolic blood pressure values increased significantly just before induction in all groups. Although there were no statistically significant differences in the heart rate values between the groups, the intra-group evaluation increased significantly 1 hour before induction. This indicates that the anxiety caused by surgery increases as the time of operation approaches and premedication is not effective enough to prevent this.

The pituitary hormones secreted in response to stress and increased sympathetic activity cause the body to transition to a new state both hemodynamically and metabolically. Therefore, heart minute volume and tissue perfusion are increased, and body temperature rises. Blood glucose is increased with the increase of catabolic hormones such as cortisol, adrenaline, and insulin, in addition to glycolysis, gluconeogenesis, and lipolysis. The serum insulin levels in our study were similar in inter- and intra-group evaluations. Serum glucose levels of group 1A (fasted, fluid restricted and premedicated group) also showed a significant change compared to other groups. The high glucose levels of group 1A may be due to the anxiety caused by fluid restriction. Catecholamines have important physiological effects in response to stress. They activate glycogenolysis, gluconeogenesis, lipolysis and ketogenesis in the liver. This is because they lower insulin and increase glucagon [18-20]. They also increase blood pressure and heart rate [21]. There are many stimuli that lead to catecholamine release, such as hypovolemia, hypoglycemia, hypoxemia, pain and fear. Hypovolemia is best correlated with catecholamine release [22]. In our research, epinephrine and norepinephrine levels were higher in group 1A compared to the other groups. These results support our view that hunger and fluid restriction increase the stress level. It is known that surgical stimulation, anesthesia, psychic, and emotional stress increase cortisol release [23]. Cortisol potentiates the effects of epinephrine and glucagon, causing hyperglycemia. It also activates gluconeogenesis, proteolysis, and lipolysis. As a result of all these processes, blood glucose rises and tries to supply the vital organs with the necessary energy.

Nesfatin-1 is a recently described molecule. Studies show that besides the central nervous system, it is secreted from the pancreas, adipose tissue, and gastric mucosa [7, 24-26]. It has been shown in human milk [27]. Food and water intake has been shown to increase Nesfatin-1 levels [7, 24, 28]. Stengel et al. [29] found low levels of Nesfatin-1 in rats that were fasted for 24 hours. Tsuchiya et al. [30] stated that there is a negative correlation between Nesfatin-1 and BMI. The increase of Nesfatin-1 secretes glucose-stimulated insulin from pancreatic beta cells [31, 32]. Foo et al. [7] showed that Nesfatin-1 administration decreases blood glucose level of hyperglycemic rats (type 2 DM) depending on the dose and time. Nesfatin-1 is also effective in the regulation of emotional and behavioral states. In experimental animal models, Nesfatin-1 activation in the rat brain increased psychological stress [8]. In their study, Hofmann et al. [33] found that plasma Nesfatin-1 level was higher in the group of high anxiety compared to patients with low anxiety**.** There was a statistically significant correlation between plasma Nesfatin-1 level, total stress score and depression score. Günay et al. [34] reported that Nesfatin-1 level was low in their study on normal weight men with general anxiety. In our study, the nestfatin-1 levels of only group 2A was significantly higher than group 2B. In the intra-group evaluation, Nesfatin1 level in group 2A was high in the second period.

The level of Nesfatin1 in Group1A was significantly higher in the 3rd period than in the 2nd period. Also, group 2A had the lowest glucose levels in comparison to other groups. This can be regarded as an indicator of the antihyperglycemic effect of Nesfatin-1. Based on our results, anxiety score was compatible in the STAI 1 test, but no correlation was observed in the STAI-2 test. We think this may be related to glucose level.

The limitations of this study are as follows: The study was performed only in operations involving general anesthesia. Therefore, the data were more limited as it did not include patients with regional anesthesia. In addition, it should be kept in mind that anxiety analyses are affected by the sociodemographic statuses of the patients.

Conclusion

According to our findings, the highest reflection of stress in patients seems to coincide with the clinical and endocrine responses just before the induction period. Preoperative fluid replacement and premedication maintain hemodynamic stability and contribute positively to energy balance by increasing the level of Nesfatin-1. If the pathophysiological mechanisms are clarified, we think that Nesfatin-1 can be used in the treatment of diseases affecting energy metabolisms such as diabetes and obesity, and in reducing perioperative complications.

References

1. Diks J, van Hoorn DEC, Nijveldt RJ, Boelens PG, Hofman Z, Bouritius H, et al. Preoperative fasting: an outdated concept? J Parenter Enteral Nutr. 2005;29:298-30.

2. Derbyshire DR, Smith G. Sympathoadrenal responses to anesthesia and surgery. Br J Anaesth. 1984;56:725-39.
3. Misiolek H, Wojcieszek E, Dyaczynska-Herman A. comparison of influence of thiopentone, propofol and midazolam on blood serum concentration of noradrenaline and cortisol in patients undergoing non-toxic struma operation. Med Sci Monit. 2000;6:319-24.
4. Su Y, Zhang J, Tang Y, Bi F, Liu JN. The novel function of Nesfatin-1: anti-hyperglycemia. Biochem Biophys Res Commun. 2010;391:1039-42.
5. Gonzalez R, Mohan H, Unniappan S. Nucleobindins: Bioactive precursor proteins encoding putative endocrine factors? Gen Comp Endocrinol. 2012;176:341-6.
6. Ito C. The role of brain histamine in acute and chronic stresses. Biomedicine & Pharmacotherapy. 2000;54:263-7.
7. Foo KS, Brauner H, Ostenson CG, Broberger C. Nucleobindin-2/Nesfatin in the endocrine pancreas: Distribution and relationship to glycemic state. J Endocrinol. 2010;204:255–63.
8. Goebel M, Stengel A, Wang L, Taché Y. Restraint stress activates Nesfatin-1-immunoreactive brain nuclei in rats. Brain Res. 2009;1300:14-24.
9. Whitty PM, Goodwin DR. Patient satisfaction with general anesthesia. Anesthesia. 1996;51:32.
10. Hume MA, Kennedy B, Asbury AJ. Patient knowledge anesthesia and perioperative care. Anesthesia. 1994;49:715-8.
11. Ramsay MA. A survey of pre-operative fear. Anesthesia. 1972;27:396–402.
12. Chew ST, Tan T, Tan SS, Ip-Yam PC. A survey of patient knowledge of anesthesia and perioperative care. Singapore Med J. 1998;39:399–402.
13. Egbert LD, Welch CE, Bartlett MK. Reduction of postoperative pain by encouragement and instruction of patients. N Engl J Med. 1964;270:7.
14. Kayhan Z (ed). Metabolic / endocrine system and anesthesia. clinical anesthesia. Logos publishing, Ankara. 2004;16:406-16.
15. Ledowski T, Bein B, Hanss R, Paris A, Fudickar W, Scholz J, et al. Neuroendocrine stress response and heart rate variability: a comparison of total intravenous versus balanced anesthesia. Anesth Analg. 2005;101:1700-5.
16. Taşdemir A, Erakgün A, Deniz MN, Çertuğ A. Comparison of preoperative and postoperative: Anxiety levels with state-trait anxiety inventory test in preoperatively informed patients. Turk J Anaesth Reanim. 2013;41:44-9.
17. Domar AD, Everett LL, Keller MG. Preoperative anxiety: Is it a predictablentity? Anesth Analg. l989;69:763-7.
18. Wallash B. Trauma Shoemoker WC. Textbook of critical care. 4nd edition. Londo WB Saunders Company 1998:1230-321.
19. Şahinoğlu AH. Intensive care problems and treatments. 2nd Edition. Trauma. Ortadoğu Advertisement Presentation and Publishing. Ankara 2003;311-30.
20. Malazgirt Z. Şahinoğlu AH. Neuroendocrine, immune and metabolic responses to trauma. Intensive Care problems and treatments. Ankara: Türkiye Klinikleri. 2003;2:305-30.
21. Lowrie A, Johnson PL, Fell D, Robinson W. Cardiovascular and plasma catecholamine responses at tracheal extubation. Br J Anaesth. 1992;68:261-3.
22. Donald SP, Whitley JM, Caral LT, Dwight DD, Dougles SD. Small volume resuscitation from hemorrhagic shock in dogs: Effects on systemic hemodynamic and systemic blood flow. Critical Care Med. 1991;19:364-71.
23. Guyton AC, Hall JE. Autonomic nervous system and adrenal gland medulla. Medical Physiology (Translation) 10th Edition, İstanbul:Nobel Tıp Kitapevleri, 2001;697-708.
24. Shimizu H, Ohsaki A, Oh-I S, Okada S, Mori M. A new anorexigenic protein, Nesfatin-1. Peptides. 2009;30:995-8.
25. Stengel A, Goebel M, Yakubov I, Wang L, Witcher D, Coskun T, et al. Identification and characterization of Nesfatin-1 immunoreactivity in endocrine cell types of the rat gastric oxyntic mucosa. Endocrinology. 2009;150:232–8.
26. Gonzalez R, Tiwari A, Unniappan S. Pancreatic beta cells colocalize insulin and proNesfatin immunoreactivity in rodents. Biochem Biophys Res Commun. 2009;381:643–8.
27. Aydin S. The presence of the peptides apelin, ghrelin and Nesfatin-1 in the human breast milk, and the lowering of their levels in patients with gestational diabetes mellitus. Peptides. 2010;31:2236-40.
28. Goebel M, Stengel A, Wang L, Taché Y. Central Nesfatin-1 reduces the nocturnal food intake in mice by reducing meal size and increasing inter-meal intervals. Peptides. 2011;32:36–43.
29. Stengel A, Taché Y. Minireview:Nesfatin-1 an emerging new player in the brain-gut, endocrine, and metabolic axis. Endocrinology. 2011;152:4033–8.
30. Tsuchiya T, Shimizu H, Yamada M, Osaki A, Oh-I S, Ariyama Y et al. Fasting concentrations of Nesfatin-1 are negatively correlated with body mass index in non-obese males. Clin Endocrinol (Oxf). 2010;73:484-90.
31. Nakata M, Manaka K, Yamamoto S, Mori M, Yada T. Nesfatin-1 enhances glucose-induced insulin secretion by promoting Ca2+ influx through L-type channels in mouse islet beta-cells. Endocr J. 2011;58:305–13.
32. Gonzalez R, Reingold BK, Gao X, Gaidhu MP, Tsushima RG, Unniappan S. Nesfatin-1 exerts a direct, glucose-dependent insulinotropic action on mouse islet beta and MIN6 cells. J Endocrinol. 2011;208:9-16.
33. Hofmann T, Stengel A, Ahnis A, Bußе P, Elbelt U, Klapp BF. NUCB2/Nesfatin-1 is associated with elevated scores of anxiety in female obese patients. Psychoneuroendocrinology. 2013;38:2502-10.
34. Gunay H, Tutuncu R, Aydin S, Dag E, Abasli D. Decreased plasma Nesfatin-1 levels in patients with generalized anxiety disorder. Psychoneuroendocrinology. 2012;37:1949-53.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):588-592.
DOI: 10.28982/josam.741869

Journal of Surgery and Medicine
e-ISSN=2602-2079

Effect of platelet large cell ratio (PLCR) and immature granulocyte (%IG) values on prognosis in surgical site infections

Berna Şermin Kılıç [1], Nil Atakul [1]

Istanbul Education and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey

ORCID ID of the author(s)
BŞK: 0000-0002-0103-0709
NA: 0000-0003-3874-8797

Corresponding Author
Berna Şermin Kılıç
İstanbul Eğitim ve Araştırma Hastanesi, Kasap İlyas Mah, Org. Abdurrahman Nafiz Gürman Cd., 34098 Fatih, İstanbul, Turkey
E-mail: berna_doctor@hotmail.com

Ethics Committee Approval
The study protocol was approved by the Ethics Committee of Istanbul Education and Research Hospital (date: 07/02/2020, issue number: 2176) All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 May 15

Abstract

Background/Aim: Surgical site infections (SSI) are serious operative complications that occur in approximately 2% of surgical procedures, although rates vary widely according to the type of procedure. Measurement of immature granulocyte percentage (%IG) and Platelet Larger Cell Ratio (PLCR) may be used as a marker of serious bacterial infections. The study aims to evaluate whether the %IG and PLCR are useful additional predictive markers of surgical site infections.

Methods: This retrospective cohort study included 50 patients with surgical site infections and 50 control individuals. Patients who were hospitalized in the Istanbul Education and Research Hospital Gynecology and Obstetrics Department between October 2017 and January 2019 were scanned. The Mann-Whitney U test was used to compare continuous variables, and the chi-square test was utilized to compare categorical data.

Results: A cut-off of 30.1 for PLRC and 0.35 for %IG had 72% sensitivity and 45% specificity, and 97% sensitivity and 78% specificity (AUC: 0.95), respectively, for the diagnosis of wound site infections. The PLRC and %IG values of the patients with and without wound site infections significantly differed (P=0.052, and P<0.05, respectively). PLRC value slightly negatively correlated with hospitalization duration (r = -0.102), and strongly negative correlated with antibiotic use (r = -0.01).

Conclusion: PLCR and %IG can be used as easy, reliable, cost-effective, and fast biomarkers for the detection and evaluation of severity in wound infection.

Keywords: Surgical site infections, Platelet large cell ratio (PLCR), Immature granulocytes (IG)

How to cite: Kılıç BŞ, Atakul N. Effect of platelet large cell ratio (PLCR) and immature granulocyte (%IG) values on prognosis in surgical site infections. J Surg Med. 2021;5(6):588-592.

Introduction

Among hospitalized patients, surgical site infection (SSI) makes up 14-16% of all nosocomial infections and is the third most frequent nosocomial infection. SSI can be classified into three categories according to the depth of the wound and the severity of the infection from superficial incisional to organ/space involvement, based on the Center for Disease Control and Prevention (CDC) reports [1].

Proper diagnosis of SSI is vital since its progression may lead to significant morbidity, and socio-economic problems if overlooked [2]. After obstetric and gynecologic procedures, SSIs are frequently encountered as a postoperative complication.

SSI is the most common reason for prolonged hospital stay and readmission. By checking the patient's routine laboratory analysis, initially white blood cell (WBC) count and C-reactive protein (CRP) levels, infections, and related complications were evaluated by physicians. In the past decade, other markers have been used to detect infections.

Platelets, 3-5μm in diameter and 4.5-11fL in volume, are cytoplasmatic fragments of megakaryocytes that are present in the bone marrow [3]. In addition to their critical role in thrombosis and hemostasis, evidence by many reports suggests that platelets contribute to the microbial host defense, inflammatory process, angiogenesis, wound healing, and remodeling [4].

Platelets act as first responders during the injury process and hemostasis. To aid tissue regeneration and wound sterilization, following surgical incision, platelets actively migrate from the inflamed or leaky vessel wall [5]. Platelet activity has been monitored by PLCR, which is defined as the percentage of circulating larger platelets (>12 fL).

PLCR and immature granulocytes are automatically measured while obtaining a complete blood count. The normal range is between 15-35% [6].

Recently, the role and several functions of platelets in the inflammation process were defined. A significant number of studies have shown that platelets play an essential role in the pathogenesis of various inflammation-related clinical circumstances.

The role of platelets from severe infection to systemic inflammatory reaction syndrome (SIRS), trauma, and thrombotic events have been researched by numerous groups who defined the activation of the coagulation system and changes in platelet volume, size, and different indices [7].

Currently, modern automated hematology analyzers are available. They measure other usable infection markers, such as PLCR and immature granulocyte percentage (%IG), to be used as parameters of severe bacterial infections [8, 9]. As a potential marker, some recent studies have searched the function of %IG to estimate the severity of infection [10, 11]. These studies were predominantly based on adult patients with a critical illness hospitalized in the intensive care units.

Our study aimed to compare the PLCR and %IG values in patients with and without SSI in the Obstetrics and Gynecology clinic and their significance in diagnosis, along with their relationship with disease severity by assessing the correlation of PLCR and %IG values with parametric values such as duration of hospitalization and antibiotic treatment.

Materials and methods

Our study was performed retrospectively in the Gynecology and Obstetrics department of a tertiary level education and research hospital. From October 2017 to January 2019, all patients diagnosed with surgical complications were evaluated for inclusion in the study. The inclusion criteria were being between 18–40 years of age, and developing incisional SSI after the gynecologic, gynecologic oncologic, or cesarean operations. Control patients were selected randomly between 18–40-year-old patients who were referred to our Gynecology and Obstetrics outpatient clinic for a routine follow-up examination without any signs of urinary tract infection or pelvic inflammatory disease. Patients with serious trauma, an infection occurring immediately after surgery, cardiac shock, those receiving immunotherapy, those with autoimmune diseases, paraneoplastic syndrome, acute versus host disease, and deep infections with organ and/or space involvement were excluded from the study. Infections which affect the skin or subcutaneous tissue within 30 days of the procedure are defined as incisional SSIs. At least one of the following signs must be documented to diagnose a patient with incisional SSI: Purulent drainage from the wound, redness and/or swelling of the incision, and wound separation.

Patients who developed SSI according to the CDC criteria were treated either in inpatient or outpatient settings. Blood samples were obtained from patients for complete blood count (CBC), CRP, and sedimentation analysis. Leukocyte count, PLCR, and% IG were measured using an automated hematological analyzer (XN-1000; SysmexCorp.), from blood samples obtained at the first admission to the outpatient clinic or the emergency room. PLCR and% IG values were calculated by semiconductor flow cytometry using the data obtained from CBC analysis. Intravenous antibiotic therapy was started with metronidazole and a second-generation cephalosporin.

Statistical analysis

Data were presented as median (interquartile) and continuous, non-normally distributed data were analyzed with the Mann–Whitney U-test. The qualitative data were analyzed by either Fisher's test or chi-square test. Correlation analysis between PLCR and %IG value and parametric variables was conducted with either Pearson's for interval scale or Spearman's for ordinal scales analysis.

The study protocol was approved by the Ethics Committee of Istanbul Education and Research Hospital (date: 07/02/2020, issue number: 2176) and conducted in accordance with the Declaration of Helsinki.

Results

Fifty females who developed SSI after surgery and 50 control individuals were enrolled in our study. Among 50 SSI patients, 9 patients had undergone a cesarean section, 14 patients, a gynecologic-oncologic operation (endometrium, ovarian and cervical cancer) and 27 patients had undergone gynecologic operations (salpingectomy, myomectomy, hysterectomy, sacrocolpopexy). All patients had superficial wound infections.

As shown in Table 1, the mean ages of the SSI and control patients were 44.1 years and 36.3 years, respectively. The median PLRC values of the SSI and control patients were 25.1 and 28.2 respectively, and the median %IG values of the SSI and control patients were 1.62 and 0.27 respectively. Significant differences were found between the PLRC and %IG values of patients with and without wound infections (P=0.052, and P<0.05, respectively). The mean BMI, CRP and WBC values of SSI patients were 32 kg/m^2, 103.9 mg/L, and 11.7x10^9/L, respectively, while those of the control patients were 29.2 kg/m^2, 6.1 mg/L and 7x10^9/L, respectively. Thirty-four out of 50 SSI patients (68%) had normal WBC count at admission to the hospital. The mean hospitalization duration was 18.2 days among SSI patients.

Table 1: Demographic data of the study population

	SSI(n=50)	Control(n=50)	*P*-value
Age (years)	44.1	36.3	<0.05
PLRC	25.1	28.2	<0.05
%IG	1.62	0.27	<0.05
BMI (kg/m^2)	32	29.2	>0.05
CRP (mean)	103.9	6.1	<0.05
ESR mean)	79.6		
WBC (x 10^9/L)	11.7	7.00	<0.05

PLRC: platelet large cell ratio, %IG: immature granulocyte percentage, BMI: body mass index, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, WBC: white blood cell

The mean %IG value of culture-negative and culture-positive SSI patients were 2.61, and 0.97, respectively (P=0.002).

A cut-off of 30.1 for PLRC and 0.35 for %IG had 72% sensitivity and 45% specificity, and 97% sensitivity and 78% specificity (AUC: 0.95), respectively, for the diagnosis of wound site infections (Figures 1 and 2).

Figure 1: ROC curve analysis of PLRC value in wound infection patients

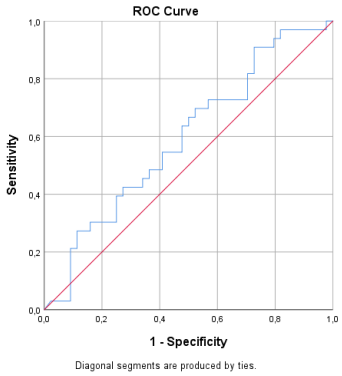
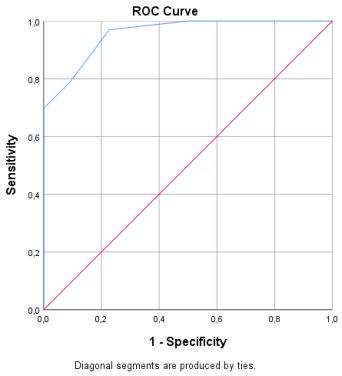


Figure 2: ROC curve analysis of %IG value in wound infection patients



PLRC value slightly negatively correlated with hospitalization duration (r = -0.102), and strongly negatively correlated with duration of antibiotic use (r = -0.01) (Figures 3 and 4), while %IG value slightly negatively correlated with hospitalization duration (r = -0.110), and slightly negatively correlated with duration of antibiotic use (r = -0.023) (Figures 5 and 6).

Among the SSI infection group, there were 30 culture-negative and 20 culture-positive patients. Among culture-positive patients, 2 had methicillin-resistant Staphylococcus aureus (MRSA), 1 had Candida spp., 3 had Escherichia coli (E.coli), 3 had Pseudomonas spp., 1 had Enterococcus spp., 1 had Klebsiella spp., 1 had S.capitis, 2 had S.epidermidis, 1 had Morganella morganii, 2 had Enterobacteria sp., 1 had S.haemolyticus, 1 had P. mirabilis, 1 had Acinetobacter infection.

Figure 3: Correlation analysis of hospitalization time with PLRC value

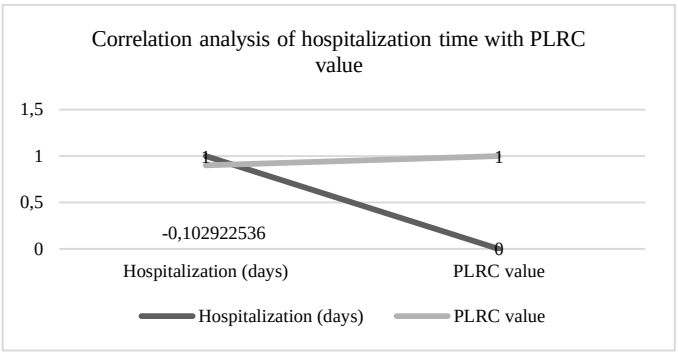


Figure 4: Correlation analysis of duration of antibiotic use with PLRC values of patients

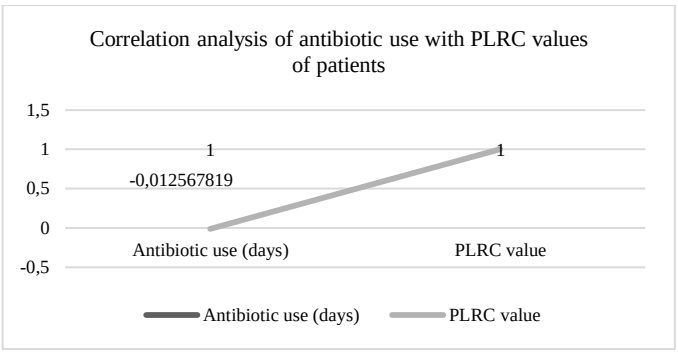


Figure 5: Correlation analysis of hospitalization time with %IG

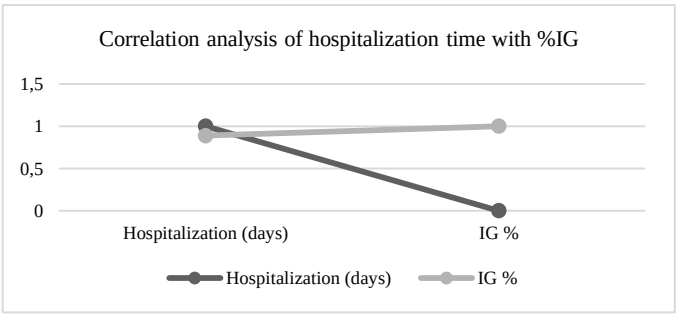
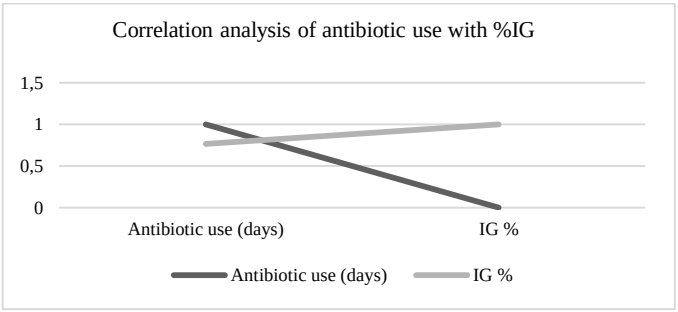


Figure 6: Correlation analysis of antibiotic use with %IG (There was a slight negative correlation between antibiotic use and %IG (correlation coefficient = -0.023).



Discussion

PLCR is another substitute marker that defines the largest size fraction of platelets for platelet volume, and an increase usually indicates the production of new platelets. Only a few reports studied PLCR value in sepsis and/or infection patients. Our study is one of the first studies to provide a PLCR cut-off value among gynecology patients. Gao et al. [12] analyzed 124 patients with septic shock retrospectively, and several important results were reported. In the non-surviving group (n=88), platelet and procalcitonin decreased while mean platelet volume (MPV), PLCR, and platelet distribution width (PDW) increased with time. PLCR was more sensitive to platelet size changes but was mostly correlated with MPV. Contrary to our results, their PLCR values were higher in their non-survivor group of patients, but their study population was critically ill. We

also found a negative correlation between PLCR and SSI severity, and we conclude that PLCR first decreases in number at the beginning of the inflammatory cascade, then starts to increase as the disease progresses to septic shock. Our findings are in concordance with the results of Zhan et al. [13] who found that PLCR value was significantly lower in patients with active periodontitis compared to the healthy control group.

Babu et al. [14] showed that the PLCR levels were parallel to MPV and PDW values and are inversely related with platelet count, which may help form a link between these two parameters. Comparative studies are needed on which one is superior and/or of equal value in estimation of progression and severity.

Some studies suggest that the %IG is a useful and an easily obtainable adjuvant marker to predict the severity and invasiveness of microbial infection in critically ill patients [15].

In earlier studies, contrary to our results, %IG was elevated in non-critically ill adults and neonates with infection [16,17,18,19,20]. Since our patients had a relatively mild infection at the beginning, as disease progresses, %IG values start to decrease, which is valuable for determining disease progression, since we found a negative correlation of %IG value with a duration of antibiotic use. More than half of our patients had normal WBC count during admission. One study showed that %IG predicts infection better than total WBC count [18]. Some studies conclude that %IG values better reflect the severity of sepsis than CRP, WBC, and procalcitonin, and attribute equivalent discrimination power to lactate [21]. We also found a negative correlation between %IG values, and disease progression and severity.

Another challenge in diagnosing sepsis is that infection is not always confirmed even if treatment is started and only in 30–40% of cases, a positive culture sepsis is present [22].

Early diagnosis and no delay in the treatment of sepsis with antibiotics can be lifesaving since sepsis is the most common cause of mortality in intensive care units [23].

However, obtaining culture results normally takes 24-48 hours, which generates a delay in treatment and diagnosis. In some clinics, broad-spectrum antibiotic therapy is initiated while waiting for culture results. However, this option is expensive and may pose a risk as unnecessary and prophylactic antibiotics may induce the development of highly resistant microorganisms [23]. More than half of our patients had negative culture results but delaying treatment while waiting for the culture results or because of non-confirmed microorganisms may put the patient's life at risk. Accordingly, examinations that allow faster diagnosis with higher specificity are required.

Nierhaus et al. [24] reported that in SIRS patients, especially within the first 48 hours, the %IG value significantly differentiates infected patients from uninfected ones ($P < 0.0001$), with a sensitivity of 89.2% and a specificity of 76.4%. They found that IG value had higher diagnostic value than other laboratory parameters such as CRP, interleukin-6 (IL-6), and lipopolysaccharide-binding protein (LBP), which had less than 68% sensitivity. The ROC curve analysis showed a higher positive predictive value for % IG compared to other parameters in the first 5 days of meeting the SIRS criteria.

Lee et al. [25] showed that blood cultures are positive only in one-third of patients who show clinical features of sepsis. Contamination of blood cultures is another aspect of difficulty in the diagnosis of sepsis which may lead to misuse of antibiotics. Even though contaminated blood cultures were excluded from their study, IG% <2.0% helped rule out sepsis even before blood culture results. Future comparative studies with contaminated culture results may help validate the discriminative power of % IG. Ansari-Lari et al. [26] also found that the %IG value was better correlated with positive blood culture results and infection than WBC count.

Contrary to our results, as we found higher %IG values in culture-negative patients, Pavare et al. [27] found that %IG added valuable information regarding the performance of children with different infection degrees in all age groups. Their results were parallel with the previous studies and suggest an association between positive blood bacterial culture and higher IG%. Furthermore, higher levels of %IG are seen in culture-positive patients and suspected septicemia [15,24].

The wound infection patients in our study group were not critically ill, and our group of patients were younger, which led to less secondary morbidities associated with changes in hematological parameters. It is safe to assume that our values give more insight into infection pathogenesis in the early phase of the inflammatory cascade.

Ours is one of the first studies investigating PLCR and %IG values in SSI after gynecological operations.

Limitations

Since PLCR and %IG were recently incorporated into total blood count analyses, comparative studies are lacking in the Gynecology and Obstetrics Department. Even though postpartum cesarean patients were small in sample size, we included both postpartum cesarean and gynecology patients in our study. Therefore, there is a need for studies that analyze these two patient groups independently, although, when plasma volume begins to increase, hematocrit values return to normal within 3-5 days after birth. However, studies evaluating the values of hemoglobin longitudinally in the postpartum period show that it takes at least 4-6 months to transform the pregnancy-associated changes to non-pregnant psychology. Since studies comparing PLRC and %IG values in postpartum cesarean and control patients are lacking, normal reference values in the postpartum population needs to be determined by further studies. Our control group was randomly selected from patients without genitourinary infection, but patients with respiratory or other site infections could not be excluded from the study.

This study could provide a basis for future large-scale studies, by making it possible to validate our results. Including PLCR, and %IG in the SSI treatment protocol, and initiating treatment earlier when needed leads to greater recovery possibilities for post-operative gynecology patients.

Conclusions

We investigated the clinical significance of the PLCR and %IG count as new markers of acute inflammation. PLCR and %IG count showed infection even without leukocytosis and in case of negative culture results. We found that low PLCR and high % IG count can be used in early diagnosis and most importantly, the tendency of PLCR value to increase from

baseline indicates that the infection is getting more complicated, and vice versa applies for %IG value. Compared with other available inflammation markers, PLRC and IG count are rapidly generated with routine CBC analysis with no delay in sample analysis and without any extra cost.

References

1. Centers for Disease Control and Prevention, National Healthcare Safety Network. CDC/NHSN. Procedure associated Module. Surgical Site Infection (SSI) Event. [Available from: https://www.cdc.gov/nhsn/pdfs/ pscmanual/9pscssicurrent.pdf
2. Olsen MA, Butler AM, Willers DM, Gross GA, Hamilton BH, Fraser VJ. Attributable costs of surgical site infection and endometritis after low transverse cesarean delivery. Infect Control Hosp Epidemiol. 2010;31(3):276–82.
3. Hoffbrand AV, Moss PAH, Pettit JE, editors. Essential Haematology. 5th ed. Carlton, Australia: Blackwell publishing Ltd, 2006.
4. Golebiewska EM, Poole AW. Platelet secretion: From haemostasis to wound healing and beyond. Blood Rev. 2015;29:153–62.
5. Mancuso ME, Santagostino E. Platelets: much more than bricks in a breached wall. Br J Haematol. 2017;178:209–19.
6. Hong H, Xiao W, Maitta RW. Steady increment of immature platelet fraction is suppressed by irradiation in single-donor platelet components during storage. PLoS One. 2014;9:e85465.
7. Thachil J. Platelets in inflammatory disorders: a pathophysiological and clinical perspective. Semin Thromb Hemost. 2015;41:572–81.
8. Sadik CD, Kim ND, Luster AD. Neutrophils cascading their way to inflammation. Trends Immunol. 2011;32:452–460.
9. Fernandes B, Hamaguchi Y. Autometed enumeration of Immature granulocytes. Am J Clin. Pathol. 2007;128:454–63.
10. Ha SO, Park SH., Park SH, Park JS, Huh JW, Lim CM, et al. Fraction of immature granulocytes reflects severity but not mortality in sepsis. Scand J Clin Lab Investig. 2015;75:36–43.
11. Mare TA, Treacher DF, Shankar-Hari M, Beale R, Lewis SM, Chambers DJ, Brown KA. The diagnostic and prognostic significance of monitoring blood levels of immature neutrophils in patients with systemic inflammation. Crit. Care. 2015;19:57.
12. Gao Y, Li Y, Yu X, Guo S, Ji X, Sun T, et al. The Impact of Various Platelet Indices as Prognostic Markers of Septic Shock. Plos One. 2014;9(8):e103761.
13. Zhan Y, Lu R, Meng H, Wang X, Sun X, Hou J. The role of platelets in inflammatory immune responses in generalized aggressive periodontitis. J Clin Periodontol. 2017;44(2):150–7.
14. Babu E, Basu D. Platelet large cell ratio in the differential diagnosis of abnormal platelet counts. Indian J Pathol Microbiol. 2004;47:202–5.
15. Van Der GPJ, Mohseni M, Brouwer R, Van Der HB, Steyerberg EW, Groeneveld A. Immature granulocytes predict microbial infection and its adverse sequelae in the intensive care unit. J Crit Care. 2014;29(4):523- 7.
16. Park BH, Kang YA, Park MS, Jung WJ, Lee SH, Lee SK, et al. Delta neutrophil index as an early marker of disease severity in critically ill patients with sepsis. BMC Infect Dis. 2001;11:299–308.
17. Simson E, Groner W. The state of the art for the automated WBC differentials. Lab Hematol. 1995;1:13–22.
18. Briggs C, Kunka S, Fujimoto H, Hamaguchi Y, Davis BH, Machin SJ. Evaluation of immature granulocyte counts by the XE-IG master: upgraded software for the XE2100 automated hematology analyzer. Lab Hematol. 2009;9:117–24.
19. Nigro KG, O'Riordan M, Molloy EJ, Walsh MC, Sandhaus LM. Performance of an automated immature granulocyte count as a predictor of neonatal sepsis. Am J Clin Pathol. 2005;123:618–24.
20. Senthilnayagam B, Kumar T, Sukumaran J, Jeya M, Rao KR. Automated measurement of immature granulocytes: performance characteristics and utility in routine clinical practise. Pathol Res Internat. 2012;2:483–9.
21. Park SH, Ha SO, Cho YU, Park CJ, Jang S, Hong SB. Immature Platelet Fraction in Septic Patients: Clinical Relevance of Immature Platelet Fraction is Limited to the Sensitive and Accurate Discrimination of Septic Patients From Non-Septic Patients, Not to the Discrimination of Sepsis Severity. Ann Lab Med. 2016;36:1-8.
22. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis- 3). JAMA. 2016;315(8):801-10.
23. Naffaa M, Makhoul BF, Tobia A, Kaplan M, Aronson D, Azzam SZ, et al. Procalcitonin and interleukin 6 for predicting blood culture positivity in sepsis. Am J Emerg Med. 2014;32(5):448- 51
24. Nierhaus A, Klatte S, Linssen J, Eismann NM, Wichmann D, Hedge J, et al. Revisiting the white blood cell count: immature granulocytes count as a diagnostic marker to discriminate between SIRS and sepsis – a prospective, observational study. BMC Immunol. 2013;14(1):1- 8.
25. Lee CH, Kim J, Park Y, Kim Y, Yoon KJ, Uh Y, et al. Delta neutrophil index discriminates true bacteremia from blood culture contamination. Clin Chim Acta. 2014;427:11- 4.
26. Ali Ansari-Lari M, Kickler TS, Borowitz MJ. Immature granulocyte measurement using the Sysmex XE-2100. Am J Clin Pathol. 2003;120:795–9.
27. Pavare, J, Grope, I, Gardovska, D. Assessment of Immature Granulocytes Percentage to Predict Severe Bacterial Infection in Latvian Children: An Analysis of Secondary Data. Medicina (Kaunas, Lithuania). 2018; 54(4):56.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):593-596.
DOI: 10.28982/josam.911665

Journal of Surgery and Medicine
e-ISSN=2602-2079

Effectiveness of greater occipital nerve blocks in chronic migraine

Esra Aciman Demirel [1], Burcu Karpuz Seren [2], Sibel Özdemir [3], Gülcan Taşçatan [1], Hüseyin Tuğrul Atasoy [1]

[1] Department of Neurology, Bulent Ecevit University School of Medicine, Zonguldak, Turkey
[2] Department of Neurology, Zonguldak Atatürk State Hospital, Zonguldak, Turkey
[3] Department of Neurology, Karaman Training and Research Hospital, Karaman, Turkey

ORCID ID of the author(s)

EAD: 0000-0002-1444-5022
BKS: 0000-0003-3171-1123
SÖ: 0000-0001-5373-7506
GT: 0000-0003-2046-6759
HTA: 0000-0003-1631-7400

Corresponding Author
Esra Aciman Demirel
Bulent Ecevit University School of Medicine, Department of Neurology, Zonguldak, Turkey
E-mail: esraaciman@yahoo.com

Ethics Committee Approval
This study was approved by Bülent Ecevit University Clinical Research Ethics Committee (No 2021/05, 10.03.2021).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 May 15

Abstract

Background/Aim: Chronic migraine (CM) is defined as headache occurring on 15 or more days per month for more than three months, which, on at least 8 days per month, has the features of a migraine headache. Greater occipital nerve (GON) blocks with local anesthetics and steroids are used in CM. GON block is widely used effectively in CM treatment. The aim of this study was to assess the effectiveness of GON blocks in CM.

Methods: This retrospective cohort study was conducted in Bulent Ecevit University Faculty of Medicine, Department of Neurology. Data of 43 CM patients who had GON block were collected. CM was diagnosed using International Classification of Headache Disorders (ICHD-3). GON blocks were repeated every week in the first month and monthly thereafter for the following 6 months. The injections were performed radially at 2 cm lateral and 2 cm inferior to the protuberantia occipitalis externa with a needle and 2 mL of 0.25% bupivacaine bilaterally. Headache attack frequency (days), headache duration (hours) and severity of pain (Visual Analog Scale (VAS)) were compared between before and after GON block in the first month.

Results: Headache attack frequency decreased from 12.8 (8.4) (pretreatment) to 3.8 (3.5), and headache severity (VAS), from 8.5 (1.2) to 4.5 (1.8) (P<0.001 for both) within one month. No serious adverse effects were observed.

Conclusion: This study showed significant decreases in headache parameters in CM. GON block is widely used effectively in CM treatment, and there is a need to standardize the application technique, dose, and frequency.

Keywords: Chronic migraine, Greater occipital nerve block, Headache attack frequency, Headache severity

How to cite: Demirel EA, Seren BK, Özdemir S, Taşçatan G, Atasoy HT. Effectiveness of greater occipital nerve blocks in chronic migraine. J Surg Med. 2021;5(6):593-596.

Introduction

Chronic migraine (CM) is defined as headache occurring on at least 15 days per month for more than three months, which, on at least 8 days per month, has the features of a migraine headache [1]. CM is characterized by recurrent moderate to severe headaches, with a severe impact on socioeconomic functioning and quality of life [2, 3]. Chronic migraine affects 1–2% of the general population, and in about 8% of patients with migraine, it usually develops from episodic migraine [3, 4]. The risk factors for chronic migraine include overuse of acute migraine medication, ineffective acute treatment, obesity, depression, and stressful life events. Age, female sex, and low educational status increase the risk of chronic migraine [3, 5].

Antidepressants are the most used prophylactic drugs. Beta blockers, antiepileptic drugs such as topiramate and valproate, and calcium channel blockers are used for treatment [2, 3]. Cognitive behavioral therapy and botulinum toxin are effective [6, 7]. Current treatments still have insufficient efficacy in migraine patients, and treatment of chronic migraines presents a challenge for the physicians.

Greater occipital nerve (GON) block with local anesthetics is another method of treatment developed because of the scarcity of prophylactic drugs. Some studies assessed the efficacy of GON block in the treatment of other headache syndromes, including cluster headache, chronic daily headache, and cervicogenic headache, trigeminal neuralgia and postdural puncture headache [8-18], but there are a few studies on CM treatment [2, 5, 19, 20]. The block method, administration frequency, the type and quantity of anesthetics used vary.

The aim of this study was to determine the effectiveness of GON block with the local anesthetic bupivacaine for CM prophylaxis in patients who do not use prophylactic agents.

Materials and methods

This retrospective cohort study was conducted in Bulent Ecevit University Faculty of Medicine, Department of Neurology between 2019-2020 on 43 CM patients who had GON block. CM was diagnosed using International Classification of Headache Disorders (ICHD-3) [1]. GON blocks were repeated every week in the first month and monthly thereafter for the following 6 months.

Exclusion criteria for this study were as follows: Having undergone occipital nerve block or occipital nerve stimulation, using prophylactic agents for migraine, having an active infection/skull defect/hemangioma in the injection area, a history of allergic reaction to the local anesthetic, a history of occipital region surgery, being pregnant or breastfeeding, having uncontrolled hypertension, uncontrolled diabetes mellitus, liver disease, congestive heart failure, history of a psychiatric disease, renal failure and using anticoagulants.

The injections were performed radially 2 cm lateral and 2 cm inferior to the protuberantia occipitalis externa with a needle and 2 mL of 0.25% bupivacaine bilaterally. The patients were kept under observation for 30 minutes to note the possible side effects.

Headache attack frequency (days), headache duration (hours) and severity of pain (Visual Analog Scale (VAS)) were compared before and after GON block in first month. Headache severity was recorded using a VAS. All patients were informed about the scale numbered from 0 (no pain) to 10 (worst pain ever experienced).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) 18.0 program. The suitability of the data to normal distribution was assessed by the Kolmogorov–Smirnov test. To summarize data obtained in the study, descriptive statistics were presented as mean (standard deviation) or median with minimum-maximum (min-max) values, depending on the distribution of the continuous variables, while categorical variables were presented as numbers and percentages. The Wilcoxon test was used to evaluate the effectiveness of GON blockade. *P*-value <0.05 was considered statistically significant.

Results

A total of 43 patients, including 39 females and 4 males, were included in the study. The median age of the patients was 40.2 (11.6) years. Table 1 shows the comparison of frequency, duration, and severity of the patients' headaches before and after bilateral GON blocks. Headache attack frequency decreased from 12.8 (8.4) (pretreatment) to 3.8 (3.5) (first month). Headache duration and severity (VAS) decreased from 17.1 (16.8) hours to 4.6 (5.3) hours, and from 8.5 (1.2) to 4.5 (1.8) (first month), respectively (P<0.001 for all). No serious adverse effects were observed.

Table 1: Pre- and post-treatment of results

n=43	Pretreatment	First month - Post-treatment	*P*-value*
Headache attack frequency (days) (per month)	12.8 (8.4)	3.8 (3.5)	<0.001
Headache duration (hours)	17.1 (16.8)	4.6 (5.3)	<0.001
VAS	8.5 (1.2)	4.5 (1.8)	<0.001

VAS: Visual Analog Scale

Discussion

Our findings showed that repeated GON block with bupivacaine bilaterally significantly decreased the number of headache days, headache duration, and VAS pain scores in patients with CM.

The effectiveness of GON block in CM has been shown in several studies [2, 5, 19-21]. The block method, administration frequency, the type and quantity of anesthetics used vary. GON block procedures are yet to be standardized.

Inan et al. [19] reported the first randomized, placebo-controlled study on GON blockade for the treatment of chronic migraine, and showed that after 3 months, repetitive GON block with bupivacaine decreased the number of headaches, headache duration, and VAS scores of CM patients. They stated that GON blockade was effective on CM treatment. Our 1- month follow-up results were similar and effective.

Dilli et al. [23] reported that GON blockade did not reduce the frequency of migraine in CM when compared with placebo. They did not use repetitive blocks.

Inan et al. [19] showed that weekly and monthly treatments were similarly effective and reported that patients

responded well to once- monthly treatment, which is more feasible than once- weekly treatment.

Unal-Artık et al. [5] reported that GON block was an effective treatment method for chronic migraine and that unilateral GON block was as effective as bilateral GON block. They showed that repeated administration was needed to achieve effective GON blockade in patients with chronic migraine. In our study, we repeated GON blocks with bupivacaine bilaterally.

In their meta-analysis, Zhang et al. [17] reported that compared to controls, GON block significantly decreases pain intensity and analgesic medication consumption but has no significant impact on headache duration. In our study, GON block decreased headache duration.

The pathophysiology of CM is not well understood, and recent advances have indicated that cortical hyperexcitability, brainstem dysfunction, and central sensitization are important in the development of CM [24].

It is related to a group of signs that originate in the autonomic nervous system. Migraine is thought to be of neurovascular origin. It is triggered by an excitation of the cerebral cortex with abnormal control of the pain-related neurons in the trigeminal nucleus which are located in the brain stem [25].

GON block treats symptoms of migraine related to modulation of afferent signals to the trigeminal nucleus caudalis, which bridges the gap between sensory regions of the ophthalmic branch of the trigeminal nerve and the greater occipital nerve. Injecting this region with a local anesthetic decreases sensory input to the trigeminal nucleus caudalis [8].

It is well known that the trigeminocervical complex is connected to the nucleus salivatorius with raphe nucleus, locus coeruleus, and hypothalamus. Painful stimulus of cranial structures is transmitted through the trigeminal nerve and the superior cervical nerve to the trigeminocervical complex and then upper centers [2, 3, 17]. There is important functional connection between the sensory occipital segments and the trigeminal nociceptive system in humans. Thus, GON block is an effective treatment option in migraine patients, and protects the patients from serious complications [2, 3, 17, 19, 21].

The response to GON block was not only dependent on the direct local anesthetic effect of the injection. The mechanism of action might have been via changes in brain nociceptive pathways. Another explanation that GON injections initiate diffuse noxious inhibitory controls, independent of anesthetic effect. Neurophysiological and clinical data suggest there is a functional connection between the sensory occipital segments and the trigeminal nociceptive system in humans. GON block for unresponsive CM should therefore be considered an effective management tool [9].

