e-ISSN:2602-2079

Volume 5
Issue 2
2021

JOURNAL of Surgery and Medicine

International Medical Journal

JOSAM

Volume: 5 - Issue: 2

Contents

Case report

J Surg Med. 2021;5(2):111-114.
DOI: 10.28982/josam.801301

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

Outcomes of intravenous thrombolytic therapy in cardioembolic strokes

Mustafa Çetiner [1], Murat Seyit [2], Neslihan Eskut [3], Gönül Akdağ [1], Fatma Akkoyun Arıkan [1], Sibel Canbaz Kabay [1]

[1] Department Of Neurology, Kütahya Health Sciences University, Kütahya, Turkey
[2] Department Of Emergency Medicine, Pamukkale University, Denizli, Turkey
[3] Department Of Neurology, University Of Health Sciences, İzmir, Turkey

ORCID ID of the author(s)

MÇ: 0000-0002-4420-6452
MS: 0000-0002-8324-9471
NE: 0000-0003-1882-8992
GA: 0000-0002-0486-6026
FAA: 0000-0002-3543-6213
SCK: 0000-0003-4808-2191

Corresponding Author
Mustafa Çetiner
Kütahya Sağlık Bilimleri Üniversitesi Tıp Fakültesi, Bölüm: Nöroloji AD, Bahçelievler mahallesi, Eryiğit sokak, No:24, Ladin sitesi. A - blok, K: 3, D-13. Kütahya, Türkiye
E-mail: drcetiner76@gmail.com

Ethics Committee Approval
The study was approved by the Dumlupinar University of Local Ethics Committee (Date: 14/11/2018, Decision no: 2018/14-8). 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 February 19

Abstract

Background/Aim: It is controversial whether intravenous recombinant tissue plasminogen activator (IV r-tPA) treatment outcomes in cardioembolic strokes differ from other types of strokes. This study aims to investigate the clinical data of patients with cardioembolic and large-vessel atherosclerosis who received IV r-tPA treatment and compare and discuss the results according to the literature.

Methods: The data of the patients who were admitted within the first 4.5 hours following the onset of symptoms, diagnosed with acute ischemic stroke in the Neurology clinic of Kütahya Evliya Çelebi Training and Research Hospital and underwent IV r-tPA were evaluated in this retrospective cohort study. Demographic data, clinical and functional results of patients were compared between the two groups (cardioembolic and large vessel atherosclerosis).

Results: Eighty-five patients with ischemic stroke who received IV r-tPA treatment due to cardioembolism and large-vessel atherosclerosis were included in the study. There were 51 patients (60%) in the cardioembolic stroke group and 34 patients (40%) in the large vascular atherosclerotic group. There was no significant difference in terms of functional results between the groups (62.7% vs 44.1%; P=0.09). While symptomatic intracerebral hemorrhage was not detected in the large-vessel atherosclerosis group, it occurred in 3.9% of the cardioembolic stroke group.

Conclusion: This study proved that functional and clinical results are similar between cardioembolic and large-vessel atherosclerosis patients who were treated with IV r-tPA treatment. Regardless of the etiology, all suitable patients with acute ischemic stroke should be treated with thrombolytic therapy.

Keywords: Acute ischemic stroke, Cardioembolic stroke, Intravenous thrombolytic therapy

How to cite: Çetiner M, Seyit M, Eskut N, Akdağ G, Arıkan FA, Kabay SC. Outcomes of intravenous thrombolytic therapy in cardioembolic strokes. J Surg Med. 2021;5(2):111-114.

Introduction

Ischemic stroke is subdivided according to etiological causes and has different prognosis and mortality rates based on the mechanisms of its formation [1,2]. It has been reported that intravenous recombinant tissue plasminogen activator (IV r-tPA), the basis of intravenous thrombolytic therapy in acute ischemic stroke, improves functional results in all strokes [3,4]. However, the response to IV r-tPA treatment may vary depending on the size, content and the source of the clot. While thrombus formed under slow blood flow in the heart cavities is rich in fibrin, that formed under fast blood flow in atherosclerotic-stenotic lesions is rich in thrombocytes. Therefore, it is assumed that the response to fibrinolytic agents such as tissue-type plasminogen activator will be superior in heart-induced embolism [5]. Studies investigating functional results of intravenous thrombolysis in patients with cardioembolic stroke are contradictory in the literature. In the study of Molina et al. [6], early recanalization following thrombolysis was more frequent, faster, and higher in cardioembolic patients with middle cerebral artery infarction, and the improvement in the three-month period was better in non-cardioembolic strokes in the study of Rocha et al. [7]. On the other hand, in the study of Nam et al., the rate of full recanalization was lower in cardioembolic strokes, the rate of poor functional recovery in the third month was higher, and heart-borne embolism was an independent determinant for the poor functional result in the third month [8]. Similarly, in the study of Kimura et al., patients with atrial fibrillation (AF) who underwent IV thrombolysis in acute ischemic stroke had worse clinical results compared to the ones without AF [9].

On the other hand, in a study reported from our country, functional results were not different in the 3rd month after thrombolytic therapy in