Another point still under discussion is the choice of medication to be used in the procedure. The current approach is to use local anesthetics and local anesthetic-steroid mixtures.

The literature does not include any study focused on the dose of local anesthetic that results in effective GON block. However, studies suggest the use of 1-2% lidocaine (10-20 mg / mL) and / or 0.25-0.5% bupivacaine (2.5-5 mg / mL) for effective GON block [26].

There are studies in which the GON block is combined with corticosteroids [23, 27, 28]. These studies revealed that corticosteroid supplementation did not reduce pain intensity but extended the duration of pain relief. More studies are needed to investigate this problem.

There are few adverse events following GON block, such as injection site pain, local infection, local hematoma and abdominal distension, paresthesia, and benign intracranial hypertension [17]. No adverse effects were observed in our study.

Limitations

This study was limited by the retrospective design, and the lack of a control group. Further placebo-controlled research involving large populations are needed.

Conclusion

Recurrent GON block is an effective treatment method of CM and protects patients from serious complications related to the side effects of drugs. This method is simple, safe, and cost-effective. Systemic side effects of other prophylactic drugs, which have limited use in liver and kidney diseases, and in case of pregnancy and breastfeeding, are avoided, as well as the high cost of chronic drug use. Botulinum toxin injections can be more painful for patients and the injection cost is higher than local anesthetics. More studies are needed to better define the safety and cost-effectiveness of the GON block for CM treatment.

References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33:629–808.
2. Gul HL, Ozon AO, Karadas O, Koc G, Inan LE. The efficacy of greater occipital nerve blockade in chronic migraine: A placebo- controlled study. Acta Neurol Scand. 2017;136(2):138-44. doi: 10.1111/ane.12716
3. May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. Nat Rev Neurol. 2016;12(8):455-64. doi:10.1038/nrneurol.2016.93
4. Buse DC, Manack AN, Fanning KM, Serrano D, Reed ML, Turkel CC, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. Headache. 2012;52(10):1456-70. doi: 10.1111/j.1526-4610.2012.02223.x
5. Unal-Artık HA, Inan LE, Atac-Ucar C, Yoldas TK. Do bilateral and unilateral greater occipital nerve block effectiveness differ in chronic migraine patients?. Neurol Sci. 2017;38(6):949-54. doi:10.1007/s10072-017-2861-5
6. Blumenfeld AM, Aurora SK, Laranjo K, Papapetropoulos S. Unmet clinical needs in chronic migraine: rationale for study and design of COMPEL, an open-label, multicenter study of the long-term efficacy, safety, and tolerability of onabotulinumtoxinA for headache prophylaxis in adults with chronic migraine. BMC Neurol. 2015;15:100. doi: 10.1186/s12883-015-0353-x
7. Sun-Edelstein C, Rapoport AM. Update on the pharmacological treatment of chronic migraine. Curr Pain Headache Rep. 2016;20(1):6. doi: 10.1007/s11916-015-0533-9
8. Allen SM, Mookadam F, Cha SS, Freeman JA, Starling AJ, Mookadam M. Greater occipital nerve block for acute treatment of migraine headache: a large retrospective cohort study. J Am Board Fam Med. 2018;31(2):211-8. doi: 10.3122/jabfm.2018.02.170188
9. Afridi SK, Shields KG, Bhola R, Goadsby PJ. Greater occipital nerve injection in primary headache syndromes–prolonged effects from a single injection. Pain. 2006;122(1–2):126–9. doi: 10.1016/j.pain.2006.01.016
10. Ashkenazi A, Matro R, Shaw JW, Abbas MA, Silberstein SD. Greater occipital nerve block using local anaesthetics alone or with triamcinolone for transformed migraine: a randomised comparative study. J Neurol Neurosurg Psychiatry. 2008;79:415–7. doi: 10.1136/jnnp.2007.124420
11. Ashkenazi A, Blumenfeld A, Napchan U, et al. Peripheral nerve blocks and trigger point injections in headache management - a systematic review and suggestions for future research. Headache. 2010;50:943–52. doi: 10.1111/j.1526-4610.2010.01675.x
12. Ozer D, Boluk C, Turk Boru U, Altun D, Tasdemir M, Koseoglu Toksoy C. Greater occipital and supraorbital nerve blockade for the preventive treatment of migraine: a single-blind, randomized, placebo-controlled study. Curr Med Res Opin. 2019;35(5):909-15. doi: 10.1080/03007995.2018.1532403
13. Tobin JA, Fitman SS. Occipital nerve blocks: effect of symptomatic medication overuse and headache type on failure rate. Headache. 2009;49(10):1479–85. doi: 10.1111/j.1526-4610.2009.01549.x
14. Gawel MJ, Rothbart PJ. Occipital nerve block in the management of headache and cervical pain. Cephalalgia. 1992;12:9–13. doi: 10.1046/j.1468-2982.1992.1201009.x
15. Inan N, Ceyhan A, Inan L, Kavaklioğlu O, Alptekin A, Unal A. C2/C3 nerve blocks and greater occipital nerve block in cervicogenic headache treatment. Funct Neurol. 2001;16:239–43. PMID: 11769869
16. Karadas O, Gul HL, Inan LE. Lidocaine injection of pericranial myofascial trigger points in the treatment of frequent episodic tension- type headache. J Headache Pain. 2013;14:44–51. doi: 10.1186/1129-2377-14-44
17. Zhang H, Yang X, Lin Y, Chen L, Ye H. The efficacy of greater occipital nerve block for the treatment of migraine: a systematic review and meta-analysis. Clin Neurol Neurosurg. 2018;165:129-33. doi: 10.1016/j.clineuro.2017.12.026
18. Terzi T, Karakurum B, Üçler S, İnan LE, Tulunay C. Greater occipital nerve blockade in migraine, tension- type headache and cervicogenic headache. J Headache Pain. 2002;3:137–41. doi: 10.1007/s101940200031

19. Inan LE, Inan N, Karadas O, Gul HL, Erdemoglu AK, Turkel Y, et al. Greater occipital nerve blockade for the treatment of chronic migraine: A randomized, multicenter, double- blind, and placebo- controlled study. Acta Neurol Scand. 2015;132(4):270-7. doi: 10.1111/ane.12393
20. Cuadrado, ML, Aledo-Serrano, Á, Navarro, P Short-term effects of greater occipital nerve blocks in chronic migraine: A double-blind, randomised, placebo-controlled clinical trial. Cephalalgia. 2017;37:864–72. doi: 10.1177/0333102416655159
21. Inan LE, Inan N, Unal-Artık HA, Atac C, Babaoglu G. Greater occipital nerve block in migraine prophylaxis: narrative review. Cephalalgia. 2019;39(7):908-20. doi: 10.1177/0333102418821669
22. Inan, N, Inan LE, Coskun O. Effectiveness of greater occipital nerve blocks in migraine prophylaxis. Arch Neuropsychiatr. 2016;53:45–8. doi: 10.5152/npa.2015.10003
23. Dilli E, Halker R, Vargas B, Hentz J, Radam T, Rogers R, et al. Occipital nerve block for the short-term preventive treatment of migraine: A randomized, double-blinded, placebo-controlled study. Cephalalgia. 2015;35:959–68. doi: 10.1177/0333102414561872
24. Su M, Yu S. Chronic migraine: A process of dysmodulation and sensitization. Mol Pain 2018;14:1-10. doi:10.1177/1744806918767697
25. Okmen K, Dagistan Y, Dagistan E, Kaplan N, Cancan E. Efficacy of the greater occipital nerve block in recurrent migraine type headaches. Neurol Neurochir Pol. 2016;50:151–4. doi: 10.1016/j.pjnns.2016.01.015
26. Blumenfeld A, Ashkenazi A, Napchan U, Bender SD, Klein BC, Berliner R,et al. Expert consensus recommendations for the performance of peripheral nerve blocks for headaches–a narrative review. Headache 2013;53(3): 437-446. doi: 10.1111/head.12053
27. Tang Y, Kang J, Zhang Y, Zhang X. Influence of greater occipital nerve block on pain severity in migraine patients: A systematic review and meta-analysis. Am J Emerg Med. 2017; 35(11):1750-4. doi: 10.1016/j.ajem.2017.08.027
28. Kashipazha D, Nakhostin-Mortazavi A, Mohammadianinejad SE, Bahadoram M, Zandifar S, Tarahomi S. Preventive effect of greater occipital nerve block on severity and frequency of migraine headache. Glob J Health Sci. 2014;6:209-13. doi: 10.5539/gjhs.v6n6p209.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):597-601.
DOI: 10.28982/josam.873383

Journal of Surgery and Medicine
e-ISSN=2602-2079

Sexual life changes in pregnant women during COVID-19 outbreak

Süleyman Eserdağ [1], Mehtap Yücedağ [2], Ali Doğukan Anğın [3], Özgür Yımaz [2], Lokman Ertekin [4], Pınar Anğın [5]

[1] Clinic of Obstetrics and Gynecology, Hera Clinic, İstanbul, Turkey
[2] Department of Obstetrics and Gynecology, Manisa City Hospital, Manisa, Turkey
[3] Clinic of Obstetrics and Gynecology, Viveste Clinic, İstanbul, Turkey
[4] Department of Obstetrics and Gynecology, Kartal Training and Research Hospital, İstanbul, Turkey
[5] Department of Obstetrics and Gynecology, Ümraniye Training and Research Hospital, İstanbul, Turkey

ORCID ID of the author(s)

SE: 0000-0001-6540-0230
MY: 0000-0002-4382-3192
ADA: 0000-0003-1954-8546
ÖY: 0000-0002-6248-1060
LE: 0000-0002-7092-1097
PA: 0000-0001-9471-268X

Corresponding Author
Ali Doğukan Anğın
Viveste Clinic, Ayşe Çavuş sok. Bağdat Caddesi, Rama Apt. No1/2, Kadıköy, İstanbul, Turkey
E-mail: dralidogukan@gmail.com

Ethics Committee Approval
This study was approved by the Ethics Committee of Kartal Dr Lütfi Kırdar Training and Research Hospital (No: 2020/514/179/6).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 June 4

Abstract

Background/Aim: Restrictions imposed after the COVID-19 outbreak have had some negative effects on the society and individuals. There are few reports on the effects of the COVID-19 pandemic, which causes stress on individuals, on sexual activity. The aim of this study is to evaluate the sexual activities of pregnant women during these restrictions.
Methods: A total of 294 pregnant women between the ages of 18-45 years and their spouses who visited the Gynecology and Obstetrics Clinic between June 2020, and August 2020 were included in this cross-sectional study. The sexual activities of pregnant women and their spouses were evaluated with the Arizona Sexual Experiences Scale (ASEX).
Results: One third of the pregnant women were in their first pregnancy, and 78.2% of those who gave birth before had a vaginal delivery. 38.8% of the pregnant women were in their second trimester. The mean ASEX scores of pregnant women and their partners during the pandemic period were significantly increased compared to the pre-pandemic period (13.47 (3.58) versus 17.01 (5.78), P=0.001, 12.14 (2.98) versus 14.49 (5.02), P=0.001, respectively). Before the pandemic, 64.62% (n=190) of the pregnant women and 51.7% (n=152) of their spouses had a sexual disorder. During the pandemic, this ratio increased in both genders and rose to 80.27% (n=136) in pregnant women and 63.60% (n=187) in their spouses.
Conclusion: We observed an increase in sexual dysfunction in both pregnant women and their partners during the COVID-19 pandemic.

Keywords: COVID-19, Pregnant women, Arizona Sexual Experiences Scale, Sexual disorder

How to cite: Eserdağ S, Yücedağ M, Anğın AD, Yımaz Ö, Ertekin L, Anğın P. Sexual life changes in pregnant women during the COVID-19 outbreak. J Surg Med. 2021;5(6):597-601.

Introduction

Coronavirus-2019 (COVID-19), which was first seen at the end of 2019 in Wuhan, a city in Hubei Province of China, and then spread rapidly all over the world, is now a pandemic [1]. SARS-CoV-2, a beta-coronavirus that can be transmitted to humans via intermediate hosts such as bats, is the biggest global challenge we have faced since World War II [2]. COVID-19 continued to spread aggressively, and on March 11, restrictions and social distancing measures were implemented in our country (Turkey). With these restrictions, the goals were to wear a mask and ensure social distancing between people to reduce and prevent the spread of the virus. Most commercial activities, especially those operating in the service sector, were closed down, and the social distance between individuals in even open areas was set to be at least 1.5 meters [3].

Measures taken after the COVID-19 outbreak have had some negative effects on society and individuals [4]. Concern about both one's own health and the health of loved ones are the first reactions to the pandemic. In addition, there was anger and boredom due to the uncertainty of how far the epidemic would progress, how it would affect life, and when life would return to "normal". High stress situations and loneliness are known to cause symptoms of depression or post-traumatic stress disorder in some people [5]. It is well known that stress has negative effects on sexual function, but the mechanisms in this relationship have not been adequately discussed. Psychologically, stress can interfere with an individual's focus on sexuality through both emotional and cognitive changes [2].

There are few reports on the effects of the COVID-19 pandemic on sexual activity [2, 6]. The sexual health of individuals who are already facing more health problems globally could be affected by COVID-19. Many people face economic and psychological pressures for fear of losing their jobs. On the other hand, it may increase the risk of experiencing adverse sexual health consequences due to the lack of access to comprehensive health services [6]. Sexual activity during pregnancy, an important aspect of quality of life, should be evaluated together with pregnant women and their spouses. Studies show that sexual activity decreases during pregnancy [7, 8]. Many factors, such as maternal age, gestational age, duration of marriage, parity, employment status, and education level have been reported to affect sexual activity during pregnancy [7]. Various scales are used to measure sexual function, such as the Arizona Sexual Experiences Scale (ASEX), the Female Sexual Function Index (FSFI), the Sexual Interaction Inventory, and the Sexual Satisfaction Questionnaire [9]. There is no study evaluating sexual activity in pregnant women during the COVID-19 pandemic. Therefore, in this study, we aimed to investigate how the COVID-19 pandemic affects sexual activity in pregnant women using the ASEX scale.

Materials and methods

This prospective cross-sectional study was approved by the institutional human study Ethics committee of the Kartal Dr Lütfi Kırdar Training and Research Hospital (No: 2020/514/179/6). This study was conducted in accordance with the tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants. A total of 294 pregnant women between the ages of 18-45 years who visited the Gynecology and Obstetrics Clinic of a Training and Research Hospital between June 2020 and August 2020 were included. Pregnant women who visited at any time during their pregnancy and their spouses were asked to fill in ASEX voluntarily, and their demographic information were recorded. ASEX was completed two times, reflecting their sexual lives before and during the pandemic (March 11, 2020).

Inclusion criteria in the study were being between the ages of 18-45, literate, willing to participate in the survey, having a singleton pregnancy, no obstetric conditions in which sexual intercourse is prohibited (placenta previa, detachment, preterm birth threat, presence of sexually transmitted disease, cervical insufficiency), not having an anomaly detected in the fetus, and not receiving any psychological treatment that may affect sexual life. Exclusion criteria were as follows: Being younger than 18 years and or older than 45 years of age, fetal anomaly detected during pregnancy follow-up, multiple pregnancy, lack of sexual partners, illiteracy, any psychological treatment that would affect sexual life, and presence of obstetric conditions for which sexual intercourse was not recommended. The demographic characteristics and ASEX results of the pregnant women and their spouses were evaluated.

Arizona Sexual Experiences Scale (ASEX)

ASEX, developed by McGahuey et al. [10], was applied to evaluate the sexual activity of the couples. The Turkish version, of which validity and reliability studies were conducted by Soykan [11], was used. The score ranges between 5 and 30, and a higher total score indicates sexual dysfunction. In this study, scores ≥11 were considered the cut-off, as suggested by Soykan.

Statistical analysis

SPPS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) statistical package program was used to evaluate the data. Variables were presented as mean (standard deviation), median (maximum-minimum), percentage, and frequency values. In addition, the homogeneity of variances, which is one of the prerequisites of parametric tests, was checked with the Levene test. Normality assumption was analyzed using the Shapiro–Wilk test. When the differences between two groups were evaluated, Student's t-test was used in cases where the parametric test met the prerequisites, otherwise, the Mann–Whitney U test was used. For comparison of three or more groups, one-way analysis of variance and Tukey's HSD test, Kruskal–Wallis, and Bonferroni–Dunn test from multiple comparison tests were used. While performing categorical data analysis, McNemar–Bowker Test, Fisher's Exact Test, Chi-Square Test, sensitivity and selectivity calculations, positive expected value, and negative expected value were calculated. In cases where the expected cells were less than 20%, the values were determined with the Monte Carlo Simulation Method to include these cells in the analysis. In the case that the relationship between two variables did not meet the parametric test prerequisites, it was evaluated with the Kendall rank correlation coefficient. Statistical significance level was $P < 0.05$.

Results

Demographic information of pregnant women and their spouses included in the study is shown in Table 1. The mean age of the pregnant women and their spouses were 27.15 (5.14) years, and 30.68 (5.74) years, respectively. Among all, 41.8% of the pregnant women had normal BMI and 36.1% were overweight. One third of the pregnant women were in their first pregnancy, and 78.2% of those who had given birth before had had a vaginal delivery. 38.8% of the pregnant women included in the study were in the second trimester.

Table 1: Demographic characteristics of pregnant women and their spouses.

	n	Mean (SD)
Age (Years)	294	27.15 (5.14)
Height (Cm)	294	162.05 (5.90)
Weight (Kg)	294	69.05 (13.06)
Spouse Age (Years)	294	30.68 (5.74)
	n	%
BMI		
Weak	4	1.4
Normal	123	41.8
Overweight	106	36.1
Stage 1 Obesity	46	15.6
Stage 2 Obesity	14	4.8
Morbid Obesity	1	0.3
Gravida		
1	97	33.0
2	81	27.6
3	72	24.5
4	29	9.9
5	11	3.7
6	1	0.3
7	2	0.7
12	1	0.3
Parity		
0	102	34.7
1	90	30.6
2	69	23.5
3	22	7.5
4	8	2.7
5	2	0.7
9	1	0.3
Form Of Birth		
Vaginal Birth	230	78.2
Cesarean Delivery	64	21.8
Pregnancy Week		
1st Trimester	88	29.9
2nd Trimester	114	38.8
3rd Trimester	92	31.3
Past Operations		
No	222	75.5
Yes	72	24.5
Comorbidity		
No	271	92.2
Yes	23	7.8
Drug Use		
No	275	93.5
Yes	19	6.5
Smoking Status		
No	275	93.5
Yes	19	6.5
Profession		
No	269	91.5
Yes	25	8.5
Education Level		
Primary School	44	15.0
Middle School	47	16.0
High School	173	58.8
University	30	10.2
Income Status (Turkish Lira)		
0-2500	32	10.8
2500-5000	220	74.8
5000-7500	32	10.9
>7500	10	3.4
Spouse Comorbidity		
No	281	95.6
Yes	13	4.4
Spouse Smoking Status		
No	149	50.7
Yes	145	49.3
Spouse Profession		
Worker	193	65.6
Officer	32	10.9
Self-Employment	65	22.1
Soldier	4	1.4
Spouse Education Level		
No Literacy	1	0.3
Primary School	31	10.5
Middle School	27	9.2
High School	197	67.0
University	38	12.9
Total	294	100.0

Before the pandemic, the mean ASEX score of pregnant women was 13.47 (3.58), and the average ASEX score of their spouses was 12.14 (2.98) (Table 2). During the pandemic, ASEX average scores of the pregnant women and their spouses significantly increased to 17.01 (5.78), and 14.49 (5.02), respectively (P=0.001 for both). The ASEX scores of the pregnant women before and after the pandemic were higher than those of their spouses.

The distribution of ≥11 ASEX scores of pregnant women and their spouses are shown in Table 3. Before the pandemic, 64.62% (n=190) of pregnant women and 51.7% (n=152) of their spouses had sexual disorders. During the pandemic, this ratio increased in both genders and rose to 80.27% (n=136) in pregnant women and 63.60% (n=187) in their spouses.

Table 2: Comparison of the Arizona Sexual Experiences Scale (ASEX) scores of pregnant women and their spouses before and during the pandemic

	Before pandemic	During pandemic	Test statistic	P-value
Pregnant ASEX	13.47 (3.58)	17.01 (5.78)	-11.118	0.001^{t*}
Spouse ASEX	12.14 (2.98)	14.49 (5.02)	-8.712	0.001^{t*}

* P<0.05, t Wilcoxon Test

Table 3: Comparison of the Arizona Sexual Experiences Scale (ASEX) ≥11 scores of pregnant women and their spouses before and during the pandemic

	Before pandemic ASEX ≥11		During pandemic ASEX ≥11		P-value
	n	%	n	%	
Pregnant	190	64.62%	236	80.27%	0.026
Spouse	152	51.7%	187	63.60%	0.083

The effects of demographic characteristics of pregnant women and their spouses on ASEX scores before and during the pandemic are shown in Table 4. The scores of those who had a previous cesarean section were higher than those who gave vaginal birth, and the scores in the third trimester were higher than other weeks of gestation. ASEX scores of those who delivered by cesarean section (P=0.001), normal deliveries (P=0.041), pregnant women in their second trimester (P=0.049), and pregnant women in their third trimesters (P=0.01) during the pandemic were higher than scores before the pandemic. There was no significant difference in terms of other demographic characteristics of pregnant women and their spouses (P>0.05 for all).

Table 4: Comparison of the demographic characteristics of pregnant women and their spouses with Arizona Sexual Experiences Scale (ASEX) scores before and after the pandemic

Variables	Before the Pandemic ASEX	During the Pandemic ASEX	*P*-value
Form Of Birth			
Vaginal Delivery (n=230)	13.20 (3.43)	16.78 (5.72)	0.041*
Cesarean Delivery (n=64)	14.43 (3.94)	17.82 (5.96)	0.001*
Test Statistics	-2.290	-1.024	
P-value	0.022€*	0.306 €	
Pregnancy Trimester			
1st Trimester	12.87 (3.07)	15.92 (5.76)	0.282
2nd Trimester	13.71 (3.43)	17.04 (5.54)	0.049*
3rd Trimester	13.75 (3.60)	18.01 (5.96)	0.01*
Test Statistics	6.189	5.356	
P-value	0.045 Ψ *	0.069 Ψ	
Education Status			
Primary School (n = 44)	13.54 (3.57)	17.45 (6.05)	0.663
Secondary School (n = 47)	13.31 (3.41)	18.48 (5.61)	0.111
High School (n = 173)	13.52 (3.65)	16.39 (5.72)	0.464
University (n = 30)	13.33 (3.57)	17.56 (5.75)	0.635
Test Statistics	0.292	5.732	
P-value	0.961 Ψ	0.125 Ψ	
Income Status (Turkish Lira)			
<2500	13.06 (2.75)	17.15 (5.54)	0.228
2500-5000	13.37 (3.62)	17.01 (5.85)	0.269
5000-7500	14.12 (3.84)	17.18 (5.70)	0.528
>7500	14.90 (3.92)	15.90 (5.97)	0.345
Test Statistics	2.372	0.499	
P-value	0.710 Ψ	0.871Ψ	
Spouse Profession			
Worker (n = 193)	12.13 (3.10)	14.28 (5.00)	0.329
Civil Servant (n = 32)	12.65 (2.81)	15.50 (5.25)	0.964
Self-Employment (n = 65)	11.87 (2.55)	14.43 (4.86)	0.596
Soldier (n = 4)	13.25 (5.05)	17.75 (6.44)	0.64
Test Statistics	1.616	3.675	
P-value	0.656 Ψ	0.299Ψ	
Spouse Education			
Primary School (n = 38)	12.32 (3.08)	13.58 (4.03)	0.185
Secondary School (n = 27)	11.88 (2.06)	13.25 (4.87)	0.584
High School (n = 197)	12.04 (3.13)	14.52 (5.05)	0.964
University (n = 38)	12.81 (2.65)	16.05 (5.44)	0.484
Test Statistics	5.590	7.564	
P-value	0.232 Ψ	0.109 Ψ	
Spouse Smoking Status			
No (n = 149)	12.10 (3.0)	14.26 (4.78)	0.115
Yes (n = 145)	12.19 (2.97)	14.73 (5.26)	0.184
Test Statistics	-0.286	-0.174	
P-value	0.775€	0.862€	
Comparison Of Pairs			
Pregnant (n = 294)	13.47 (3.58)	17.01 (5.78)	0.001
Spouse (n = 294)	12.14 (2.98)	14.49 (5.02)	0.001
Test Statistics	-4.632	-5.532	
P-value	0.001*€	0.001*€	

*$P<0.05$, ¥ Independent Two Group t-test (Student's t test), € Mann–Whitney U test, Δ One-way analysis of variance (ANOVA), ψ Kruskal–Wallis Test

Discussion

In this worldwide alarming atmosphere, changes in lifestyle are inevitable, which may affect people's quality of life and sexual function due to social constraints and uncertainties about the future [12]. It has been reported that the psychological effect is caused by high stress, depression, anxiety, and dissatisfaction [13]. In the first phase of the COVID-19 outbreak in China, female gender, being a student, and having certain physical symptoms were associated with higher stress, anxiety, and depression [14]. It is known that a stressful lifestyle affects a woman's sexual desire and frequency of sexual intercourse. Decreased sexual desire and frequency of sexual intercourse have been reported with high levels of chronic stress and after earthquakes [15, 16]. In contrast, it has been shown that sexual activity increases among women during stressful times [17].

After restrictions were announced in most countries with the COVID-19 pandemic, studies on how sexual life was affected were published. In a study conducted in Poland, they found a decrease in all areas of FSFI scores during the pandemic. They observed the greatest decrease in FSFI scores in women who had never worked [9]. In a study conducted in Turkey during the pandemic, despite an increase in the average weekly frequency of sexual intercourse (1.9 vs. 2.4), decreases in the FSFI scores (17.56 against 20.52) were found. They reported that the field scores for arousal, orgasm, and satisfaction from the FSFI subfields were significantly higher before the pandemic. Also, although the use of contraception during the pandemic decreased (24 participants versus 10), they found a decrease in the number of women who were thinking of becoming pregnant (19 versus 3) [18]. In a study conducted in Italy, it was determined that there was a decrease in sexual function and quality of life in women within the social restriction period during the COVID-19 pandemic [2]. They found that, compared to before the pandemic, the number of women who had sexual intercourse four times a month dropped from 89 to 52. They also reported lower FSFI scores in women with higher education levels, those with parity ≥ 1, and women living with their partner [2]. In a study conducted in the UK, they determined that 60.1% of 868 people participating in the study were not sexually active during the pandemic. They reported that being male, younger, married, and consuming alcohol were associated with more sexual activity [19]. Li et al. found that both sexual activity and sexual satisfaction of young men and women decreased during the peak of the COVID-19 outbreak in China [4]. Similarly, in another study of 967 participants in China, 22% (n=212) of the participants reported a decrease in sexual desire, and 41% (n=396) reported a decrease in the frequency of intercourse [6].

Pregnancy can be defined as an important stress that changes the pre-pregnancy lifestyle and quality of life of both partners, including sexual activity. The main factors that can lead to sexual dysfunction during pregnancy stem from physical, hormonal, and psychological factors [20]. It is known that sexual activity usually decreases during pregnancy. Aslan et al. reported that orgasmic activity, sexual interest, and frequency of sexual intercourse among pregnant women gradually decreased [8]. The prevalence of female sexual disorder (FSD) among pregnant women was reported as 50-80% [7, 21]. Studies conducted in Turkey revealed FSD rates during pregnancy as high as 80-90% [22]. Although it is well known that sexual activity decreases in pregnant women and the previously mentioned studies show decreased sexual activity during the pandemic among non-pregnant individuals, there are no studies regarding sexual activity during the pregnancy period during the pandemic. Ours is the first study evaluating sexual activity in pregnant women during the pandemic period. As a result of the survey conducted in our study, we determined that 64.62% of pregnant women before the pandemic and 51.7% of their spouses had sexual disorders. After the pandemic, this ratio increased in both genders and rose to 80.27% in pregnant women and 63.60% in their spouses. Angin et al. [23] compared the sexual activities of pregnant women and their spouses before pregnancy. In their study, they determined that the pre-pregnancy spouses' ASEX scores increased from 23.2% to 55.6%. The 51.7% ASEX in our study is similar to the results of this study. However, the results of pregnant women and their spouses evaluated in our study are consistent with the increased FSD results after COVID-19 in other countries.

In a study conducted on 220 women, they reported that younger age, shorter duration of marriage, and multiparity were positively associated with female sexuality [24]. In studies from Turkey, age, parity, and duration of marriage do not affect the sexual activity of women; however, it was found that nulliparous women had higher sexual desire and satisfaction scores [21, 25]. In our study, pre-pandemic ASEX scores of pregnant women in the third trimester were significantly higher compared to other weeks of gestation, and those who had previous cesarean section had scores that were significantly higher than those who had vaginal birth. In addition, ASEX scores of pregnant women in the second and third trimester were higher than before the pandemic. We can say that pregnant women with a further week of gestation are more affected by the COVID-19 pandemic. Corbacıoglu-Esmer et al. [21] reported that sexual dysfunction in third trimester in which FSFI scores were significantly lower compared to the first two trimesters. Similarly, Aslan et al. [8] found a decrease in all domains of FSFI in the last trimester. In our study, the high ASEX scores and FSD rate in the third trimester are consistent with the literature.

Limitations

This is the first study to investigate sexual activity in pregnant women during COVID-19 self-isolation/social distancing. However, our study has some limitations. First, participants were asked to potentially introduce a self-report bias to the findings, as they were asked to self-assess their sexual activity. Another limitation is that we did not evaluate the pre-pregnancy period. If ASEX were evaluated before pregnancy, we could have had more clear information about the effect of COVID-19. This study can serve as an example for further research.

Conclusion

In this first study evaluating sexual activity in pregnant women due to the COVID-19 epidemic, we observed a decrease in sexual activity in pregnant women and their partners during the pandemic period. Being in the third trimester of pregnancy and having a previous cesarean section were associated with increased ASEX scores before the pandemic. We can say that pregnant women with a further week of gestation are more affected by the COVID-19 pandemic. Larger studies are needed on the subject.

References

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020;395(10223):470-3. doi: 10.1016/S0140-6736(20)30185-9. Epub 2020 Jan 24. Erratum in: Lancet. 2020 Jan 29. PMID: 31986257; PMCID: PMC7135038.
2. Schiavi MC, Spina V, Zullo MA, Colagiovanni V, Luffarelli P, Rago R, et al. Love in the Time of COVID-19:Sexual Function and Quality of Life Analysis During the Social Distancing Measures in a Group of Italian Reproductive-Age Women. J Sex Med. 2020;17:1407-13.
3. Nicoli F, Gasparetto A. Italy in a Time of Emergency and Scarce Resources:The Need for Embedding Ethical Reflection in Social and Clinical Settings. J Clin Ethics. 2020;31(1):92-4. PMID: 32213700.
4. Li W, Li G, Xin C, Wang Y, Yang S. Challenges in the Practice of Sexual Medicine in the Time of COVID-19 in China. J Sex Med. 2020;17:1225-8.
5. Cao W, Fang Z, Hou G, Han M, Xu X, Dong J, et al. The psychological impact of the COVID-19 epidemic on college students in China. Psychiatry Res. 2020;287:112934. doi: 10.1016/j.psychres.2020.112934. Epub 2020 Mar 20. PMID: 32229390; PMCID: PMC7102633.
6. Li G, Tang D, Song B, Wang C, Qunshan S, Xu C, et al. Impact of the COVID-19 Pandemic on Partner Relationships and Sexual and Reproductive Health:Cross-Sectional, Online Survey Study. J Med Internet Res. 2020;22 (8):e20961.
7. Ahmed MR, Madny EH, Sayed Ahmed WA. Prevalence of female sexual dysfunction during pregnancy among Egyptian women. J Obstet Gynaecol Res. 2014;40(4):1023-9. doi: 10.1111/jog.12313. Epub 2014 Mar 10. PMID: 24612115.a
8. Aslan G, Aslan D, Kizilyar A, Ispahi C, Esen A. A prospective analysis of sexual functions during pregnancy. Int J Impot Res. 2005;17(2):154-7. doi: 10.1038/sj.ijir.3901288. PMID: 15538394.
9. Fuchs A, Czech I, Sikora J, Fuchs P, Lorek M, Skrzypulec-Plinta V, et al. Sexual Functioning in Pregnant Women. Int J Environ Res Public Health. 2019;16(21):4216. doi: 10.3390/ijerph16214216. PMID: 31671702; PMCID: PMC6862185.
10. McGahuey CA, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL, McKnight KM, Manber R. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther. 2000;26(1):25-40. doi: 10.1080/009262300278623. PMID: 10693114.
11. Soykan A. The reliability and validity of Arizona sexual experiences scale in Turkish ESRD patients undergoing hemodialysis. Int J Impot Res. 2004;16:531-4.
12. Lima CKT, Carvalho PMM, Lima IAAS, Nunes JVAO, Saraiva JS, de Souza RI, et al. The emotional impact of Coronavirus 2019-nCoV (new Coronavirus disease). Psychiatry Res. 2020;287:112915. doi: 10.1016/j.psychres.2020.112915. Epub 2020 Mar 12. PMID: 32199182; PMCID: PMC7195292.
13. Li Z, Ge J, Yang M, Feng J, Qiao M, Jiang R, et al. Vicarious traumatization in the general public, members, and non-members of medical teams aiding in COVID-19 control. Brain Behav Immun. 2020;88:916-919. doi: 10.1016/j.bbi.2020.03.007. Epub 2020 Mar 10. PMID: 32169498; PMCID: PMC7102670.
14. Duan L, Zhu G. Psychological interventions for people affected by the COVID-19 epidemic. Lancet Psychiatry. 2020;7(4):300-2. doi: 10.1016/S2215-0366(20)30073-0. Epub 2020 Feb 19. PMID: 32085840; PMCID: PMC7128328.
15. Hamilton LD, Meston CM. Chronic stress and sexual function in women. J Sex Med. 2013;10(10):2443-54. doi: 10.1111/jsm.12249. Epub 2013 Jul 10. PMID: 23841462; PMCID: PMC4199300.
16. Liu S, Han J, Xiao D, Ma C, Chen B. A report on the reproductive health of women after the massive 2008 Wenchuan earthquake. Int J Gynaecol Obstet. 2010 Feb;108(2):161-4. doi: 10.1016/j.ijgo.2009.08.030. Epub 2009 Nov 4. PMID: 19892335.
17. Hall KS, Kusunoki Y, Gatny H, Barber J. Stress symptoms and frequency of sexual intercourse among young women. J Sex Med. 2014;11(8):1982-90. doi: 10.1111/jsm.12607. Epub 2014 Jun 3. PMID: 24894425; PMCID: PMC4115031.
18. Yuksel B, Ozgor F. Effect of the COVID-19 pandemic on female sexual behavior. Int J Gynaecol Obstet. 2020;150:98-102.
19. Jacob L, Smith L, Butler L, Barnett Y, Grabovac I, McDermott D, et al. Challenges in the Practice of Sexual Medicine in the Time of COVID-19 in the United Kingdom. J Sex Med. 2020;17(7):1229-36. doi: 10.1016/j.jsxm.2020.05.001. Epub 2020 May 14. PMID: 32411271; PMCID: PMC7221385.
20. Erol B, Sanli O, Korkmaz D, Seyhan A, Akman T, Kadioglu A. A cross-sectional study of female sexual function and dysfunction during pregnancy. J Sex Med. 2007;4(5):1381-7. doi: 10.1111/j.1743-6109.2007.00559.x. Epub 2007 Jul 25. PMID: 17651387.
21. Corbacioglu Esmer A, Akca A, Akbayir O, Goksedef BP, Bakir VL. Female sexual function and associated factors during pregnancy. J Obstet Gynaecol Res. 2013;39:1165-72.
22. Aydin M, Cayonu N, Kadihasanoglu M, Irkilata L, Atilla MK, Kendirci M. Comparison of Sexual Functions in Pregnant and Non-Pregnant Women. Urol J. 2015;12(5):2339-44. PMID: 26571317.
23. Ağın AD, Özkaya E, Çetin M, Gün I, Sakin O, Ertekin LT, et al. Comparison of female sexual function and sexual function of their partners between groups of pregnant and non-pregnant women. Ginekol Pol. 2020;91(5):235-239. doi: 10.5603/GP.2020.0062. PMID: 32495927.
24. al Bustan MA, el Tomi NF, Faiwalla MF, Manav V. Maternal sexuality during pregnancy and after childbirth in Muslim Kuwaiti women. Arch Sex Behav. 1995;24(2):207-15. doi: 10.1007/BF01541581. PMID: 7794108.
25. Küçükdurmaz F, Efe E, Malkoç Ö, Kolus E, Amasyalı AS, Resim S. Prevalence and correlates of female sexual dysfunction among Turkish pregnant women. Turk J Urol. 2016;42(3):178-83. doi: 10.5152/tud.2016.49207. PMID: 27635293; PMCID: PMC5012445.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):602-605.
DOI: 10.28982/josam.887312

Journal of Surgery and Medicine
e-ISSN=2602-2079

Effects of preoperative and postoperative albumin levels on postoperative arrhythmias after open heart surgeries with cardiopulmonary bypass

Kevser Tural [1], Ali Alper Kahraman [2]

[1] Kafkas University, School of Medicine, Department of Cardiovascular Surgery, Kars, 36100, Turkey
[2] Kafkas University, Health Research and Application Center, Perfusionist, Kars, 36100, Turkey

ORCID ID of the author(s)
KT: 0000-0003-4490-037X
AAK: 0000-0003-2924-2655

Corresponding Author
Kevser Tural
Kafkas University, Faculty of Medicine, Department of Cardiovascular Surgery, Kars, Turkey
E-mail: ktrl2011@hotmail.com

Ethics Committee Approval
Kafkas University, Faculty of Medicine, Local Ethic Commitee, Date:06.05.2020, No:133. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 May 15

Abstract

Background/Aim: Ischemia-reperfusion injury is associated with transient contractility disorders and lethal arrhythmias. The main reason for this is the increase in the oxidants and the decrease in the antioxidants. This study aimed to investigate the relationship between albumin, known to have antioxidant properties, and arrhythmias seen in the early postoperative period in patients undergoing open heart surgery.

Methods: Adult patients undergoing open heart surgery with cardiopulmonary bypass within 5 years were included in this single-center, retrospective cohort study. The relationship of arrhythmias within the first 24 hours after the operation with the albumin levels obtained within 6 hours before the operation and within 4 hours after the operation was investigated. The difference between preoperative and postoperative albumin levels was evaluated using the Wilcoxon test and the relationship between albumin levels and arrhythmias, using the Mann-Whitney U test. The relationship between the results was evaluated by Pearson's correlation analysis, and the interaction of the results with correlations was evaluated by regression analysis.

Results: A total of 56 patients were included in the study. The average age of the patients was 63.07 years (11.24) (range, 42-89). The mean preoperative and postoperative albumin levels were 4.04 (0.51) g/dL, and 3.21 (0.45) g/dL, respectively. The mean postoperative albumin level was significantly lower than the preoperative mean albumin level ($P<0.001$). In the analyses performed to find the relationship between albumin levels and postoperative arrhythmias, the effects of postoperative albumin levels on postoperative arrhythmias were significant ($P=0.016$). In the regression analysis, there was an interaction between postoperative albumin levels and preoperative albumin levels ($P<0.001$), postoperative arrhythmia status ($P=0.005$), postoperative sinus tachycardia status ($P=0.002$), and postoperative lactate levels ($P=0.005$).

Conclusion: The present study suggests that high albumin levels may have a protective effect against postoperative arrhythmias. For all that, prospective studies may be planned with more patients and by examining the biochemical mechanism more comprehensively.

Keywords: Cardiopulmonary bypass, Ischemia-reperfusion injury, Arrhythmia, Sinus tachycardia, Albumin

How to cite: Tural K, Kahraman AA. Effects of preoperative and postoperative albumin levels on postoperative arrhythmias after open heart surgeries with cardiopulmonary bypass. J Surg Med. 2021;5(6):602-605.

Introduction

Heart diseases are still among the major causes of mortality worldwide [1, 2]. Cardiopulmonary bypass (CPB) is a system that provides blood circulation and oxygen needs of the body by undertaking the function of the heart and lungs during cardiac surgery [3]. CPB provides a stationary and bloodless surgical area, which is considered as the optimum condition in cardiac surgical treatment. During CPB, the selected cardiac arrest method creates a stationary surgical environment and a transient ischemic condition occurs. Hemodilution is also required for CPB [4].

Cardiac arrhythmias are associated with various conditions, such as heart failure and myocardial ischemia. Arrhythmias due to myocardial ischemia and ischemia-reperfusion (I-R) damage are among the most important causes of death of the myocardium. In addition, arrhythmias due to ischemia and I-R damage occur with oxidative and inflammatory responses leading to impaired myocardial electrical stability [5, 6]. Although reperfusion is necessary for the survival of ischemic tissue, it causes cell damage [7, 8]. The main reason for this damage is the increase in the number of oxidants [9]. When this increase in oxidants exceeds the antioxidant defense capacity, oxidative stress increases with a detrimental effect on the functional and structural integrity of the tissue and organ [10].

Serum albumin (SA) is seen as the most important antioxidant in the blood. It has a prognostic value in many cardiovascular diseases. Serum albumin contains abundant thiol groups that make up >80% of total thiols in plasma-clearing reactive oxygen and nitrogen species. Some substances such as nitric oxide and bilirubin are carried by SA and provide additional protection against oxidative stress [11]. SA creates its antioxidant effects largely by maintaining colloid osmotic pressure and hemostasis [12]. In addition, human serum albumin has N-terminal regions that detoxify oxidant agents. In the case of ischemia-reperfusion, N terminal areas of SA are damaged by oxidant agents [13, 14], antioxidant systems are damaged after reperfusion [15], and reduction in the amount of SA [4] occurs due to hemodilution during CPB. In this study, our aim was to investigate the relationship between preoperative and postoperative albumin levels, and postoperative arrhythmias in patients undergoing open heart surgery.

Materials and methods

In this retrospective cohort study, we analyzed 56 patients who underwent open heart surgery in our center between January 2015 and December 2020. The data were obtained from file scans and electronic records. All patients with normal sinus rhythm were included in the study in the preoperative period. In the preoperative period, patients with arrhythmia, those who underwent cardiopulmonary resuscitation, received ventilator, inotropic, or intra-aortic balloon pump support to ensure normal hemodynamics were excluded in the study. In addition, patients with malignancy, liver disease, collagen tissue disease, steroid use, psychosis, and a history of inflammatory disease including infection or sepsis were not included in the study. The STROBE checklist was used in the study design and drafting of the manuscript [16]. This study was approved by the ethics committee of Kafkas University, School of Medicine Ethics Committee (Date: 06.05.2020, No: 80576354-050-99/133), and conducted in accordance with the principles of the Declaration of Helsinki.

Arrhythmias occurring within the first 24 hours in the postoperative period were evaluated. Human albumin was not used in CPB circuits. Cold blood cardioplegia was used as the cardiac arrest method during CPB. In the study, serum albumin levels obtained from the antecubital vein within 6 hours before the operation and within 4 hours after the operation were evaluated. Albumin levels were analyzed by Cobas® 6000 c501-e601, Roche®, Switzerland, and lactate levels, by Radiometer ABL 90 Series, Radiometer, Denmark. Hemoglobin levels were assessed with Horiba ABX-120, Horiba, Japan. The definitions of arrhythmia are based on those detailed in the Lambeth Conventions [5], and electrocardiography results were determined by examining the patient files.

Statistical analysis

The statistical significance levels of the results were determined with SPSS® Statistic Version 20 (IBM®, USA). Continuous variables are expressed as mean (standard deviation) (min-max) and categorical variables, as numbers and percentages. The difference between preoperative and postoperative albumin levels was evaluated using the Wilcoxon test and the relationship between albumin levels and arrhythmias, using the Mann-Whitney U test. The relationship between the results was evaluated by Pearson's correlation analysis, and the interaction of the results with correlations was evaluated by regression analysis. Any p value less than 0.05 was considered statistically significant.

Results

The mean age of the patients included in the study was 63.07 years (11.24) (range, 42-89) and 42 were male and 14 were female. Demographic, preoperative, and intraoperative data of the patients are given in Table 1.

Table 1: Demographic and operation data of patients

Parameter	Value
	n=56
Gender n (%)	
Male	42 (75)
Female	14 (25)
Age (mean (SD) (min-max))	63.07 (11.24) (42-89)
Hypertension n (%)	19 (33.92)
Chronic renal failure n (%)	2(3.57)
Diabetes mellitus n (%)	10(17.85)
Chronic obstructive lung disease n (%)	5(8.92)
Cerebrovascular disease n (%)	1(1.78)
CABG n (%)	51 (91.07)
AVR n (%)	2 (3.57)
CABG+ AVR n (%)	1(1.78)
MVR n (%)	1 (1.78)
ASD repair n (%)	1 (1.78)
Ejection Fractions (EF) n (%)	
%30-40	8 (14.28)
%41-50	27 (48.21)
>%51	21 (37.5)
EuroSCORE (mean (SD) (min-max))	2.04 (2.02) (0.65-10.69)
CPB Time (mean (SD) (min-max)) (minute)	112.28 (32.09) (44-193)
Cross-Clamp Time (mean (SD) (min-max)) (minute)	62.07 (23.69) (18-126)

CABG: coronary artery bypass graft, AVR: aortic valve replacement, MVR: mitral valve replacement, ASD: atrial septal defect, SD: standard deviation

A comparison of the means of albumin, lactate, and hemoglobin levels in the preoperative and postoperative period showed that albumin and hemoglobin levels decreased significantly while lactate levels significantly increased (P<0.001, P<0.001, P=0.004, respectively) (Table 2). The means of the preoperative and postoperative albumin, lactate,

and hemoglobin levels of the patients are given in Table 2. Postoperative arrhythmia rates are presented in Table 3.

Table 2. The mean of preoperative and postoperative albumin, hemoglobin, and lactate levels of patients

	Preoperative Mean (SD) (min-max)	Postoperative Mean (SD) (min-max)	Z	*P*-value
Albumin (g/dL)	4.04 (0.51) (2.79-5.26)	3.21 (0.45) (2.02-4.24)	-6.249	<0.001
Hemoglobin (gr/dL)	13.81 (2.07) (8.34-18.80)	10.30 (1.43) (7.10-13.50)	-6.469	<0.001
Lactate (u/Lt.)	2.15 (2.68) (0.40-19.0)	3.55 (3.83) (0.60-21.0)	-2.904	0.004

Table 3: Postoperative arrhythmia results

Postoperative Electrocardiographic Rhythm Status	n (%)
Normal Sinus Rhythm (NSR)	26 (46.42)
Total Arrhythmia	30 (53.57)
Sinus Tachycardia (ST)	27 (48.21)
Atrial Fibrillation (AF)	2 (3.57)
Ventricular Fibrillation (VF)	1 (1.78)

In the comparisons made to evaluate whether there is a relationship between preoperative and postoperative albumin, lactate, and hemoglobin levels and postoperative arrhythmias, a significant association was found between postoperative albumin levels and postoperative arrhythmias (P=0.016) (Table 4). In the comparisons made to evaluate whether there is a relationship between preoperative and postoperative albumin, lactate and hemoglobin levels and postoperative sinus tachycardia formation, a significant association was found between preoperative and postoperative albumin levels and postoperative sinus tachycardia development (P=0.032 and P=0.010, respectively) (Table 5).

Table 4: The relationship of preoperative and postoperative albumin lactate and hemoglobin levels with postoperative arrhythmia formation

	Preoperative Albumin(g/dL) Mean (SD) (min-max)	Postoperative Albumin(g/dL) Mean (SD) (min-max)	*P*-value (Wilcoxon)
Postoperative Arrhythmia + (n=30)	3.93 (0.57) (2.79-4.77)	3.07 (0.49) (2.02-3.90)	<0.001
P-value	0.230	0.016	
	Preoperative Hemoglobin(gr/dL) Mean (SD) (min-max)	Postoperative Hemoglobin(gr/dL) Mean (SD) (min-max)	*P*-value (Wilcoxon)
Postoperative Arrhythmia + (n=30)	13.76 (2.32) (9.20-18.80)	10.09 (1.41) (7.80-13.40)	<0.001
P-value	0.895	0.200	
	Preoperative Lactate(u/Lt.) Mean (SD) (min-max)	Postoperative Lactate(u/Lt.) Mean (SD) (min-max)	*P*-value (Wilcoxon)
Postoperative Arrhythmia + (n=30)	2.62 (3.50) (0.40-19.00)	4.60 (4.92) (0.70-21.00)	0.050
P-value	0.411	0.143	

Table 5: Relationship between preoperative and postoperative albumin lactate and hemoglobin levels and postoperative sinus tachycardia

	Preoperative Albumin(g/dL) Mean (SD) (min-max)	Postoperative Albumin(g/dL) Mean (SD) (min-max)	*P*-value (Wilcoxon)
Postoperative sinus Tachycardia + (n=27)	3.87 (0.56) (2.79-4.77)	3.04 (0.49) (2.02-3.90)	<0.001
P-value	0.032	0.010	
	Preoperative Hemoglobin(gr/dL) Mean (SD) (min-max)	Postoperative Hemoglobin(gr/dL) Mean (SD) (min-max)	*P*-value (Wilcoxon)
Postoperative sinus Tachycardia + (n=27)	13.61 (2.40) (9.20-18.80)	10.06 (1.46) (7.80-13.40)	<0.001
P-value	0.501	0.184	
	Preoperative Lactate(u/Lt.) Mean (SD) (min-max)	Postoperative Lactate(u/Lt.) Mean (SD) (min-max)	*P*-value (Wilcoxon)
Postoperative sinus Tachycardia + (n=27)	2.77 (3.66) (0.40-19.00)	4.04 (3.95) (0.70-17.00)	0.118
P-value	0.275	0.317	

An inverse correlation was found between preoperative albumin levels and postoperative sinus tachycardia status (P=0.011), and between postoperative albumin levels and postoperative arrhythmia status (P=0.011), postoperative sinus tachycardia status (P=0.004), postoperative lactate levels (P=0.009), and cross clamp time (P=0.035). An inverse correlation was found between postoperative lactate levels and postoperative arrhythmia status (P=0.028). Regression analysis revealed an interaction between postoperative albumin levels and preoperative albumin levels (P<0.001), postoperative arrhythmia status (P=0.005), postoperative sinus tachycardia status (P=0.002), postoperative lactate levels (P=0.005), and cross clamp time (P=0.018).

Discussion

In our study, a significant relationship was found between decreased postoperative albumin levels and postoperative sinus tachycardia/arrhythmias status, and between preoperative albumin levels and postoperative sinus tachycardia status. Postoperative decreased albumin levels were significantly related with postoperative increased lactate levels and cross-clamping time.

In addition to its positive effects for open heart surgery, CPB also has negative effects, cardiac arrest being the leading one. Cardiac arrest has a direct relationship with I-R damage in myocardium [17]. Another negative effect of CPB is the decrease in albumin levels as in other biochemical parameters due to the hemodilution required during CPB [4]. In our study, postoperative albumin levels decreased significantly with the increase of cross-clamping time and postoperative lactate levels.

A study examining the I-R damage reported the effects of antioxidant systems on myocardial protection and their importance in inhibiting harmful cardiac changes during the damage caused by I-R in myocardium [18]. In another study, oxidative stress increase due to the increase in oxidants and the decrease in antioxidants after ischemia was shown as the main cause of I-R-related damage [15]. Albumin is known as an important antioxidant [11] and low albumin levels have been linked to increased oxidative stress [19]. It was reported that low albumin levels may be an independent predictor of heart failure and poor prognosis in patients with ischemic heart disease [20]. van Beeket al. [4] reported that albumin levels had effects on the contraction of the heart, and low albumin levels in the postoperative period were associated with an increase in myocardial damage. It was reported that low albumin levels caused the formation of myocardial edema, thereby contributing to worsening of heart diseases, and was associated with an increased incidence of atrial fibrillation [11]. On the other hand, albumin has N-terminal regions detoxifying oxidant substances, but the structure of albumin changed in the case of ischemia and thus the oxidant agent binding capacity of albumin reduced [13]. In addition, albumin provides a cardioprotective effect in the postoperative period due to its nitric oxide-sparing effect, which can potentially reduce nitric oxide-induced vasodilation [21].

Di Filippo et al. [5] investigated whether increasing the number of antioxidants has positive effects on arrhythmias and reported that the increase in the number of antioxidant systems significantly reduced the incidence of ventricular tachycardia and ventricular fibrillation and increased the survival rate. It was also reported that low serum albumin levels were associated with

atrial fibrillation (AF) formation [22]. He et al. [23] suggested that hypoalbuminemia is an independent risk factor of paroxysmal AF. On the other hand, although serum albumin level was inversely related with AF incidence in a linear pattern in the study of Liao et al. [19], no causal role of serum albumin in AF etiology was found by two-sample Mendelian randomization.

In the light of these studies, we tried to determine the effects of preoperative and postoperative albumin levels and changes in the postoperative albumin levels on postoperative arrhythmias. The significant postoperative decrease in albumin levels, as well as the decreases in the antioxidant amounts due to I-R injury, may be explained by hemodilution [4] [15]. There was also an inverse correlation between postoperative albumin levels and postoperative lactate levels. This outcome was significant in the regression analysis.

When the albumin levels and postoperative arrhythmias were examined by correlation and regression tests, the level of preoperative albumin was not associated with postoperative arrhythmias, and there was no significant difference in the comparisons between the binary groups. However, there was an inverse relationship between preoperative albumin levels and postoperative sinus tachycardia. As the preoperative albumin levels decreased, postoperative sinus tachycardia increased. On the other hand, as the difference between preoperative and postoperative albumin levels increased, the frequency of sinus tachycardia increased.

When the relationship between postoperative arrhythmias and sinus tachycardia with postoperative albumin levels was examined, an inverse correlation was observed. In addition, this outcome was significant in regression analysis and comparisons between the binary groups. These analyses suggest that low albumin levels may cause arrhythmias in patients underwent CPB, in agreement with other studies.

Among the limitations of our study are the low number of subjects. Another limitation was that the basic mechanism of damage could not be understood since more extensive tests could not be performed due to its retrospective nature. Despite these limitations, the results of our study support the idea that low albumin levels may lead to the development of postoperative arrhythmias in patients who underwent CPB.

Conclusion

In the light of these results, it can be concluded that disturbance between oxidant and antioxidant mechanisms affects myocardial functions. Furthermore, high albumin levels may have a protective effect against postoperative sinus tachycardia/arrhythmias. To explain these effects more clearly, prospective studies can be planned by increasing the number of subjects and examining the mechanism of the relationship between arrhythmias and albumin levels extensively.

References

1. Colantonio LD, Muntner P. It Is Time for Reducing Global Cardiovascular Mortality. Circulation 2019;140(9):726-8.
2. Argacha JF, Bourdrel T, van de Borne P. Ecology of the cardiovascular system: A focus on air-related environmental factors. Trends Cardiovasc Med. 2018;28(2):112-26.
3. Lee YS, Kim WY, Yoo JW, Jung HD, Min TJ. Correlation between regional tissue perfusion saturation and lactate level during cardiopulmonary bypass. Korean J Anesthesiol. 2018;71(2):361-7.
4. van Beek DEC, van der Horst ICC, de Geus AF, Mariani MA, Scheeren TWL. Albumin, a marker for post-operative myocardial damage in cardiac surgery. J Crit Care 2018;47:55-60.
5. Di Filippo C, Cervone C, Rossi C, di Ronza C, Marfella R, Capodanno P, et al. Antiarrhythmic effect of acute oxygen-ozone administration to rats. Eur J Pharmacol. 2010;629(1-3):89-95.
6. Dhalla NS, Elmoselhi AB, Hata T, Makino N. Status of myocardial antioxidants in ischemia–reperfusion injury. Cardiovasc Res. 2000;47(3):446-56.
7. Tural K, Ozden O, Bilgi Z, Kubat E, Ermutlu CS, Merhan O, et al. The protective effect of betanin and copper on heart and lung in end‐organ ischemia reperfusion injury. BratislLekListy. 2020;121(3):211-7.
8. Taghizadieh M, Hajipour B, Ahmadi Asl N, Khodadadi A, Somi MH, Banei M. Combination effect of melatonin and dexamethasone on liver ischemia/reperfusion injury. BratislLekListy. 2016;116(1):47-53.
9. Ahmed LA, Salem HA, Mawsouf MN, Attia AS, Agha AM. Cardioprotective effects of ozone oxidative preconditioning in an in vivo model of ischemia/reperfusion injury in rats. Scand J Clin Lab Invest. 2012;72(5):345-54.
10. Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. Am J Physiol Heart Circ Physiol. 2011;301(6):2181-90.
11. Arques S. Human serum albumin in cardiovascular diseases. Eur J Intern Med. 2018;52:8-12.
12. Anraku M, Chuang VT, Maruyama T, Otagiri M. Redox properties of serum albumin. BiochimBiophysActa2013;1830(12):5465-72.
13. Kanko M, Yavuz S, Duman C, Hosten T, Oner E, Berki T. Ischemia-modified albumin use as a prognostic factor in coronary bypass surgery. J Cardiothorac Surg. 2012;7:3.
14. Eryılmaz R, Demir C, Aslan R, Demir H, Taken K. Can ischemia modified albumin (IMA) and total sulfhydryl level (TSH) be used as a biomarker in the diagnosis of bladder tumor? A prospective case-control study. J Surg Med. 2020;4(12):1104-7.
15. Zweier JL, Talukder MAH. The role of oxidants and free radicals in reperfusion injury. Cardiovasc Res. 2006;70(2):181-90.
16. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology 2007;18(6):805-35.
17. De Lange F, Yoshitani K, Podgoreanu MV, Grocott HP, BurkhardMackensen G. A novel survival model of cardioplegic arrest and cardiopulmonary bypass in rats: a methodology paper. J Cardiothorac Surg. 2008;3:51.
18. Napoli P Di, Taccardi AA, Caterina R De, Barsotti A. Pathophysiology of ischemia-reperfusion injury: experimental data. Ital Heart J.2002;3(4):24-8.
19. Liao LZ, Zhang SZ, Li WD, Liu Y, Li JP, Zhuang XD, et al. Serum albumin and atrial fibrillation: insights from epidemiological and mendelian randomization studies. Eur J Epidemiol. 2020;35(2):113–22.
20. Zhu L, Chen M, Lin X. Serum albumin level for prediction of all-cause mortality in acute coronary syndrome patients: A meta-analysis. Biosci Rep.2020;40(1):1-8.
21. Kingeter AJ, Raghunathan K, Munson SH, Hayashida DK, Zhang X, Iyengar S, et al. Association between albumin administration and survival in cardiac surgery: a retrospective cohort study. Can J Anesth. 2018:65(11):1218-27.
22. Arques S. Serum albumin and cardiovascular diseases: A comprehensive review of the literature. Ann Cardiol Angeiol. 2018;67(2):82-90.
23. He YM, Yang XJ, Hui J, Jiang TB, Song JP, Liu ZH, et al. Low serum albumin levels in patients with paroxysmal atrial fibrillation: what does it mean? Acta Cardiol. 2006;61(3):333-7

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):606-610.
DOI: 10.28982/josam.935556

Journal of Surgery and Medicine
e-ISSN=2602-2079

Sleep quality, perceived stress, and quality of life of healthcare professionals working in direct contact with COVID-19 (+) patients: A comparative study

Sümeyye Barut [1], Esra Sabanci Baransel [2], Tuba Uçar [2]

[1] Department of Midwifery, Faculty of Health Sciences, Fırat University, Elazığ, Turkey
[2] Department of Midwifery, Faculty of Health Sciences, İnönü University, Malatya, Turkey

ORCID ID of the author(s)
SB: 0000-0002-1222-9692
ESB: 0000-0001-6348-2084
TU: 0000-0002-4450-6826

Corresponding Author
Esra Sabancı Baransel
İnönü University Central Campus (Elazig Road 15.km) PC: 44280 Bulgurlu Battalgazi / Malatya, Turkey
E-mail: esraa.sabancii@gmail.com.tr

Ethics Committee Approval
Scientific Research and Editorial Ethics Board of Health Sciences of Inönü University, 22/12/2020, 2020/1428.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Previous Presentation
This research was given as an oral presentation at the 4th International Conference on COVID-19 Studies, April 17-19, 2019, İstanbul, Turkey

Published
2021 May 15

Abstract

Background/Aim: Healthcare workers can be psychologically and physically affected by the COVID-19 pandemic. This study was conducted to evaluate the sleep quality, perceived stress, and quality of life of healthcare professionals during the COVID-19 pandemic.
Methods: This cross-sectional and comparative study was conducted with employees of a city hospital in Turkey between 01-20 January 2021. Personal Information Form, Jenkins Sleep Scale, Perceived Stress Scale, and Quality of Life Test Short Form-36 (SF-36) were used to collect data during face-to-face interviews conducted with the hospital staff by the researchers. The sample of the study consisted of a healthcare team providing service for COVID-19 patients in the city hospital (Group 1) and a healthcare team working without direct contact with COVID-19 patients (Group 2). The results obtained from the study were compared between these two groups. There were 213 volunteers in Group 1, and 163 volunteer healthcare workers (doctors, nurses, midwives, medical secretaries, patient transfer staff, and patient support staff) in Group 2.
Results: Sleep problems and stress levels were significantly higher among healthcare professionals who had direct contact with COVID-19 (+) patients compared to those who did not ($P<0.05$). Healthcare professionals in Group 1 had lower levels of emotional wellbeing, vitality (energy), mental health, and social function, which are subscales of the SF-36 scale, while the pain and general perception of health subscale scores were higher compared to Group 2 ($P<0.05$). Logistic regression analysis showed that stress (OR: 1.045) and pain (OR: 1.018) were increased in those working in direct contact with COVID-19 (+) patients.
Conclusion: This study showed that healthcare workers who had contact with COVID-19 (+) patients had more sleep problems, their perceived stress levels were higher, and their quality of life was lower.

Keywords: COVID-19, Sleep quality, Perceived stress, Quality of life

How to cite: Barut S, Baransel ES, Uçar T. Sleep quality, perceived stress, and quality of life of healthcare professionals working in direct contact with COVID-19 (+) patients: A comparative study. J Surg Med. 2021;5(6):606-610.

Introduction

The COVID-19 pandemic, reported in December 2019 from Wuhan, China, has affected the world [1, 2]. In this pandemic, which is associated with the respiratory tract, hospitals and other health institutions carry the highest risk of infection [3, 4].

Special services related to the pandemic are carried out along with routine healthcare services. The personnel working in the healthcare sector have essential and decisive roles in the fight against the pandemic. In the execution of these services, healthcare workers who provide radiation, track contact, make a diagnosis, and decide on treatment and post-treatment process are in the front line, while support personnel and public employees are at the back, also fighting for the same cause. Publications from China during the early outbreak reported that 29% of those who got sick were healthcare workers [5]. In an article published in the USA, it was reported that 68.6% of the healthcare workers who got sick were working during the contagious phases of their disease and 47.9% had contact with a patient or a colleague with COVID-19 [6]. Another article reported that 52% of 2457 healthcare workers contracting COVID-19 were nurses and 33% were doctors [7]. According to data released in September, health workers constitute 10.9% of cases in Turkey [8]. In different countries, healthcare workers suffering from COVID-19 constitute 3.46-33.6% of all cases [5-10].

COVID-19 pandemic affects individuals psychologically, and according to the level of exposure and conditions, the graveness of psychological response can increase [9, 10]. The emotional, cognitive, behavioral, physical, or social responses to the pandemic depend on the situation and perceived stress of the person [9-12]. Along with an increasing and unpredictable pace of work among the healthcare workers during this period, there are also factors such as a high risk of infection and contamination, overworking, providing care to terminal or seriously ill patients, experiencing relationship and task sharing problems in the workplace, disturbance of sleep, night shifts and dealing with relatives and economic problems, all of which can lead to stress, tension and a feeling of burnout [13, 14]. The feeling of burnout in business and professional life causes psychological problems, such as increased depressive complaints, impaired quality of life [15-18], fatigue, sleep disturbances, irritability, job dissatisfaction, and inhibition of professionalism. These psychological problems not only affect health workers' attention, understanding, and decision-making ability but also hinder the fight against COVID-19. Additionally, they may result in a lasting effect on the healthcare workers' health [19].

For effective pandemic management and the continuation of healthcare services after the epidemic, there is a need to protect and empower those working in the field of health, as well as risk identification. It is especially important to protect the mental health of healthcare professionals who care for COVID-19 positive patients so that mental disorders can be prevented before they occur [20]. During the pandemic, many studies have been conducted on the physical and mental health of healthcare workers, but no study investigated how the working status affects the sleep quality, perceived stress, and quality of life of healthcare personnel in direct contact with COVID-19 positive patients. In line with this information, we aimed to determine the effect of working in direct contact with patients during the COVID-19 pandemic on sleep quality, perceived stress, and quality of life of healthcare professionals. This study was designed to answer the following research questions:

1. During the COVID-19 outbreak, is there a difference in sleep quality, perceived stress, or quality of life between groups working and not working in direct contact with patients?

2. How effective is working in direct contact with patients during the COVID-19 pandemic on sleep quality, perceived stress, and quality of life?

Materials and methods

Study design and sample

This cross-sectional study was conducted between January 1 and January 20, 2021, with employees of a city hospital in the east of Turkey. The sample of the study consisted of a healthcare team providing service for COVID-19 patients in the city hospital and a healthcare team working in units without direct contact with COVID-19 patients. The effect of providing service for COVID-19 patients with a definitive diagnosis was compared between the two groups of healthcare teams. Group 1 consisted of the healthcare team that provided care to hospitalized COVID-19 patients diagnosed by infectious diseases and chest disease specialists with serological and imaging methods. Group 2 consisted of a medical team working in units such as operating rooms, and polyclinics without direct contact with COVID-19 patients.

At the time of the study, 16 COVID services and 6 COVID intensive care services were active in the hospital. No sampling method was used, and all healthcare staff working in COVID-19 units and all employees who agreed to participate in the study were included. The comparison group was selected among the employees in other units with similar sociodemographic characteristics. Participants included doctors, nurses, midwives, medical secretaries, patient transfer, and patient support staff. OpenEpi version 3 statistics software, which is open for general use, was used to calculate the sample size (http://www.openepi.com). In the power analysis, the sample size was calculated as 374 with a 5% margin of error, 95% confidence interval, 0.80 power of representation, and two-way significance level. After the groups were formed, a total of 376 volunteers (213 primary and 163 secondary group employees) were included in the study following the obtaining of informed consent forms.

The research data were collected by the researcher using face-to-face interviews with hospital staff (doctor, midwife, nurse, and other healthcare personnel) in the hospital. The researchers told the participants that the data obtained would be used for scientific purposes, without using their names, and that they could leave the study at any time. The research was evaluated and approved by the Scientific Research and Editorial Ethics Board of Health Sciences of Inönü University (Decision no: 2020/1428). In addition, a COVID-19 Scientific research permit was obtained from the Ministry of Health of the Republic of Turkey (Form code: 2020-12-18T03_35_12).

Data collection tools

Personal Information Form, Jenkins Sleep Scale (JSEQ), Perceived Stress Scale (PSS), and Quality of Life Test Short Form-36 (SF-36) were used to collect data.

Personal Information Form

This form was prepared by researchers through a literature review to determine various characteristics of healthcare professionals. It includes the socio-demographic (age, gender, marital status, presence of children, education level, etc.) and professional characteristics (profession, working years, etc.) of the healthcare professionals.

Jenkins Sleep Scale (JSEQ)

The Turkish validity and reliability of the scale, developed by Jenkins to evaluate sleep problems, was conducted by Duruöz [21, 22]. This six-point Likert-type scale consists of four items assessing sleep problems within the last four weeks. Higher scores indicate increased sleep disturbance. The reliability of the scale (Cronbach's alpha) is 0.86 [22]. This value was 0.85 in our study.

Perceived Stress Scale (PSS)

Developed by Cohen et al. in 1983, this scale measures the stress perceptions regarding various events that occur in the life of the individual. The Turkish validity and reliability of the scale were conducted by Eskin et al. [23, 24]. It is a five-point Likert type consisting of 14 questions. It is rated from "never (0)" to "very often (4)". Reverse scoring is used for seven items with positively worded questions (4, 5, 6, 7, 9, 10, 13). The higher the scores obtained from the scale, the higher the perception of stress. Cronbach's alpha reliability coefficient of the scale is 0.84 [24]. In our study, the Cronbach's alpha reliability coefficient of the scale was 0.67.

Quality of Life Test Short Form-36 (SF-36)

The scale was developed by Rand (1983) to measure the quality of life of the individual. The Turkish validity and reliability of the scale were conducted by Koçyiğit et al. (1999) [25, 26]. The scale consists of 36 items and 8 subscales: Physical function (10 items), social function (2 items), physical role (4 items), emotional roles (3 items), mental health (5 items), vitality (energy) (4 items), pain (2 items) and general health (5 items). Each subscale is scored between 0 and 100, and the higher the score, the higher the quality of life. Zero points indicate poor quality of life while 100 points indicate good quality of life. In the Turkish validity and reliability study, Cronbach's alpha values of its subscales vary between 0.73-0.76 [25, 26]. In this study, the Cronbach's alpha reliability coefficient of the scale ranged between 0.67-0.84.

Statistical analysis

The data were analyzed with the Statistical Package for the Social Sciences version 25.0 for Windows software (SPSS, Chicago, IL, USA). When reporting the results, healthcare professionals were divided into two groups: Group 1 consisted of workers in direct contact with COVID-19-positive patients while Group 2 had no direct contact. The Chi-square test was used to compare the difference between the groups, and the t-test was used to compare the mean scores of the variables meeting the parametric test conditions. Binary Logistic Regression analysis was used to identify the optimal set of predictors in terms of sleep problems, stress, and quality of life of healthcare professionals who had direct contact with COVID-19 (+) patients. Significant variables in univariate analysis (P<0.05) were added to the regression model. For this purpose, both the existence of direct contact with COVID-19 patients, which was the dependent variable, and the scale scores (JSEQ, PSS, subscales of SF-36: Emotional roles, Mental health, Vitality, Pain and General health), constituting the independent variables, were added to the model. A P-value <0.05 was considered statistically significant.

Results

A comparison of sociodemographic characteristics between the groups is presented in Table 1. Females, singles, those with children, doctors, and those with a history of COVID-19 positivity had higher rates of contact with COVID-19 positive patients (P<0.05). Also, those working in contact with COVID-19 positive patients were younger and had worked for fewer years (P<0.05) (Table 1).

Table 1: Comparison of sociodemographic characteristics between the groups (n = 376)

Variables	Direct contact with COVID-19 (+) patients (n=213)		No direct contact with COVID-19 (+) patients (n=163)		Total (n=376)		Test and P-value
Age (y), Mean (SD)	35.02(7.54)		38.73(8.77)		36.63(8.29)		t=4.306 P<0.001
Years in profession Mean (SD)	12.01(7.83)		14.82(8.98)		13.24(8.46)		t=-3.194 P=0.002
	n	%	n	%	n	%	
Gender							
Female	157	60.9	101	39.1	258	68.6	χ^2=5.916
Male	56	47.5	62	52.5	118	31.4	P=0.015
Educational level							
High school	25	53.2	22	46.8	47	12.5	χ^2=0.261
University and upper	188	57.1	141	42.9	329	87.5	P=0.609
Marital status							
Married	129	49.8	130	50.2	259	68.9	χ^2=15.866
Single	84	71.8	33	28.2	117	31.1	P<0.001
Presence of children							
Yes	80	65.6	42	34.4	254	67.6	χ^2=5.858
No	133	52.4	121	47.6	122	32.4	P=0.016
Profession							
Doctor	30	76.9	9	23.1	39	10.7	χ^2=30.858
Midwife	32	55.2	26	44.8	58	15.9	P<0.001
Nurse	113	67.3	55	32.7	168	46.2	
Other healthcare professionals	36	36.4	63	63.6	99	27.2	
History of COVID-19 (+)	82	70.1	35	29.9	117	31.1	χ^2=12.487
Yes	131	50.6	128	49.4	259	68.9	P<0.001
No							

Comparison of the inter-group JSEQ, PSS, and SF-36 scale averages are presented in Table 2. The mean JSEQ and PSS scores were significantly higher among workers in direct contact with COVID-19 positive patients (P<0.05). This finding suggests that Group 1 has more sleep problems compared to Group 2, and their stress levels are higher. Among those who work in direct contact with COVID-19 positive patients, while the emotional wellbeing, vitality (energy), mental health levels were lower, the mean scores of the sub-dimensions of pain and general health perception were higher (P<0.05). SF-36 physical function, physical role, and social function sub-dimensions mean scores were insignificantly higher in Group 1 (P>0.05) (Table 2). Logistic regression analysis showed increased stress (OR: 1.045) and pain (OR: 1.018) among employees who had direct contact with COVID-19 positive patients (Table 3).

Table 2: Comparison of JSEQ, PSS and SF-36 scales mean scores between the groups (n=376)

Variables	Direct contact with COVID-19 (+) patients (n=213)	No direct contact with COVID-19 (+) patients (n=163)	Test[a]	*P*-value
JSEQ	13.76(5.04)	12.36(5.49)	2.563	0.001
PSS	31.11(5.88)	29.78(6.04)	2.141	0.033
SF-36				
Physical Function	65.09(24.45)	68.58(22.54)	-1.420	1.156
Physical Role	27.58(33.01)	32.82(34.75)	-1.491	0.137
Emotional Role	30.82(29.21)	37.64(32.09)	-2.120	0.035
Vitality (energy)	54.95(11.02)	57.63(3.42)	-2.378	0.018
Mental Health	45.24(13.83)	49.30(12.97)	-2.891	0.004
Social Function	46.95(24.40)	50.83(23.55)	-1.549	0.122
Pain	56.20(26.30)	50.39(28.12)	2.060	0.040
General Health	40.57(14.66)	44.67(14.22)	-2.726	0.007

JSEQ: Jenkins Sleep Scale, PSS: Perceived Stress Scale, [a] Independent samples t-test

Table 3: Binary Logistic Regression analysis for predictors of sleep problems, stress, and quality of life among healthcare professionals in direct contact with COVID-19 (+) patients

Predictors	B	*P*-value	OR	95% CI	
				Lower	Upper
JSEQ	0.043	0.068	1.044	0.997	1.094
PSS	0.044	0.023	1.045	1.006	1.085
Emotional Role	-0.004	0.264	0.996	0.989	1.003
Vitality(energy)	-0.020	0.066	0.981	0.960	1.001
Mental Health	-0.021	0.050	0.979	0.961	0.998
Pain	0.017	<0.001	1.018	1.008	1.027
General Health	-0.014	0.110	0.986	0.970	1.003

JSEQ: Jenkins Sleep Scale, PSS: Perceived Stress Scale, B: Regression Coefficient; OR: Odds Ratio; CI: Confidence Interval. Dependent variable in the model: whether direct contact with COVID-19 patients. Independent variables in the model: JSEQ, PSS, subscales of SF-36: Emotional roles, Mental health, Vitality, Pain and General health

Discussion

The COVID-19 disease, declared as a pandemic as of March 2020, has vitally affected people physically and psychologically. Medical personnel are at the top of the occupational groups affected by the pandemic. Our study aims to determine the quality of sleep, perceived stress levels, and quality of life of health professionals who have direct contact with patients diagnosed with COVID-19.

COVID-19 has infected millions of people around the world and continues to be transmitted. This disease causes not only physical damage to humans but also negatively affects the quality of sleep, hindering their psychological health [8-27]. In this study, it was found that health workers in direct contact with COVID-19 positive patients had more sleep problems. In a meta-analysis, the quality of sleep of medical personnel in contact with COVID-19 patients was 2.57 times worse than medical personnel without contact. In another study, 67.2% of those who provided care for COVID-19 positive patients and 47.7% of those who did not had poor sleep quality [27]. Wang et al. found that 38.0% of health workers had poor sleep quality and 7.0% were anxious [28]. The results of the previously conducted studies resemble our results.

In pandemics, the workload of health care systems and the stress of healthcare professionals increase markedly [29]. In our study, the stress levels of healthcare workers in direct contact with COVID-19 positive were higher, and the perceived stress was 1.045 times more compared to those working without direct contact with COVID-19 positive patients. In a study conducted with healthcare professionals, 18.9% of the personnel had elevated stress symptoms. In another study examining the workload of 180 nurses working in the clinic during the pandemic, participants reported high levels of stress [30]. Another study reported that anxiety and depression scores were significantly higher among health workers providing care for patients with COVID-19 with 3 hours of contact and over [31]. In line with these results, it can be said that COVID clinics have more stressful working conditions than other units.

We found that healthcare workers who have direct contact with COVID-19 positive patients have poorer emotional wellbeing, energy-vitality, and mental health statuses, and higher levels of pain and general health perception. In a study by Stojanov et al. conducted on 201 healthcare professionals, the effects of working with COVID-19 positive patients on the quality of life, symptoms of depression, and anxiety levels were examined. Working with COVID-19 positive patients caused elevated levels of anxiety and depression among healthcare workers, and their quality of sleep and life were negatively affected. In the same study, it was stated that healthcare workers working with COVID-19 positive patients were afraid of infecting their family members; therefore, their general health and social function levels were lower, and they had lower emotional and mental scores. This above-mentioned study with 201 healthcare workers supports our findings [32]. In our study, there was no significant difference between physical function, physical role, and social functionality sub-dimension scores between groups. This may be due to different characteristics such as COVID-19 transmission status and contact time.

In our study, females, bachelors, those with children, doctors, and those with a positive history of COVID-19 had higher rates of working in contact with COVID-19 positive patients, and those in contact with COVID-19 positive patients were younger and had worked for fewer years. In their study on 2457 health workers in Wuhan, China, Zheng et al. determined that 72% of the employees were females, and 33.6% were doctors. In the same study, 64.8% of the married workers had children. These results are similar to our findings [33].

Limitations

This study had some limitations. First, this is a cross-sectional study, which makes it difficult to determine the exposure and outcome relationships between the variables examined and the results. Also, prior knowledge of the situation may affect the determination of exposure or outcome, leading to recall bias. Non-response is a specific problem affecting cross-sectional studies and may cause bias in outcome measures. This is a particular problem when the characteristics of the non-responders differ from those of the respondents. Because the pandemic is ongoing, a control group could not be formed, and the sleep quality, perceived stress level, and quality of life of the healthcare personnel were not evaluated outside the pandemic conditions. Lastly, the results cannot be generalized since the study was completed in a single center. In later studies, a broader sample group may be covered for more accurate results.

Conclusion

Our study revealed an important aspect of the psychology of healthcare professionals during the COVID-19 pandemic. These psychological problems not only affect health workers' attention, understanding, and decision-making ability but also hinder the fight against COVID-19. It was determined that hospital employees who had contact with COVID-19 had more sleep problems, their perceived stress was higher, and their quality of life was lower. Since this threatens the current and future lives of healthcare workers, better personalized care and support should be provided to healthcare workers during and after the pandemic.

In summary, the pandemic has led to psychological problems among healthcare workers. For this reason, support programs for healthcare workers, including psychotherapy options, need to be implemented quickly.

Acknowledgments

We would like to thank the participants who volunteered to take part in this study.

References

1. World Health Organization. World Health Organization coronavirus disease (COVID-19) dashboard. 2020.
2. Bhaumik S, Moola S, Tyagi J, Nambiar D, Kakoti M. Community health workers for pandemic response: a rapid evidence synthesis. BMJ Glob Health. 2020;5(6):e002769. doi: 10.1136/bmjgh-2020-002769.
3. Styra R, Hawryluck L, Robinson S, Kasapinovic S, Fones C, Gold WL. Impact on health care workers employed in high-risk areas during the Toronto SARS outbreak. J Psychosom Res. 2008;64(2):177-83. doi: 10.1016/j.jpsychores.2007.07.015.
4. Fessell D, Cherniss C. Coronavirus Disease 2019 (COVID-19) and Beyond: Micropractices for Burnout Prevention and Emotional Wellness. J Am Coll Radiol. 2020;17(6):746-8. doi: 10.1016/j.jacr.2020.03.013. Epub 2020 Mar 24. PMID: 32208139; PMCID: PMC7146659.
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. doi: 10.1001/jama.2020.1585.
6. Hartmann S, Rubin Z, Sato H, OYong K, Terashita D, Balter S. Coronavirus 2019 (COVID-19) Infections Among Healthcare Workers, Los Angeles County, February - May 2020. Clin Infect Dis. 2020;17:ciaa1200. doi: 10.1093/cid/ciaa1200.
7. Zheng L, Wang X, Zhou C, Liu Q, Li S, Sun Q, et al. Analysis of the Infection Status of Healthcare Workers in Wuhan During the COVID-19 Outbreak: A Cross-sectional Study. Clin Infect Dis. 2020;71(16):2109-13. doi: 10.1093/cid/ciaa588.
8. Pala SÇ, Metintas S. COVID-19 pandemisinde sağlık çalışanları. ESTÜDAM Halk Sağlığı Dergisi. 2020;5:175-87. doi: 10.35232/estudamhsd.789806
9. Tönbül Ö. Koronavirüs (Covid-19) salgını sonrası 20-60 yaş arası bireylerin psikolojik dayanıklılıklarının bazı değişkenler açısından incelenmesi. Humanistic Perspective. 2020;2:159-74.
10. Birinci M, Bulut T. Covıd-19'un sosyo-ekonomik yönden dezavantajlı gruplar üzerindeki etkileri: sosyal hizmet bakış açısından bir değerlendirme. Sosyal Çalışma Dergisi. 2020;4:62-8.
11. Göksu Ö, Kumcağız H. Covid-19 salgınında bireylerde algılanan stres düzeyi ve kaygı düzeyleri. Electronic Turkish Studies. 2020;15.
12. Kırlı U, Binbay T, Elbi H, Alptekin K. COVID-19 pandemisi ve psikotik belirtiler. Klinik Psikiyatri Dergisi. 2020;23. doi: 10.5505/kpd.2020.27122
13. Kaçmaz N. Tükenmişlik sendromu. İst Tıp Fak Derg. 2005;68:29-32.
14. French SE, Lenton R, Walters V, Eyles J. An empirical evaluation of an expanded Nursing Stress Scale. J Nurs Meas. 2000;8(2):161-78.
15. Maslach C, Schaufeli WB, Leiter MP. Job burnout. Annu Rev Psychol. 2001;52:397-422. doi: 10.1146/annurev.psych.52.1.397.
16. Collins S, Long A. Working with the psychological effects of trauma: consequences for mental health-care workers--a literature review. J Psychiatr Ment Health Nurs. 2003;10(4):417-24. doi: 10.1046/j.1365-2850.2003.00620.x.
17. Sabin-Farrell R, Turpin G. Vicarious traumatization: implications for the mental health of health workers? Clin Psychol Rev. 2003;23(3):449-80. doi:10.1016/s0272-7358(03)00030-8.
18. Cullen A. Burnout. Why do we blame the nurse? Am J Nurs. 1995;95(11):23-8.
19. Kang L, Li Y, Hu S, Chen M, Yang C, Yang BX, et al. The mental health of medical workers in Wuhan, China dealing with the 2019 novel coronavirus. Lancet Psychiatry. 2020;7(3):e14. doi: 10.1016/S2215-0366(20)30047-X.
20. Asmundson GJG, Taylor S. Coronaphobia: Fear and the 2019-nCoV outbreak. J Anxiety Disord. 2020;70:102196. doi: 10.1016/j.janxdis.2020.102196.
21. Jenkins CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol. 1988;41(4):313-21. doi: 10.1016/0895-4356(88)90138-2.
22. Duruöz MT, Erdem D, Gencer K, Ulutatar F, Baklacıoğlu HŞ. Validity and reliability of the Turkish version of the Jenkins Sleep Scale in psoriatic arthritis. Rheumatol Int. 2018;38(2):261-5. doi: 10.1007/s00296-017-3911-2.
23. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96.
24. Eskin M, Harlak H, Demirkıran F, et al. Algılanan stres ölçeğinin Türkçeye uyarlanması: güvenirlik ve geçerlik analizi. In New/Yeni Symposium Journal. 2013;51:132-40.
25. Stewart AL, Hays RD, Ware JE Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care. 1988;26(7):724-35. doi: 10.1097/00005650-198807000-00007.
26. Koçyiğit H, Aydemir Ö, Ölmez N, et al. SF-36'nın Türkçe için güvenilirliği ve geçerliliği. İlaç ve Tedavi Dergisi. 1999;12:102-6.
27. Qi J, Xu J, Li BZ, Huang JS, Yang Y, Zhang ZT, et al. The evaluation of sleep disturbances for Chinese frontline medical workers under the outbreak of COVID-19. Sleep Med. 2020;72:1-4. doi: 10.1016/j.sleep.2020.05.023.
28. Wang S, Xie L, Xu Y, Yu S, Yao B, Xiang D. Sleep disturbances among medical workers during the outbreak of COVID-2019. Occup Med (Lond). 2020;70(5):364-9. doi: 10.1093/occmed/kqaa074.
29. Enli Tuncay F, Koyuncu E, Özel Ş. Pandemilerde sağlık çalışanlarının psikososyal sağlığını etkileyen koruyucu ve risk faktörlerine ilişkin bir derleme. Ankara Medical Journal. 2020;20:488-504. doi: 10.5505/amj.2020.02418.
30. Mo Y, Deng L, Zhang L, Lang Q, Pang H, Liao C, et al. Anxiety of Nurses to support Wuhan in fighting against COVID-19 Epidemic and its Correlation With Work Stress and Self-efficacy. J Clin Nurs. 2021;30(3-4):397-405. doi: 10.1111/jocn.15549.
31. Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. Psychiatry Res. 2020;288:112954. doi: 10.1016/j.psychres.2020.112954.
32. Stojanov J, Malobabic M, Stanojevic G, Stevic M, Milosevic V, Stojanov A. Quality of sleep and health-related quality of life among health care professionals treating patients with coronavirus disease-19. Int J Soc Psychiatry. 2020;16:20764020942800. doi: 10.1177/0020764020942800.
33. Zhang R, Hou T, Kong X, Wang G, Wang H, Xu S, et al. Effects of region, epidemic stage, and demographic characteristics on sleep quality and mental disturbances among health care workers during COVID-19 outbreak. Europe PMC. 2020. doi: 10.21203/rs.3.rs-23260/v1.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):611-614.
DOI: 10.28982/josam.941178

Journal of Surgery and Medicine
e-ISSN=2602-2079

The association of vitamin D with semen quality and fertility hormones in idiopathic recurrent pregnancy loss without the female factor

Banuhan Şahin [1], Erkan Alataş [2]

[1] Amasya University, Sabuncuoğlu Şerefeddin Training and Research Hospital, Department of Obstetrics and Gynecology, Amasya, Turkey
[2] University of Pamukkale, Faculty of Medicine, Department of Obstetrics and Gynecology, Denizli, Turkey

ORCID ID of the author(s)
BŞ: 0000-0002-8711-1584
EA: 0000-0001-6423-5106

Corresponding Author
Banuhan Şahin
Amasya University, Sabuncuoğlu Şerefeddin Training and Research Hospital, Department of Obstetrics and Gynecology, 05000, Amasya, Turkey
E-mail: banuhansahin@gmail.com

Ethics Committee Approval
Ethics Committee of Pamukkale University, 13/02/2014-No: 014-11.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 June 20

Abstract

Background/Aim: There is a lack of data about male contribution to idiopathic recurrent pregnancy loss (IRPL). The study aimed to investigate the factors associated with males, including Vitamin D, semen parameters, fertility hormones, and some demographical features in IRPL.
Methods: In this cross-sectional study, the data of 41 men whose partners were diagnosed with recurrent pregnancy loss between February 2014 to February 2015 were collected. Female partners were examined fully, including thrombophilia factors, and no cause was detected. The karyotypes of both partners were normal. Men's 25-hydroxy-vitamin D (25-OH-VD) levels, semen parameters (ejaculate volume, total sperm count per ejaculate, sperm concentration, sperm progressive motility, and sperm morphology), and fertility hormones (follicle-stimulating hormone, luteinizing hormone, total testosterone, estradiol, and prolactin) were assessed.
Results: Mean 25-OH-VD was lower (18.4 (9.6) ng/ml) than the normal range. We found that testosterone was significantly lower in the group with 25-OH-VD ≤19 ng/dl when compared to the group with 25-OH-VD ≥20 ng/ml. There is a positive correlation between 25-OH-VD and testosterone levels. Although it was not statistically significant, there was a tendency for decreased sperm morphology.
Conclusion: Serum testosterone levels of men whose partners were diagnosed with IRPL decreased with lower 25-OH-VD levels. In addition to standard female factors, male factors should also be taken into consideration when evaluating the risk of IRPL.

Keywords: Idiopathic recurrent pregnancy loss, Male factors, Vitamin D, Testosterone, Spermiogram

How to cite: Şahin B, Alataş E. The association of vitamin D with semen quality and fertility hormones in idiopathic recurrent pregnancy loss without the female factor. J Surg Med. 2021;5(6):611-614.

Introduction

Recurrent pregnancy loss (RPL) is defined as a female patient having two or more clinical pregnancy losses (miscarriages) before 20 weeks of gestation and affects 1–5% of reproductive-age women. Yet, clinicians recommend medical evaluation after just two miscarriages [1], which mainly focuses on female partners. Many factors may be involved in RPL, such as genetic, endocrinological, and anatomical abnormalities, autoimmune disorders, and infectious and systemic maternal diseases [2, 3]. Despite the extensive and expensive investigation of female partners, greater than 50% of cases are unexplained and defined as idiopathic recurrent pregnancy loss (IRPL) [4].

In recent years, an increasing number of researchers have investigated the effect of male factors on IRPL [5-7]. However, infertility clinics routinely evaluate paternal chromosomes. Recently, with the assisted reproductive technology procedures, the role of sperm factors has gained importance.

Semen parameters, including ejaculate volume, total sperm count per ejaculate, sperm concentration, progressive sperm motility, and sperm morphology provide useful insight into the quality of semen. However, the correct interpretation of these semen parameters for IRPL remains unclear [8–10]. Defective sperm DNA, with and without abnormal sperm parameters, is considered a reason of IRPL [9]. This led researchers to explore what may damage the sperm DNA. Regulation of male reproduction via modulation of the hypothalamus-pituitary-testes axis is important. As is known, hormones affect semen quality and sperm DNA [12]. Vitamin D (VD) levels may also affect spermatogenesis and serum androgen levels in men [13-16]. VD Receptor (VDR) which mediates the biological actions of VD, has been observed in reproductive tissues such as the ovary, uterus, prostate, testis, and human sperm [17, 18]. VD–metabolizing enzymes have been observed in the human testis, the ejaculatory tract, and mature sperm cells; therefore, VD plays an essential role in the maturation of sperm cells [19]. In one infertility study, vitamin D was positively associated with testosterone (T), and free androgen index but negatively associated with sex hormone-binding globulin (SHBG) [16]. However, there is a lack of data about the relationship between IRPL and VD levels in men as a male factor.

In this study, we aimed to investigate the association between 25- hydroxy-Vitamin D (25-OH-VD) serum levels and semen quality and reproduction hormones of men whose partners were diagnosed with IRPL.

Materials and methods

Patient selection

In this cross-sectional study, the data of 41 couples with a history of IRPL were collected. They had lost a minimum of two embryos during the first trimester and were referred to Infertility Clinic in the Medical School of Pamukkale University between February 2014 and February 2015. The female partners of the couples were examined fully and no cause was detected. These couples had not attempted assisted reproduction treatments at that time. On the other hand, the karyotypes of these couples were normal. No men had any history of radiotherapy, chemotherapy, chronic illness, or a family history of any diseases.

We noted age, smoking status, and previous varicocele operation history in all subjects. This protocol was approved by the local ethics committee and all patients were informed about the study.

Semen Analysis

Semen samples (one per subject) were collected by masturbation after 3-4 days of sexual abstinence in sterile plastic containers and left to liquefy at 37°C for 30 minutes. All semen analyses were performed by the same technician. Basic semen parameters (volume, count, concentration, and motility) were assessed according to the World Health Organization guidelines [20]. Sperm morphologies were assessed according to Kruger's criteria.

Hormonal analysis

Follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (T), estradiol (E_2), and prolactin (PRL) were assayed with an electrochemiluminescence immunoassay (ECLIA) (Elecsys Kit; Roche Diagnostics, Germany). Serum vitamin D levels were assessed by measuring serum 25-OH-VD levels using chemiluminescence immunoassay (Liaison Assay; Diasorin, Italy). 25-OH-VD levels were divided into two categories: 25-OH-VD ≤19 ng/ml (VD deficiency) and 25-OH-VD ≥20 ng/ml (normal) [21]. We had no subjects with 25-OH-VD ≥50 ng/ml. Seasonal variation of VD was excluded.

Statistical analysis

The Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis for the obtained values. The arithmetic mean of descriptive data, standard deviation, and percentage distributions were made. Mann-Whitney U test was used for non-parametric data and correlation analysis was performed. A *P*-value <0.05 was considered statistically significant.

Results

The mean age of the men who participated in the study was 31.7 (4.3) years. The mean duration of marriage and infertility were 5.34 (3.3) years, and 1.73 (0.8) years, respectively. The mean number of miscarriages was 2.7 (1.8), and the mean number of packages smoked per year was 2.6 (4.7). Only 13.9% of men had undergone varicocele operation.

The mean 25-OH-VD level was 18.4 (9.6) ng/ml. The mean 25-OH-VD levels of 27 patients (65.8%) were ≤19 ng/ml, while that of 14 patients (34.2%) were ≥20 ng/ml. The mean FSH, LH, T, E2 and PRL levels were 4.1 (2) mIU/mL, 4.5 (1.7) mIU/mL, 4 (1.7) ng/mL, 21.8 (8.5) pg/mL and 13 (8) ng/mL, respectively. The mean abstinence day, ejaculate volume, total sperm count per ejaculate, sperm concentration, percentage of progressive sperm motility and sperm morphology were 3.24 (0.4), 3.1 (1.5) ml, 291 (188) million, 102 (70) million/ml, 61% (16%) and 4% (4%), respectively.

Testosterone levels were lower in the IRPL group with 25-OH-VD ≤19 ng/ml when compared with the IRPL group with 25-OH-VD ≥20 ng/ml (P=0.008). There was no significant difference between these two groups in terms of other hormonal values (Table 1).

In our study, the semen parameters insignificantly changed with 25-OH-VD values. The ejaculate volume, total sperm count per ejaculate, progressive sperm motility, sperm morphology were numerically decreased in the low VD group (P>0.05).

Table 1: Demographical, hormonal and semen parameters per category of serum 25-hydroxy-Vitamin D level

	Serum 25-hydroxy-Vitamin D level		
	0-19 ng/ml (n=27)	20-50 ng/ml (n=14)	*P*-value
Duration of infertility (years)	1.8 (0.9)	1.5 (0.8)	0.190
Miscarriage	3 (2.1)	2.2 (0.4)	0.281
Smoking (packet x year)	3.25 (0.89)	5.03 (2.66)	0.136
FSH (mIU/mL)	4.1 (2.1)	4 (1.9)	0.941
LH (mIU/mL)	4.7 (1.5)	4.2 (2)	0.266
Testosterone (ng/mL)	3.1 (1.8)	4.3 (1.6)	0.008*
E_2 (pg/mL)	21.7 (10.2)	22.1 (4.5)	0.686
PRL (ng/mL)	12.9 (9.6)	13.1 (4)	0.571
Ejaculate volume (ml)	2.8 (1.3)	3.6 (1.7)	0.180
Total sperm count per ejaculate (million)	278.4 (187.2)	315.9 (194.6)	0.590
Sperm concentration (million/ml)	108 (79.7)	92.3 (49.2)	0.711
Progressive sperm motility (percent)	60.8 (16.3)	62.2 (18.6)	0.635
Sperm morphology (percent)	3.7 (2.1)	4.7 (2.1)	0.191

FSH: Follicle stimulating hormone, LH: luteinizing hormone, T: total testosterone, E_2: estradiol, PRL: prolactin. * P<0.05

Discussion

In the present study, we found that men whose partners were diagnosed with IRPL had decreased serum levels of 25-OH-VD. We also found that there was a significant relationship between serum 25-OH-VD and T levels. Because of the positive correlation between T and VD, serum T levels were lower in the VD deficient group. To the best of our knowledge, the role of VD on IRPL was not studied before. The literature about the role of VD on reproductive functions is preliminary, but VDR and VD metabolizing enzymes have been investigated in the reproductive tissues of males [21, 22]. Similarly, in an early study, VD was positively associated with T and free androgen index and inversely associated with SHBG [16]. Similar results were reported in some animal studies. VDR null mice had insufficient gonadal function with low sperm parameters and abnormal testis histology [23]. They were diagnosed with hypergonadotropic hypogonadism with high FSH and LH levels, and low T and E_2 levels due to reduced gonadal aromatase activity. Although the mating capacity was normal in VD-deficient male rats, they had decreased overall fertility [24].

The main reason for decreased T synthesis is lacking; however, 1,25-OH-VD treatment upregulates various genes for spermatogenesis in Sertoli cells [25]. The presence of VDR in human sperm displays a role in the capacitation and survival of sperm [26]. On the other hand, some researchers did not find a relationship between serum VD and T, E_2, LH, inhibin B [27]. Likewise, in another study, no significant differences were observed in terms of various hormonal parameters with different categories of 25-OH-VD levels [28]. The relationship of VD and fertility hormones is not reported in that study, probably because they chose participants from young healthy volunteers without any desire of procreating. With recent research, it became obvious that VD has a role in the reproductive proves, but related pathophysiological mechanisms require further larger investigations. We hypothesized that deficiency of 25-OH-VD is correlated with low testosterone levels in men with partners diagnosed with IRPL.

We also found that there was an insignificant association between 25-OH-VD levels and semen parameters. Ejaculate volume, total sperm count per ejaculate, progressive sperm motility, sperm morphology were lower in the VD deficient group when compared to the normal VD group with IRPL. There is scant data in the literature about the relationship between VD and semen parameters. Research showed that high levels of VD were related to lower total sperm count and normal morphology percentage, but low levels of VD were not related to sperm parameters [29]. They demonstrated that high VD might have caused toxicity in the male reproductive system. The findings of our study about sperm parameters in patients with normal VD levels are similar to those of the previous study. In our study, there were no patients with high 25-OH-VD levels (≥50 ng/ml) so we could only compare low and normal VD levels. Although statistical significance could not be shown, our data supported that low VD levels correlated negatively with most semen parameters. Blomberg et al. showed that low VD levels were correlated with reduced sperm motility, but high VD levels did not negatively affect sperm parameters [15]. Similarly, in a recent study, the association between low VD levels and semen parameters was asserted [30]. They found that VD deficiency was related to lower total progressive motile sperm count and lower total sperm count, but not related to sperm concentration, progressive motility, and morphology. Although we could not show the connection between VD and semen morphology in our study, poor semen quality, especially morphologic features, were the main characteristics of our IRPL group. In a recent study, the incidence of DNA fragmentation was increased in patients with poor sperm morphology compared with men with normal semen quality [31]. As expected, fertilization by spermatozoa with fragmented DNA results in a poor-quality embryo, decreased implantation rates, and higher pregnancy loss [32].

The relatively small study population limits the extrapolation of our study results. Further studies with larger populations are needed to validate our findings and explore the mechanism.

Conclusion

We found a negative association between 25-OH-VD levels and testosterone, which affects semen quality. Our results showed that poor sperm morphology and VD deficiency were related to pregnancy success. This study will hopefully make way for the development of new diagnostic methods in evaluating recurrent pregnancy losses without the female factor in the future.

Acknowledgments

We thank all staff in the infertility department.

References

1. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012;98(5):1103–11. doi: 10.1016/j.fertnstert.2012.06.048.
2. Allison JL, Schust DJ. Recurrent first trimester pregnancy loss: revised definitions and novel causes. Curr Opin Endocrinol Diabetes Obes. 2009;16:446–50. doi: 10.1097/MED.0b013e3283327fc5.
3. Kiwi R. Recurrent pregnancy loss: evaluation and discussion of the causes and their management. Cleve Clin J Med. 2006;73:913–21. doi: 10.3949/ccjm.73.10.913.
4. El Hachem H, Crepaux V, May-Panloup P, Descamps P, Legendre G, Bouet PE. Recurrent pregnancy loss: current perspectives. Int J Womens Health. 2017;9:331–45. doi: 10.2147/IJWH.S100817.
5. Puscheck EE, Jeyendran RS. The impact of male factor on recurrent pregnancy loss. Curr Opin Obstet Gynecol. 2007;19:222–8. doi: 10.1097/GCO.0b013e32813e3ff0.
6. Ruixue W, Hongli Z, Zhihong Z, Rulin D, Dongfeng G, Ruizhi L. The impact of semen quality, occupational exposure to environmental factors and lifestyle on recurrent pregnancy loss. J Assist Reprod Genet. 2013;30:1513–8. doi: 10.1007/s10815-013-0091-1.
7. Dickey R, Ramasamy R. Role of Male Factor Testing in Recurrent Pregnancy Loss or In Vitro Fertilization Failure. Reprod Syst Sex Disord. 2015;4(3):1000e122. doi: 10.4172/2161-038X.1000e122.

8. Cao X, Cui Y, Zhang X, Lou J, Zhou J, Wei R. The correlation of sperm morphology with unexplained recurrent spontaneous abortion: A systematic review and meta-analysis. Oncotarget. 2017;8:55646–56. doi: 10.18632/oncotarget.17233.
9. Talebi AR, Vahidi S, Aflatoonian A, Ghasemi N, Ghasemzadeh J, Firoozabadi RD, et al. Cytochemical evaluation of sperm chromatin and DNA integrity in couples with unexplained recurrent spontaneous abortions. Andrologia. 2012;44:462–70. doi: 10.1111/j.1439-0272.2011.01206.x.
10. Absalan F, Ghannadi A, Kazerooni M, Parifar R, Jamalzadeh F, Amiri S. Value of sperm chromatin dispersion test in couples with unexplained recurrent abortion. J Assist Reprod Genet. 2012;29(1):11–4. doi: 10.1007/s10815-011-9647-0.
11. Esteves SC, Zini A, Coward RM, Evenson DP, Gosálvez J, Lewis SEM, et al. Sperm DNA fragmentation testing: Summary evidence and clinical practice recommendations. Andrologia. 2021;53:13874. doi: 10.1111/and.13874.
12. Jayasena CN, Radia UK, Figueiredo M, Revill LF, Dimakopoulou A, Osagie M, et al. Reduced Testicular Steroidogenesis and Increased Semen Oxidative Stress in Male Partners as Novel Markers of Recurrent Miscarriage. Clin Chem. 2019;65:16–9. doi: 10.1373/clinchem.2018.289348.
13. Corbett ST, Hill O, Nangia AK. Vitamin D receptor found in human sperm. Urology. 2006;68(6):1345–9. doi: 10.1016/j.urology.2006.09.011.
14. Aquila S, Guido C, Middea E, Perrotta I, Bruno R, Pellegrino M, et al. Human male gamete endocrinology: 1alpha, 25-dihydroxyvitamin D3 (1.25(OH)2D3) regulates different aspects of human sperm biology and metabolism. Reprod Biol Endocrinol. 2009;7:140. doi: 10.1186/1477-7827-7-140.
15. Blomberg Jensen M, Nielsen JE, Jørgensen A, Rajpert-De Meyts E, Kristensen DM, Jørgensen N, et al. Vitamin D receptor and vitamin D metabolizing enzymes are expressed in the human male reproductive tract. Hum Reprod. 2010;25(5):1303–11. doi: 10.1093/humrep/deq024.
16. Wehr E, Pilz S, Boehm BO, März W, Obermayer-Pietsch B. Association of vitamin D status with serum androgen levels in men. Clin Endocrinol (Oxf). 2010;73:243–8. doi: 10.1111/j.1365-2265.2009.03777.x.
17. Johnson JA, Grande JP, Roche PC, Kumar R. Immunohistochemical detection and distribution of the 1,25-dihydroxyvitamin D3 receptor in rat reproductive tissues. Histochem Cell Biol. 1996;105(1):7–15. doi: 10.1007/BF01450873.
18. Aquila S, Guido C, Perrotta I, Tripepi S, Nastro A, Andò S. Human sperm anatomy: ultrastructural localization of 1alpha,25-dihydroxyvitamin D receptor and its possible role in the human male gamete. J Anat. 2008;213(5):555–64. doi: 10.1111/j.1469-7580.2008.00975.x.
19. Kinuta K, Tanaka H, Moriwake T, Aya K, Kato S, Seino Y. Vitamin D is an important factor in estrogen biosynthesis of both female and male gonads. Endocrinology. 2000;141:1317–24. doi: 10.1210/endo.141.4.7403.
20. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16(3):231–45. doi: 10.1093/humupd/dmp048.
21. Costanzo PR, Knoblovits P. Vitamin D and male reproductive system. Horm Mol Biol Clin Investig. 2016;28:151–9. doi: 10.1515/hmbci-2016-0049.
22. Lorenzen M, Boisen IM, Mortensen LJ, Lanske B, Juul A, Blomberg Jensen M. Reproductive endocrinology of vitamin D. Mol Cell Endocrinol. 2017;453:103–12. doi: 10.1016/j.mce.2017.03.023.
23. Zanatta L, Zamoner A, Zanatta AP, Bouraïma-Lelong H, Delalande C, Bois C, et al. Nongenomic and genomic effects of 1α,25(OH)2 vitamin D3 in rat testis. Life Sci. 2011;89:515–23. doi: 10.1016/j.lfs.2011.04.008.
24. Zamani A, Saki F, Hatami N, Koohpeyma F. Stereological assessment of the effects of vitamin D deficiency on the rat testis. BMC Endocr Disord. 2020;20(1):162. doi: 10.1186/s12902-020-00642-0.
25. Menegaz D, Barrientos-Duran A, Kline A, Silva FR, Norman AW, Mizwicki MT, et al. 1alpha,25(OH)2-Vitamin D3 stimulation of secretion via chloride channel activation in Sertoli cells. J Steroid Biochem Mol Biol. 2010;119:127–34. doi: 10.1016/j.jsbmb.2010.01.011.
26. de Angelis C, Galdiero M, Pivonello C, Garifalos F, Menafra D, Cariati F, et al. The role of vitamin D in male fertility: A focus on the testis. Rev Endocr Metab Disord. 2017;18:285–305. doi: 10.1007/s11154-017-9425-0.
27. Ramlau-Hansen CH, Moeller UK, Bonde JP, Olsen J, Thulstrup AM. Are serum levels of vitamin D associated with semen quality? Results from a cross-sectional study in young healthy men. Fertil Steril. 2011;95:1000–4. doi: 10.1016/j.fertnstert.2010.11.002.
28. Hammoud AO, Meikle AW, Peterson CM, Stanford J, Gibson M, Carrell DT. Association of 25-hydroxy-vitamin D levels with semen and hormonal parameters. Asian J Androl. 2012;14(6):855–9. doi: 10.1038/aja.2012.77.
29. Lerchbaum E, Pilz S, Trummer C, Rabe T, Schenk M, Heijboer AC, et al. Serum vitamin D levels and hypogonadism in men. Andrology. 2014;2:748–54. doi: 10.1111/j.2047-2927.2014.00247.x.
30. Rehman R, Lalani S, Baig M, Nizami I, Rana Z, Gazzaz ZJ. Association Between Vitamin D, Reproductive Hormones and Sperm Parameters in Infertile Male Subjects. Front Endocrinol (Lausanne). 2018;9:607. doi: 10.3389/fendo.2018.00607.
31. Barratt CL. Male infertility joins the translational medicine revolution. Sperm DNA: from basic science to clinical reality. Mol Hum Reprod. 2010;16(1):1–2. doi: 10.1093/molehr/gap094.
32. Carrell DT. Elucidating the genetics of male infertility: understanding transcriptional and translational regulatory networks involved in spermatogenesis. Int J Androl. 2008;31:455–6. doi: 10.1111/j.1365-2605.2008.00913.x.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):615-619.
DOI: 10.28982/josam.867945

Research article

Journal of Surgery and Medicine
e-ISSN=2602-2079

Value of serum thiol/disulphide in chronic prostatitis

Halil Ferat Öncel [1], Remzi Salar [1], Engin Özbay [1], İbrahim Halil Dikici [2], Mehmet Demir [3], Ayhan Verit [4]

[1] University of Health Sciences, Medical Faculty, Mehmet Akif Inan Hospital, Department of Urology, Sanliurfa, Turkey
[2] University of Health Sciences, Medical Faculty, Mehmet Akif Inan Hospital, Department of Biochemistry, Sanliurfa, Turkey
[3] Harran University, Faculty of Medicine, Department of Urology, Sanliurfa, Turkey
[4] University of Health Sciences, Medical Faculty, Fatih Sultan Mehmet Hospital, Department of Urology, Istanbul, Turkey

ORCID ID of the author(s)

HFÖ: 0000-0003-4043-5597
RS: 0000-0002-5078-9367
EÖ: 0000-0001-7102-3064
İHD: 0000-0002-9427-5974
MD: 0000-0002-3618-0547
AV: 0000-0002-1602-9698

Corresponding Author
Halil Ferat Öncel
Department of Urology, University of Health Sciences, Medical Faculty, Mehmet Akif Inan Hospital, Esentepe Mah. Ertuğrul Cad. Sanliurfa, Turkey
E-mail: halilferat.oncel@gmail.com

Ethics Committee Approval
Ethics Committee of Harran University, date: 10.12.2018, number: HRU/10.12.18
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 June 20

Abstract

Background/Aim: Thiols are an important part of the antioxidant system which destroy reactive oxygen molecules, especially in inflammatory reactions. Maneuvers expressing the prostate fluid required for the diagnosis of chronic prostatitis are not practical and are rarely used in clinical practice. We aimed to compare the level of native thiol/disulphide as a supportive biomarker in patients with chronic abacterial prostatitis.

Methods: Twenty patients diagnosed with chronic prostatitis and 20 healthy volunteers were included in this prospective-case control study. Both groups were compared in terms of native thiol disulphide homeostasis, IPSS, QoL and PSA levels.

Results: In the chronic prostatitis group, the native thiol level was significantly lower (P=0.043), the % disulfide/natural thiol was higher (P=0.037), the international prostate symptom score was higher (P=0.006), the quality of life was higher (P=0.023) and the maximum flow rate was lower (P=0.009) compared to the healthy volunteers.

Conclusion: In this study, we found that the native thiol (SH) level in patients with chronic prostatitis was low and their disulphide level was high; therefore, we think that the level of native thiol/total thiol may assist in supporting the diagnosis of chronic prostatitis.

Keywords: Oxidative stress, Prostatitis, Quality of life, Reactive oxygen species, Thiol disulphide

How to cite: Öncel HF, Salar R, Özbay E, Dikici İH, Demir M, Verit A. Value of serum thiol/disulphide in chronic prostatitis. J Surg Med. 2021;5(6):615-619.

Introduction

The term prostatitis describes a wide range of inflammatory diseases from acute bacterial infection of the prostate to chronic pain syndromes, in which the prostate is inflamed. All these diseases seriously affect patients' quality of life and social life. The etiopathogenesis of prostatitis is not yet fully understood [1]. It is reported that the prevalence of prostatitis-like complaints or the diagnosis of prostatitis varies between 2 and 10% in the world [2]. Although chronic prostatitis is mostly known as a disease of the young, studies emphasize that men from any age group can be affected. Many studies were conducted on the relationship between oxidative stress and prostate cancer, benign prostatic hyperplasia (BPH), and prostate inflammation [3]. The incomplete understanding of the etiopathogenesis of chronic prostatitis causes difficulties in diagnosis and treatment. Although there were publications supporting the role of oxidative stress in etiopathogenesis, the number of these publications is limited.

Oxidative stress is a process in which the prooxidant-antioxidant balance in the body and tissues is disrupted. The occurrence of Reactive oxygen species (ROS), known as prooxidants, is a natural result of normal aerobic life. The presence and development of cells in oxygen-containing environments is not possible without powerful antioxidant and non-enzyme antioxidant systems. In aerobic life, continuously produced prooxidants need to be regularly absorbed and balanced by antioxidants; otherwise, oxidative damage occurs, which may lead to various pathologies [4]. Free oxygen radicals having a destructive effect, which are generated as a result of any extra or intracellular oxidative stress, are bound by thiols and inactivated. This reaction leads to the emergence of freeS-S bound molecules. Thiols are an important part of the antioxidant system in that they destroy reactive oxygen molecules and other free radicals produced by enzymatic and non-enzymatic pathways. Various methods are available to evaluate the effects of oxidative stress on the body, and for this purpose, different markers have been investigated. The automatic spectrophotometric analysis, an inexpensive, fast, and practical technique developed by Erel and Neselioğlu, is currently used to measure native thiol / disulphide bonds (SH/SS) homeostasis and allows for the specific measurements of SH and SS levels. The impairment of SH/SS homeostasis in favor of SS has been shown to affect disease pathogenesis. SH/SS homeostasis is impaired in cases such as cardiovascular diseases, diabetes mellitus, Parkinson's disease, chronic renal failure, liver disorders, rheumatic, and oncological diseases. While plasma SS levels are high in smokers, diabetes mellitus, obesity, pneumonia, multiple myeloma, bladder cancer, kidney cancer, and colon cancer patients, low levels of SS are found in patients with aggressive tumors [5].

Diagnosing chronic prostatitis is difficult and time-consuming in clinical practice. In addition, the lack of a marker used in diagnosis and follow-up is one of the main problems for the clinician. There are very few studies examining the relationship between isolated chronic prostatitis and thiol balance. In the current study, we aimed to compare the level of SH/SS as a supportive biomarker for diagnosis in patients with prostatitis classified in categories other than acute bacterial prostatitis (National Institutes of Health, Category I) and healthy individuals.

Materials and methods

Twenty patients who presented to the urology outpatient clinic of our hospital and were diagnosed with chronic prostatitis by four-glass test [2] between December 2018 and December 2019, and 20 healthy volunteers were included in the study. After obtaining detailed history and physical examination, the International Prostate Symptom Score (IPSS) and the Quality of life (QoL) Form, which measures quality of life according to urinary symptoms, were completed by all patients diagnosed with chronic prostatitis and healthy individuals. The Prostate specific antigen (PSA) level and the maximum flow rate (Q_{max}) values were also noted. The participants filled in the IPSS and QoL forms independently during the examination, with no interference. Uroflowmetry was performed at the third hour after oral hydration. Patients with a complaint of less than three months, those who received antibiotics or anti-inflammatory therapy within the last month, with a history of urethral or prostatic surgery, using pentoxifylline and vitamin preparations/antioxidants, and patients with diabetes mellitus, hypertension, a history of prostate cancer/malignancy, sleep apnea, and chronic kidney damage were excluded from the study. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Prior to the study, approval was obtained from the Ethics Committee of Harran University Faculty of Medicine (date/number: 2018/18-12-15).

Sample collection and biochemical analysis

Venous blood samples were obtained from all participants after 12 hours of fasting and placed in tubes containing ethylenediaminetetraacetic acid, and the serum was immediately separated by centrifugation at 1,500 rpm for 10 minutes. The separated sera were kept at -80 °C after coding, and SH/SS homeostasis tests were conducted. SH/SS homeostasis was assayed using a new and automatic analysis technique found by Erel and Neşelioğlu [5]. The ratios of disulphide bonds / total thiol (SS/TT), SS/SH and SH/TT were calculated as percentages. The PSA and free PSA values were measured by the immunoassay method using an ARCHITECT i2000SR analyzer (Abbott Diagnostics).

Statistical analysis

Statistical Package for the Social Science for Windows program, version 24.0 was used to evaluate the data obtained in the research. The mean and standard deviation values for the parameters evaluated in the study were examined in all patients. The independent samples t-test was used to compare the test values of the patients with chronic prostatitis and the control group. Within the scope of the research, power analysis was performed to measure the adequacy of the sample size using G*Power program. For a d of 1.4352 and an actual power of 0.9548, the required sample size was 28 patients, 14 patients in each group. The fact that "d" which is the Cohen effect value, is above 0.80, shows that the study has a high effect level, and the statistical power of above 0.90 indicates that the sample size is sufficient [6-7].

Results

The mean ages of the patients with prostatitis and healthy volunteers were 41.55 (10.26) (27-69) years and 38.85 (12.6) (16-61) years, respectively (Table 1). There was no significant difference between the two groups in terms of age. The SH, TT, SS, %SH/TT, %SS/SH, %SS/TT and PSA levels of prostatitis patients were 329.4 (52.4) µmoL/L, 373.16 (59.0) µmoL/L, 21.88 (8.7) µmoL/L (Figure 1), 88.34 (3.8), 6.69 (2.38), 5.82 (1.9), and 1.19 (1.18) ng/ml, respectively. Their IPSS, QoL and Qmax were 7.3 (4.66), 0.75 (0.44) (Figure 2), and 14.65 (3.03) ml/sec, respectively.

Table 1: Comparison of the values between the chronic prostatitis and control groups

	Chronic prostatitis (n=20) Mean (SD) Min-Max	Control group (n=20) Mean (SD) Min-Max	t	*P*-value
Age	45.55(10.26) 27-69	38.85(12.6) 16-61	0.743	0.462
SH	329.4(52.4) 178.5-426.8	345.61(61.1) 155.5-429.5	-1,901	0.43*
TT	373.16(59) 207.9-437.3	384.9(67.76) 185.8-460.9	-1,586	0.561
SS	21.88(8.7) 5.25-36.05	19.66(8.89) 2.35-39.45	0.797	0.431
%SH/TT	88.34(3.8) 82.39-97.59	89.77(4.17) 82.88-98.72	-1.126	0.267
% SS/SH	6.69(2.38) 1.23-10.68	5.81(2.57) 0.64-10.32	2.121	0.37*
%SS/TT	5.82(1.9) 1.2-8.8	5.11(2.08) 0.63-8.55	1.126	0.267
IPSS	7.3(4.66) 1-16	4.05(1.7) 1-8	2.925	0.06**
QoL	1.4(1..4) 0-4	0.75(0.44) 0-1	2.371	0.23*
PSA	1.19(1.18) 0.4-6	1.07(0.85) 0.2-3.7	0.387	0.702
Qmax	14.65(3.03) 9-19	17.11(2.58) 11-22	-2.766	0.09**

Independent samples t-test, * $P<0.05$, ** $P<0.01$, SD: standard deviation, SH: native thiol, SS: disulfide, TT: total thiol, IPSS: International Prostate Symptom Score, QoL: Quality of Life Form, Q_{max}: maximum flow rate, PSA: prostate-specific antigen

Figure 1: Comparison of the native thiol, total thiol and disulfide levels of chronic prostatitis and control groups (in µmol units)

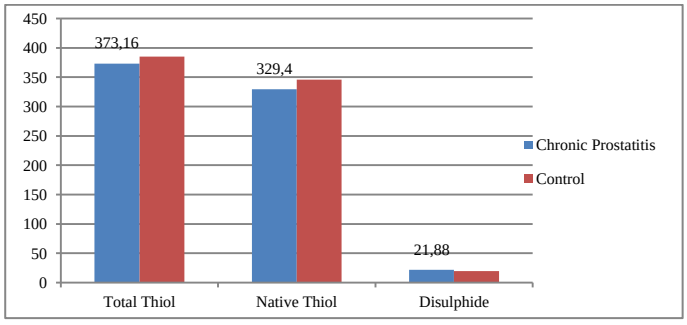
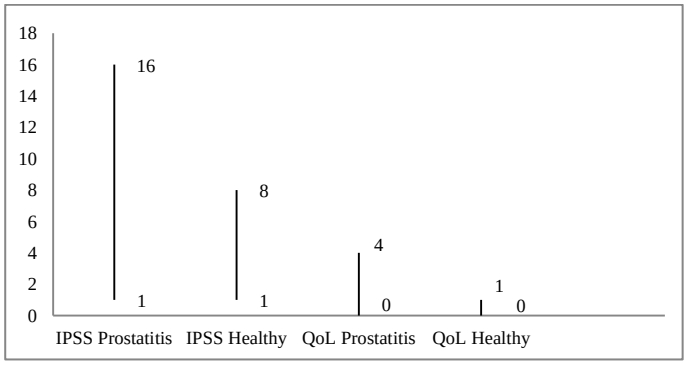


Figure 2: IPSS and QoL scores of the prostatitis and healthy groups



The SH, TT, SS, %SH/TT, %SS/SH, %SS/TT and PSA levels of the healthy volunteers were 45.61 (61.1) µmoL/L, 384.94 (67.76) µmoL/L, 19.66 (8.89) µmoL/L (Fig.1), 89.77 (4.17), 5.81 (2.57), 5.11 (2.08), and 1.07 (0.85) ng/ml, respectively. Their IPSS, QoL and Qmax were

4.05 (1.7), 1.4 (1.14) (Figure 2), and 17.11 (2.58) ml/sec, respectively. The chronic prostatitis patients and healthy controls significantly differed in terms of SH (P=0.043), SS/SH (P=0.037), IPSS (P=0.006), QoL (P=0.023), and Q_{max} (P=0.009) (Table 1). According to these results, the SH and Q_{max} values were significantly lower and the %SS/SH, IPSS and QoL values were significantly higher in the chronic prostatitis group compared to the control group.

Discussion

In urological practice, prostatitis a common condition seen more frequently among young and middle-aged men. It is estimated that around two million men admitted to hospital annually are diagnosed with prostatitis. However, true bacterial infections of the prostate constitute the minority of these cases [2]. In a study in which 409 men with prostatitis were retrospectively evaluated, bacterial cultures in prostate fluid were positive in only 10% [1]. This is due to the lack of parameters that would help in diagnosis. Maneuvers expressing the prostate fluid required for the diagnosis of chronic prostatitis are not practical, and thus rarely used in clinical practice. Clinicians need more practical biomarkers in the diagnosis and follow-up.

Prostatitis, the result of recurrent bacterial infections in chronic prostatitis, is classified as Category II. Diagnosis can be made by isolating bacteria in the prostatic fluid culture. However, the physiopathology of the chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) or Category III prostatitis is still not fully understood. Types of inflammatory (IIIA) or non-inflammatory (IIIB) prostatitis can be classified according to whether there are leukocytes in the prostate fluid. The available information on CP/CPPS is limited, and its etiopathogenesis is still poorly understood. For these reasons, the diagnosis and treatment criteria have not yet been precisely determined.

The causes of CP/CPPS include infection, autoimmunity, inflammation, and neurological conditions. Recently, the role of oxidative stress in CP/CPPS has also been investigated. Many studies show the role of oxidative stress in patients with chronic prostatitis, regardless of the etiological basis of CP/CPPS. Since inflammation in the tissue is always accompanied by oxidative stress in patients with chronic prostatitis, products of oxidative stress are seen in this condition [8]. In our study, we hypothesized that patients with chronic prostatitis would have more oxidative stress because we detected that the body reacted to destroy the radical products produced by stress, during which SH/SS homeostasis was impaired in favor of SS.

There are many publications regarding the relationship between inflammation and oxidative stress [8]. Different markers have been studied for ROS. In a healthy organism in which detoxifying and anti-inflammatory molecules effective against oxidative stress and inflammatory mediators are in balance, free radicals are at a normal level and necessary to a certain extent. Sometimes, while these free radicals cause damage, they can also promote repair [9]. Oxidative stress plays a key role in acute and chronic inflammation at various levels. There are many studies that reveal the effects of oxidative stress on chronic prostatitis, and oxidative stress markers have been identified in the urine and genital secretions of patients with prostatitis [10-13]. Studies have been conducted to explore the relationship between oxidative stress and prostate cancer, BPH and prostate inflammation [14]. Normal oxidative stress markers such as nitric oxide synthases and malonyl dialaldehyde are still in use today. However, the analysis technique found by Erel and Neselioglu is faster, cheaper, practical, and a fully automatic

spectrophotometric examination for the measurement of the plasma dynamic SH/SS homeostasis [5]. Dynamic SH/SS imbalance has been associated with various disorders, such as diabetes mellitus, cancer, migraine, hyperemesis gravidarum, obstructive sleep apnea, and chronic kidney failure [15].

Recently, the thiol metabolism has attracted attention as potential biomarkers of oxidative stress. Thiol protein groups are antioxidant buffers that regulate the redox system. Oxidative protein damage manifests itself with an increase in carbonyl levels and a decrease in thiol levels [16-18]. Decreased levels of thiol protein groups are associated with decreased serum antioxidant power. Therefore, SH/SS homeostasis can be considered an oxidative stress marker similar to lipid hydroperoxide, total antioxidant/oxidant status, and paraoxonase. Changes in SH/SS balance caused by oxidative stress provide valuable information concerning various abnormal biochemical processes [19]. It is known that thiol groups play a prominent role in ROS detoxification, and the reduction of thiol causes the failure of the antioxidant defense mechanism. SH/SS homeostasis and thiol oxidation have critical regulatory activities in oxidative stress, detoxification, regulation of enzymes, and protection against essential cellular pathways, such as signal transmission and pro-apoptotic and anti-apoptotic signaling [20]. If there is an increase in ROS in the environment, the organism uses thiol to destroy these harmful radicals, and as a result, the disulfide level increases. While oxidative stress products increase in inflammation, SH/SS homeostasis will be impaired in favor of SS. In their study comparing the BPH and control groups, Minciullo et al. [3] reported that the oxidative stress parameters were higher and antioxidant parameters were lower in prostate cancer [3]. This supports the shift of SH/SS homeostasis toward SS. Measuring this balance biochemically led us to consider that it could be an indicator of an inflammatory process associated with oxidative stress in tissue.

In a study on rats, the effects of oxidation on inflammation were demonstrated in subjects with chronic prostatitis. It was revealed that the use of antioxidants, such as diene conjugates, malonic dialdehyde, superoxide dismutase, and succinate dehydrogenase positively affected treatment in combating this inflammation [21], which indirectly supports our results. If the healing process is accelerated using antioxidants, this means that oxygen radicals accumulate in the tissue in cases of prostatitis. In our study, we found that the SH/SS homeostasis was impaired in favor of SS. This suggests that oxidative stress products are generated as a result of prostatitis. IPSS is a reproducible, validated index designed to determine disease severity and response to treatment. The use of IPSS alone is not safe in diagnosing BPH related lower urinary tract symptom (LUTS), but it is a quantitative measure of LUTS after diagnosis [22]. In LUTS, especially in BPH, IPSS is completed by patients. QoL is measured by adding further questions to IPSS.

Since chronic prostatitis causes LUTS, a significant difference was observed in the IPSS levels between the patients and healthy volunteer groups included in the study. In addition, the Q8 value, which was the QoL criterion based on urinary symptoms, was higher in the chronic prostatitis group than in the control group. Therefore, we consider that the use of IPSS and QoL forms in the follow-up of patients with chronic prostatitis will guide the evaluation of response to treatment.

The Q_{max} values of the patients with the complaints of LUTS were adversely affected. Bladder outlet obstruction can be safely diagnosed in men with a Qmax lower than 10 mL/s and an IPSS higher than 16 [23]. In a study conducted by Ghobish demonstrating the relationship between chronic prostatitis and voiding dysfunction, it was reported that Q_{max} value was decreased in patients with prostatitis compared to the control group [24].

We achieved similar results in our study. Q_{max} decreases not only in chronic prostatitis but also in bladder outlet obstruction or urethral stenosis. Thus, although Q_{max} alone is not sufficient for a diagnosis, we think it can aid in this process.

Chronic prostatitis negatively affects the quality of life. The procedures required for the diagnosis of chronic prostatitis in urology practice are not practical for the patient or the physician. Therefore, having a marker that can be used in diagnosis, treatment and follow-up may facilitate procedures to improve the patients' quality of life. Determining an impairment in SH/SS homeostasis through the method we used in the current study can assist clinicians in diagnosis. In addition, some studies have found that combating oxidative stress through anti-oxidants accelerates the improvement of the inflammatory process. We consider that positive changes in SH/SS homeostasis in the follow-up of the treatment can confirm the accuracy of the treatment during the inflammation process. It is also necessary to consider that diseases, such as oncological diseases, diabetes mellitus, and kidney disorders can also disrupt this balance.

Limitations

The main limitations of this study include the limited number of the study groups and the evaluation of changes in the level of SH/TT in other diseases, such as diabetes and cancer. Large-scale studies with a higher number of participants are needed.

Conclusions

We found that the SH level in patients with chronic prostatitis was low and their SS level was high; therefore, we think that the level of SH/TT may assist in supporting the diagnosis of chronic prostatitis. In addition, future studies investigating the role and efficacy of antioxidant treatment in chronic prostatitis can use this parameter to assess the effectiveness of treatment.

References

1. De la Rosette JJ, Hubregtse MR, Meuleman EJ, Stolk-Engelaar MV, Debruyne FM. Diagnosis and treatment of 409 patients with prostatitis syndromes. Urology. 1993;41:301-7.
2. Krieger JN, Nyberg L, Curtis Nickel JC. NIH Consensus Definition and Classification of Prostatitis. JAMA. 1999;282:236-7.
3. Minciullo PL, Inferrera A, Navarra M, Calapai G, Magno C, Gangemi S. Oxidative stress in benign prostatic hyperplasia: a systematic review. Urol Int. 2015;94:249–54.
4. Sies H. Oxidative stress: from basic research to clinical application. Am J Med. 1991;9:30-8.
5. Erel O, Neselioğlu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014;47:326-32.
6. Goodwin CJ. Research in psychology methods and design. Sixth ed. New Jersey: John Wiley&Sons, Inc: 2010. p.157-61.
7. Çapkın C. Statistical power analysis and it's use in nursing studies. Journal of Anatolia Nursing and Health Sciences. 2014:17:p271.
8. Ihsan AU, Khan FU, Khongorzul P. Role of oxidative stress in pathology of chronic prostatitis/chronic pelvic pain syndrome and male infertility and antioxidants function in ameliorating oxidative stress. Biomed Pharmacother. 2018 Oct;106:714-23.
9. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature. 2000;408:239-47.
10. Paulis G. Inflammatory mechanisms and oxidative stress in prostatitis: the possible role of antioxidant therapy. Res Rep Urol. 2018;10:75–87.
11. Pasqualotto FF, Sharma RK, Potts JM, Nelson DR, Thomas AJ, Agarwal A. Seminal oxidative stress in patients with chronic prostatitis. Urology. 2000;55:881–5.

12.Shahed AR, Shoskes DA. Oxidative stress in prostatic fluid of patients with chronic pelvic pain syndrome: correlation with gram positive bacterial growth and treatment response. J Androl. 2000;21:669–75.
13.Kullisaar T, Türk S, Punab M, Mändar R. Oxidative stress – cause or consequence of male genital tract disorders? Prostate. 2012;72:977–83.
14.Solakhan M, Cicek H, Orhan N, Yildirim M. Role of native Thiol, total Thiol and dynamic Disulphide in diagnosis of patient with prostate cancer and prostatitis. Int Braz J Urol. 2019;45:495-502.
15.Topaktaş R, Ürkmez A, Kutluhan MA, Çalışkan S, Erel Ö. Does plasma thiol and disulphide be a new marker for prostate cancer in prostate-specific antigen level between 10 and 20 ng/ml? Aging Male. 2019 May 10:1-5.
16.Reznick AZ, Packer L. Oxidative damage to proteins: spectrophotometric method for carbonyl assay. Methods Enzymol. 1994;233:357–63.
17.Levine RL, Williams JA, Stadtman ER, Shacter E. Carbonyl assays for determination of oxidatively modified proteins. Methods Enzymol. 1994;233:347–57.
18.Hu ML. Measurement of protein thiol groups and glutathione in plasma. Methods Enzymol. 1994;233:380–5.
19.Sönmez MG, Kozanhan B, Deniz ÇD, Göger YE, Kilinç MT, Neşelioglu S, et al. Is oxidative stress measured by thiol/disulphide homeostasis status associated with prostate adeno carcinoma? Cent Eur J Immunol. 2018;43:174-9.
20.Hanikoglu F, Hanikoglu A, Kucuksayan E, Alisik M, Gocener AA, Erel O, et al. Dynamic thiol/disulphide homeostasis before and after radical prostatectomy in patients with prostate cancer. FreeRadicRes. 2016;50:S79-84.
21.Bratchikov OI, Dubonos PA, Tyuzikov IA. Justification of a Use of Additional Antioxidant Therapy in Experimental Models of Chronic Bacterial Prostatitis Urologiia. 2019;1:16-22.
22.D'Silva KA, Dahm P, Wong CL. Does this man with lower urinary tract symptoms have bladder outlet obstruction?: The Rational Clinical Examination: a systematic review. JAMA. 2014;312:535.
23.Porru D, Jallous H, Cavalli V, Sallustu F, Rovereto B. Prognostic value of a combination of IPSS, flow rate and residual urine volume compared to pressure-flow studies in the preoperative evaluation of symptomatic BPH. Eur Urol. 2002;41:246.
24.Ghobish A. Voiding Dysfunction Associated with "Chronic Bacterial Prostatitis". Eur Urol. 2002;42:159–62.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):620-622.
DOI: 10.28982/josam.807627

Journal of Surgery and Medicine
e-ISSN=2602-2079

The effect of isosorbide-mononitrate on proteinuria in patients with diabetic nephropathy

Recep Demirci [1], Okan Akyüz [2]

[1] Department of Nephrology, University of Health Sciences Kanuni Sultan Suleyman Training and Research Hospital, Turkey
[2] Department of Nephrology, University of Health Sciences Kartal Kosuyolu Heart and Research Hospital, Turkey

ORCID ID of the author(s)

RD: 0000-0001-5609-9634
OA: 0000-0003-2460-9577

Corresponding Author
Recep Demirci
Department of Nephrology, University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital, 34303
Kucukcekmece/Istanbul, Turkey
E-mail: rcpdemirci@windowslive.com

Ethics Committee Approval
The study protocol was approved by the Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (2013-KAEK-64).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 June 25

Abstract

Background/Aim: Diabetic nephropathy (DN) occurs in approximately 40% of patients with Type 1 and Type 2 diabetes mellitus (DM) and is one of the most common causes of end-stage renal disease (ESRD). New treatment strategies are needed to prevent DN. This study aims to investigate the effect of the use of isosorbide-mononitrate (IMN) on diabetic nephropathy.
Methods: In this study, patients with type 2 diabetes mellitus were divided into two groups, as those using and not using IMN to evaluate whether IMN reduces proteinuria. Biochemical parameters and proteinuria values were recorded and comparatively analyzed.
Results: The urea and creatinine values of patients with type 2 DM who were using IMN were significantly higher and e-GFR values were significantly lower than those of the control group (P=0.049, P=0.001, P=0.013, respectively). However, the proteinuria amounts of Type 2 DM patients using IMN (0.98 g/day [0.52-1.43]) were significantly lower than those who were not (1.61 g/day [1.02-2.69] (P=0.001)).
Conclusion: The addition of nitrate to angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) in the treatment of patients with DN may be a new alternative for reducing proteinuria.

Keywords: Diabetic nephropathy, Isosorbide-mononitrate, Proteinuria

How to cite: Demirci R, Akyüz O. The effect of isosorbide-mononitrate on proteinuria in patients with diabetic nephropathy. J Surg Med. 2021;5(6):620-622.

Introduction

Diabetes Mellitus (DM) is a metabolic disease associated with micro-and macrovascular complications. One of the most important microvascular complications is diabetic nephropathy (DN) [1]. DN is among the most common causes of end-stage renal disease (ESRD), which occurs in approximately 40% of patients with DM [2]. Accompanying diabetes proteinuria has been associated with kidney failure, cardiovascular events, and the risk of premature death, and it has been reported that these risks increase with the amount of proteinuria [3-5]. Today's proteinuria treatment strategy is based on the inhibition of the renin-angiotensin-aldosterone system (RAAS) using angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), which provide hypertension control [6, 7]. In some cases, ACEIs and ARBs fail to reduce proteinuria/albuminuria, and unfortunately, there is no other class of drugs recommended by guidelines to correct it. In this context, studies are underway to develop some new treatment agents, but most of these studies are at an early stage [8, 9]. Studies evaluating the effect of isosorbide-mononitrate (IMN) on proteinuria are quite limited. In a study in rats, IMN was used as a nitrite oxide donor in rats with exercise-induced proteinuria and a decrease in proteinuria was observed [10]. Roccatello et al. reported a decrease in proteinuria when IMN was administered to patients with Ig A nephropathy and proteinuria [11]. There is still a need for novel studies on this subject. In this study, the effect of IMN on proteinuria was investigated in patients with type 2 DM-related nephropathy.

Materials and methods

The files and records of type 2 DM patients with proteinuria despite using ACEI and/or ARB for more than 6 months who visited the nephrology outpatient clinic of Istanbul Health Sciences Kanuni Sultan Suleyman Training and Research Hospital were retrospectively analyzed and those who met the inclusion criteria were included in this study. Demographic features, drugs used, body mass indexes (BMI), some biochemical parameters (Creatinine, Urea, Na, K, Ca, P, total protein, albumin), glomerular filtration rate (e-GFR), and proteinuria values were analyzed. Creatinine clearance was calculated with the Cockcroft-Gault formula.

Ethical approval

This case-control study protocol was approved by Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (2013-KAEK-64). The study was conducted by the principles of the Helsinki Declaration.

Study population

In the power analysis performed with the G*power 3.1 program, the effect size was 0.65 to evaluate the antiproteinuric activity of isosorbide-mononitrate (alpha error probability=0.05), and the sample size was calculated with a power of 0.80 [12].

A total of 29 patients with symptomatic ischemic heart and peripheral vascular diseases and Type 2 DM using oral IMN were included in the study. Forty-six patients with diabetic nephropathy (DN) using ACEI and/or ARB with similar demographic characteristics but who did not receive IMN treatment were included in the control group. Patients who actively used other proteinuria reducing agents such as cyclophosphamide, azathioprine, mycophenolate mofetil, prednisolone, and rituximab were not included in the study.

Statistical analysis

All statistical analyses were performed using SPSS software version 21.0 (SPSS Inc, Chicago, IL, USA). Data that did not conform to the normal distribution were shown as median (interquartile range [IQR]), while normally distributed data were given as mean±standard deviation. Mann-Whitney U test was used to compare non-normally distributed numerical data. The categorical variables in the study were compared using the chi-square or Fisher's exact tests. Values with $P<0.05$ were considered statistically significant.

Results

There were 29 patients (39%) in the IMN group and 46 patients (61%) in the control group. The female/male distribution of those in the IMN and control groups were 13(72%)/16 (28%) and 33(45%)/13(55%), respectively. The rate of females was significantly higher in the IMN group (p=0.02). Also, the mean age of patients in the IMN group (62(12) years) was significantly higher than that of the control group (55(10) years) (P=0.009). The BMIs of both groups were similar (P=0.242) (Table 1). Eighty-six percent (n=25) of the patients in the IMN group and 74% (n=34) of those in the control group were hypertensive. The smoker rates in the IMN and control groups were 35% (n=10), and 33% (n=15), respectively.

Table 1: Demographic data of the cases

Parameters		Control group	IMN group	*P*-value
Gender	Female (n)	33	13	0.020
	Male (n)	13	16	
Age (years)		55 (10)	62 (12)	0.009
Height (cm)		162 (1.58-1.65)	168 (1.61-1.72)	0.131
Weight (kg)		74 (68-83)	78 (75-83)	0.040
BMI (kg/m^2)		27.48 (26.50-28.41)	28.58 (26.37-30.80)	0.242
Creatinine (mg/dL)		0.85 (0.70-1.38)	1.20 (1.08-1.50)	0.001
Urea (mg/dL)		41 (29-60)	52 (41-65)	0.049
Na (mmol/L)		141 (139-142)	140 (139-142)	0.974
K (mmol/L)		4.9 (0.5)	4.8 (0.5)	0.216
Ca (mg/dL)		9.5 (9.1-9.8)	9.5(8.9-10.0)	0.870
P (mg/dL)		3.8 (0.4)	3.5 (0.7)	0.039
Protein (g/dL)		7.30 (6.80-7.50)	7.10 (6.80-7.50)	0.506
Albumin (g/dL)		4.1 (3.9-4.4)	4.3 (3.6-4.4)	0.948
e-GFR (mL/min/1.73m^2)		73 (46-96)	50 (41-72)	0.013
Proteinuria (g/day)		1.61 (1.02-2.69)	0.98 (0.52-1.43)	0.001

BMI: Body mass index, Na: Sodium, K: Potassium, Ca: Calcium, P: Phosphorus, GFR: glomerular filtration rate

The number of patients using ACEIs, ARBs and combined ACEI/ARBs in the IMN and control groups were 11, 16, 1 and 22, 22, and 2, respectively. The creatinine and urea values of patients with Type 2 DM using IMN in our study were significantly higher compared to the control group (P=0.001, P=0.049, respectively).

The Na, K, and Ca values were similar between the groups ($P>0.05$), while mean the serum phosphorus level of patients in the IMN group was significantly lower compared to the control group (P=0.039).

In terms of total protein and albumin values, there was no significant difference between Type 2 DM patients using and not using IMN ($P>0.05$).

The e-GFR values of the patients in the IMN group were significantly lower than those of patients in the control group (P=0.013). Despite this, proteinuria amounts of Type 2

DM patients using IMN were significantly lower compared to non-users (*P*=0.001) (Table 2).

Table 2: Comparison of biochemical data of patients in IMN and control group

	IMN group (n=29)	Control group (n=46)	*P*-value
Proteinuria (g/day)	0.98 (0.48-1.46)	1.61 (1.02-2.69)	0.001
e-GFR (mL/min/1.73 m^2)	50 (41-72)	73 (46-96)	0.013
Albumin (g/dL)	4.05 (0.61)	4.09 (0.48)	0.745
Total protein (g/dL)	7.03 (0.75)	7.09 (0.66)	0.721
Calcium (mg/dL)	9.4 (0.65)	9.3 (0.80)	0.591
Sodium (mmol/L)	140 (3.1)	140 (2.2)	0.103
Potassium (mmol/L)	4.75 (0.46)	4.89 (0.47)	0.216
Phosphorus (mg/dL)	3.48 (0.67)	3.75 (0.44)	0.039

Discussion

In this study, the proteinuria amounts of type 2 DM patients with DN who did and did not use IMN were compared. There are a limited number of studies on the effect of IMN in reducing proteinuria in DN. However, some studies evaluated the effect of IMN on proteinuria in various diseases. In a study conducted by Gündüz et al. [10], rats with exercise-induced proteinuria used IMN as a nitrite oxide donor and had decreased proteinuria.

In another study, when patients with IgA nephropathy and proteinuria were given IMN, a decrease in proteinuria was reported [11]. In our study, creatinine clearance was calculated with the Cockcroft-Gault formula [13]. The creatinine and urea values were higher and e-GFR was lower among IMN users compared to non-users. Despite this, patients in the IMN group had significantly lower proteinuria values, which shows that IMN use may have a proteinuria-reducing effect among DN patients.

Approximately 40% of diabetic patients have diabetic nephropathy. The treatment aims to prevent the progression of micro and macroalbuminuria, protect kidney function in patients with macroalbuminuria, and prevent cardiovascular events [14]. Besides, changes in serum glucose levels, especially hypoglycemia, in diabetic patients cause endothelial dysfunction by affecting cardiac functions [15]. DN is an independent risk factor for cardiovascular disease and one of the leading causes of end-stage renal failure (ESRD) worldwide [16].

Limitations

There are some limitations to the study. First, this study is a retrospective, single-center study with small sample size. Second, when comparing DN patients who did and did not use IMN, linear regression analysis, in which many factors such as hypertension, smoking, gender, age, and duration of diabetes disease were evaluated together, could not be performed due to the limited data.

Conclusion

The addition of IMN therapy to ACEI or ARB may be a novel alternative in the treatment of proteinuria in DN patients. It would be beneficial to conduct prospective, randomized, controlled, and multicenter studies to examine the effect of IMN treatment on proteinuria in patients with DN.

References

1. Gnudi L, Coward RJ, Long DA. Diabetic nephropathy: perspective on novel molecular mechanisms. Trends Endocrinol Metab. 2016;27(11):820-30. doi: 10.1016/j.tem.2016.07.002.
2. Gross JL, De Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes care. 2005;28(1):164-76. doi: 10.2337/diacare.28.1.164.
3. de Zeeuw D, Remuzzi G, Parving HH, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation. 2004;110(8):921-7. doi: 10.1161/01.CIR.0000139860.33974.28.
4. Macisaac RJ, Jerums G. Diabetic kidney disease with and without albuminuria. Curr Opin Nephrol Hypertens. 2011;20(3):246-57. doi: 10.1097/MNH.0b013e3283456546.
5. Valmadrid CT, Klein R, Moss SE, Klein BE. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. Arch Intern Med. 2000;160(8):1093-100. doi: 10.1001/archinte.160.8.1093.
6. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Ann Intern Med. 2008;148(1):30-48. doi: 10.7326/0003-4819-148-1-200801010-00190.
7. Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851-60. doi: 10.1056/NEJMoa011303.
8. Fernandez-Fernandez B, Ortiz A, Gomez-Guerrero C, Egido J. Therapeutic approaches to diabetic nephropathy—beyond the RAS. Nat Rev Nephrol. 2014;10(6):325. doi: 10.1038/nrneph.2014.74.
9. Gallagher H, Suckling RJ. Diabetic nephropathy: where are we on the journey from pathophysiology to treatment? Diabetes Obes Metab. 2016 Jul;18(7):641-7. doi: 10.1111/dom.12630.
10. Gündüz F, Kuru O, Sentürk UK. Effect of nitric oxide on exercise-induced proteinuria in rats. J Appl Physiol (1985). 2003 Nov;95(5):1867-72. doi: 10.1152/japplphysiol.00599.2003.
11. Roccatello D, Mengozzi G, Ferro M et al. Isosorbide 5 mononitrate administration increases nitric oxide blood levels and reduces proteinuria in IgA glomerulonephritis patients with abnormal urinary endothelin/cyclic GMP ratio. Clin Nephrol. 1995;44(3):163-9.
12. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007 May;39(2):175-91. doi: 10.3758/bf03193146.
13. Lin J, Knight EL, Hogan ML, Singh AK. A comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. J Am Soc Nephrol. 2003 Oct;14(10):2573-80. doi: 10.1097/01.asn.0000088721.98173.4b.
14. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care. 2005;28(1):164-76. doi: 10.2337/diacare.28.1.164.
15. Akhan O, Ardahanli I. Hypoglycemia in the emergency, is there any effect on endothelial and diastolic functions? Echocardiography. 2021 Mar;38(3):450-459. doi: 10.1111/echo.14988.
16. Kim MK. Treatment of diabetic kidney disease: current and future targets. Korean J Intern Med. 2017 Jul;32(4):622-630. doi: 10.3904/kjim.2016.219.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):623-627.
DOI: 10.28982/josam.930254

Journal of Surgery and Medicine
e-ISSN=2602-2079

Neutrophil-to-lymphocyte and fibrinogen-to-albumin ratios may be indicators of worse outcomes in ICU patients with COVID-19

Ahmet Atlas, Nuray Altay, Mahmut Alp Karahan, Veli Pehlivan, Başak Pehlivan, Erdoğan Duran, Mehmet Kenan Erol

Department of Anesthesiology and Reanimation, Harran University Medical Faculty, Sanliurfa, Turkey

ORCID ID of the author(s)
AA: 0000-0001-5999-0510
NA: 0000-0002-7111-7893
MAK: 0000-0002-7210-9481
VP: 0000-0001-5661-4499
BP: 0000-0001-6985-343X
ED: 0000-0002-9606-8266
MKE: 0000-0003-1493-8828

Corresponding Author
Ahmet Atlas
Department of Anesthesiology and Reanimation, Harran University Medical Faculty, Sanliurfa, Turkey
E-mail: ahmetatlas@harran.edu.tr

Ethics Committee Approval
Harran University Clinical Research Ethics Committee; Document Date and Number: 28/09/2020-E.37467.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 June 25

Abstract

Background/Aim: Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a pandemic. Early diagnosis of complications and mortality caused by this disease will guide the treatment process in patients with COVID-19. We aimed to investigate whether the neutrophil/lymphocyte and fibrinogen/albumin ratios can predict mortality in COVID-19 patients.

Methods: A total of 102 adult patients (≥18 years) who were followed up in the intensive care unit (ICU) between May and August 2020 because of COVID-19 were included in this retrospective cohort study. Demographic data, comorbid diseases, and hematological parameters of the patients during admission to the ICU were examined. Hematological parameters such as leukocyte, neutrophil, lymphocyte, platelet counts, C-reactive protein (CRP), D-dimer, and lactate data were recorded. The neutrophil-to-lymphocyte ratio (NLR) and fibrinogen-to-albumin ratio (FAR) were calculated, and their effects on mortality were examined.

Results: Of the patients, 71 (69.6%) were male and the mean age of all patients was 69.1 (14.3) (24–103) years. Comorbid diseases of the patients were as follows: Hypertension (n=40, 39.2%), diabetes mellitus (n=28, 27.4%), chronic obstructive pulmonary disease (n=20, 19.6%), coronary artery disease (n=14, 13.7%), heart failure (n=4, 3.9%), and cerebrovascular disease (n=3, 2.9%). Mortality was higher in older patients (median age = 72; range = 62–80 years) (P=0.043), and bilateral infiltration was observed in lung computed tomography images of all patients who died. Mortality was higher in patients with NLR>9.16, FAR>0.15, D-dimer>2.01 mg/L, CRP >11.6 mg/dL, lactate >2.3 mmol/L.

Conclusion: Elevated levels of neutrophil-to-lymphocyte Ratio, fibrinogen-to-albumin ratio, D-dimer, CRP, and lactate were associated with worse outcomes among COVID-19 patients in the ICU.

Keywords: COVID-19, Mortality, Neutrophil-to-lymphocyte ratio

How to cite: Atlas A, Altay N, Karahan MA, Pehlivan V, Pehlivan B, Duran E, Erol MK. Neutrophil-to-lymphocyte and fibrinogen-to-albumin ratios may be indicators of worse outcomes in ICU patients with COVID-19. J Surg Med. 2021;5(6):623-627.

Introduction

A novel coronavirus called "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" causes COVID-19 disease, which is highly contagious and progresses to pneumonia. Although COVID-19 has been documented to occur primarily as a respiratory infection, emerging data have suggested that it should be considered a systemic disease involving multiple systems, including cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems [1-3]. Although death rates of COVID-19 are lower than SARS and Middle East respiratory syndrome, COVID-19 is more lethal than seasonal flu [4]. Elderly people and those with comorbid diseases are at increased risk of death from COVID-19, but young individuals without underlying major diseases can also experience potentially fatal complications such as fulminant myocarditis and disseminated intravascular coagulation [5, 6].

In most severe COVID-19 cases, several abnormal hematological parameters such as lymphopenia, neutrophilia, high D-dimer and fibrinogen levels, increased leukocyte count, and neutrophil-to-lymphocyte ratio (NLR) have been reported, as well as low percentages of monocytes, eosinophils, and basophils [7-9].

The fibrinogen-to-albumin ratio (FAR) is widely used as an effective marker of inflammation and tends to be highly elevated in various conditions, such as severe infection and malignant disorders [10]. An increased FAR level may be associated with cytokine storms induced by virus invasion [11].

NLR is a convenient index that can be calculated from a complete blood count, and numerous studies have shown that the NLR has a prognostic value in a variety of conditions such as sepsis, cardiovascular disease, and malignant tumors [12-15]. Normal NLR value ranges between 0.78 and 3.53 and is a simple parameter to easily assess a patient's inflammatory status [16].

In our study, we examined the correlation between hematological parameters and the severity of COVID-19 disease. We aimed to predict mortality and detect possible complications in the early period of the disease by examining the hematological parameters during admission to the intensive care unit (ICU).

Materials and methods

In this retrospective cohort study, 102 adult patients aged ≥18 years and hospitalized in the third-level ICU with the diagnosis of COVID-19 between May and August 2020 were included. After obtaining permission from the Ethics Committee for Clinical Research of the Harran University (Document Date and Number: 19.02.2021-12864), patient files were reviewed retrospectively. The data of patients diagnosed with COVID-19 were accessed and evaluated via the hospital information processing system, ICU nurse observations, and patient files.

Demographic data, comorbid diseases, and hematological parameters, complete blood count, coagulation profile, arterial blood gas analysis, blood biochemistry, and inflammation biomarkers of the patients at admission to the ICU were examined. Hematological parameters such as leukocyte, neutrophil, lymphocyte, platelet counts, C-reactive protein (CRP), D-dimer, and lactate data were recorded. NLR and FAR values were calculated. The length of stay in the ICU, duration of mechanical ventilator use, and the length of hospitalization of the patients were analyzed retrospectively.

The COVID-19 treatment protocol in our center comprised pharmacotherapy and respiratory support modalities. Based on the protocol published by the Ministry of Health, pharmacotherapy included antiviral drugs, antibiotics, corticosteroids, and anticoagulants. The patients were administered hydroxychloroquine. Among antiviral drugs, they were prescribed Favipiravir. Corticosteroids (1–2 mg/kg methylprednisolone for 5–7 days) were prescribed to patients with widespread lung infiltration or rapid progression and antibiotics, to those with a secondary bacterial infection. Low-molecular-weight heparin was administered to the patients with high thrombosis risk along with hyperfibrinogenemia.

Patients who met the criteria for admission to the ICU (dyspnea, tachypnea, respiratory rate>30/min, oxygen saturation below 93%, PaO2/FiO2 <300, and/or >50% increase in lung infiltration within 24–48 hours) were admitted to the ICU. Discharge criteria were as follows: Patients with no respiratory failure, oxygen saturation of 94% while receiving 2 L/min nasal oxygen, oxygen saturation of 92% at room air, no need for mechanical ventilation, and having passed 48 hours after extubation, no need for vasopressors, and clinically stability. These patients were transported from the ICU to the wards.

Statistical analysis

The distribution of continuous variables was evaluated by Shapiro–Wilk test. Mann–Whitney U test was used to compare two independent groups of non-normally distributed data, and Cohen's d effect size was calculated for numerical variables. Binary logistic regression analysis was performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curve analysis was performed to determine diagnostic values of some numerical measurements. Statistical analysis was performed with SPSS for Windows version 24.0, and a *P*-value <0.05 was considered statistically significant.

Results

In our hospital, 732 patients diagnosed with COVID-19 were treated between May and August 2020. A total of 35 patients aged <18 years and 595 patients treated in the normal wards were excluded from the study. In total, 102 COVID-19 patients who were followed up in the ICU were included in our study (Figure 1). The mean age of the patients was 69.1 (14.3) (24–103) years, and 71 (69.6%) were male. Comorbid diseases of these patients were as follows: Hypertension (HT) (n=40, 39.2%), diabetes mellitus (DM) (n=28, 27.4%), chronic obstructive pulmonary disease (COPD) (n=20, 19.6%), coronary artery disease (CAD) (n=14, 13.7%), heart failure (n=4, 3.9%), and cerebrovascular disease (CVD) (n=3, 2.9%) (Table 1). More than one comorbid disease was found in 30 patients (29.4%). The number of patients without a comorbid disease was 19 (18.6%). The most common comorbid disease was hypertension. Of the patients, 80.7% received mechanical ventilation support. Bilateral pneumonia proven by chest computed tomography (CT) was reported in 91.2% of the patients.

Figure 1: The patient inclusion and exclusion diagram

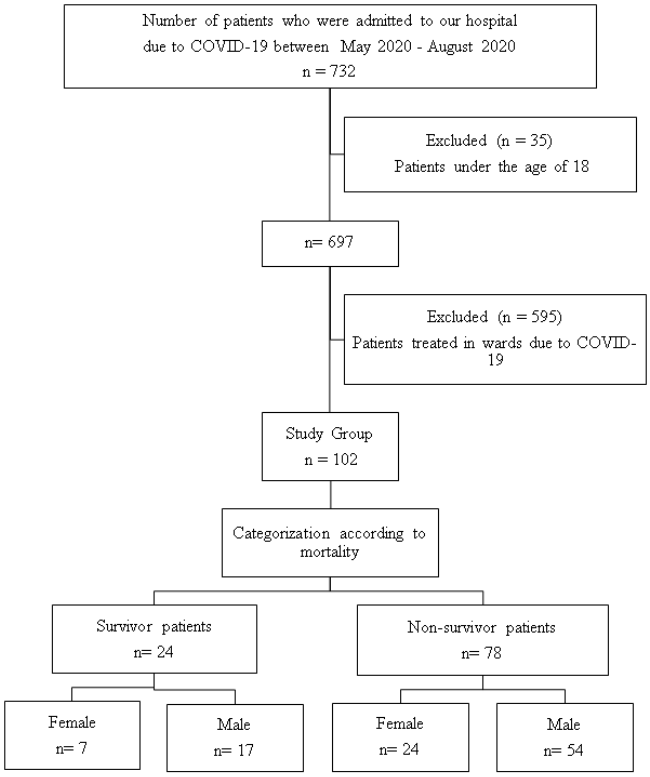


Table 1: Demographic data

Variables		Patient (n = 102)
Age (mean (SD))		69.1 (14.3)
Gender, n (%)		
Male		71 (69.6)
Female		31 (30.4)
Comorbid disease, n (%)		
DM	Yes	28 (27.5)
	No	74 (72.5)
HT	Yes	40 (39.2)
	No	62 (60.8)
COPD	Yes	20 (19.6)
	No	82 (80.4)
CAH	Yes	14 (13.7)
	No	88 (86.3)
Heart failure	Yes	4 (3.9)
	No	98 (96.1)
CVD	Yes	3 (2.9)
	No	99 (97.1)
CT findings	Bilateral	93 (91.2)
	Unilateral	9 (8.8)

SD: Standard deviation, DM: Diabetes Mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, CAH: Coronary artery disease, CVD: Cerebrovascular disease, CT: Computed tomography

Laboratory examination during admission to the ICU revealed abnormalities, particularly in the peripheral blood cell and coagulation profile. The mean hemoglobin level, neutrophil, lymphocyte, and platelet counts of the patients were 12.8 (1.9) g/dl, 10.3 (3.6) $\times 10^3$/L, and 0.74 (0.3) $\times 10^3$/L, and 272 (117)$\times 10^3$/L, respectively. The mean NLR, FAR, D-dimer, CRP, lactate levels of the patients were 16.1(8.2), 0.19 (0.04), 10.5 (15.5) mg/L, 15.2 (8.5) mg/dl, and 2.9 (1.9) mmol/L, respectively. The mean length of stay in the ICU was 8.8 (8.9) days, the mean duration of mechanical ventilation, 5.5 (8.8) days, and the mean length of hospital stay, 12.7 (10.5) days (Table 2).

The demographic and hematological parameters of the non-surviving and surviving patients were compared. Twenty-four patients (23.5%) survived their stay in the ICU and were transported to the normal wards, while 78 patients (76.5%) died. The two groups were similar in terms of gender, comorbid diseases, and hemoglobin levels. Results indicated that mortality was higher in older patients (median = 72 years; range = 62–80 years), and lung CTs of all the non-survivors showed bilateral infiltration (P=0.043; P=0.004). DM was detected in 29.5%, HT in 37.2%, and COPD in 20.5% of the non-survivors (Table 3). Among them, the median neutrophil and lymphocyte counts were 10.8 (8.76–13.2) × 109/L, and 0.55 (0.48–0.75) × 109/L, respectively (P=0.001). Their NLR and FAR values were 18.25 (14–22.3) and 0.2 (0.18–0.23), respectively (P=0.001). Median CRP, D-dimer and lactate values of the non-survivors were 15.85 (12.4–21.1) mg/dL, 7.03 (3.36–17.7) mg/L, and 2.9 (2.2–3.9) mmol/L, respectively (P=0.001; Table 4). The neutrophil, NLR, FAR, CRP, D-dimer, and lactate levels of the non-survivors were significantly higher, while their lymphocyte levels were significantly lower compared with the survivors ($p < 0.05$). ROC and area under the curve (AUC) values of hematological and inflammatory indices were calculated between the two groups (Figure 2). According to ROC curve analysis, we observed that NLR, FAR, D-dimer, CRP, and lactate data were successful in predicting mortality in patients with COVID-19. The AUCs for NLR, FAR, D-dimer, CRP, and lactate were 0.969, 0.989, 0.927, 0.913, and 0.893, respectively. We found that mortality increased in patients with NLR>9.16, FAR>0.15, D-dimer >2.01 mg/L, CRP >11.6 mg/dL, and lactate >2.3 mmol/L.

Table 2: Clinical and laboratory data of the patients

Data (n:102)	Mean (SD)	Median (min–max)
Hb (g/dL)	12.85 (1.97)	12.95 (8.45–18.2)
WBC ($\times 10^3$/L)	11.72 (3.94)	11.6 (1.89–20.7)
Neutrophil ($\times 10^3$/L)	10.28 (3.63)	10.5 (1.14–18.1)
Lymphocyte ($\times 10^3$/L)	0.74 (0.33)	0.65 (0.21–1.75)
NLR	16.11 (8.19)	16.45 (2.47–50.9)
Platelet ($\times 10^3$/L)	272.1 (117.8)	255 (43–718)
Fibrinogen (g/L)	5.63 (1.18)	5.64 (3.2–8.47)
Albumin (g/L)	30.12 (2.69)	30 (22–36)
FAR	0.19 (0.04)	0.19 (0.11–0.29)
CRP (mg/L)	15.22 (8.59	14.55 (1.71–47.2)
D-dimer (mg/L)	10.47 (15.53)	3.74 (0.34–80)
Lactate (mmol/L)	2.91 (1.94)	2.4 (1.1–11.8)
Mechanical ventilator time/day	5.5 (8.8)	2 (0–60)
ICU stay/day	8.8 (8.9)	6 (1–60)
Hospital stay/day	12.7 (10.5)	10 (1–65)

SD: Standard deviation, min: Minimum, max: Maximum, Hb: Hemoglobin, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, FAR: Fibrinogen-to-albumin ratio, CRP: C-reactive protein, ICU: Intensive care unit

Table 3: Relationship between mortality and categorical variables

Variables		Non-survivor (n = 78) n (%)	Survivor (n = 24) n (%)	OR [95% CI]	*P*-value
Gender	Male	54 (69.2)	17 (70.8)	1.08 [0.39–2.94]	0.881
	Female	24 (30.8)	7 (29.2)	1 (reference)	
CT findings	Bilateral	78 (100)	15 (62.5)	46.8 [5.52–397.2]	*0.004**
	Unilateral	0 (0)	9 (37.5)	1 (reference)	
DM		23 (29.5)	5 (20.8)	1.59 [0.53–4.77]	0.409
HT		29 (37.2)	11 (45.8)	1.43 [0.57–3.61]	0.449
COPD		16 (20.5)	4 (16.7)	1.29 [0.39–4.31]	0.679

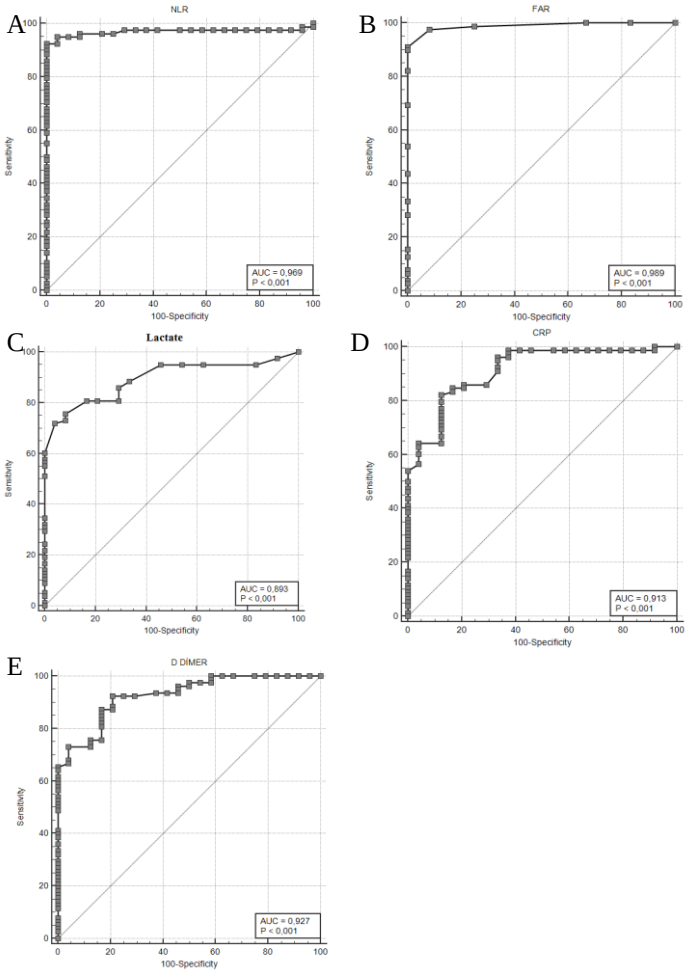
*significant at 0.05 level. Univariate binary logistic regression analysis. OR: Odds ratio, CI: Confidence interval, CT: Computed tomography, DM: Diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease

Table 4: Comparison of clinical and laboratory data of patients with and without mortality

Variables	Non-survivor (n = 78) Median (min–max)	Survivor (n = 24) Median (min–max)	Cohen's *d* effect size	*P*-value
Age (year)	72 (62–80)	66 (52–75.5)	0.55	0.043 *
Hb (g/dL)	13 (11.7–14)	12.85 (9.95–14.2)	0,30	0.435
WBC ($\times 10^3$/L)	12.2 (10.1–14.3)	9.67 (7.52–11.45)	0.66	0.004 *
Neutrophil ($\times 10^3$/L)	10.8 (8.76–13.2)	7.64 (6.36–10.03)	0.79	0.001 *
Lymphocyte ($\times 10^3$/L)	0.55 (0.48–0.75)	1.02 (0.95–1.32)	*1.89*	0.001 *
NLR	18.25 (14–22.3)	7.35 (6.52–7.82)	*1.78*	0.001 *
Platelet ($\times 10^3$/L)	247 (192– 354)	310 (234– 350)	0.37	0,193
Fibrinogen (g/L)	5.85 (5.46–6.67)	4.2 (4.1–4.4)	*2.28*	0.001 *
Albumin (g/L)	30 (28–31)	31 (30.5–32)	0.82	0.001 *
FAR	0.2 (0.18–0.23)	0.13 (0.12–0.14)	*2.43*	0.001 *
CRP (mg/L)	15.85 (12.4–21.1)	6.6 (4.55–9.4)	*1.40*	0.001 *
D-dimer (mg/L)	7.03 (3.36–17.7)	1.59 (0.82–2)	0.78	0.001 *
Lactate (mmol / L)	2.9 (2.2–3.9)	1.5 (1.3–1.9)	0.96	0.001 *
ICU hospitalization period/day	6 (3–13)	5 (3–9.5)	0,26	0.534
Mechanical ventilator time/day	4 (1–9)	0 (0–0)	0.76	0.001 *
Hospital stay/day	9 (5–16)	14.5 (9–18)	0.33	0.017 *

*significant at 0.05 level, Median [25%–75%], Mann–Whitney U test. Hb: Hemoglobin, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, FAR: Fibrinogen-to-albumin ratio, CRP: C-reactive protein, ICU: Intensive care unit.

Figure 2: Results of neutrophil-to-lymphocyte ratio (NLR), fibrinogen-to-albumin ratio (FAR), lactate, C-reactive protein (CRP), and D-dimer receiver operating characteristic (ROC) curve analyses in patients with COVID 19. A: NLR ROC curve analysis; B: FAR ROC curve analysis; C: Lactate ROC curve analysis; D: CRP ROC curve analysis; E: D-dimer ROC curve analysis



Discussion

In this study, we found that older age, high neutrophil count, NLR, FAR, D-dimer, CRP, and lactate successfully predicted mortality. FAR (AUC=0.989) and NLR (AUC = 0.969) had the highest AUC values. A previous study reported that the mean age of patients hospitalized because of COVID-19 was 46.6 (12) (22–77) years, 60% were male, and 17.3% had underlying comorbidities. A bilateral ground-glass image was observed in the lung CT of 76% of these patients. Moreover, 21.3% of the patients were followed up in the ICU [17]. In their study examining 245 patients diagnosed with COVID-19, Liu et al. reported that the mean age was 53.95 (16.90) years and 46.53% of the patients were male. They stated that 3.2% of patients had COPD, 21.22% had HT, and 9.39% had DM and the in-hospital mortality rate was 13.47% [18]. In our study, we found that gender was not significant in terms of mortality; however, mortality increased with older age.

In their study investigating 1,099 COVID-19 cases, Guan et al [7] reported that most patients presented with lymphocytopenia (83.2%), 36.2% had thrombocytopenia and 33.7% had leukopenia. Huang et al. [8] and Wang et al. [11] emphasized the relationship between lymphopenia and admission to the ICU. Wu et al. [19] demonstrated a relationship between lymphopenia and the development of acute respiratory distress syndrome (ARDS). In their study, they retrospectively analyzed the risk factors for ARDS and mortality in 201 patients with COVID-19 pneumonia and found that increased risk of ARDS during the disease was associated with increased neutrophil and decreased lymphocyte count by bivariate Cox regression analysis. They reported a positive correlation between increased neutrophil count and mortality rate. In our study, consistent with the literature, we found a strong correlation between increased neutrophil count and mortality.

Fan et al. [20] found that patients needing ICU support initially had significantly lower lymphocyte levels. Lymphopenia was reported in 85% of patients in another retrospective study involving 52 critically ill patients in Wuhan, China [21]. Other studies have also shown that lymphopenia was prominent in critically ill patients with COVID-19 [22, 23]. The mortality rate was higher in patients with lymphopenia during hospitalization [11]. Patients with severe diseases and fatal outcomes have been reported to have a decreased lymphocyte/white blood cell ratio both at admission and during hospitalization [9, 24]. Tan et al. [25] reported that patients with lymphocytes <20% on days 10–12 and <5% on days 17– 19 from the onset of symptoms had a poor prognosis. In our study, similar to the literature, we found that mortality was higher in patients with lymphopenia.

The hyperactivity of fibrinolysis usually results in increased platelet consumption. Although widely used to treat patients with severe COVID-19, corticosteroids can also cause thrombocytopenia [26]. Lippi et al. [27] reported that thrombocytopenia was associated with an increased risk of serious illness and death in patients with COVID-19. In our study, there was no significant relationship between the decrease in platelet count and mortality.

NLR was proposed as a new biomarker for systemic inflammation in which both neutrophil and lymphocyte count are considered [28]. High NLR occurs due to increased neutrophil and decreased lymphocyte counts. The inflammatory response can stimulate neutrophil production and accelerate the apoptosis of lymphocytes [29]. Qin et al. [9] reported that severe cases of COVID-19 had higher neutrophil, but lower lymphocyte counts than non-severe cases; therefore, NLR was higher in patients with severe infection. In their study examining 155 patients with COVID-19, Mo et al. [30] found that patients who did not respond to treatment had higher neutrophil levels. In our study, there was a direct relationship between increased NLR and mortality.

FAR is widely used as an effective marker of inflammation, and it tends to be elevated in various conditions, such as severe infection and malignant disorders [10]. An increased FAR level may be associated with cytokine storms induced by virus invasion [11]. In our study, the median FAR values of the non-survivors and survivors were 0.2 (0.18–0.23) and 0.13 (0.12–0.14), respectively. We found that the mortality rate was high in patients with high FAR.

Studies have reported that high CRP is an indicator of poor prognosis. Guan et al. [7] reported that CRP increased in 60.7% of the patients. The severity of the disease was associated with high CRP, and they detected high CRP levels in 81.5% (110 / 135) of the severe cases. Wu et al. [19] found a relationship between high CRP and the development of ARDS. Deng et al. [24] reported that the mortality rate was high in patients with high CRP levels at the time of admission. Consistent with the

literature, we found that mortality increased in patients with high CRP values during hospitalization.

In patients with COVID-19, the incidence of coagulation disorders increases with the severity of the disease [24, 31]. A multicenter retrospective study showed that 46.4% of 560 patients with laboratory-confirmed COVID-19 infection had high D-dimer levels [7]. It has been reported that high D-dimer levels were associated with poor prognosis in patients with community-acquired pneumonia [32]. High D-dimer (>1.5 mg/L) was detected in 36% of the patients in a study of 99 COVID-19 cases in Wuhan, China [26]. Another retrospective study on 41 patients in China reported that D-dimer and prothrombin time levels were higher at admission among patients requiring ICU support (median D-dimer was 2.4 mg/L within the ICU and 0.5 mg/L outside the ICU) [8]. Wang et al. [11] reported that the patients needing ICU support had high D-dimer levels. In accordance with the literature, we found a relationship between high D-dimer levels and mortality.

Limitations

The single-center retrospective design of our study is its major limitation.

Conclusion

Elevated levels of neutrophil-to-lymphocyte ratio, fibrinogen-to-albumin ratio, D-dimer, CRP, and lactate were associated with worse outcomes among COVID-19 patients in the ICU. These parameters should be closely monitored in hospitalized COVID-19 patients. Morbidity and mortality can be prevented with early interventions by evaluating these parameters. More studies are needed to confirm these findings.

References

1. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. J Am Coll Cardiol. 2020 May 12;75(18):2352-71. doi: 10.1016/j.jacc.2020.03.031.
2. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol. 2020 Jun;5(6):529-30. doi: 10.1016/S2468-1253(20)30084-4.
3. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395(10229):1033-4. doi: 10.1016/S0140-6736(20)30628-0.
4. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr 7;323(13):1239-42. doi: 10.1001/jama.2020.2648.
5. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020 Apr;18(4):844-7. doi: 10.1111/jth.14768.
6. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol. 2020 Jul 1;5(7):831-40. doi: 10.1001/jamacardio.2020.1286.
7. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-20. doi: 10.1056/NEJMoa2002032.
8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5.
9. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020 Jul 28;71(15):762-8. doi: 10.1093/cid/ciaa248.
10. Sun DW, An L, Lv GY. Albumin-fibrinogen ratio and fibrinogen-prealbumin ratio as promising prognostic markers for cancers: an updated meta-analysis. World J Surg Oncol. 2020 Jan 13;18(1):9. doi: 10.1186/s12957-020-1786-2.
11. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061-9. doi: 10.1001/jama.2020.1585.
12. Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, de Jager CPC, et al. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: A systematic review and meta-analysis. J Infect. 2019 May;78(5):339-48. doi: 10.1016/j.jinf.2019.02.006.
13. Huguet E, Maccallini G, Pardini P, Hidalgo M, Obregon S, Botto F, et al. Reference Values for Neutrophil to Lymphocyte Ratio (NLR), a Biomarker of Cardiovascular Risk, According to Age and Sex in a Latin American Population. Curr Probl Cardiol. 2021 Mar;46(3):100422. doi: 10.1016/j.cpcardiol.2019.04.002.
14. Park JS, Seo KW, Choi BJ, Choi SY, Yoon MH, Hwang GS, et al. Importance of prognostic value of neutrophil to lymphocyte ratio in patients with ST-elevation myocardial infarction. Medicine (Baltimore). 2018 Nov;97(48):e13471. doi: 10.1097/MD.0000000000013471.
15. Mei Z, Shi L, Wang B, Yang J, Xiao Z, Du P, et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: A systematic review and meta-analysis of 66 cohort studies. Cancer Treat Rev. 2017 Jul;58:1-13. doi: 10.1016/j.ctrv.2017.05.005.
16. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes. 2017 Jan 3;10(1):12. doi: 10.1186/s13104-016-2335-5.
17. Fu J, Kong J, Wang W, Wu M, Yao L, Wang Z, et al. The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: A retrospective study in Suzhou China. Thromb Res. 2020 Aug;192:3-8. doi: 10.1016/j.thromres.2020.05.006.
18. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020 Jul;81(1):e6-e12. doi: 10.1016/j.jinf.2020.04.002.
19. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020 Jul 1;180(7):934-43. doi: 10.1001/jamainternmed.2020.0994.
20. Fan BE. Hematologic parameters in patients with COVID-19 infection: a reply. Am J Hematol. 2020 Aug;95(8):E215. doi: 10.1002/ajh.25847.
21. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475-81. doi: 10.1016/S2213-2600(20)30079-5.
22. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA. 2020 Apr 28;323(16):1612-4. doi: 10.1001/jama.2020.4326.
23. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med. 2020 May 21;382(21):2012-22. doi: 10.1056/NEJMoa2004500.
24. Deng Y, Liu W, Liu K, Fang YY, Shang J, Zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: a retrospective study. Chin Med J (Engl). 2020 Jun 5;133(11):1261-7. doi: 10.1097/CM9.0000000000000824.
25. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020 Mar 27;5(1):33. doi: 10.1038/s41392-020-0148-4. Erratum in: Signal Transduct Target Ther. 2020 Apr 29;5(1):61. doi: 10.1038/s41392-020-0148-4.
26. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507-13. doi: 10.1016/S0140-6736(20)30211-7.
27. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta. 2020 Jul;506:145-8. doi: 10.1016/j.cca.2020.03.022.
28. Yıldırım ÖT, Akşit E, Aydın F, Aydın AH, Dağtekin E. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio can be used as biomarkers for non-dipper blood pressure. J Surg Med. 2019;3(1):4-7. doi: 10.28982/josam.436951
29. Forget P, Moreau N, Engel H, Cornu O, Boland B, De Kock M, et al. The neutrophil-to-lymphocyte ratio (NLR) after surgery for hip fracture (HF). Arch Gerontol Geriatr. 2015 Mar-Apr;60(2):366-71. doi: 10.1016/j.archger.2014.11.008.
30. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis. 2020 Mar 16:ciaa270. doi: 10.1093/cid/ciaa270.
31. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-62. doi: 10.1016/S0140-6736(20)30566-3.
32. Snijders D, Schoorl M, Schoorl M, Bartels PC, van der Werf TS, Boersma WG. D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomised clinical trial. Eur J Intern Med. 2012 Jul;23(5):436-41. doi: 10.1016/j.ejim.2011.10.019.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):628-632.
DOI: 10.28982/josam.859388

Journal of Surgery and Medicine
e-ISSN=2602-2079

Association of circulating preptin with non-alcoholic fatty liver disease: A case-control study

Derya Argun [1], Pelin Basım [2], Betul Borku Uysal [3], Ferit Argun [1]

[1] Istanbul Aydın University, Medical Faculty, Department of Internal Medicine, Istanbul, Turkey
[2] Istanbul Medipol University, Medical Faculty, Department of General Surgery, Istanbul, Turkey
[3] Istanbul Biruni University, Medical Faculty, Department of Internal Medicine, Istanbul, Turkey

ORCID ID of the author(s)

DA: 0000-0002-0141-3515
PB: 0000-0002-9452-9276
BBU: 0000-0001-9292-5024
FA: 0000-0002-2192-9084

Corresponding Author
Derya Argun
Beşyol, Florya, Akasya Sk. No:4 D:1, 34295
Küçükçekmece, Istanbul, Turkey
E-mail: dr.deryaargun@gmail.com

Ethics Committee Approval
The study protocol was approved by the Medipol University Ethics Committee (10840098-604.01.01-E.175 number:1191).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 June 25

Abstract

Background/Aim: Non-alcoholic fatty liver disease (NAFLD) is the hepatic component of metabolic disorders and identifying patients with a high risk of fibrosis is crucial. A scoring system, the FIB-4 score, based on clinical and biochemical parameters was developed to predict fibrosis. NAFLD is associated with various peptide hormones. However, the relationship of preptin, a newly discovered peptide critical for regulating energy metabolism, with NAFLD remains unclear. Therefore, we aimed to determine the relationship of preptin with NAFLD and evaluate whether there was an association between serum preptin levels and FIB-4 score.

Methods: In this prospective study, serum biochemical parameters and serum preptin levels of 51 patients with grade 2-3 hepatosteatosis proven by ultrasonography and 35 healthy controls with similar demographic characteristics were compared. Serum preptin levels were measured using ELISA. The FIB-4 scores were calculated and recorded.

Results: The serum preptin levels were higher in the NAFLD group than in the control cases (P<0.001). Among the patients, the sensitivity, specificity, positive predictive, and negative predictive values of preptin above a cut-off value of ≥62.3 were 85.7%, 56.9%, 85.3%, and 57.7%, respectively, with an accuracy of 68.6%. The preptin level was negatively correlated with the FIB-4 score and AST in the patient group (P=0.004 and P=0.014, respectively). The linear regression model revealed that there was a significant relationship between the FIB-4 score and preptin (P<0.05). Each 1 unit increase in the FIB-4 score induced a decrease of 86.37 units in preptin values (R^2=%8.5).

Conclusion: We demonstrated that the serum preptin levels were higher in patients with NAFLD than healthy individuals and negatively correlated with the FIB-4 score and AST levels. Preptin may have a role in the pathogenesis of NAFLD, is likely to distinguish patients with mild and severe liver damage and may be a useful marker in predicting a high risk for progression to fibrosis. Further studies establishing a stratification system including plasma preptin level and the FIB-4 score and its verification with liver biopsies are required.

Keywords: Preptin, Hepatosteatosis, Non-alcoholic fatty liver disease

How to cite: Argun D, Basım P, Uysal BB, Argun F. Association of circulating preptin with non-alcoholic fatty liver disease: A case-control study. J Surg Med. 2021;5(6):628-632.

Introduction

Non-alcoholic fatty liver disease (NAFLD), defined as liver dysfunction with excessive fat deposition in the liver parenchyma without evidence of significant alcohol consumption or other secondary etiologies of liver disease, is acknowledged as the most common cause and form of chronic liver disease and estimated to affect 20-30% of the general population [1]. NAFLD encompasses simple steatosis (SS), non-alcoholic steatohepatitis (NASH), liver cirrhosis, and hepatocellular carcinoma (HCC). SS is the most common type and has been considered the most benign presentation of the disease [2]. Unfortunately, about 30 percent of patients with SS progress to NASH, which is defined as the presence of NAFL plus inflammation with hepatocyte damage, fibrosis, and cirrhosis, or HCC [3, 4]. Therefore, it is important to identify groups of patients with a higher risk of advanced fibrosis to optimally conduct follow-up and treatment.

Although liver biopsy is the gold standard for diagnosing and staging liver fibrosis, various non-invasive estimation methods have been developed based on the clinical and biochemical parameters to assess fibrosis without a liver biopsy. Based on this idea, the FIB-4 score consisting of age, liver function tests, and platelet counts of the patient has been established to forecast advanced fibrosis in patients with NAFLD [5]. However, the complexity of NAFLD pathogenesis and various biological deflections make it difficult to distinguish NASH and SS with a single biomarker.

Recently, NAFLD was found to be associated with various peptide hormones synthesized in a multitude of tissues [6-8]. Preptin, the importance of which is just beginning to be understood, is a 34-amino acid peptide derived from proinsulin-like growth factor II (pro-IGF-II) [9]. This peptide hormone is synthesized in pancreatic β-cells and co-secreted from cells with insulin in response to glucose [10]. Preptin has also been found in the salivary glands, breast tissue, and kidneys [11]. Previous studies have demonstrated that preptin induces insulin secretion via a variety of biochemical pathways. In experimental studies, intravenous preptin infusion in rats has been shown to cause a decrease in blood glucose level associated with insulin secretion during glucose loading. Glibenclamide and preptin, which stimulate insulin secretion by blocking ATP-sensitive potassium channels in pancreatic β-cells, have similar effects on insulin secretion [12]. Additionally, human studies showed that preptin levels were increased in metabolic disorders such as gestational diabetes mellitus (GDM), polycystic ovary syndrome (PCOS), diabetes mellitus (DM), and high blood pressure, and there was a significant relationship between preptin and body mass index (BMI) [11-19].

Despite the serious damage caused by NAFLD, the underlying pathological mechanism has not yet been fully elucidated. Although the effects of metabolic factors, reactive oxygen metabolites, cytokines, endotoxins, and mitochondrial changes have been proven in the etiopathogenesis of fatty liver disease [20], the effects of peptide hormones are still a matter of debate. In this study, we aimed to determine the relationship between preptin and NAFLD and evaluate the possible association between serum preptin levels and the FIB-4 score in this patient group.

Materials and methods

Study design

This single-centered study was planned and conducted prospectively with 86 patients aged 17 to 70 years who presented to the internal medicine outpatient clinic of Medipol Mega University Hospital between January 2020 and April 2020. The patient group of our study consisted of 51 patients with grade 2-3 hepatosteatosis according to liver ultrasonography. Thirty-five healthy individuals with similar demographics were included in the study as a control group. To avoid possible effects of blood glucose disorders, patients with insulin resistance and diabetes mellitus were excluded, as well as patients with a history of hypertension, kidney diseases, and malignancies, viral/autoimmune hepatitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, primary sclerosing cholangitis, biliary system diseases, an alcohol consumption of >20 g/day, those using hepatotoxic drugs, herbal products, those receiving hormone replacement therapy or antidiabetic medication and pregnant women.

Ethical approval and patient consent

All patients were given detailed information that the study was not part of their treatment, and informed consent of all participants was obtained. The study protocol was approved by Medipol University Ethics Committee (10840098-604.01.01-E.175 number:1191) and conducted per the principles of the Declaration of Helsinki.

Blood sample test

Blood samples were taken from the patients after 10 to 12 hours of fasting. Laboratory data, including the levels of serum glucose, HbA1c, total cholesterol, low-density lipoprotein cholesterol (LDL), triglyceride, high-density lipoprotein-cholesterol (HDL), urea, creatinine, aspartate transaminase (AST), alanine transaminase (ALT) levels were analyzed using routine methods with an autoanalyzer. During routine blood tests, an extra tube of blood was collected from the participants into EDTA tubes and centrifuged at 1,000g for 15 min, and the obtained sera were stored at -80 °C until preptin analysis.

The height and weight of the participants were measured, and the value obtained by dividing the body weight by the square of height was recorded as BMI (kg/m²). In all cases, the blood pressure, measured with a sphygmomanometer after 10 minutes of rest, was recorded.

Measurement of serum preptin by ELISA

Serum preptin levels were measured using an enzyme-linked immunosorbent test kit in a human double antibody sandwich (catalog number E-EL-H0913 96T; Donghu Hi-Tech Development Area, Wuhan, Hubei, China). Measurement with preptin immunosorbent test kits was performed by the ELISA method per the manufacturer's protocol. The results were expressed as picograms per milliliter (pg/mL). The coefficient of variation (CV) is <10 %, sensitivity is 37.50 pg/ml, and detection range is 50-4.000 pg/mL for the preptin ELISA kit.

Ultrasound examination protocol

The liver of all patients was evaluated by the same radiologist using an X brand ultrasonography device after at least

eight hours of fasting. The degree of hepatosteatosis was divided into four groups: Normal (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3), depending on the increase in the parenchymal echo, the thickness of intrahepatic vascular structures, diaphragm and gallbladder wall, and whether there was clear visualization of the fatty liver with an increased parenchymal echo.

Calculation of the FIB-4 score

The following formula was used to calculate the FIB-4 score: [age (years) × (AST)] / [platelet counts ($\times 10^9$/L) × √ALT U/L].

Statistical analysis

The power analysis for the mean preptin level differences between the two groups was performed using G power 3.1.6 for Windows. The minimum required size of the study population was calculated as 90 subjects for a large effect size at a 95% confidence interval for α=0.05. The data were collected, transferred to the Microsoft Excel program, organized, cleaned, and rendered suitable for analysis. Mann Whitney U, T-Test, ROC Curve Analysis, Spearman Correlation Tests, and Linear Regression Analysis were used for assessment. Data were tested using the IBM SPSS Statistics 26.0 (Statistical Package for Social Science) package programs. A *P*-value of <0.05 was considered statistically significant.

Results

The demographical and clinical characteristics of the participants are shown in Table 1. The study was conducted with 86 patients as four out of ninety participants reported that they wanted to leave the study. Fifty-one patients diagnosed with grade 2-3 hepatosteatosis and 35 healthy control cases were included.

Table 1: Demographic and disease-related characteristics

	Hepatosteatosis group (n = 51)	Control group (n = 35)	*P*-value
Age (years) Mean (SD)	40.69 (9.19)	36.23 (11.94)	0.054
Male	27 (52.9)	19 (54.3)	0.539
Gender			
Female	24 (47.1)	16 (45.7)	
BMI (kg/m²) Mean (SD)	25.15 (1.81)	25.13 (1.05)	0.951
SBP (mmHg) Mean (SD)	122.88 (8.93)	120.03 (10.86)	0.186
DBP (mmHg) Mean (SD)	75.02 (6.3)	74.63 (6.62)	0.782
FIB-4	0.58 (0.24)	-	-

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

The laboratory data of the participants are summarized in Table 2. The serum preptin, AST, ALT, and triglyceride levels of the NAFLD group were significantly higher than those of the control cases (*P*<0.001, and *P*<0.01 for the latter three, respectively). In addition, serum HDL levels were significantly lower in the NAFLD group compared to the control group (*P*<0.001).

Table 2: Laboratory findings of the NAFLD and control groups

	NAFLD group		Control group		*P*-value
	Mean (SD)	Range	Mean (SD)	Range	
Glucose (mg/dl)	92.19 (4.37)	92-16.6	92.04 (4.34)	92-15	0.873
Urea (mg/dl)	26.65 (5.74)	26.4-28.2	25.31 (6.05)	25-20.5	0.299
Creatinine (mg/dl)	0.92 (0.14)	0.93-0.59	0.86 (0.18)	0.86-0.72	0.129
AST (IU/L)	23.95 (9.43)	22.8-45.1	18.31 (12.93)	16-76	<0.001*
ALT (IU/L)	44.69 (25.19)	39.5-126.2	17.31 (8.9)	16-40.7	<0.001*
TC (mg/dl)	197.37(39.22)	196.6-181.4	188.42 (30.36)	186-134	0.259
LDL-C (mg/dl)	119.14 (37.34)	123-166	113.54 (28.04)	109-114	0.454
HDL-C (mg/dl)	42.36 (9.23)	39.9-38	55.09 (11.76)	56-42	<0.001*
TG (mg/dl)	194.16 (102.35)	167.1-517.4	99.68 (45.53)	92-214	<0.001*
HbA1c (%)	5.25 (0.32)	5.3-1.46	5.23 (0.3)	5.22-1.25	0.824
Preptin (pg/ml)	83.73 (71.11)	64.01-472.32	56.52 (8.08)	54.24-40.83	<0.001*

*Statistically significant at 0.05, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride.

The minimum-maximum, 25-75% percentile, and median values of serum preptin levels were higher in the patient group compared to the control group (Figure 1). In the patient group, the serum preptin level's area under the curve (AUC) in ROC analysis, its cut-off, sensitivity, specificity, positive and negative predictive values, and accuracy were 0.767 (95% CI 0.668-0.866) (Figure 2), ≥62.3, 85.7%, 56.9%, 85.3%, 57.7%, and 68.6%, respectively (Table 3).

Figure 1: Minimum, maximum, 25-75% percentile and median values of serum preptin levels of the participants

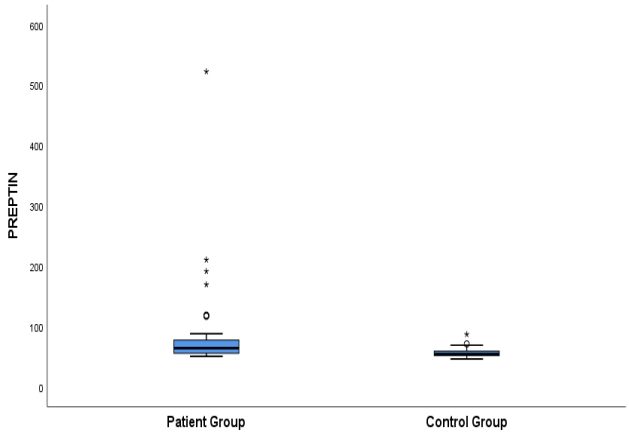


Figure 2: The receiver operating characteristic curve for determining the serum preptin level of the patient group (AUC):0.767 %95 CI 0.668-0.866

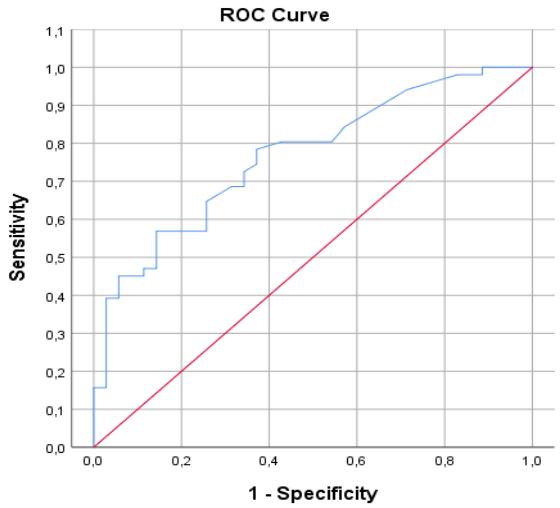


Table 3: The sensitivity, specificity, PPV and NPV of preptin to predict NAFLD

	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
Preptin	62.33	85.7%	56.9%	85.3%	57.7%	68.6%

PPV: positive predictive value, NPV: negative predictive value

The preptin level was significantly negatively correlated with the FIB-4 score and AST level in the patient group (*P*=0.004 and *P*=0.014, respectively), while in the control group, preptin was significantly negatively correlated with urea and creatinine and positively correlated with triglyceride (*P*=0.029, *P*=0.034 and *P*=0.038, respectively) (Table 4).

The results of the linear regression model are given in detail in Table 5. Accordingly, the FIB-4 score was significantly related to preptin (*P*<0.05). One unit increase in FIB-4 values induces a decrease of 86.37 units in preptin values (R^2=%8.5) (Table 5) (Figure 3).

Table 4: Spearman's correlation analyses between preptin and other variables

	General	Hepatosteatosis	Control
Age (years)	0.00 (*P*=0.973)	-0.25 (*P*=0.079)	0.06 (*P*=0.723)
Glucose (mg/dl)	-0.02 (*P*=0.841)	-0.06 (*P*=0.668)	0.04 (*P*=0.823)
Urea (mg/dl)	-0.18 (*P*=0.099)	-0.18 (*P*=0.210)	-0.37 (*P*=0.029*)
Creatinine (mg/dl)	0.03 (*P*=0.753)	0.19 (*P*=0.177)	-0.36 (*P*=0.034*)
AST (IU/L)	-0.04 (*P*=0.746)	-0.34 (*P*=0.014*)	-0.17 (*P*=0.340)
ALT (IU/L)	0.19 (*P*=0.079)	-0.18 (*P*=0.197)	-0.22 (*P*=0.211)
TC (mg/dl)	0.06 (*P*=0.611)	-0.10 (*P*=0.496)	0.11 (*P*=0.527)
LDL-C (mg/dl)	0.03 (*P*=0.764)	-0.05 (*P*=0.740)	0.05 (*P*=0.777)
HDL-C (mg/dl)	-0.37 (*P*<0.001*)	-0.18 (*P*=0.206)	-0.10 (*P*=0.551)
TG (mg/dl)	0.50 (*P*<0.001*)	0.22 (*P*=0.129)	0.35 (*P*=0.038*)
BMI (kg(m²)	0.05 (*P*=0.651)	0.18 (*P*=0.203)	-0.22 (*P*=0.203)
SBP (mmHg)	0.12 (*P*=0.275)	0.06 (*P*=0.652)	0.19 (*P*=0.267)
DBP (mmHg)	0.15 (*P*=0.180)	0.15 (*P*=0.302)	0.16 (*P*=0.344)
HBA1C (%)	0.27 (*P*=0.012*)	0.23 (*P*=0.104)	0.24 (*P*=0.170)
FIB-4	-0.40 (*P*=0.004*)	-0.40 (*P*=0.004*)	

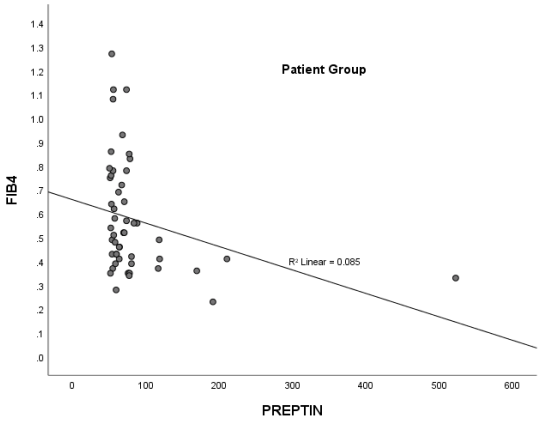
*Statistically significant at 0.05. Spearman correlation analyses, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride.

Table 5: Regression analysis for preptin levels of the NAFLD group (dependent: preptin, independent: investigated variables)

	B	t	*P*-value	R Square	Durbin-Watson
Constant	133.482	5.286	<0.001*	0.085	2.308
FIB-4	-86.367	-2.131	0.038*		

*Statistically significant at 0.05, B: Backward method

Figure 3: Correlation analysis between serum preptin levels and FIB-4 score in the hepatosteatosis group



Discussion

In this study, we aimed to investigate preptin levels in patients with grade 2-3 hepatosteatosis. We primarily showed that the serum preptin levels in patients with hepatosteatosis were increased compared to the healthy individuals. Our second aim was to determine the possible relationship between preptin and the FIB-4 score, a non-invasive method that was developed to assess fibrosis without a liver biopsy. We demonstrated that the preptin level had a significant negative correlation with the FIB-4 and AST levels in NAFLD. To the best of our knowledge, this is the first study investigating the relationship between the serum levels of preptin and NAFLD.

NAFLD is of great importance because it is the most common chronic liver disease and the hepatic component of metabolic syndrome. The mechanism of the development of both NAFLD and metabolic syndrome is based on glucose metabolism disorders [2]. Glucose metabolism is arranged by various enzymes and hormones. A newly discovered hormone, preptin, has a role in the carbohydrate mechanism by moderating the release of glucose-mediated insulin [10]. In immunohistochemical studies, the demonstration of the presence of pro-IGF-II and insulin at the same location in secretory granules of the pancreas indicates that pancreatic β-cells synthesize not only insulin but also preptin [12]. In an experimental study, the effect of preptin on glucose metabolism was demonstrated with the IGF-II receptor and activation of the protein kinase C and phospholipase C pathways. Furthermore, preptin was found to enhance, but not initiate, insulin secretion in a calcium-dependent manner under high glucose levels [10].

In the literature, there are a limited number of human studies on preptin levels. In these studies, the common characteristic of metabolic disorders is increased insulin levels and/or insulin resistance. In a study on patients with T2DM, preptin levels were higher than in healthy individuals [16]. The other two studies showed increased preptin levels in the serum and colostrum of mothers with GDM as well as in the fetal cord blood [11, 13]. Furthermore, Celik et al. [14] determined that the serum preptin levels were higher in patients with PCOS than in healthy volunteers. In our study, in which insulin resistance and diabetes patients were excluded, preptin levels were significantly higher in the NAFLD group compared to the controls. The result of our study suggests that hepatosteatosis increases preptin levels regardless of insulin resistance.

We also expected the increase in preptin levels to be more pronounced in correlation with the increase of FIB-4 score. Surprisingly, we found that preptin had a statistically negative correlation with the FIB-4 score and AST level in the patient group. In addition, using the factors that significantly determine the preptin level in the univariate analysis, we constructed a logistic regression model, and the FIB-4 score was the most significant factor. This negative correlation between the FIB-4 score and preptin can be explained by several mechanisms. First, the decreased preptin level in patients with NAFLD may be a result of reduced secretion and/or increased catabolism of preptin. Since the liver is the major organ of the synthesis of plasma proteins such as pro-IGF-II, from which preptin derivates, the synthesis of preptin is likely to decrease due to the loss of liver function with the development of fibrosis.

Second, although the mechanisms leading to NAFLD have not yet been clarified, the role of chronic inflammation is evident in the development and progression of NAFLD. Reduction of pro-IGF-II expression caused by inflammatory cytokines may be involved not only with the development of NAFLD but also the grade of NAFLD progression. In addition to all these probabilities, inflammatory cytokines themselves may have caused a decrease in preptin levels, as well as a decrease in protein synthesis in the liver. Unfortunately, there are only limited data on the association of preptin with inflammation. In a clinical study of Dogan et al. [21], the preptin levels were lower in psoriasis and Behçet's disease, both inflammatory diseases. Additionally, in their study, even when they excluded patients with insulin resistance to prevent metabolic parameters from influencing outcomes, the decrease in serum preptin levels in the patient group was unchanged. These findings support our thesis of the probability of a relationship between inflammation and preptin.

In our study, while preptin levels were affected by urea, creatinine, and triglyceride levels in healthy individuals, these three parameters did not affect the preptin level of NAFLD patients. We found this result is worth mentioning as it indicates that the FIB-4 score is the only factor affecting the preptin levels in NAFLD patients.

Our main aim was to compare serum preptin levels in patients with NAFLD and determine whether there was a

diagnostic difference compared to healthy individuals. We found that the preptin levels achieved a diagnostic accuracy of 68.6% in NAFLD. Although not very high, we could not find any report in the literature that we could compare this value with; thus, we decided to present this as a contribution to the literature. In addition, we determined the sensitivity of preptin as 85.7%, while its specificity was 56.9%. According to these results, preptin is effective in identifying the patients with NAFLD and can be considered a new marker with its disease-diagnostic feature in this specific patient group. The low specificity can be explained by the presence of other undiagnosed diseases in the NAFLD group that may increase the preptin level. We could not make any comparisons, since sensitivity and specificity analyses were not conducted for preptin in any of the previous studies.

Studies have shown that there is an association between plasma preptin levels and blood pressure. In a study, preptin levels were positively correlated with systolic blood pressure in patients with T1DM [17]. Similarly, Yang et al. [16] found that plasma preptin levels were positively correlated with diastolic blood pressure in patients with T2DM. Cai et al. [18] determined that patients with essential hypertension had lower plasma preptin levels compared to the control group. Conversely, Wang et al. [22] did not observe a significant difference between the preptin levels between women with preeclampsia and those with normal pregnancies. Similarly, in our study, we did not find any significant differences between the serum preptin levels and blood pressure. Due to the previous studies in which controversial results have been obtained, further investigations regarding circulating preptin levels in hypertension need to be carried out.

In previous studies, an association between serum preptin and BMI has been reported [19, 23, 24]. Nevertheless, we did not determine a correlation between preptin and BMI. Yang et al. [16], who examined patients with T2DM, reported that plasma preptin levels were lower in men compared to women. However, in our study, we did not observe any significant differences between the preptin levels of males and females.

Some limitations of this study must be considered. First, although we excluded some diseases that could affect preptin levels, various other diseases with unknown preptin expression may have been overlooked in our study population. In addition, the patient group has been lacking liver biopsy protocol, which is the only method to demonstrate the real-time severity of the damage. Lastly, pro-inflammatory cytokines and the correlation of oxidant-antioxidant status with preptin were not studied. On the other hand, the superiority of our study is that we have shown that preptin can distinguish fibrosis in NAFLD and may be a useful marker in predicting its progression. In fact, with the finding that the increase of the FIB-4 score associated with the severity of NAFLD leads to a decrease in serum preptin levels, the idea of creating a new classification that includes preptin levels in NAFLD scoring seems worthwhile. However, to obtain more accurate information about this issue, further studies should be planned with a greater number of cases to compare the results with liver biopsy findings. Despite these limitations, we believe that this study contributes to the understanding of the association between NAFLD and preptin.

Conclusion

This study provides a new insight that higher circulating preptin levels are associated with an increased risk of NAFLD. The results of this study demonstrated that the serum preptin levels were significantly higher in patients with NAFLD than healthy individuals. We also determined that the preptin level was significantly negatively correlated with the FIB-4 and AST levels in NAFLD. These findings suggest that preptin plays a potential role in the pathogenesis of NAFLD, is likely to distinguish patients with mild and severe liver damage and may be a useful marker in predicting elevated risk for progression to fibrosis. In patients with NAFLD, which is common in clinical practice and mostly asymptomatic, creating a risk profile for predicting severe liver damage should be the main goal. For this purpose, further studies establishing a stratification system with serum preptin levels and the FIB-4 score and verification with liver biopsy are required.

References

1. Milić S, Lulić D, Štimac D. Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations. World J Gastroenterol. 2014;20:9330-7.
2. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-57.
3. Fazel Y, Koenig AB, Sayiner M, Goodman ZD, Younossi ZM. Epidemiology and natural history of non-alcoholic fatty liver disease. Metabolism 2016;65:1017-25.
4. Mishra A, Younossi ZM. Epidemiology and natural history of non-alcoholic fatty liver disease. J Clin Exp Hepatol. 2012;2:135-44.
5. Mallet V, Parlati L, Vallet-Pichard A, Terris B, Tsochatzis E, Sogni P, et al. FIB-4 index to rule-out advanced liver fibrosis in NAFLD patients. Presse Med. 2019;48:1484-88.
6. Adolph TE, Grander C, Grabherr F, Tilg H. Adipokines and Non-Alcoholic Fatty Liver Disease: Multiple Interactions. Int J Mol Sci. 2017;29:1649.
7. Kutlu O, Altun Ö, Dikker O, Aktaş Ş, Özsoy N, Arman Y, et al. Serum Adropin Levels Are Reduced in Adult Patients with Nonalcoholic Fatty Liver Disease. Med Princ Pract. 2019;28:463-9.
8. Dallio M, Masarone M, Caprio GG, Sarno RD, Tuccillo C, Sasso FC, et al. Endocan Serum Levels in Patients with Non-Alcoholic Fatty Liver Disease with or without Type 2 Diabetes Mellitus: A Pilot Study. J Gastrointestin Liver Dis. 2017;26:261-268.
9. Cornish J, Callon KE, Bava U, Watson M, Xu X, Lin JM, et al. Preptin, another peptide product of the pancreatic β-cell, is osteogenic in vitro and in vivo. Am J Physiol Endocrinol Metab. 2007;292:117-22.
10. Buchanan CM, Philips AR, Cooper GJ. Preptin derived from proinsulin-like growth factor II (proIGF-II) is secreted from pancreatic islet beta-cells and enhances insulin secretion. Biochem J. 2001;360:431-9.
11. Aydın S, Celik O, Gurates B, Sahin I, Ulas M, Yilmaz M, et al. Concentrations of preptin, salusins and hepcidins in plasma milk of lactating women with or without gestational diabetes mellitus. Peptides 2013;49:123-30.
12. Aydin S. Three new players in energy regulation: preptin, adropin and irisin. Peptides. 2014;56:94-110.
13. Aslan M, Celik O, Karsavuran N, Celik N, Dogan DG, Botan E, et al. Maternal serum and cord blood preptin levels in gestational diabetes mellitus. J Perinatol. 2011;31:350–5.
14. Celik O, Celik N, Hascalik S, Sahin I, Aydin S, Ozerol E. An appraisal of serum preptin levels in PCOS. Fertil Steril. 2011;95:314–16.
15. Mierzwicka A, Kuliczkowska-Plaksej J, Kolačkov K, Bolanowski M. Preptin in women with polycystic ovary syndrome. Gynecol Endocrinol. 2018;34:470-475.
16. Yang G, Li L, Chen W, Liu H, Boden G, Li K. Circulating preptin levels in normal, impaired glucose tolerance, and type 2 diabetic subjects. Ann Med. 2009;41:52–6.
17. Abd El Dayem SM, Battah AA, El Shehaby A, Allah NA. Assessment of human cartilage glycoprotein 39 (YKL-40), preptin, and nitric oxide in adolescent patients with type 1 diabetes and its relation to cardiorenal affection. J Pediatr Endocrinol Metab. 2015;28:309-14.
18. Cai H, Liu Q, Dong X, Cai Y, Yao J, Liu Y. Plasma preptin levels are decreased in patients with essential hypertension. Pharmazie 2018;73:274-8.
19. Ozkan Y, Timurkan ES, Aydın S, Sahin I, Timurkan M, Citil C, et al. Acylated and desacylated ghrelin, preptin, leptin, and nesfatin-I peptide changes related to the body mass index. Int J Endocrinol. 2013;2013:1-7.
20. Abenavoli L, Peta V. Role of adipokines and cytokines in non-alcoholic fatty liver disease. Rev Recent Clin Trials 2014;9:134-40.
21. Doğan FB, Cicek D, Aydın S, Dertlioglu SB, Halisdemir N, Ucak H, et al. Serum preptin and amylin values in psoriasis vulgaris and Behçet's patients. J Clin Lab Anal. 2016;30:165-8.
22. Wang H, Gao B, Wu Z, Wang H, Dong M. Alteration of serum adropin level in preeclampsia. Pregnancy Hypertens. 2017;8:6-8.
23. Wang R, Xue A, Zheng W, Wang L, Yan F, Hu W, et al. Elevated serum preptin concentrations in patients with diabetic nephropathy. J Investig Med. 2019;67:1048-52.
24. Glück M, Glück J, Wiewióra M, Rogala B, Piecuch J. Serum irisin, adropin, and preptin in obese patients 6 months after bariatric surgery. Obes Surg. 2019;29:3334-41.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):633-637.
DOI: 10.28982/josam.855197

Research article

Journal of Surgery and Medicine
e-ISSN=2602-2079

Reelin levels in inflammatory bowel disease: A case-control study

Selman Gencer [1], Müçteba Can [2], İlhami Yüksel [3]

[1] Department of Internal Disease, Aksaray Education and Research Hospital, Aksaray, Turkey
[2] Department of Intensive care unit, Ankara City Hospital, Ankara, Turkey
[3] Department of Gastroenterology, Yıldırım Beyazıt University. Ankara. Turkey

ORCID ID of the author(s)

SG: 0000-0003-3936-4146
MC: 0000-0002-8316-5075
İY: 0000-0002-9730-2309

Corresponding Author
Selman Gencer
Aksaray University, Training and Research Hospital, Department of Internal Disease, 06300, Ankara, Turkey
E-mail: selmangencer@hotmail.com

Ethics Committee Approval
Ethics committee approval (TC Ministry of Health Ankara Provincial Health Directorate Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethical Committee (15.12.2014, 18/19) was obtained, and all participants gave informed consent before inclusion in the study.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 June 25

Abstract

Background/Aim: Crohn's Disease (CD) and Ulcerative Colitis (UC) are grouped as Inflammatory Bowel Diseases (IBD). There are many similarities between these two diseases, and CD and UC cases cannot be separated at a rate varying between 5% and 10%. Reelin is an extracellular matrix protein first known for its vital role in neuronal migration. Studies in rodent small intestine suggested that reelin protects the organism from intestinal pathologies. In a 5-year retrospective case-control study, we aimed to detect the effectiveness of serum reelin level in patients with IBD in determining the severity and activation of the disease and compare healthy volunteers with patients in terms of inactivation and remission.
Methods: The data of all 194 IBD patients diagnosed at Beyazit Training and Research Hospital between 2011-2015 were retrospectively reviewed. The patients were matched with 30 healthy volunteers. Risk factors were assessed by multivariate logistic regression analysis.
Results: The serum reelin levels were similar between UC and CD patients, the control group, UC and CD groups (P=0.067), and those with active disease or disease in remission, and did not differ according to disease behavior or location of involvement.
Conclusions: Our study shows that Reelin cannot be used as an activation/remission marker in IBD. In addition, it does not differentiate between UC and CD.

Keywords: Reelin, Inflammatory bowel diseases, Crohn's disease, Ulcerative colitis

How to cite: Gencer S, Can M, Yüksel İ. Reelin levels in inflammatory bowel disease: A case-control study. J Surg Med. 2021;5(6):633-637.

Introduction

Inflammatory Bowel Diseases (IBD) refer to inflammatory diseases involving the colon and small intestine (Baumgart and Carding, 2007). These can be idiopathic and recur chronically to cause inflammation in the gastrointestinal tract. It has two main subtypes: Ulcerative Colitis (UC) and Crohn's Disease (CD), and a third subtype in the form of indeterminate colitis [1].

Clinically, UC and CD share similar symptoms such as diarrhea, hematochezia, and abdominal pain, but differ in terms of the location and depth of inflammation, as well as complications and prevalence [2].

In ulcerative colitis, submucosal tissue and inflammation of the colonic mucosa are present, and involvement is not seen in deeper parts except for the fulminant type. While it starts with rectal involvement in most patients, the lesions progress proximally without space in between, thus becoming continuous [3]. In ulcerative colitis, the target tissue is the colon. If only the rectum is involved, the disease is called hemorrhagic proctitis or ulcerative proctitis. If only the sigmoid colon and rectum are involved, it is called ulcerative colitis with distal involvement [4]. Crohn's disease, on the other hand, can involve the gastrointestinal tract from the mouth to the anus, and it is most seen in the terminal ileum. Intact mucosal areas as well as intermittent lesions can be observed. All layers of the gut are inflamed [5].

Chronic inflammatory bowel diseases, namely, Crohn's disease, and ulcerative colitis, constitute an essential part of gastrointestinal diseases in children and adults. Inflammatory bowel diseases worldwide are typical in regions such as the United States, England, and Scandinavia [6]. The age of onset of Crohn's Disease ranges between 20-30 years [7, 8]. While 5% to 15% of patients are older than 60 years of age, 25% are diagnosed before the age of 18 years [9]. Phenotype and natural disease history may differ according to the age of onset [10]. For example, pediatric-onset ulcerative colitis is characterized by a high spread rate and surgical treatment is performed in approximately 20% of children in the first ten years of follow-up after diagnosis [11]. On the other hand, although the clinical course of elderly inflammatory bowel disease patients seems mild due to a more minimal disease progression over time, they are more vulnerable, and due to the numerous side effects related to treatment, the risk of infections, malignancy, bone disease, eye disease, malnutrition, and thrombotic complications are increased [12, 13].

It is also quite surprising that the prevalence of inflammatory diseases differs according to age, gender, ethnicity, time, and geographical distribution [7, 14, 15]. Significant efforts have been made to determine the cause. Studies suggest that various types of bacteria, such as Heliobacter hepaticus, Pseudomonas maltophilia, Bacteroides fragilis, Bacteroides necrophorum, Blastocystis hominis, Edwardsiella tarda, Plesiomonas shigelloides, Aeromonas hydrophila, Chlamydia trachomatis, Yersinia enterocolitica, Campylobacterfetus jejuni, Aerobacter bifidobacteria, Aerobacter coprococcus, Aerobacteraerogenes, Bacillus vulgatus, Pseudomonas maltophilia, Mycobacteria kansasii, Mycobacteria paratuberculosis, Mycobacteria tuberculosis, Escherichia coli, Bacillus morgagni, Spherophorus necrophorus, Bacillus pyocyaneus, Bacillus proteus, Bacilluscoli, fungi such as Monilia and Histoplasma, viruses such as lymphopathia venereum, viruses such as Behcet virus, cytomegalovirus, paramyxovirus, Poliovirus, reovirus, coxsackie A and B, herpes, measles, influenza, rotavirus, Epstein-Barr, adenovirus, and Echo A, B, parasites and protozoans such as Escherichia histolytica, calcium phosphate, silicon oxide, titanium and aluminum microparticles from soil, dust, toothpaste, and diet, non-steroidal anti-inflammatory drugs and oral contraceptives, sugar, fat, and protein components from fast food, coke, coffee, farm products, margarine, vegetables, and fruits, glycoalkaloid compounds in potatoes, smoking, and other factors such as frozen products transported with cold chain play a role [16-23]. Despite this, the increasing incidence of inflammatory bowel diseases, especially in recent years, has led experts and researchers to view this situation as an expanding global health problem of industrial-urbanized societies [24]. In this context, it has become essential to study inflammatory bowel diseases in more detail and determine the factors that play a role in their etiology.

Reelin is an extracellular glycoprotein secreted by Cajal-Retzius cells and GABAergic interneurons in the adult brain during embryonic brain development. The full-length Reelin is about 460 kDa and has a signal peptide, an F-spondin-like domain, eight Reelin repeats (R1-R8), and a positively charged sequence at the C-terminal [25]. It modulates neuronal function and synaptic plasticity in the mature brain and regulates tau phosphorylation, axonal growth, and dendritic spine morphology [26]. Studies show that Reelin deficiency is associated with bipolar disorder and major depression, autism, epilepsy, and schizophrenia [27-30]. There are also studies suggesting that Reelin may play a role in inflammatory bowel diseases [31-33]. Additionally, studies show its function in crypto-villus homeostasis and that Reelin regulation plays a protective role against diseases such as acute colitis [31, 34]. However, no previous study directly examined the role of Reelin in inflammatory bowel diseases in the local or international literature. In this respect, this study aims to determine the role of Reelin in inflammatory bowel diseases and contribute to the literature.

Materials and methods

Design and sample

The present hospital-based case-control study retrospectively collected the data of cases and controls aged between 25-65 years who reside in Ankara.

This study was completed in the Dışkapı Yıldırım Beyazıt Training and Research Hospital Gastroenterology - IBD Clinic located in Ankara, Turkey. According to IBD clinic records between 2011-2015, the diagnoses of 194 individuals were confirmed as Crohn's Disease and Ulcerative Colitis. Using the telephone numbers included in the files, investigators contacted the individual regarding whether they wanted to be included in the study. Information about the aim and method was provided over the phone, and the individuals were invited to the IBD clinic for collection of the data. A total of 194 patients agreed to participate in this study as the case group.

Individuals with similar sociodemographic characteristics as the case group were chosen from visitors at the same hospital to be included in the control group. A total of 30 volunteers, aged 25 years and above, who were not diagnosed with IBD or any other illness, were identified as potential control group members. All those who were invited to participate in the study were informed that participation was on voluntary basis, they could withdraw at any time, and their privacy would be respected. Researchers contacted the subjects at the hospital, both the cases and the controls, and gave them questionnaires to collect data.

Data were collected from patient files and the hospital's information processing system. CD Activity Index "CDAI" and the Truelove activity index were calculated for Ulcerative Colitis, and serum Reelin levels were determined in the hospital's biochemistry laboratory.

Data collection

Researchers conducted face-to-face interviews with both the case and control groups at the hospital. The investigators introduced themselves, explained the study's purpose, and obtained informed consent from all subjects before the interview. A customized questionnaire and personal interviews were used to collect demographic and risk factor data from each participant.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the chi-square test and logistic regression analysis with the SPSS 22.0 software. The chi-square test was used to compare Reelin levels. The non-paired student t-test was used to analyze parametric data. The relationship between blood Reelin concentration and clinical parameters was assessed with Spearman's correlation analysis. Statistical significance was defined as a probability (p) value of less than 0.05. Power analysis was performed using the computer-aided statistics program G-power. According to previous studies [27, 28] in the literature, the smallest sample size to represent the population with 95% strength was 52 participants at 0.8 power and a 5% alpha error margin.

Ethical considerations

Ethics committee approval (TC Ministry of Health Ankara Provincial Health Directorate Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethical Committee (15.12.2014, 18/19) was obtained, and all participants gave informed consent before inclusion in the study. This study complied with the principles of the Declaration of Helsinki.

Results

General characteristics and demographic data of the participants in the study are presented in Table 1. Ninety-nine of 194 patients had UC and 89 had CD. The mean ages of the UC and CD patients were 41.77 (7.77) years and 39.63 (15.55) years, respectively. There were 40 females and 59 males in the UC group, and 36 females and 43 males in the CD group.

The serum Reelin levels were similar between the UC and CD groups (P=0.419), and between UC, CD, and control groups (P=0.059) (Table 2, 3). There were no significant differences in terms of serum Reelin levels when the UC and CD groups were compared with the control group separately (P=0.910, P=0.436, respectively) (Table 3).

Table 1: Demographic features of study group

	Ulcerative colitis (UC)	Crohn's disease (CD)	Control group
Age (SD)	41.77(7.77)	39.63(15.55)	28(6.3)
Female	40	36	15
Male	59	59	15
Active	50	49	
Remission	49	46	
Localization			
Proctitis	22		
Left Side Involvement	48		
Extensive	29		
Ileal		32	
Colonic		9	
Ileocolonic		51	
Disease behavior			
Inflammatory		64	
Stricturing		3	
Penetrant		10	
Inflammatory + Perianal		7	
Inflammatory + Stricturing		6	

Table 2: Average reelin level in all groups

	n	Reelin ng/ml
Total of UC	97	0.6216(1.0835)
Total of CD	92	0.3993(0.5101)
Control group	30	0.5576(0.6142)
Active CD	49	0.3675(0.5789)
Active UC	48	0.3846(0.4850)
CD in Remission	43	0.4354(0.5789)
UC in Remission	49	0.8538(1.4161)

Table 3: Comparison of all groups

Total	UC	CD	*P*-value UC + CD vs. control group	*P*-value UC vs. control group	*P*-value CD vs. control group
n=189	n=97	n=92	0.419	0.910	0.436

The serum Reelin levels of 49 CD patients who were in active disease period and 46 who were in remission were similar (P=0.518) (Table 4). Serum Reelin levels according to disease location of all CD patients, and those with active CD and CD at remission are shown in Table 5. Table 5 shows that Reelin levels do not differ significantly according to the location of involvement among all patients with CD (X^2=0.109; P=0.947), or among those with active CD (X^2=0.299; P=0.861) and CD in remission (X^2=0.653; P=0.721).

Table 4: Relationship between groups and Reelin level

	n	*P*-value
Active UC	48	
UC in remission	49	0.618
Active CD	49	
CD in remission	43	0.518
UC+ proctitis	22	
UC+ left segment involvement	48	0.266
UC+ extensive	29	
CD, ileal	32	
CD, colonic	9	0.947
CD, ileocolonic	51	
CD, inflammatory	64	
CD, stricturing	3	
CD, penetrating	10	0.741
CD, penetrating, inflammatory	7	
CD, stricturing, inflammatory	6	

Table 5: Disease localization of Reelin level

Location		n	X^2	*P*-value
CD	Ileal	32	0.109	0.947
	Colonic	9		
	Ileocolonic	51		
CD+ active	Ileal	16	0.299	0.861
	Colonic	6		
	Ileocolonic	26		
CD+ remission	Ileal	16	0.653	0.721
	Colonic	3		
	Ileocolonic	25		

The Kruskal Wallis H test results according to the behavior of the disease in patients with CD, patients with active CD, and patients with CD in remission are shown in Table 6. As seen in Table 6, Reelin levels do not significantly differ with behavior of the disease among all CD patients (X^2=1.971;

P=0.741), or among those with active CD (X^2=1.845; P=0.764) or CD in remission (X^2=1.986; P=0.738).

The Kruskal Wallis H test results of Reelin levels in patients with UC, active UC, and UC in remission according to the disease location are seen in Table 7. Among the 97 UC patients included in the study, 48 were in their active period, and 49 were in remission. The serum Reelin levels did not significantly differ according to disease state (P=0.359). Also, no difference was found between the Reelin values of the patients with active UC and the control group (P=0.618).

Table 6: Reelin levels of type of disease behavior

	Type of disease behavior	n	X^2	P-value
CD	Inflammatory	64		
	Stricturing	3		
	Penetrating	10	1.971	0.741
	Inflammatory + Perianal Disease	7		
	Inflammatory+ Stricturing	6		
CD+ active	Inflammatory	32		
	Stricturing	2		
	Penetrating	5	1.845	0.764
	Inflammatory + Perianal Disease	4		
	Inflammatory+ Stricturing	4		
CD+ remission	Inflammatory	32		
	Stricturing	1		
	Penetrating	5	1.986	0.738
	Inflammatory + Perianal Disease	3		
	Inflammatory+ Stricturing	4		

Table 7: Disease localization of Reelin levels in patients

Location		n	X^2	P-value
UC	Proctitis	21	2.647	0.266
	Left Type	48		
	Extensive	28		
Active UC	Proctitis	10	0.820	0.664
	Left Type	24		
	Extensive	14		
UC in remission	Proctitis	11	1.978	0.372
	Left Type	24		
	Extensive	14		

According to the segment of involvement, the serum Reelin levels were similar between all UC patients (X^2=0.109; P=0.055), in those with active UC (X^2=0.820; P=0.072), and in patients with UC in remission (X^2=1.978; P=0.065).

ANOVA test revealed no significant differences in terms of serum Reelin levels between CD and UC patients and the healthy control group (X^2=1.007, P=0.605) according to involved segments (Table 8).

Table 8: Results of Reelin level of group

Group	n	X^2	P-value
CD	94	1.007	0.605
UC	97		
Control group	30		

Discussion

The entire surface area of the human intestine reaches 200-400 m^2 [35]. As well as being the barrier of the innate immune system, the inner cell lining of the intestines is also where interactions with commensal microorganisms occur. These interactions are precisely modulated by the intestinal immune system and contribute to immune homeostasis [36, 37].

The epithelium of the mammalian gastrointestinal tract has the fastest turnover rate of any tissue in the body and requires precisely modulated homeostasis, carefully regulated cell proliferation, growth arrest, migration/differentiation, and apoptosis programs to contribute to the immune system. In rodents, the epithelium of the small intestine is completely replaced every 2-3 days. Cell proliferation is confined to crypts of Lieberkühn, where stem cells lead to progenitor cells amplified by continuous division across the lower two-thirds of the crypts. Cell involvement and differentiation occur when the cell progenitors reach the crypt-villi junction, and the villi differentiate and form the functional compartment. Absorptive enterocytes, hormone-secreting enteroendocrine cells, opioid-producing brush cells, microfold cells, and mucus-producing Goblet cells emerge from the crypts and complete the differentiation of adjacent villi in the consistent vertical columns [38]. When mature cells approach the apical extrusion site of the villi, they undergo apoptosis and are dumped into the intestinal lumen; thus, the continuous production of new cells is balanced [39].

Epithelial cell regeneration is tightly controlled by cell-cell and cell-extracellular matrix interactions [40]. A thin and continuous cell-extracellular matrix layer separates the basement membrane epithelial cells from the interstitial connective tissue, and its composition defines the requirements. Mutual interactions between the epithelium and the underlying basement membrane regulate proliferation, migration, differentiation, apoptosis, morphogenesis, tissue repair, inflammation, and immune response [31]. Many receptors have been identified for cell-extracellular matrix molecules in intestinal epithelial cells, many of which are integrins [32]. However, the nature of cell-basement membrane interactions and their intracellular processing is largely undefined. Various components, such as myofibroblasts, cytokines, growth factors, chemokines, hormones, neurotransmitters, inflammatory mediators, and adhesion proteins, are expressed and secreted under the epithelium in the cell-extracellular matrix. Express receptors for many of these ligands allow information flow in both directions to the gut epithelium and the cell-extracellular matrix. Consequently, myofibroblasts are considered to regulate functions ranging from peripheral immune tolerance to the control of epithelial regeneration processes and provide immune homeostasis [31, 41]. Idiopathic intestinal inflammations such as inflammatory bowel diseases can occur when this homeostasis deteriorates for various reasons [36, 37].

Many markers that correlate with the clinical picture of IBD have been identified and are still being studied. In the literature, increased ADA levels were found in IBD patients compared to healthy controls [42]. In another study, it was shown that PTX3 value workup would be appropriate during the follow-up of UC patients [43].

In the studies conducted, it was determined that the expressions of Reelin among Reelin receptors, apolipoprotein E receptor (ApoER2), very low-density lipoprotein receptor (VLDLR), and effector protein Disabled-1 (DAB1) in the mucosa of the rat small intestine are limited to myofibroblasts [31, 38]. It is also known that Reelin secreted by Cajal-Retzius cells in the brain is critical for the positioning of migrating neurons during the development of the nervous system [41]. The reason is that the differentiation of the intestinal epithelium requires the migration of cells along the crypt-villus axis [31]. This suggests that Reelin, which plays a vital role in intestinal epithelial dynamics, also plays an essential role in inflammatory bowel diseases.

Based on the result of our study, we concluded that serum Reelin levels did not significantly differ between UC and CD, their active or remission periods, between the patients and the control group or according to segment of involvement. There

was no relationship between Reelin levels of the participants in the study and their diseases.

Limitations

The findings of this study must be viewed in the context of some limitations. First, the study was conducted over five years in a small group of 194 cases. Another study limitation is that all the data came from a single center and one nationality. Furthermore, no reference values for serum RELN concentrations were established. Therefore, we cannot verify our findings or compare them to those found in the international literature. However, at this stage of research, where case-control studies are the method of choice for increasing our knowledge of this intriguing signal, this is not a critical point. The study's findings and limitations are instrumental in contributing to the advancement of research in this field. Furthermore, because this research was conducted in a developing country, lifestyle changes may reveal important information about IBD. Widespread future studies are warranted to explore significant differences in clinical scores or intestinal inflammation depending on the level of RELN.

Conclusions

The study showed that Reelin could not be used as a marker of activation/remission in inflammatory bowel diseases and that there is no marker in the differential diagnosis between UC and CD. Although its routine use is not yet recommended, ADA level helps determine the clinical activity of IBD and can be preferred in selected cases. Additionally, before the widespread use of ADA levels is recommended, it should be ensured that it is easily applicable in larger populations.

References

1. Valdovinos-García R, Martínez-Vázquez M. Diagnostic approach to inflammatory bowel. IBD Reviews. 2018;4:30-8.
2. Kim DH, Cheon JH. Pathogenesis of Inflammatory Bowel Disease and Recent Advances in Biologic Therapies. Immune Netw. 2017 Feb;17(1):25- 40. doi: 10.4110/in.2017.17.1.25.
3. Danese S, Fiorino G, Peyrin-Biroulet L, Lucenteforte E, Virgili G, Moja L, Bonovas S. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. Ann Intern Med. 2014 May 20;160(10):704-11. doi: 10.7326/M13-2403.
4. Ökten A. Gastroenterohepatoloji. İstanbul: Nobel Medicine Publication. 2001
5. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012 Nov 3;380(9853):1590-605. doi: 10.1016/S0140-6736(12)60026-9.
6. Hendrickson BA, Gokhale R, Cho JH. Clinical aspects and pathophysiology of inflammatory bowel disease. Clin Microbiol Rev. 2002 Jan;15(1):79-94. doi: 10.1128/CMR.15.1.79-94.2002.
7. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1):46-54.e42; quiz e30. doi: 10.1053/j.gastro.2011.10.001.
8. Kurata JH, Kantor-Fish S, Frankl H, Godby P, Vadheim CM. Crohn's disease among ethnic groups in a large health maintenance organization. Gastroenterology. 1992;102:1940–8.
9. Malik TA. Inflammatory Bowel Disease: Historical Perspective, Epidemiology, and Risk Factors. Surg Clin North Am. 2015 Dec;95(6):1105-22. doi: 10.1016/j.suc.2015.07.006
10. Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nat Rev Gastroenterol Hepatol. 2015 Apr;12(4):205-17. doi: 10.1038/nrgastro.2015.34.
11. Andres PG, Friedman LS. Epidemiology and the natural course of inflammatory bowel disease. Gastroenterology Clinics of North America. 1999;28(2):255-81.
12. Taleban S. Challenges in the Diagnosis and Management of Inflammatory Bowel Disease in the Elderly. Curr Treat Options Gastroenterol. 2015 Sep;13(3):275-86. doi: 10.1007/s11938-015-0059-6
13. Foxworthy DM, Wilson JA. Crohn's disease in the elderly. Prolonged delay in diagnosis. J Am Geriatr Soc. 1985 Jul;33(7):492-5. doi: 10.1111/j.1532-5415.1985.tb05462.x.
14. Russel MGVM. Changes in the incidence of inflammatory bowel disease: what does it mean? European Journal of Internal Medicine. 2000;11(4):191-6.
15. Ekbom, A. The changing faces of Crohn's disease and ulcerative colitis. In: Targan SR, Shanahan F, Karp LC. Inflammatory bowel disease: from bench to bedside (pp. 5-20) New York: Springer. 2005.
16. Kirsner JB. The historical basis of the idiopathic inflammatory bowel diseases. Inflammatory Bowel Diseases. 1995;1(1):2-26.
17. Korzenik JR. Past and current theories of etiology of IBD: toothpaste, worms, and refrigerators. J Clin Gastroenterol. 2005 Apr;39(4 Suppl 2):S59-65. doi: 10.1097/01.mcg.0000155553.28348.fc.
18. Kirsner JB. Historical origins of current IBD concepts. World J Gastroenterol. 2001 Apr;7(2):175-84. doi: 10.3748/wjg.v7.i2.175.
19. Lomer MC, Thompson RP, Powell JJ. Fine and ultrafine particles of the diet: influence on the mucosal immune response and association with Crohn's disease. Proc Nutr Soc. 2002 Feb;61(1):123-30. doi: 10.1079/pns2001134.
20. Carbonnel F, Jantchou P, Monnet E, Cosnes J. Environmental risk factors in Crohn's disease and ulcerative colitis: an update. Gastroenterol Clin Biol. 2009 Jun;33 Suppl 3:S145-57. doi: 10.1016/S0399-8320(09)73150-1.
21. Kefalakes H, Stylianides TJ, Amanakis G, Kolios G. Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality? Eur J Clin Pharmacol. 2009 Oct;65(10):963-70. doi: 10.1007/s00228-009-0719-3.
22. Patel B, Schutte R, Sporns P, Doyle J, Jewel L, Fedorak RN. Potato glycoalkaloids adversely affect intestinal permeability and aggravate inflammatory bowel disease. Inflammatory Bowel Dis. 2002 Sep;8(5):340-6. doi: 10.1097/00054725-200209000-00005.
23. Hugot JP, Alberti C, Berrebi D, Bingen E, Cézard JP. Crohn's disease: the cold chain hypothesis. Lancet. 2003 Dec 13;362(9400):2012-5. doi: 10.1016/S0140-6736(03)15024-6.
24. Yamamoto-Furusho JK, Sarmiento-Aguilar A, Toledo-Mauriño JJ, Bozada-Gutiérrez KE, Bosques-Padilla FJ, Martínez-Vázquez MA, et al.; EPIMEX Study Group. Incidence and prevalence of inflammatory bowel disease in Mexico from a nationwide cohort study in a period of 15 years (2000-2017). Medicine (Baltimore). 2019 Jul;98(27):e16291. doi: 10.1097/MD.0000000000016291.
25. Santana J, Marzolo MP. The functions of Reelin in membrane trafficking and cytoskeletal dynamics: implications for neuronal migration, polarization and differentiation. Biochem J. 2017 Sep 7;474(18):3137-65. doi: 10.1042/BCJ20160628.
26. Byrne DJ, Harmon MJ, Simpson JC, Blackstone C, O'Sullivan NC. Roles for the VCP co-factors Npl4 and Ufd1 in neuronal function in Drosophila melanogaster. J Genet Genomics. 2017 Oct 20;44(10):493-501. doi: 10.1016/j.jgg.2017.06.003.
27. Fatemi SH, Earle JA, McMenomy T. Reduction in Reelin immunoreactivity in hippocampus of subjects with schizophrenia, bipolar disorder and major depression. Mol Psychiatry. 2000 Nov;5(6):654-63, 571. doi: 10.1038/sj.mp.4000783.
28. Fatemi SH, Snow AV, Stary JM, Araghi-Niknam M, Reutiman TJ, Lee S, Brooks AI, Pearce DA. Reelin signaling is impaired in autism. Biol Psychiatry. 2005 Apr 1;57(7):777-87. doi: 10.1016/j.biopsych.2004.12.018.
29. Haas CA, Frotscher M. Reelin deficiency causes granule cell dispersion in epilepsy. Exp Brain Res. 2010 Jan;200(2):141-9. doi: 10.1007/s00221-009-1948-5.
30. Özkul T , Gölgeli A . Deneysel şizofreni modellerinin oluşturulması ve deneysel yöntemlerle şizofreni belirtilerinin değerlendirilmesi. Mersin Üniversitesi Sağlık Bilimleri Dergisi. 2019;12(2):351-9.
31. Carvajal AE, Vázquez Carretero MD, García Miranda P, Peral Rubio MJ, Calonge Castrillo ML, Ilundáin Larrañeta MA. A. Reelin expression is up-regulated in mice colon in response to acute colitis and provides resistance against colitis. Biochimica et Biophysica Acta Molecular and Cell Biology of Lipids. 2017;1863(2):462-73.
32. Carvajal AE, Serrano-Morales JM, Vázquez-Carretero MD, García-Miranda P, Calonge ML, Peral MJ, et al. Reelin protects from colon pathology by maintaining the intestinal barrier integrity and repressing tumorigenic genes. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2017;1863(9):2126-34.
33. Groeger SE, Meyle J. Epithelial barrier and oral bacterial infection. Periodontol 2000. 2015 Oct;69(1):46-67. doi: 10.1111/prd.12094.
34. García-Miranda P, Vázquez-Carretero MD, Sesma P, Peral MJ, Ilundain AA. Reelin is involved in the crypt-villus unit homeostasis. Tissue Eng Part A. 2013 Jan;19(1-2):188-98. doi: 10.1089/ten.TEA.2012.0050.
35. Schulenburg H, Kurz CL, Ewbank JJ. Evolution of the innate immune system: the worm perspective. İmmunology Rev. 2004 Apr;198:36-58. doi: 10.1111/j.0105-2896.2004.0125.x
36. Cader MZ, Kaser A. Recent advances in inflammatory bowel disease: mucosal immune cells in intestinal inflammation. Gut. 2013 Nov;62(11):1653-64. doi: 10.1136/gutjnl-2012-303955.
37. Maloy KJ, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. Nature. 2011 Jun 15;474(7351):298-306. doi: 10.1038/nature10208.
38. Viggiano D, Ianiro G, Vanella G, Bibbò S, Bruno G, Simeone G, Mele G. Gut barrier in health and disease: focus on childhood. Eur Rev Med Pharmacol Sci. 2015;19(6):1077-85.
39. García-Miranda P, Peral MJ, Ilundain AA. Rat small intestine expresses the reelin-Disabled-1 signalling pathway. Exp Physiol. 2010 Apr;95(4):498-507. doi: 10.1113/expphysiol.2009.050682.
40. García-Miranda P, Vázquez-Carretero MD, Sesma P, Peral MJ, Ilundain AA. Reelin is involved in the crypt-villus unit homeostasis. Tissue Eng Part A. 2013 Jan;19(1-2):188-98. doi: 10.1089/ten.TEA.2012.0050.
41. Carvajal A, Vázquez-Carretero M, Peral M, Ilundáin A, Calonge M. (2015). DSS-induced inflammation and regulation of reelin gene expression in mouse colon: P4-4. Acta Physiologica. 2015.
42. Gökden Y , Hot S , Gönen C , Kalyon S , Akkan Çetinkaya Z . The value of adenosine deaminase level in assessing activation of inflammatory bowel disease. Journal of Surgery and Medicine. 2020;4(8):654-59. doi: 10.28982/josam.769877
43. Kalyon S, Gökden Y, Oyman F. A new biological marker in inflammatory bowel disease: Pentraxin 3. Journal of Surgery and Medicine. 2020;4(10):875-8. doi: 10.28982/josam.791156.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):638-641.
DOI: 10.28982/josam.954130

Journal of Surgery and Medicine
e-ISSN=2602-2079

Doppler ultrasound in standing position is superior to demonstrate nutcracker phenomenon in children with varicocele

Ali Tekin [1], Eren İsmailoğlu [2]

[1] Department of Pediatric Surgery, Division of Pediatric Urology, Ege University Faculty of Medicine, Izmir, Turkey
[2] Department of Radiology, Bakircay University, Faculty of Medicine, Cigli Training Hospital, Izmir, Turkey

ORCID ID of the author(s)
AT: 0000-0002-6988-0806
Eİ: 0000-0001-9998-6081

Corresponding Author
Ali Tekin
Ege Universitesi, Tıp Fakültesi, Çocuk Cerrahi AD, İzmir, Turkey
E-mail: dralitekin@gmail.com

Ethics Committee Approval
Sağlık Bilimleri University, İzmir Dr. Behçet Uz Childrens Hospital, Clinical Research Ethics Committee, 04.07.2019, 2019/11-07
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 June 26

Abstract

Background/Aim: The nutcracker phenomenon refers to the entrapment of the left renal vein between the superior mesenteric artery and the aorta. It is named nutcracker syndrome if accompanied by symptoms such as flank pain, hematuria, proteinuria, and varicocele. This study aimed to determine the rate of nutcracker phenomenon in children with varicocele by left renal vein Doppler US measurements in standing and supine positions.

Methods: The hospital records of patients admitted to our clinic with grades 2 and 3 left varicocele between 2017 and 2019 were reviewed retrospectively. Demographic data, BMI values, blood pressure values, and urinalysis results of the patients were recorded.

The diameter and the peak velocity (PV) of the left renal vein were measured at the level of the hilus and in the aortomesenteric part, both in supine and standing positions by Doppler ultrasonography (US).

Results: Twenty-six cases were included in the study. No additional pathology was found other than varicocele. The diameter of the aortomesenteric part of the renal vein decreased, the hilar part of the renal vein increased, and the rate and the diameter ratio increased at the standing position. The incidence of the nutcracker phenomenon was 42.3-57.7% with different thresholds in the supine position, and 88-96.2% in the standing position.

Conclusion: Doppler ultrasonography in the standing position is superior to that performed in the supine position in detecting the nutcracker phenomenon in patients with varicocele.

Keywords: Varicocele, Nutcracker Phenomenon, Nutcracker Syndrome, Doppler Ultrasonography, Children

How to cite: Tekin A, İsmailoğlu E. Doppler ultrasound in standing position is superior to demonstrate nutcracker phenomenon in children with varicocele. J Surg Med. 2021;5(6):638-641.

Introduction

The nutcracker phenomenon refers to the entrapment of the left renal vein between the superior mesenteric artery and the aorta [1]. It is named nutcracker syndrome if accompanied by symptoms such as flank pain, hematuria, proteinuria, and varicocele. Many studies have shown that Doppler ultrasonography can be used in the diagnosis by measuring the difference in diameter or peak velocity between the aortomesenteric and the hilar parts of the renal vein [2–4]. However, different threshold values were defined in these studies. The theory that varicocele occurs with the increase in left renal vein (LRV) pressure and the fact that this pressure will increase in the standing position suggests that the measurements should be made in different positions. This study aimed to determine the rate of nutcracker phenomenon in children with varicocele detected by left renal vein Doppler US measurements in standing and supine positions.

Materials and methods

The hospital records of patients admitted to our clinic with grades 2 and 3 left varicocele between 2017 and 2019 were reviewed retrospectively. Cases evaluated with Doppler US were included in the study.

All patients were examined by a single physician. On physical examination, varicose veins that can be palpated but not seen at rest were classified as grade 2, and their presence during rest was classified as grade 3.

Doppler ultrasonography of the left renal vein was evaluated in all patients after 6-8 hours of fasting. All examinations were performed by a single radiologist using a 2-6 Mhz convex transducer (Philips Affiniti 50, Philips Healthcare Netherlands). The diameter of the left renal vein was measured at the level of the hilus (HLRVD) and in the aortomesenteric part (AMLRVD) in the supine position. Then, peak velocity (PV) measurements were made in the same segments (peak velocity at the level of the hilus: HLRVPV, peak velocity at the level of the aortomesenteric part: AMLRVPV) with a Doppler angle of lower than 60º. All measurements were repeated at the standing position. The sampling interval used to obtain the Doppler spectra of the LRV was chosen as 2-4 mm at the hilar level and 4-10 mm at the aortomesenteric level. All measurements were repeated twice.

Body mass index (BMI) was calculated as the ratio of weight in kilograms (kg) divided by height in meters-squared (m2). BMI percentile values were determined according to the study of Neyzi et al. [5]. Blood pressure measurements of all cases were noted. Care was taken to perform urine dipstick tests in the afternoon not to miss possible orthostatic proteinuria. An informed consent form was obtained from all patients and parents. Ethics approval for this study was obtained from Sağlık Bilimleri University, İzmir Dr. Behçet Uz Children's Hospital, Clinical Research Ethics Committee, 04.07.2019, 2019/11-07.

Selection bias was avoided by recruiting every patient diagnosed with varicocele in the outpatient clinic between the specified dates and including those with Doppler ultrasonography screening.

Statistical analysis

All data were recorded with the Microsoft Excel program. Analyses were performed with the McNemar test, Chi-Square test, Students' T-test, and Kolmogorov-Smirnov test. IBM Statistics SPSS 23.0 for Windows (V 23.0, United States of America, IBM) was used for statistical analyses. A *P*-value of less than 0.05 was considered statistically significant.

Results

Twenty-six cases were included in the study. The mean age was 13.92 (1.72) years. Twelve cases (46.2%) had grade 2 and 14 cases (53.8%) had grade 3 varicocele. Testicular dimensions were compatible with the ages. No additional pathology was found other than varicocele. The overall mean BMI, and those of patients with grades 2 and 3 varicocele were 18.24 (3.91) kg/m^2, 20.13 (5.03) kg/m^2, and 16.62 (1.38) kg/m^2, respectively (P=0.02, Student T-Test). When the BMI data were compared with the BMI values of Turkish children, it was observed that 8 cases were below the 5th percentile, 7 of which (87.5%) had grade 3, and one of which (12.5%) had grade 2 varicocele (P=0.036, Chi-Square).

Doppler US results of all cases are given in Table 1. The diameter of the aortomesenteric part of the renal vein decreased, the hilar part of the renal vein increased, and the rate and the diameter ratio increased at the standing position compared to the supine position. The incidence of the nutcracker phenomenon in our cases according to different threshold values defined in different studies is given in Table 2. When the diameter ratio (DR) and peak velocity ratio (PVR) thresholds were taken as 4.7 or 5 based on the studies of Kim et al. [6] and Cheon et al. [7], the rate of nutcracker phenomenon was significantly higher at the standing position than in the supine position (P=0.01, McNemar Test).

Table 1: Doppler Measurements of left renal vein

Position		Mean
Supine position	AMLRVPV (cm/sec)	100.27 (45.01)
	HLRVPV (cm/sec)	25.23 (6.76)
	AMLRVD (mm)	2.05 (0.63)
	HLRVD (mm)	8.76 (1.32)
	PVR	4.26 (2.14)
	DR	4.61 (1.51)
Standing position	AMLRVPV (cm/sec)	147.19 (42.31)
	HLRVPV (cm/sec)	18.35 (4.27)
	AMLRVD (mm)	1.51 (0.34)
	HLRVD (mm)	10.36 (1.48)
	PVR	8.54 (3.39)
	DR	7.21 (1.89)

AMLRVPV: Aortomesenteric peak velocity of left renal vein, HLRVPV: Hilar peak velocity of left renal vein, AMLRVD: Aortomesenteric diameter of left renal vein, HLRVD: Hilar diameter of left renal vein, PVR: Peak velocity ratio= AMLRVPV/HLRVPV, DR: Diameter ratio=HLRVD/AMLRVD

Table 2: Nutcracker prevalence of patients with different threshold values

Study	Specified threshold value	Measurement position	Nutcracker Phenomenon Positive n (%)	Nutcracker Phenomenon Negative n (%)
Hangge et al. [9]	DR>2.25	Supine	26 (100)	0
		Standing	26 (100)	0
Kim et al. [6]	DR>5	Supine	11 (42.3)	15 (57.7)
		Standing	24 (92.5)	2 (7.7)
	PVR>5	Supine	11 (42.3)	15 (57.7)
		Standing	23 (88.5)	3 (11.5)
Cheon et al. [7]	PVR>4.7	Supine	11 (42.3)	15 (57.7)
		Standing	23 (88.5)	3 (11.5)
	DR> 4.7	Supine	11 (42.3)	15 (57.7)
		Standing	24 (92.3)	2 (7.7)
Romera-Villegas [13]	PVR>2.99	Supine	15 (57.7)	11 (42.3)
	PVR>3.73	Standing	25 (96.2)	1 (3.8)
	DR>3.85	Supine	16 (61.5)	10 (38.5)
	DR>4.12	Standing	25 (96.2)	1 (3.8)

PVR: Peak velocity ratio (AMLRVPV/HLRVPV), DR: Diameter ratio (HLRVD/AMLRVD)

Protein positivity was found in 6 cases in dipstick urinalysis. Among them, the supine peak velocity ratio was 5.27 (1.36), the supine diameter ratio was 5.12 (1.64), the standing PVR was 9.47 (3.20), and the standing DR was 7.42 (2.07). These values were insignificantly higher than the mean values in cases without protein in the urinalysis (P=0.20, P=0.35, P=0.45 and P=0.76, respectively Students' T test). There was no significant difference in peak velocity or diameter ratios when BMI values below the 5th percentile were compared with those without (P=0.55, P=0.92 respectively Chi-Square). In addition, no hematuria or flank pain was found in the cases, which are other clinical manifestations of nutcracker syndrome.

With this sample size, the effect size was 0.97%, and the power was 94%, with a margin of error of 5%, in the standing position and supine AMLRVPV. Furthermore, the standard effect size was 1.07%, and the power was 97% with a 5% margin of error in the standing position and supine nutcracker phenomenon rates.

A total of 3 cases were operated. Two had testicular pain, and one had a disorder in sperm analysis. One of these patients, who was operated in a different clinic, was admitted with recurrence. In this patient, the PVR and DR were 2.20 and 3.9, respectively, in the supine position, and 7.56 and 8.16, respectively, in the standing position.

Discussion

Increased pressure in the left renal vein is considered among the causes of varicocele. The Nutcracker phenomenon is the most important known cause of this pressure increase. The gold standard in diagnosis is to measure the pressure difference between the left renal vein and the vena cava by selective angiography [6]. Computerized tomography (CT) and Doppler US were also used for diagnosis instead of this highly invasive method [2, 7]. It is possible to reveal the difference caused by stenosis by measuring the renal vein flow velocity and diameter after and before the stenotic segment with Doppler US. Many researchers have shown that the left renal vein narrows in the aortomesenteric section, and the peak flow velocity in this section increases significantly in patients with varicocele [4, 8, 9]. In this study, we observed that the peak velocity in AMLRV increased more than four times compared to HLRV and the diameter decreased more than 4.5 times in children with varicocele in the supine position. This result is compatible with other studies in the literature.

Hangge et al. [9] showed that the mean value of DR was higher in the patient group with CT. They stated that with a cutoff value of 2.25, nutcracker can be diagnosed with high sensitivity and specificity. Kim et al. [6] defined the threshold of PVR and DR as 5 in their study according to Doppler US measurements. In the study of Cheon et al. [7] it was shown that the nutcracker phenomenon could be detected with high sensitivity and specificity with a PVR threshold of 4.7. In this study, the rate of nutcracker phenomenon was 42.3% when PVR and DR threshold values were 5 or 4.7. This data was consistent with the rate of 30.1-56.2%, reported in the literature [8, 9]. When this ratio was taken as 2.25, as in the study of Hangge et al. [9], all of our cases had nutcracker phenomenon.

The standing position increases the renal vein pressure by narrowing the aortomesenteric angle and visceral ptosis [3, 12]. Therefore, the researchers thought that standing Doppler US would be more sensitive in demonstrating the nutcracker phenomenon. Romero-Villegas et al. [13] stated that PVR measurement with standing Doppler US would show the nutcracker phenomenon with the best sensitivity and specificity by analyzing Doppler US results in patients with intermittent hematuria of unknown cause. Unlu et al. [4] also showed that the Doppler measurements while standing defined the nutcracker phenomenon better than those performed in the supine position without a sharp threshold. In our study, a significant increase was observed in both PVR and DR values while standing. As a result of this, the rate of nutcracker phenomenon when standing up has more than doubled, reaching almost 90% with different threshold values. These high rates are not surprising when varicocele is considered a manifestation of nutcracker syndrome. We think that ultrasonic measurements while standing are necessary to resolve the causes of varicocele.

Many studies have shown an inverse relationship between BMI and varicocele frequency and grade [14, 15]. This has been attributed to the fact that as the BMI increases, the adipose tissue around the renal vein increases and prevents compression, and the fat tissue makes it difficult to examine the spermatic cord [16]. In our study, we also found an inverse relationship between the varicocele grade and BMI. Almost all children with a BMI below the 5th percentile had a grade 3 varicocele. However, no significant difference was found in ultrasonographic measurements between these underweight children and the others.

Orthostatic proteinuria is one of the symptoms of nutcracker syndrome [1]. It is usually a benign finding and does not require treatment. Park et al. [2] showed that DR and PVR were increased in patients with orthostatic proteinuria compared to healthy volunteers. The mean DR was reported as 5.31 and PVR as 5.21 in cases with proteinuria. Proteinuria was found in 6 cases with the dipstick test, and DR and PVR rates were 5.12 and 5.27, respectively, which were very close to the aforementioned study. Although the mean velocity and diameter ratios in both supine and standing cases were higher in these 6 cases compared to the others, no significance was found. However, we think that this difference can be demonstrated statistically by conducting studies with a larger number of cases.

Limitations

The most important limitations of our study are its retrospective nature and the lack of a control group, which may both cause bias. Performing both standing and supine ultrasonic measurements and comparing them with different parameters such as BMI, proteinuria, and varicocele grade are the strengths of our study.

Conclusion

Doppler ultrasonography in the standing position is superior to that performed in the supine position in detecting the nutcracker phenomenon in patients with varicocele. Furthermore, in almost all cases with varicocele, the Doppler US detected the nutcracker phenomenon at the standing position, based on every threshold value. Future randomized controlled studies with

Doppler US at the standing position may reveal that the nutcracker phenomenon might be the main cause of varicocele.

References

1. Kurklinsky AK, Rooke TW. Nutcracker phenomenon and nutcracker syndrome. Mayo Clin Proc. 2010;85:552–9.
2. Park SJ, Lim JW, Cho BS, Yoon TY, Oh JH. Nutcracker syndrome in children with orthostatic proteinuria: Diagnosis on the basis of Doppler sonography. J Ultrasound Med. 2002;21:39-45.
3. Cho BS, Choi YM, Kang HH, Park SJ, Lim JW, Yoon TY. Diagnosis of nut-cracker phenomenon using renal Doppler ultrasound in orthostatic proteinuria. Nephrol Dial Transplant. 2001;16:1620–5.
4. Unlu M, Orguc S, Serter S, Pekindil G, Pabuscu Y. Anatomic and hemodynamic evaluation of renal venous flow in varicocele formation using color Doppler sonography with emphasis on renal vein entrapment syndrome. Scand J Urol Nephrol. 2007;41:42–6.
5. Neyzi O, Günöz H, Furman A, Bundak R, Gökçay G, Darendeliler F, et al. Türk çocuklarında vücut ağırlığı, boy uzunluğu, baş çevresi ve vücut kitle indeksi referans değerleri. Çocuk Sağlığı ve Hastalıkları Dergisi. 2008;51:1-14.
6. Kim SH, Cho SW, Kim HD, Chung JW, Park JH, Han MC. Nutcracker syndrome: Diagnosis with Doppler US. Radiology 1996;198:93–7.
7. Cheon JE, Kim WS, Kim IO, Kim SH, Yeon KM, Ha IS, et al. Nutcracker syndrome in children with gross haematuria: Doppler sonographic evaluation of the left renal vein. Pediatr Radiol. 2006;36:682–6.
8. Nishimura Y, Fushiki M, Yoshida M, Nakamura K, Imai M, Ono T, et al. Left renal vein hypertension in patients with left renal bleeding of unknown origin. Radiology. 1986;160:663–7.
9. Hangge P, Gupta N, Khurana A, Quencer K, Albadawi H, Alzubaidi S, et al. Degree of Left Renal Vein Compression Predicts Nutcracker Syndrome. J Clin Med. 2018;7:107.
10. Hannick JH, Blais AS, Kim JK, Traubici J, Shiff M, Book R, et al. Prevalence, Doppler Ultrasound Findings, and Clinical Implications of the Nutcracker Phenomenon in Pediatric Varicoceles. Urology. 2019;128:78–83.
11. Mohamadi A, Ghasemi-Rad M, Mladkova N, Masudi S. Varicocele and nutcracker syndrome: Sonographic findings. J Ultrasound Med. 2010;29:1153–60.
12. Turner TT. Varicocele: Still an enigma. J Urol. 1983;129:695–9.
13. Romera-Villegas A, Vila-Coll R, Cairols-Castellote R, Poveda-Monge R, Masuet-Aumatell C, Grinyó-Boira M. The importance of a standing position in the diagnosis of nutcracker phenomenon by duplex sonography. Int Angiol. 2009;28(6):461-8.
14. Pham KN, Sandlow JI. The effect of body mass index on the outcomes of varicocelectomy. J Urol. 2012;187:219–21.
15. Hassanzadeh K, Yavari-kia P, Soleymanpour H, Ebrahimpour-tolouei N, Alikhah H. Effect of Body Mass Index on severity and prevalence of varicocele. Pak J Biol Sci. 2011;14:869–75.
16. Tsao CW, Hsu CY, Chou YC, Wu ST, Sun GH, Yu DS, et al. The relationship between varicoceles and obesity in a young adult population. Int J Androl. 2009;32:385–90.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):642-647.
DOI: 10.28982/josam.951898

Journal of Surgery and Medicine
e-ISSN=2602-2079

Pilates workouts can improve the labor and newborn outcomes: A case control study

Pınar Kırıcı [1], Mehmet Can Nacar [1], Talip Karaçor [1], Mehmet Bülbül [1], Merve Baktıroğlu [2], Nihal Mavral [3], Necla Kaya [1]

[1] Adıyaman University, Faculty of Medicine, Department of Obstetrics and Gynecology, Adıyaman, Turkey
[2] Istanbul University, Faculty of Medicine, Department of Gynecological Oncology, Istanbul, Turkey
[3] Hitit University Training and Research Hospital, Department of Obstetrics and Gynecology, Corum, Turkey

ORCID ID of the author(s)

PK: 0000-0001-7616-4181
MCN: 0000-0001-5463-4197
TK: 0000-0003-1349-1569
MB: 0000-0001-5695-2586
MB: 0000-0001-8931-8397
NM: 0000-0002-0622-8415
NK: 0000-0001-7354-8366

Corresponding Author
Pınar Kırıcı
Adıyaman Üniversitesi School of Medicine, Atatürk Blv. No: 411, 02200 Merkez, Adıyaman, Turkey
E-mail: kiricipinar@hotmail.com

Ethics Committee Approval
The study was approved by the Non-Interventional Clinical Research Ethics Boards of the Adıyaman University (approval number 2019/8-11).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2021 June 25

Abstract

Background/Aim: Physical activity during pregnancy assumes an important role in the health of both the pregnant and newborn. Our study aims to evaluate the effects of Pilates workouts on labor and newborn outcomes.
Methods: This retrospective case control study was conducted with the nulliparous pregnant women admitted to our obstetrics clinic. We evaluated the effects of a Pilates workout program for 70-80 minutes per day, once a week for eight weeks, on the labor and newborn outcomes. We defined the labor outcomes as the type of delivery and the gestational age at delivery and the newborn outcomes as one-minute (APGAR-1) and five-minute Apgar scores (APGAR-5).
Results: The incidences of episiotomy, vacuum-assisted vaginal delivery, and cesarean section (CS) were significantly lower in pregnant women who participated in Pilates workouts ($P<0.001$). Pilates workouts increased the chance of normal vaginal delivery. The gestational age at delivery was significantly lower, and the APGAR-1 and APGAR-5 scores were significantly higher among those in the Pilates group ($P<0.001$).
Conclusion: A supervised Pilates workout is an effective and achievable exercise method decreasing cesarean delivery and assisted vaginal delivery. It also has no negative effects on newborns, supported by the higher APGAR scores of babies whose mothers were in the Pilates group.

Keywords: Pilates, Pregnancy, Pregnant women, Normal delivery, Cesarean delivery, Newborn

How to cite: Kırıcı P, Nacar MC, Karaçor T, Bülbül M, Baktıroğlu M, Mavral N, Kaya N. Pilates workouts can improve the labor and newborn outcomes: A case control study. J Surg Med. 2021;5(6):642-647.

Introduction

The worldwide rate of cesarean delivery has increased since 2000, and Turkey has one of the highest rates of cesarean-section, reported as over 50% [1, 2]. This rise in C-sections (CS) is a global phenomenon, which is an issue of concern as a cesarean delivery is not without risk to the mother and fetus [2, 3]. Maternal risks during a CS are major abdominal surgery complications, placental problems during future pregnancies, respiratory complications, reaction to anesthesia, and longer hospitalization. Besides, neonatal respiratory difficulties and poor sucking reflex are known risk factors for the newborn [3-5].

Exercise during pregnancy contributes to feeling healthy by improving fitness, reducing symptoms of depression, and decreasing gestational weight gain [6, 7]. The strengthening of the muscle of the area involved in regulating labor reduces the pain and the effort needed to give birth [8]. In the absence of complications, pregnant women should be encouraged to join recommended physical activities, which appear to be helpful and reliable for both the mother and fetus [6]. The American Congress of Obstetricians and Gynecologists (ACOG) recommends that all pregnant women should be engaged in moderate-intensity exercise for 30 minutes or more per day on most—if not all—days of the week [9-11].

Among exercise methods, the Pilates workout has become more popular worldwide than other physical activities [12]. For both healthy and unhealthy adults, modern Pilates workout programs are useful and beneficial for increasing feelings of happiness and well-being, reducing anxiety and stress, gaining muscular strength and flexibility, and improving posture [12-15]. Considering that pregnancy leads to several changes in a woman's body, participating in a Pilates workout not only leads to the benefits mentioned, but it also helps the pregnant woman adapt to the physical changes within her body [16, 17].

While there are no international clinical guidelines for Pilates exercises during pregnancy, brief unauthorized recommendations exist in the literature [11, 14]. Several studies investigate the effects of physical exercise on weight gain, type of delivery, and birth outcomes, and a few studies were found in the literature involving a physical exercise program using the Pilates method [16, 17]. The aim of the present study is, therefore, to assess the potential effects of Pilates workouts during the 24th and 40th gestational weeks on labor and newborn outcomes.

Materials and methods

Study design and setting

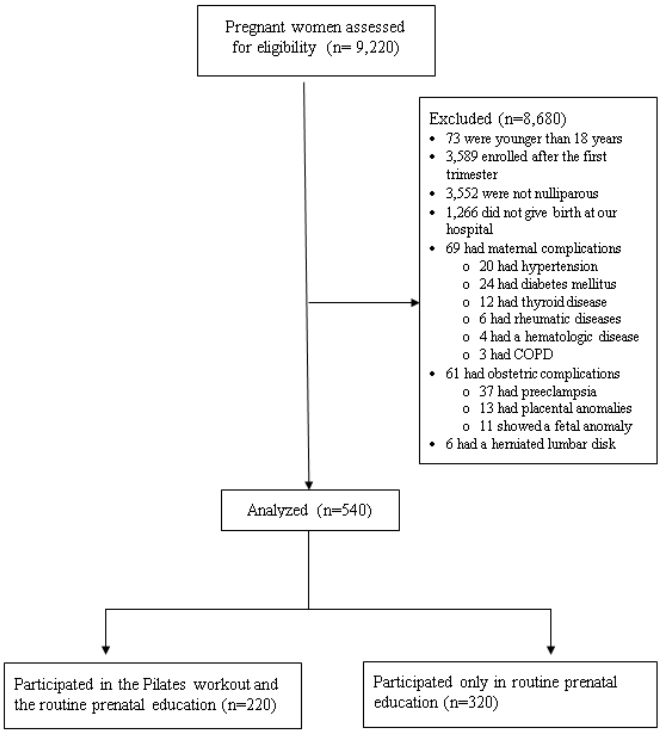
This retrospective case control study was conducted under the Declaration of Helsinki, and according to the STROBE guidelines [18]. The study was approved by the Non-Interventional Clinical Research Ethics Boards of the Adıyaman University (approval number 2019/8-11) and is based on the obstetric registry data from our hospital between 01.01.2017 and 30.09.2019. Ours is a tertiary care hospital with an obstetrics and gynecology bed capacity of 110. Our obstetric registry includes maternal demographics, medical and obstetric history, obstetric follow-up visit information, labor and delivery outcomes, and post-natal outcomes for the mothers and the newborns. Because of the nature of our study, we were not required to obtain informed consent from participants.

Study size and participants

We intended to include all pregnant women who met the inclusion criteria for the study, which included (1) being aged 18 years and older, (2) having visited our obstetrics clinic in the first trimester of a nulliparous pregnancy, and (3) having delivered at our hospital. The exclusion criteria were as follows: (1) Having obstetric complications such as preeclampsia, placental anomalies, or fetal anomalies, (2) having a herniated lumbar disk, (3) having a chronic illness such as hypertension, diabetes mellitus, thyroid diseases, rheumatic diseases, chronic hematologic diseases, or chronic obstructive pulmonary disease (COPD), or (4) having had uterine surgery.

This study was performed with the data of the pregnant women admitted to our obstetrics clinic (OC) who gave birth in our hospital. We assessed 9,220 pregnant women for eligibility for the study. After excluding 8,680 women, 540 pregnant women were included in the analyses. We further divided the study cohort into two groups based on their participation in the workout program (Pilates group vs. control group). Of the 540 women in the study, 220 pregnant women (40.7%) participated in the Pilates workout program (Figure 1).

Figure 1: Flow diagram of the study



As a standard procedure, all pregnant women who register at our clinic get prenatal education on topics such as medications, dental care, nutrition, weight gain, exercise, and workplace practices. The exercise topic includes describing which physical activities are safe and unsafe, evaluating the patient for any medical conditions that would lead to having to avoid exercise, and recommending appropriate physical exercises. Also, we started a Pilates exercise program modified for pregnancy on January 1, 2017. The Pilates instructors were trained by a senior Pilates instructor, an obstetrician, and a midwife to ensure that the modified exercise program would be safe for pregnant women. Any pregnant women followed up at

our clinic may voluntarily participate in this Pilates exercise program.

The pregnant women participated in the exercise program for 70-80 minutes a minimum of once a week for 8 weeks between the 24th and 40th gestational weeks. The daily workout was designed as a 10-minute warm-up routine, a main exercise session of 50-60 minutes, and a 10-minute cool-down routine. This program was based on official Pilates methods used by the New York Pilates Academy International (PAI) and the San Francisco Balanced Body University (BBU) [19]. It is used to promote good posture and alignment, strengthen the legs to help carry the increased body weight, prevent edema and pain from varicose veins, strengthen the abdominal muscles, protect the cardiovascular system, strengthen the pelvic floor muscles to be used during labor, and strengthen the arms for childcare after childbirth.

Data and variables

We obtained the following data: Age, occupation, education, height and weight, obstetric and medical history, due date, whether they smoked or not, whether they had consulted with a prenatal dietician (in addition to our prenatal education program), previous Pilates experience, their participation in our Pilates exercise program, and the maternal and newborn outcomes from the hospital registry system. Using a three-step control mechanism, the data was compared against the hospital registry for errors including incorrect entries, duplicate records, and user errors. The hospital data processing unit checked the system daily, and the medical service and statistics units checked it monthly. During the final step, the provincial health authorities checked the data and registries and the ministry of health checked the records four times a year.

We calculated pregestational body mass index (BMI), and based on these calculations, we categorized them as underweight (less than 18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (30.0 kg/m^2 and over). We defined the weight gain during pregnancy as the difference between the weight at labor and the weight on conception.

There are four primary outcomes of the study, of which two are labor outcomes, and two are newborn outcomes. The labor outcomes are the delivery method and the gestational age at delivery. We defined the delivery as normal vaginal delivery (with/without episiotomy or vacuum assistance) and cesarean delivery. The ACOG guidelines were used for selecting the delivery at our hospital [20-22]. We categorized the gestational age at delivery as preterm (less than 37 0/7 weeks), early-term (37 0/7-38 6/7 weeks), full-term (39 0/7-40 6/7 weeks), late-term (41 0/7-41 6/7 weeks), and post-term (42 0/7 weeks and beyond).

The newborn outcomes are based on one-minute (APGAR-1) and five-minute APGAR scores (APGAR-5). A pediatrician calculated the APGAR scores for all newborns one and five minutes after birth.

Statistical analysis

Statistical analyses were conducted using SPSS Statistics version 20.0 (IBM Corp., Armonk, NY). Descriptive data are presented as median with interquartile range (IQR) for numerical variables, and as frequency and percentage for categorical variables. The Shapiro–Wilk and Kolmogorov–Smirnov tests were used to evaluate the distribution of the numerical data. The Mann–Whitney U test was used to compare non-normally distributed numerical data between two study groups. Pearson's chi-squared (χ^2) and Fisher's exact tests were used for comparing categorical variables. We used univariate logistic regression analysis to assess the effect of Pilates on the delivery. Also, we built three multivariate logistic regression models for adjusting covariates (occupation, education level, pregestational BMI, weight gain during pregnancy, previous Pilates experience, and prenatal dietician consultation) to analyze the effect of the Pilates workouts on the delivery. $P<0.05$ was considered statistically significant.

Results

The median age was 26.0 years in each study group. Of those in the Pilates group, almost half were housewives, while 63.7% of the control group were housewives. Among these pregnant women, 48.2% of the Pilates group and 44.7% of the control group had an education level of university or higher. Of the Pilates group, 2.7% were underweight and 9.1% were overweight; however, there were no underweight women among the controls while 10.6% of the women in that group were overweight. The median weight gain during pregnancy within the groups was 9.0 kg and 12.0 kg, respectively. Of these pregnant women, 18.6% and 23.5% were smokers in the Pilates and control groups, respectively. The incidences of episiotomy, vacuum-assisted vaginal delivery, and CS were significantly lower among the Pilates group than the control group ($P<0.001$). Among the Pilates group, 31.8% of the women had previous experience with Pilates, while no one in the control group had had previous experience doing Pilates exercises. Women in the Pilates group consulted with a prenatal dietician nearly five times more than the women in the control group. The median gravida was 1, and there had been zero abortions in either study group (Table 1).

Table 1: Characteristics of the pregnant women

Characteristics	Pilates group n= 220 (40.7%)	Control group n= 320 (59.3%)	*P*-value
Age (years), median (IQR)	26.0 (23.0-29.0)	26.0 (23.0-29.0)	0.753
Occupation, n (%)			0.026
Housewife	116 (52.7)	204 (63.7)	
Blue-collar worker	32 (14.5)	42 (13.1)	
White-collar worker	72 (32.7)	74 (23.1)	
Level of education, n (%)			0.006
Secondary school	11 (5.0)	3 (0.9)	
High school	103 (46.8)	174 (54.4)	
University	106 (48.2)	143 (44.7)	
Pregestational BMI, n (%)			0.009
Underweight	6 (2.7)	0 (0.0)	
Normal weight	194 (88.2)	286 (89.4)	
Overweight	20 (9.1)	34 (10.6)	
Weight gain during pregnancy (kg), median (IQR)	9.0 (8.0-10.0)	12.0 (11.0-14.0)	< 0.001
Type of delivery, n (%)			< 0.001
NVD	142 (64.6)	44 (13.8)	
NVD with episiotomy	61 (27.7)	144 (45.0)	
NVD with vacuum extraction	6 (2.7)	54 (16.9)	
CS	11 (5.0)	78 (24.4)	
Smokers, n (%)	41 (18.6)	75 (23.5)	0.176
Previous Pilates experience, n (%)	70 (31.8)	0 (0.0)	< 0.001
Prenatal dietician consultation, n (%)	106 (48.2)	32 (10.0)	< 0.001
Gravida, median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	
Abortions, median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	

IQR: Interquartile range, BMI: Body mass index

The odds ratio of Pilates workouts to the routine prenatal education was 6.1 (95% CI: 3.2-11.8) for the chance of normal delivery compared to the cesarean delivery in the univariate analysis. In the multivariate analyses, we also found

the Pilates workout to significantly affect the type of delivery independent from demographics, pregestational BMI, weight gain during pregnancy, previous Pilates experience, or prenatal dietician consultation (OR (95% CI): 3.2 (1.5-6.8) and *P*= 0.003) (Table 2).

Table 2: Univariate and multivariate logistic regression analysis for the effect of the Pilates workout participation on the type of delivery

Delivery type	Pilates group n (%)	Control group n (%)	Univariate analysis			Multivariate model 1*			Multivariate model 2**			Multivariate model 3***		
			P	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI
Normal	209 (95.0)	242 (75.6)	<0.001	6.1	3.2-11.8	<0.001	5.5	2.6-11.6	0.001	3.6	1.7-7.7	0.003	3.2	1.5-6.8
Cesarean	11 (5.0)	78 (24.4)												

ORs show the chance of the normal delivery (with/without episiotomy and/or vacuum aid) compared to cesarean delivery. * Adjusted for occupation, education level, pregestational BMI, and weight gain during pregnancy. ** Adjusted for occupation, education level, pregestational BMI, weight gain during pregnancy, and previous Pilates experience. *** Adjusted for occupation, education level, pregestational BMI, weight gain during pregnancy, previous Pilates experience, and prenatal dietician consultation.

The gestational age at delivery was significantly lower in the Pilates group compared to the control group (*P*<0.001). However, there was neither preterm nor post-term labor in either group. In the Pilates group, the rates of newborns with birth weights of 2500-3000 gr and 3000-3500 gr were significantly higher when compared to the control group (*P*<0.001) (Table 3).

The one-minute and the five-minute APGAR scores were significantly higher in the Pilates group than the control group (*P*<0.001 and *P*<0.001, respectively) (Table 4 and Figure 2).

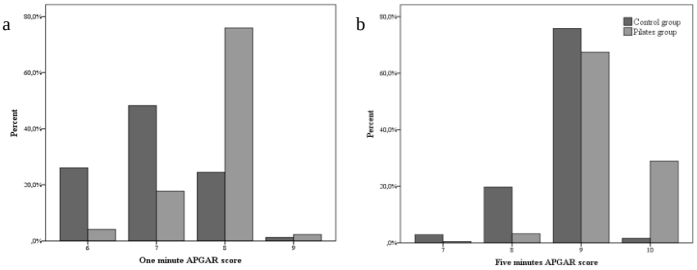
Table 3: Comparison of gestational age on delivery and birth weight among the study groups

	Pilates group n= 220 (40.7%)	Control group n= 320 (59.3%)	*P*-value
Gestational age at delivery, n (%)			
Early term	60 (27.3)	30 (9.4)	<0.001
Full term	159 (72.3)	227 (70.9)	
Late term	1 (0.4)	63 (19.7)	
Birth weight, n (%)			
2500-2999 gr	79 (35.9)	59 (18.4)	<0.001
3000-3499 gr	120 (54.5)	132 (41.2)	
3500-3999 gr	20 (9.1)	117 (36.6)	
≥ 4000 gr	1 (0.5)	12 (3.8)	

Table 4: Comparison of one-minute and five-minute APGAR scores of the newborns among the study groups

APGAR score		Pilates group n= 220 (40.7%)	Control group n= 320 (59.3%)	*P*-value
One minute	Mean (SD)	7.8 (0.6)	7.0 (0.7)	< 0.001
	Median (IQR)	8.0 (8.0-8.0)	7.0 (6.0-8.0)	
Five minutes	Mean (SD)	9.3 (0.5)	8.8 (0.5)	< 0.001
	Median (IQR)	9.0 (9.0-10.0)	9.0 (9.0-9.0)	

Figure 2: Distribution of (a) one-minute and (b) five-minute APGAR scores of the newborns



Discussion

Our study includes a relatively large number of pregnant women in both intervention and control groups, when compared to similar studies focusing on the benefits of exercise [8, 13]. Our study demonstrated that Pilates workouts significantly decrease the rate of cesarean and instrumented vaginal deliveries. We performed additional models for adjusting covariates to analyze the effect of the Pilates workouts on the type of delivery, finding that the Pilates workout was associated with a significantly higher incidence of vaginal delivery, and a significantly lower incidence of cesarean delivery independent of demographics, pregestational BMI, weight gain during pregnancy, previous Pilates experience, and prenatal dietician consultation. No adverse events were noted during or after the Pilates sessions in our study.

To date, several studies investigating the effects of physical exercise on type of delivery have been found in the literature. While some of the studies report that physical exercise does not affect the type of delivery [23, 24], other studies state that physical exercise during pregnancy decreases the risk of Cesarean delivery and increases the likelihood of vaginal delivery [3, 25, 26]. Also, several recently published reviews agree on the effects of physical activity on type of delivery; however, a general lack of consensus exists because the individual trials included in these reviews differ somewhat in terms of how they define exercise, the intensity of exercise, time, and duration of exercise [4, 27-31]. Also, the focus of those authors was not on the type of delivery; hence, detailed information on the indications for performing the cesarean section was rarely reported [4, 24]. The researchers of those studies also stated that lots of confounding factors may affect the main conclusions such as which type of physical activity was carried out, and how the participants were assessed [26].

Several studies were based on data from self-administered questionnaires [6, 24], which are not objective assessment tools. There is little information in the studies on a supervised exercise program, and many studies report observations on leisure time and physical activity related to occupation [3, 24]. Besides, the period of physical activity in these studies varies. While some include early pregnancy through the third trimester, others include only the second or third trimester [3, 6].

Excessive gestational weight gain is associated with an increased risk of complications such as instrumental vaginal delivery and cesarean delivery [25, 32]. Excessive weight gain during pregnancy is also related to an increased risk of weight retention after delivery, with approximately 25% of women experiencing weight retention of 4.5 kg or more [32, 33]. Linne et al. [34] showed that 45.6% of women of normal weight who gained too much weight during pregnancy (an average of 18.8 kg) shifted from normal weight to overweight during a 15-year follow-up period. However, a combined intervention including dietary counseling and physical exercise during pregnancy showed a significantly higher probability of returning to pregestational weight at 6 months postpartum [35, 36]. Therefore, preventive strategies among pregnant women are needed to prevent excessive weight gain during pregnancy. This could help fight the obesity epidemic, because the pregnant women who participated in Pilates workout gained less weight than those in the control group.

Recently, many reports have emphasized that moderate exercise does not increase the risk of preterm delivery [6, 25, 27, 28]. In our study, there was neither preterm nor post-term labor in either group. By using the global-standard APGAR score of the newborns, one- and five-minute APGAR scores of newborns whose mothers participated in Pilates workouts were significantly higher than those in the control group, showing that the overall health status of the newborn was not adversely affected by the Pilates workouts. Moreover, newborn baby weights were significantly higher in the control group. It has

been stated that moderate exercises that start after the 20th gestational week can positively affect fetal development and APGAR scores of these newborns compared to newborn babies of women who do not exercise [37]. Contrary to this study, there was no significant difference between the 1st and 5th minute APGAR scores in a previous study [38].

Several studies are investigating the effects of Pilates exercises on pain control, type of delivery, or strengthening the pelvic floor muscles of pregnant women. Dias et al. [13] investigated the effects of a Pilates exercise program on pelvic floor muscle strength in pregnant women. They found that the program was not able to change pelvic floor muscle strength but emphasized that small sample size (24 pregnant women in the Pilates group and 12 in the control group) may have limited their findings. Rodriguez-Diaz et al. [8] similarly conducted a study of 105 pregnant women (50 in the Pilates group and 55 in the control group) to assess the effectiveness and safety of the Pilates method on functional and labor parameters. They concluded that a Pilates routine increases the rate of normal birth and decreases the need for an episiotomy or a CS.

For many women, it is difficult to find the motivation to start a physical exercise program [4]. It was demonstrated that the percentage of pregnant women who participated in a physical activity program during pregnancy was low [9, 25]. Besides, women who engaged in an exercise program stopped exercising, particularly in the third trimester as they found it difficult to move due to their increased body mass [39]. However, several studies have stated that pregnancy represents a "teachable moment" to adopt healthy behaviors as gravid women are often young and reliably seek healthcare [33, 40].

We believe that the increasing popularity of Pilates workouts over the last few decades may contribute to a greater adherence to Pilates exercises among pregnant women compared to other exercise programs. Domenjos et al. [4] state that pregnancy could be a critical moment to cease the sedentary life if physical exercise is approved to be effective and beneficial for pregnancy outcomes for both mother and fetus. Dias et al. [13] suggested that their Pilates group had good compliance with the intervention. All pregnant women in the Pilates group had completed the program through the last trimester of pregnancy, and that supports this approach.

Limitations

The main limitation of this study was its retrospective design, and the gathering of the data from the hospital registry. However, we have a three-step quality control system to prevent errors and account for missing data. Another limitation is having no data on the dietary habits of the participants, which is an important confounding variable between exercise and its outcomes on health. Furthermore, the baseline characteristics of the pregnant women such as occupation, education level, and pregestational BMI were not balanced among the study groups; however, we performed additional multivariate logistic regression models for adjusting these covariates to analyze the effect of the Pilates workouts on the type of delivery. Also, we used only APGAR-1 score, APGAR-5 score, and birth weight as newborn outcomes, though there are many other outcomes such as the need for intensive care and the neonatal death rate that can demonstrate the health and well-being of the newborns.

Conclusion

In conclusion, the results of our study demonstrate that a supervised Pilates workout is an effective and achievable exercise method decreasing cesarean delivery and assisted vaginal delivery with episiotomies or vacuum extraction. Such an exercise program also has no negative effects on newborns, as supported by the higher APGAR scores. More comprehensive and prospective studies should be conducted to generalize these results.

References

1. Owe KM, Nystad W, Stigum H, Vangen S, Bo K. Exercise during pregnancy and risk of cesarean delivery in nulliparous women:a large population-based cohort study. Am J Obstet Gynecol. 2016;215:791.e1-.e13.
2. OECD (2017), "Caesarean sections", in Health at a Glance 2017:OECD Indicators, OECD Publishing, Paris.
3. Barakat R, Pelaez M, Lopez C, Montejo R, Coteron J. Exercise during pregnancy reduces the rate of cesarean and instrumental deliveries:results of a randomized controlled trial. J Matern Fetal Neonatal Med. 2012;25:2372-6.
4. Domenjoz I, Kayser B, Boulvain M. Effect of physical activity during pregnancy on mode of delivery. Am J Obstet Gynecol. 2014;211:401.e1-11.
5. Akgun N, Keskin HL, Ustuner I, Pekcan G, Avsar AF. Factors affecting pregnancy weight gain and relationships with maternal/fetal outcomes in Turkey. Saudi Med J. 2017;38:503-8.
6. Takami M, Tsuchida A, Takamori A, et al. Effects of physical activity during pregnancy on preterm delivery and mode of delivery:The Japan Environment and Children's Study, birth cohort study. PLoS One 2018;13:e0206160.
7. Poyatos-Leon R, Garcia-Hermoso A, Sanabria-Martinez G, Alvarez-Bueno C, Sanchez-Lopez M, Martinez-Vizcaino V. Effects of exercise during pregnancy on mode of delivery:a meta-analysis. Acta Obstet Gynecol Scand. 2015;94:1039-47.
8. Rodriguez-Diaz L, Ruiz-Frutos C, Vazquez-Lara JM, Ramirez-Rodrigo J, Villaverde-Gutierrez C, Torres-Luque G. Effectiveness of a physical activity programme based on the Pilates method in pregnancy and labour. Enferm Clin. 2017;27:271-7.
9. Nascimento SL, Surita FG, Cecatti JG. Physical exercise during pregnancy:a systematic review. Curr Opin Obstet Gynecol. 2012;24:387-94.
10. Artal R, O'Toole M. Guidelines of the American College of Obstetricians and Gynecologists for exercise during pregnancy and the postpartum period. Br J Sports Med. 2003;37:6-12.
11. ACOG Committee Opinion No. 650:Physical activity and exercise during pregnancy and the postpartum period. Obstet Gynecol. 2015;126:e135-42.
12. Wells C, Kolt GS, Bialocerkowski A. Defining Pilates exercise:a systematic review. Complement Ther Med. 2012;20:253-62.
13. Dias NT, Ferreira LR, Fernandes MG, Resende APM, Pereira-Baldon VS. A Pilates exercise program with pelvic floor muscle contraction:Is it effective for pregnant women? A randomized controlled trial. Neurourol Urodyn. 2018;37:379-84.
14. Mazzarino M, Kerr D, Morris ME. Pilates program design and health benefits for pregnant women:A practitioners' survey. J Bodyw Mov Ther. 2018;22:411-7.
15. Fleming KM, Herring MP. The effects of pilates on mental health outcomes:A meta-analysis of controlled trials. Complement Ther Med. 2018;37:80-95.
16. Mazzarino M, Kerr D, Wajswelner H, Morris ME. Pilates method for women's health:systematic review of randomized controlled trials. Arch Phys Med Rehabil. 2015;96:2231-42.
17. Oktaviani I. Pilates workouts can reduce pain in pregnant women. Complement Ther Clin Pract. 2018;31:349-51.
18. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg. 2014;12:1495-9.
19. Kim H-J, Kim J, Kim C-S. The effects of pilates exercise on lipid metabolism and inflammatory cytokines mRNA expression in female undergraduates. J Exercise Nutr Biochem. 2014;18:267-75.
20. Caughey AB, Cahill AG, Guise JM, Rouse DJ. Safe prevention of the primary cesarean delivery. Am J Obstet Gynecol. 2014;210:179-93.
21. ACOG Practice Bulletin No. 198:Prevention and Management of Obstetric Lacerations at Vaginal Delivery. Obstet Gynecol. 2018;132:e87-e102. doi: 10.1097/aog.0000000000002841
22. ACOG Practice Bulletin No. 154:Operative Vaginal Delivery. Obstet Gynecol. 2015;126:e56-65.
23. Barakat R, Ruiz JR, Stirling JR, Zakynthinaki M, Lucia A. Type of delivery is not affected by light resistance and toning exercise training during pregnancy:a randomized controlled trial. Am J Obstet Gynecol. 2009;201:590.e1-6.
24. Bovbjerg ML, Siega-Riz AM. Exercise during pregnancy and cesarean delivery:North Carolina PRAMS, 2004-2005. Birth 2009;36:200-7.
25. Wang C, Wei Y, Zhang X, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. Am J Obstet Gynecol. 2017;216:340-51.
26. Morgan KL, Rahman MA, Hill RA, et al. Physical activity and excess weight in pregnancy have independent and unique effects on delivery and perinatal outcomes. PLoS One 2014;9:e94532.
27. Magro-Malosso ER, Saccone G, Di Tommaso M, Roman A, Berghella V. Exercise during pregnancy and risk of gestational hypertensive disorders:a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2017;96: 921-31.
28. Magro-Malosso ER, Saccone G, Di Mascio D, Di Tommaso M, Berghella V. Exercise during pregnancy and risk of preterm birth in overweight and obese women:a systematic review and meta-analysis of randomized controlled trials. Acta Obstet Gynecol Scand. 2017;96:263-73.
29. Di Mascio D, Magro-Malosso ER, Saccone G, Marhefka GD, Berghella V. Exercise during pregnancy in normal-weight women and risk of preterm birth:a systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol. 2016;215:561-71.
30. Ming WK, Ding W, Zhang CJP, et al. The effect of exercise during pregnancy on gestational diabetes mellitus in normal-weight women:a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2018;18:440.
31. Muktabhant B, Lawrie TA, Lumbiganon P, Laopaiboon M. Diet or exercise, or both, for preventing excessive weight gain in pregnancy. Cochrane Database Syst Rev 2015:Cd007145.
32. Sagedal LR, Overby NC, Lohne-Seiler H, et al. Study protocol:fit for delivery-can a lifestyle intervention in pregnancy result in measurable health benefits for mothers and newborns? a randomized controlled trial. BMC Public Health. 2013;13:132.
33. Phelan S. Pregnancy:a "teachable moment" for weight control and obesity prevention. Am J Obstet Gynecol. 2010;202:135.e1-8.

34.Linne Y, Dye L, Barkeling B, Rossner S. Long-term weight development in women:a 15-year follow-up of the effects of pregnancy. Obes Res. 2004;12:1166-78.
35.Huang TT, Yeh CY, Tsai YC. A diet and physical activity intervention for preventing weight retention among Taiwanese childbearing women:a randomised controlled trial. Midwifery. 2011;27:257-64.
36.Phelan S, Phipps MG, Abrams B, Darroch F, Schaffner A, Wing RR. Randomized trial of a behavioral intervention to prevent excessive gestational weight gain:the Fit for Delivery Study. Am J Clin Nutr. 2011;93:772-9.
37.Aktan B. The effect of clinical Pilates exercise and childbirth education on the delivery outcomes (Master Thesis). Ankara:Hacettepe University;2015.
38.Miquelutti MA, Cecatti JG, Makuch MY. Evaluation of a birth preparation program on lumbopelvic pain, urinary incontinence, anxiety and exercise:a randomized controlled trial. BMC Pregnancy Childbirth 2013;13:154.
39.Coll CV, Domingues MR, Hallal PC, et al. Changes in leisure-time physical activity among Brazilian pregnant women:comparison between two birth cohort studies (2004-2015). BMC Public Health 2017;17:119.
40.Bohrer J, Ehrenthal DB. Other adverse pregnancy outcomes and future chronic disease. Semin Perinatol. 2015;39:259-63.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):648-650.
DOI: 10.28982/josam.795843

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Sacral erector spinae plane block for analgesia after hip surgery

Ayşegül Bilge [1], Şule Arıcan [2]

[1] Department of Anesthesia and Reanimation, Gumushane State Hospital, Gumushane, Turkey
[2] Department of Anesthesia and Reanimation, Necmettin Erbakan University, Konya, Turkey

ORCID ID of the author(s)
AB: 0000-0003-2804-9589
ŞA: 0000-0002-8634-1150

Corresponding Author
Ayşegül Bilge
Department of Anesthesia and Reanimation, State Hospital Gumushane, Gumushane, Turkey
E-mail: aysegulbilge@gmail.com

Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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

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

Published
2021 May 15

Abstract

Erector spinae plane block (ESPB) is an interfascial plane block used for providing analgesia in acute or chronic perioperative/postoperative pain for various indications. The case reports presented here describe the use of sacral ESPB for postoperative pain control in two patients who were operated on for a femur fracture. One underwent spinal anesthesia and the other underwent general anesthesia. The sacral ESPB technique has been described and the pain scores and the analgesia requirements of the patients during postoperative 48 hours have been reported. We observed that sacral ESPB is an effective method for postoperative analgesia in patients undergoing surgery for the treatment of a femoral fracture through a posterolateral approach.

Keywords: Erector spinae block, Hip surgery, Ultrasonography

Introduction

Erector spinae plane block (ESPB) was first described as an interfascial plane block performed at the upper thoracic levels to alleviate neuropathic pain [1]. Later, its use has been reported in many thoracic procedures including mastectomy, video-assisted thoracoscopy (VATS), and heart surgery, and at lumbar levels for abdominal surgery, prostatectomy, lumbar spine surgery, total hip arthroplasty, and proximal femur surgery [2].

Sacral ESPB has been recently described. Case reports are showing that it is useful in various types of surgery. In case presentations, it has been reported as effective in providing analgesia in the posterior branches of the sacral nerves in pilonidal sinus surgery, in the treatment of radicular pain at the L5 - S1 level, after a sex reassignment operation and hypospadias surgery, and its use in combination with lumbar ESPB for analgesia was reported after hip prosthesis surgery [3-8].

Severe pain occurs after general anesthesia following hip surgery either because the spinal anesthesia wears off or the patient is not given adequate doses of opioids to avoid potential respiratory problems and hospital morbidity. Severe pain acts on a variety of factors from patient mobilization to the length of hospital stay. We herein reported the effect of sacral ESPB in providing postoperative analgesia by presenting the VAS scores and the need for analgesics in the first 48 hours after surgery in two patients. One of these patients underwent intramedullary nail treatment of an intertrochanteric femoral fracture and the other one underwent prosthetic replacement of the femoral head.

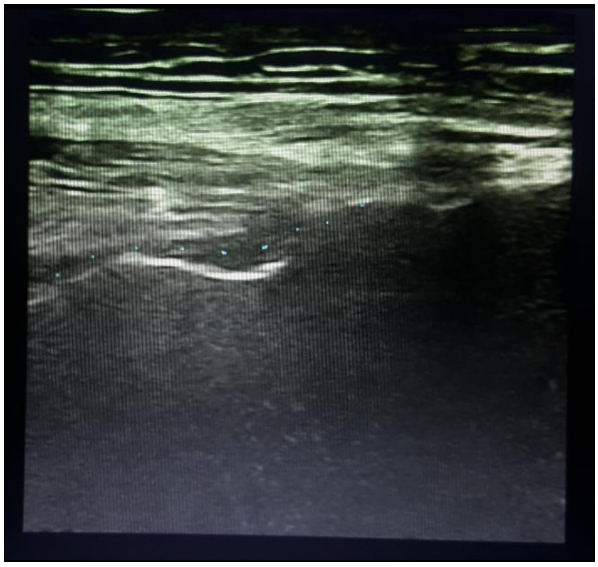
How to cite: Bilge A, Arıcan Ş. Sacral erector spinae plane block for analgesia after hip surgery. J Surg Med. 2021;5(6):648-650.

Case presentation

The first patient was a 71-year-old female with a history of rheumatoid arthritis who underwent intramedullary nail treatment due to a trochanteric fracture in her right femur. Written informed consent was obtained from the patient. The surgical procedure was performed without the use of opioids in approximately 2.5 hours under spinal anesthesia by administering 12 milligrams of bupivacaine through the intervertebral space between the L4 and L5 vertebrae.

When the patient was in the lateral decubitus position, the curvilinear (curved) transducer was placed parallel to the median sacral crest pointing towards the caudal direction. After visualizing the S1 median sacral crest, the transducer was shifted caudally. When the S3 level was reached, the transducer was moved 3-4 cm laterally. Then, the intermediate crest (IC) was detected in the parasagittal plane. At the S3-4 level, a 21-gauge, 80-mm-block needle (Pajunk, Geisingen, Germany) was advanced in the caudo-cranial direction under the erector spinae muscle until it contacted the bone. Then, a 30 ml solution containing 60 mg bupivacaine and 240 mg prilocaine was injected. The caudal-cranial spread of the solution and the elevation of the erector spinae muscle over the bone were observed (Figure 1). Motor block was not detected in the lower extremities of the patient, who was re-evaluated in the inpatient unit 2 hours after the block. There was no pain at the incision site, where the posterolateral approach was used. The pain severity with joint motion was scored as 2/10 using the numeric pain rating scale (NRS). Because the visual analog scale (VAS) score of the patient was 4/10 at the end of the 6th hour, paracetamol infusion was administered. The VAS score was still 2/10 at the end of 24 hours. No other analgesics were required within 48 hours. The patient was mobilized on the postoperative first day and discharged on day 4.

Figure 1: Linear distribution of local anesthesia after application of sacral erector spinae plane block



Total hip replacement surgery was planned for an 83-year-old female patient with congestive heart failure. Her ejection fraction (EF) was 40%; she had atrial fibrillation and was considered ASA III according to the American Society of Anesthesiologists Classification. The operation lasted 3 hours following the standard anesthesia induction. The patient was awakened and extubated without any problems and transferred to the inpatient unit. The VAS of the patient was 9/10 at the end of the first postoperative hour; therefore, the patient was scheduled to undergo sacral ESPB. Informed written consent for all procedures and permission to publish data was obtained from the patient. The patient was placed in the lateral decubitus position and the block was performed with the same method as described above. Fifteen minutes after the injection, the patient's VAS score decreased to 1/10. The patient did not complain of pain or need any analgesics for 24 hours. In the 25th hour, the VAS score of the patient was 5/10. Therefore, tramadol 50 mg was administered. In the 32nd hour, the VAS score of the patient was 4/10, necessitating the administration of 1 g paracetamol. The patient was discharged from the hospital on day 5.

Discussion

Hip fracture is a widespread problem, especially in the geriatric population. Because the cutaneous innervation of the hip area is complex, the success rate of effective anesthesia in completely covering the incision depends not only on the type of the surgical incision but the nerve block techniques as well. Surgical incisions for hip surgery are usually made near the greater trochanter of the femur. The posterolateral approach is usually the preferred method. The nerves that innervate the hip joint originate from the ventral branch of the spinal nerve roots of the lower part of the lumbar plexus (L2-4) and the upper part of the sacral plexus (L4-S1) [8].

The reduction in the need for opioid use by postoperative pain relief may allow to avoid respiratory complications and the early ambulation of the patient, help engage the patient in physical therapy programs that are less uncomfortable, improve patient satisfaction and shorten the time to hospital discharge. Peripheral nerve blockage is one of the preferred methods for postoperative multimodal analgesia in patients operated for hip fractures. Accordingly, we found that the postoperatively performed ESPB provided effective analgesia for 24 hours in two of our patients who underwent surgery for a hip fracture.

ESPB is a regional plane block that blocks the dorsal and ventral roots of the spinal nerve, providing somatic and visceral analgesia. It allows the widespread distribution of local anesthetics in the craniocaudal direction and the blockade of multiple dermatomes [9].

Because the sacral anatomical structures involved in ESPB have not been clarified yet, it has been argued that ESPB can alternatively be called sacral retrolaminar block or sacral multifidus plane block [10, 11]. ESPB can potentially block the pudendal nerve (S2-S4) at sacral levels. Also, the cephalad spread of anesthesia may result in the blockade of a part of the lumbar plexus. Previous studies suggested the potential of the epidural spread as it has been observed that extra analgesics were not needed after the block [4, 7]. Indeed, alleviation of pain both at the incision site and decreased severity of motion-induced pain after high-volume sacral ESPB in both of our patients yielded clinical data showing that the dorsal and ventral branches of the spinal nerves were blocked. Sacral ESPB is easy to perform under ultrasound guidance because it is applied relatively more superficially, and the intervention site is not close to major

vascular and neural structures. Also, we found that it can widely spread under the muscle depending on the volume applied and allow long-term analgesia without causing a motor block.

Because our study was limited to only 2 cases, further studies are needed to confirm the benefits of sacral ESPB for postoperative analgesia in hip fracture operations.

References

1. Forero M, Adhikary SD, Lopez H, Tsui C, Chin KJ. The erector spinae plane block: a novel analgesic technique in thoracic neuropathic pain. Reg Anesth Pain Med. 2016;41(5):621–7.
2. Cassai A, Bonvicini D, Correale C, Sandei L, Tulgar S, Tonetti T. Erector spinae plane block: a systematic qualitative review. Minerva Anestesiol. 2019;85(3):308–19.
3. Tulgar S, Senturk O, Thomas DT, Deveci U, Ozer Z. A new technique for sensory blockage of posterior branches of sacral nerves: ultrasound guided sacral erector spinae plane block. J Clin Anesth. 2019;57:129–30.
4. Piraccini E, Antioco M, Maitan S. Ultrasound guided sacral erector spinae plane block: a useful tool for radicular pain treatment. J Clin Anesth. 2019;59:11–2.
5. Kukreja P, Deichmann P, Selph JP, Hebbard J, Kalagara H. Sacral Erector Spinae Plane Block for Gender Reassignment Surgery. Cureus. 2020;12(4):e7665.
6. Kilicaslan, A, Uyel Y. Novel lumbosacral approach for erector spinae plane block (LS-ESPB) in hip surgery. Journal of Clinical Anesthesia. 2020;60:83–84.
7. Aksu C, Gürkan Y. Sacral erector spinae plane block with longitudinal midline approach: Could it be the new era for pediatric postoperative analgesia? J Clin Anesth. 2020:59:38-9.
8. Birnbaum K, Prescher A, Hessler S, Heller KD. The sensory innervation of the hip joint an anatomical study. Surg Radiol Anat. 1997; 19(6):371-5.
9. Kalagara HK, Deichmann P, Brooks B, Nagi P, Kukreja P. T1 erector spinae plane block catheter as a novel treatment modality for pancoast tumor pain. Cureus. 2019;11(11):e6092.
10. Hamilton DL. The erector spinae plane block: Time for clarity over anatomical nomenclature. J Clin Anesth. 2020;62:109699.
11. Piraccini E, Taddei S. Sacral multifidus plane block: The correct name for sacral erector spinae plane block. J Clin Anesth. 2020;63:109754.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):651-653.
DOI: 10.28982/josam.799391

Journal of Surgery and Medicine
e-ISSN: 2602-2079

A case of bilateral hip and knee osteonecrosis in a patient with ankylosing spondylitis who used steroids due to immune thrombocytopenic purpura

Sena Öztekin [1], Rafet Sönmez [2], Ayşe Sarsan [1], Hakan Alkan [1]

[1] Pamukkale University Medicine Faculty, Department of Physical Medicine and Rehabilitation, Denizli, Turkey
[2] Sirnak State Hospital, Department of Physical Medicine and Rehabilitation, Sirnak, Turkey

ORCID ID of the author(s)
SÖ: 0000-0002-9237-782X
RS: 0000-0003-0838-2659
AS: 0000-0002-6930-6441
HA: 0000-0001-8461-9131

Corresponding Author
Sena Öztekin
Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Pamukkale University, 20070 Kınıklı, Denizli, Turkey
E-mail: senaoztekin@gmail.com

Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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

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

Previous Presentation
This case report was presented at the "RADER Asistan Okulu'18" congress held in Famagusta, Cyprus on 21-23 September 2018.

Published
2021 May 15

Abstract

We aim to present a case of bilateral hip and knee osteonecrosis due to steroid use in an ankylosing spondylitis (AS) patient who developed immune thrombocytopenic purpura (ITP) after the use of nonsteroidal anti-inflammatory drugs (NSAID). A 60-year-old male patient was diagnosed with AS with bilateral sacroiliitis and inflammatory low back pain on sacroiliac radiography 10 years ago. He was followed up with NSAIDs. Intravenous steroid treatment was started in the hematology clinic to the patient who had developed ITP due to NSAID usage. The patient presented to our clinic with bilateral hip pain that developed after steroid therapy. He had limited hip joint movement and bilateral destructive hip joints in pelvic radiography. Bilateral total hip arthroplasty (THA) was performed by the Orthopedics and Traumatology Department at 1-year intervals because of osteonecrosis associated with steroid use. When he presented to our clinic 3 years later with bilateral knee pain, we detected osteonecrosis in the distal segments of bilateral femurs and proximal tibial diaphysis on knee MRI. We implemented a rehabilitation program with the conservative treatment recommendation of orthopedics. Comorbidities or drug side effects should be examined more carefully while treating peripheral joint involvement in patients with AS.

Keywords: Osteonecrosis, Meloxicam, Immune thrombocytopenic purpura, Ankylosing spondylitis

Introduction

Osteonecrosis (ON) is a bone disorder that results with the demolition of the bone and bone marrow cells [1]. Immune Thrombocytopenic Purpura (ITP) is a hematological disease associated with autoantibody activity against glycoprotein structures on platelets due to primary or secondary causes [2]. We present a case with bilateral hip and knee osteonecrosis due to steroid use of patients with ankylosing spondylitis (AS) who developed ITP after nonsteroidal anti-inflammatory drug (NSAID) use. The patient was 60 years old. After the first diagnosis of AS, he presented with bilateral hip ON first, then bilateral knee ON over the next 4 years. Orthopedics was consulted to learn whether if surgery was an option, but conservative treatment was recommended. This is the first case report to present ON in the lower extremities in 4 different regions in the patient who has AS.

How to cite: Öztekin S, Sönmez R, Sarsan A, Alkan H. A case of bilateral hip and knee osteonecrosis in a patient with ankylosing spondylitis who used steroids due to immune thrombocytopenic purpura. J Surg Med. 2021;5(6):651-653.

Case presentation

A 60-year-old male patient was admitted to our clinic with inflammatory back pain 8 years ago. He also had morning stiffness which lasted more than 30 minutes due to thoracolumbar limitation and bilateral heel pain. He had no disease other than insulin-dependent diabetes mellitus for the last 13 years, hyperlipidemia for the last 12 years and he was operated on for meniscopathy. There were bilateral sacroiliitis in sacroiliac magnetic resonance imaging (MRI), syndesmophytes in the lateral thoracic radiography (Figure 1), and bilateral enthesitis on the lateral foot x-ray (Figure 2). He was HLA B27 negative and had a CRP value of <0.5mg/dl. Other laboratory values were also within normal ranges.

Figure 1: Lateral thoracic radiography

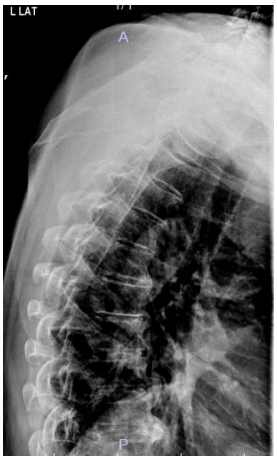
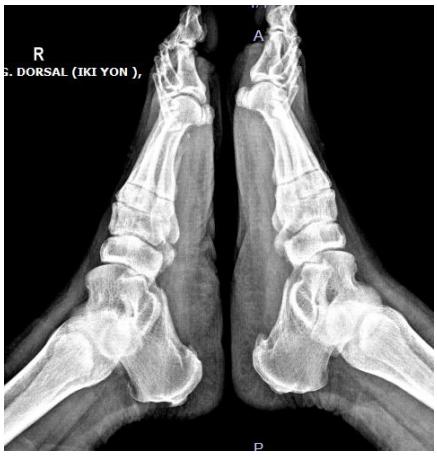
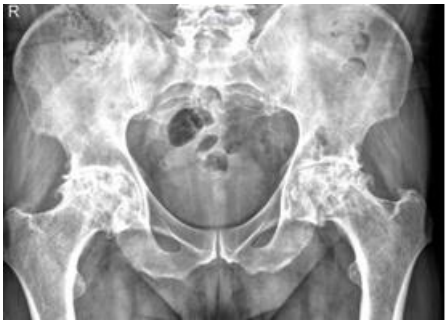


Figure 2: Lateral view of foot in x-ray, enthesitis is observed on bilateral calcaneal areas



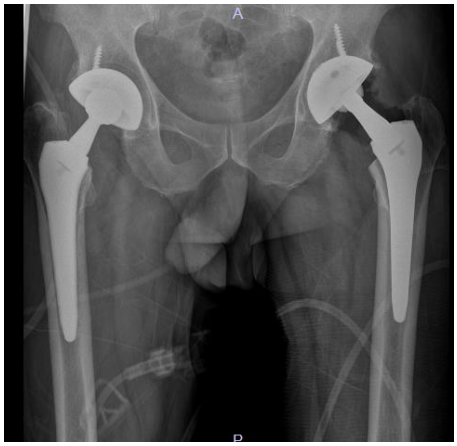
The patient was diagnosed with AS. The initial treatment was meloxicam at a daily dose of 15 mg. The patient was invited for follow-up 14 days later, but he missed the appointment. During this time, he went to another health institution and was diagnosed with thrombocytopenia. He received intravenous (IV) methylprednisolone at 10 mg/kg/dose for 3 days. Steroid treatment was tapered and terminated within 4 weeks. One year later, after the ITP treatment finished, the patient presented to the clinic with bilateral hip pain. On physical examination, limitation of movement was observed within the hip joint. Pelvic radiographs (Figure 3) showing bilateral destruction of the hip joints prompted us to consult with the orthopedics and traumatology clinic regarding surgical treatment for avascular necrosis.

Figure 3: Pelvic radiography, destructive hip appearance due to the avascular necrosis



Bilateral total hip arthroplasty (THA) had been performed 1 year apart (Figure 4).

Figure 4: Pelvic radiography, Bilateral total hip replacement, postoperative view.



During the follow-up of AS and bilateral THA, the patient presented to our clinic with more severe bilateral knee pain in the left knee after 4 years. Bilateral knee radiography showed lesions in the distal femur and proximal tibia (Figure 5). The bone infarct areas of 2x1 cm in the femur and 2.5x1.5 cm in the tibia were detected in the left knee MRI (Figure 6).

The patient with AS who developed ITP after NSAID usage had ON in four joints due to the use of high-dose steroids for ITP treatment. He is currently under treatment in our clinic.

Figure 5: A two-way bilateral knee X-ray of the distal femur and proximal tibia on the border of irregular sclerotic lesions.

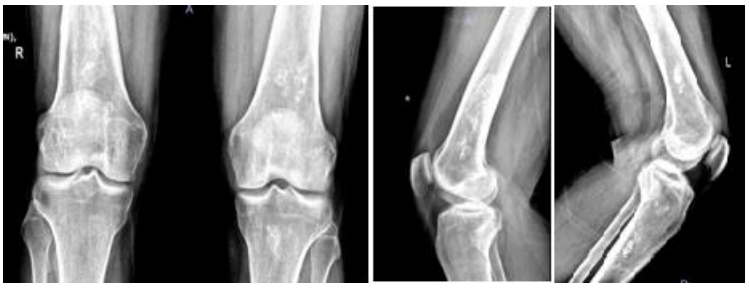
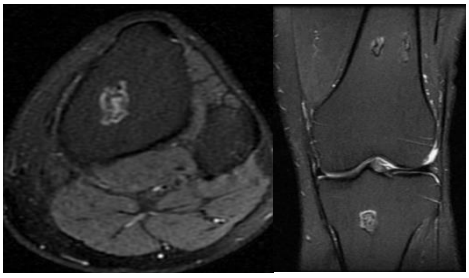


Figure 6: MRI of the left knee, two lesions of 2x1 cm in the femur and one lesion of 2.5x1.5 cm in the tibia.



Discussion

Osteonecrosis (ON, avascular necrosis) is caused by ischemic injury of bone and bone marrow cellular components. It is more common in the hip joint (90%) but can be detected in the knee joint with a lower incidence (10%) [1]. Steroid use is the most common reason for ON. Many osteonecrosis cases related to steroid use have been reported in the literature. Even though there are many publications, there is no case of avascular necrosis observed in 4 joints in a patient with AS.

The side effects of steroids depend on the dose and time. ON can usually be detected by imaging 1-6 months after high-dose corticosteroid (>0.5 mg/kg/day) treatment [3]. However, some publications report osteonecrosis cases after low-dose steroid intake [4]. In 1996, Usui et al. [5] reported that 4 women who received steroids, one for ITP and 3 for lupus, were diagnosed with femoral head fractures due to femoral head osteonecrosis. In in a case report published by Yildiz et al. [6] in 2008, a 64-year-old female patient reportedly received pulse steroid therapy for 3 weeks, starting at 1000 mg/day, reducing the dose every 3 days. Two weeks after starting the treatment, there was unilateral pain in his left knee and hip, and after 4 weeks he was unable to walk without support. A diagnosis of ON was made with unilateral right knee and hip MRI. After rehabilitation, hip and knee arthroplasty was recommended. In 2015, a 17-year-old patient diagnosed with ITP received pulse steroid therapy for 4 days, at a dose of 40 mg/day every 4 months. After 2 years of treatment, he had severe hip pain during heavy lifting. MRI showed ON in the right femoral head at the second year of treatment and in the left femoral head at the third year. The patient's age was appropriate for core decompression therapy rather than bilateral total hip replacement surgery [7].

ITP is a hematologic disease caused by autoantibodies that target glycoprotein structures on the platelets for primary or secondary reasons. Secondary reasons include autoimmune diseases (lupus, antiphospholipid syndromes), infections (HBV, HCV, HIV, CMV), and medical treatments (NSAIDs, heparin, quinidine). Secondary thrombocytopenia results from immune-mediated platelet destruction associated with medical therapy. The reduction in the platelet count occurs within a few hours to 1-2 weeks after drug use [2]. The most common side effects of meloxicam in the NSAID group are gastrointestinal complaints such as diarrhea and dyspepsia, neurological symptoms such as dizziness and headache, and dermatological complaints such as rash. Thrombocytopenia is a rare side effect that occurs in less than %2 of the patients [8]. The first case of meloxicam-induced thrombocytopenia was verified in India. According to the case report, a 57-year-old woman who took 75 mg/day meloxicam for arthralgia had ITP symptoms in 24 hours after taking two doses. The patient’s platelet count reached basal levels during a year of observation. In another case, reported by Ranieri MM in Philadelphia in 2014 [9], the platelet count of the patient was 2000/mm^3 with the clinical symptoms of ecchymosis and gastrointestinal bleeding after one week of meloxicam use. According to the Hill criteria for causality, the patient was diagnosed with immune thrombocytopenia secondary to meloxicam.

There were no data on the development of ON after steroid treatment in both above-mentioned cases. In our case, ITP developed after the use of NSAIDs, as in the previous 2 cases, and also, ON occurred in the late period after steroid use for ITP treatment. In the literature, there are no cases of ONs in 4 joints due to steroid intake. In this case report, while treating AS, we detected ITP, which is a rare side effect of meloxicam. We also found ON which developed in 4 joints in the late period of steroid treatment after ITP.

Comorbidities or drug side effects should be examined more carefully while treating peripheral joint involvement in patients with AS.

References

1. Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). N Engl J. 1992;326:1473-9. doi: 10.1056/NEJM199205283262206
2. Van den Bemt PMLA, Meyboom RHB, Egberts ACG. Drug-induced thrombocytopenia. Drug Saf. 2004;27:1243–52. doi: 10.2165/00002018-200427150-00007.
3. Lafforgue P. Pathophysiology and natural history of avascular necrosis of bone. Joint Bone Spine. 2006;73:500-7. doi: 10.1016/j.jbspin.2006.01.025.
4. Bekler H, Uygur AM, Gökçe A, Beyzadeoğlu T. Steroid kullanımının femur başı avasküler nekrozu patogenezindeki yeri: Deneysel hayvan modeli. Acta Orthop Traumatol Turc. 2007;41(1):58-63.
5. Usui M, Inoue H, Yukihiro S, Abe N. Femoral neck fracture following avascular necrosis of the femoral head. Acta Med Okayama. 1996;50(2):111-7. doi: 10.18926/AMO/30487.
6. Yildiz N, Ardic F, Deniz S. Very Early Onset Steroid-Induced Avascular Necrosis of the Hip and Knee in a Patient with Idiopathic Thrombocytopenic Purpura. Inter Med. 2008;47:1989-92. doi: 10.2169/internalmedicine.47.1038.
7. Fotopoulos VCh, Mouzopoulos G, Floros T, Tzurbakis M. Steroid-induced femoral head osteonecrosis in immune thrombocytopenia treatment with osteochondral autograft transplantation. Knee Surg Sports Traumatol Arthrosc. 2015; 23(9):2605-10. doi: 10.1007/s00167-014-3239-3.
8. Boehringer-Ingelheim Pharmaceuticals, Inc. Mobic (meloxicam) package insert. Ridgefield, CT. 2012.
9. Ranieri MM, Bradley EF, Simon AB. Meloxicam-induced thrombocytopenia. Pharmacotherapy. 2014;34(2):e14-7. doi: 10.1002/phar.1372.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(6):654-656.
DOI: 10.28982/josam.821735

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Internal carotid artery agenesis and contralateral middle cerebral artery infarction

Fatma Şimşek [1], Filiz Aktaş [2]

[1] Atatürk University, Faculty of Medicine, Department of Neurology, Erzurum, Turkey
[2] University of health sciences education research hospital neurology, Konya, Turkey

ORCID ID of the author(s)
FŞ: 0000-0003-1662-5534
FA: 0000-0003-2973-916X

Abstract

Internal carotid artery agenesis is usually an asymptomatic condition. It is detected incidentally by radiological imaging performed for other reasons. It may rarely present with clinical manifestations such as subarachnoid hemorrhage associated with aneurysm, transient ischemic attack, or stroke. Agenesis can be erroneously interpreted as occlusion in case of insufficient clinical experience. The absence of the carotid canal on the bone window in the computed tomography scan of the brain helps confirm the diagnosis. The well-developed collateral circulation in patients with internal carotid artery agenesis is an effective factor in recovering from cerebrovascular diseases with less damage. Here, a rare case of agenesis of the right internal carotid artery and contralateral middle cerebral artery infarction is presented.

Keywords: Internal carotid artery, Ischemic stroke, Agenesis, Magnetic resonance angiography

Introduction

The agenesis of the internal carotid artery (ICA) occurs due to abnormal regression of the first and third aortic arch, with an unclear exact etiology [1, 2]. Carotid agenesis is a rare condition that can be unilateral or bilateral. Documented cases with absent ICA are mostly unilateral and most frequently reported on the left side [3, 4]. Most cases are clinically silent due to the well-developed collateral circulation [5]. Most patients are detected by radiological imaging methods, such as ultrasonography, magnetic resonance imaging, computed brain tomography, performed for a different reason. Inadequate collateral flow may result in cerebrovascular events and/or intracranial bleeding, which may emerge as cerebrovascular disease [6, 7]. We here report a case with agenesis of the right ICA and contralateral middle cerebral artery infarction, a rare phenomenon.

Corresponding Author
Fatma Şimşek
Atatürk Üniversitesi Tıp fakültesi Nöroloji Anabilim Dalı, Erzurum, Turkey
E-mail: klamaks@hotmail.com

Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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

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

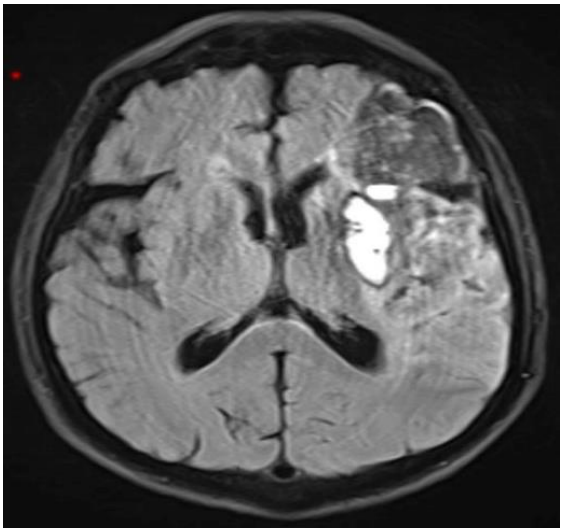
Published
2021 Jun 9

How to cite: Şimşek F, Aktaş F. Internal carotid artery agenesis and contralateral middle cerebral artery infarction. J Surg Med. 2021;5(6):654-656.

Case presentation

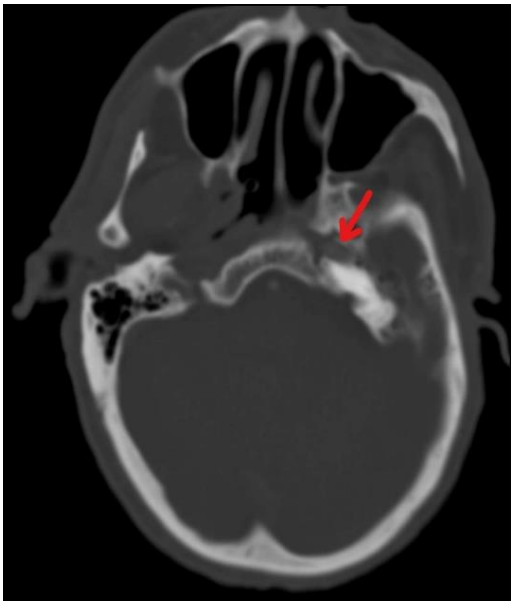
A 64-year-old male patient with no history of systemic disease was admitted to the emergency department due to sudden right-sided weakness. In the neurological examination, the patient was somnolent with partial space-time orientation and cooperation. He had central facial paralysis on the left and 3/5 motor strength on the right with extensor reflex responses. The patient had a history of smoking one packet of cigarettes a day for 25 years. The family history was insignificant. Intravenous thrombolytic therapy could not be administered due to the hemorrhagic infarction in the left middle cerebral artery watershed area, revealed by the computed tomography of the brain (CT) performed in the emergency department. The admission magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) failed to reveal the right internal carotid artery. There was a hemorrhagic infarct area on the left on MRI (Figure 1).

Figure 1: The FLAIR MRI sequence shows hemorrhagic infarction in the middle cerebral artery watershed area on the left side



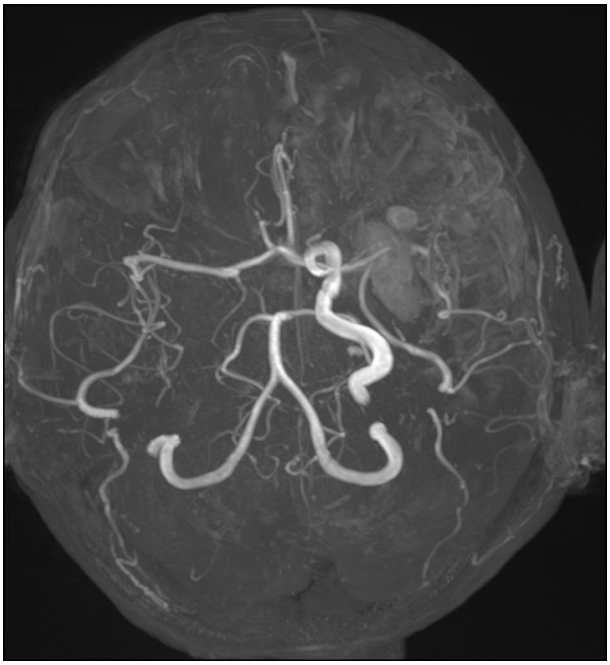
The right ICA was thought to be totally occluded. The bone window in the CT scan of the brain showed the carotid canal on the left while the carotid canal was absent on the right, confirming the diagnosis of agenesis of the right ICA (Figure 2).

Figure 2: The bone window in the CT scan of the brain shows the carotid canal on the left (red arrow), while the right carotid canal is absent.



Aneurysm is a common accompanying pathology in patients with ICA agenesis. In our patient, MRA revealed no aneurysm showing that the right middle cerebral artery and right anterior cerebral artery received collateral circulation through the anterior communicating artery and the left ICA, which appeared dolichoectatic (Figure 3).

Figure 3: MRA shows the right middle cerebral artery and right anterior cerebral artery receiving collateral circulation through the anterior communicating artery while the left ICA appears dolichoectatic.



The patient's cardiac examination (Echocardiography and 24-hour rhythm Holter), blood lipids, HbA1C, homocysteine level and blood pressure were normal. The patient, who had no risk factors other than smoking, was discharged after 4 weeks with a moderate-well condition and 4/5 motor strength on the right side. At the 3-month follow-up, he was able to walk with one-sided support and perform daily activities without help. Informed consent was obtained from the patient for scientific presentation.

Discussion

Agenesis of the ICA and hypoplasia are rare congenital anomalies occurring in less than 0.01% of the population [8]. The left ICA is affected by dysgenesis three times more often than the right one [4].

Our patient had agenesis of the right ICA and left middle cerebral artery infarction. Agenesis of the right ICA was confirmed when the bone window in the CT scan of the brain showed no carotid canal, although it was interpreted as total occlusion of the right ICA in the initial MRI. The presence of ICA is necessary for the development of the carotid canal, the absence of which can confirm ICA agenesis. It is a rare condition that can be erroneously interpreted as stenosis or occlusion in case of insufficient clinical experience. Although our patient had agenesis of the right ICA and left MCA infarction, his clinical condition was not very severe. This was thought to be associated with the well-developed collateral circulation due to cerebral vascular anomaly. The fact that the patient remained asymptomatic until the age of 65 years supports the well-development of collateral circulation in these patients.

While collateral flow through the Willis circle is usually sufficient to prevent cerebral ischemia during carotid clamping, an incomplete and dysfunctional circle poses increased risk [9, 10]. Agenesis of the ICA is a rare condition that alters the collateral circulation in the circle. Cross-clamping the side with ICA during surgery in a patient with ICA agenesis can disrupt the blood supply of the whole brain, causing irreversible damage. Ultrasonography, an easy and inexpensive method, can be used to monitor ICAs to prevent possible complications in surgical procedures as a protective factor in reducing the risk of possible cerebrovascular complications. The other ICA should be checked, especially in the presence of a dolichoectatic ICA, as in our patient.

References

1. Kunishio K, Yamamoto Y, Sunami N, Asari S. Agenesis of the left internal carotid artery, common carotid artery, and main trunk of the external carotid artery associated with multiple cerebral aneurysms. Surgical neurology. 1987;27(2):177-81. doi: 10.1016/0090-3019(87)90292-8.
2. Cohen JE, Gomori JM, Leker RR. Internal carotid artery agenesis: diagnosis, clinical spectrum, associated conditions and its importance in the era of stroke interventions. Neurological research. 2010;32(10):1027-32. doi: 10.1179/016164110X12767786356273.
3. Alurkar A, Karanam LSP, Oak S, Kori S. Congenital absence of internal carotid artery with rare type of intercavernous anastamosis and ruptured cerebral aneurysm. Journal of clinical and diagnostic research:JCDR. 2016;10(4):TD03. doi: 10.7860/JCDR/2016/17797.7549.
4. Taşar M, Yetişer S, Taşar A, Uğurel Ş, Gönül E, Sağlam M. Congenital absence or hypoplasia of the carotid artery: radioclinical issues. American journal of otolaryngology. 2004;25(5):339-49. doi: 10.1016/j.amjoto.2004.04.008.
5. Ryan FH, Kline LB, Gomez C. Congenital Horner's syndrome resulting from agenesis of the internal carotid artery. Ophthalmology. 2000;107(1):185-8. doi: 10.1016/S0161-6420(99)00006-8.
6. Damry N, Hanquinet S, Christophe C, Janssen F, Delatte P, Perlmutter N. Bilateral congenital absence of the internal carotid artery with a primitive transmaxillary arterial anastomosis. Pediatric radiology. 1994;24(3):200-3.
7. Farhat W, Ahdab R, Hosseini H. Congenital agenesis of internal carotid artery with ipsilateral Horner presenting as focal neurological symptoms. Vascular Health and Risk Management. 2011;7:37. doi: 10.2147/VHRM.S16642.
8. Given II CA, Huang-Hellinger F, Baker MD, Chepuri NB, Morris PP. Congenital absence of the internal carotid artery: case reports and review of the collateral circulation. American Journal of Neuroradiology. 2001;22(10):1953-9.
9. Kim GE, Cho YP, Lim SM. The anatomy of the circle of Willis as a predictive factor for intra-operative cerebral ischemia (shunt need) during carotid endarterectomy. Neurological research. 2002;24(3):237-40. doi: 10.1179/016164102101199846.
10. Moritz A, Koci G, Steinlechner B, Hölzenbein T, Nasel C, Grubhofer G, et al. Contralateral stroke during carotid endarterectomy due to abnormalities in the circle of Willis. Wiener klinische Wochenschrift. 2007;119(21):669-73.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.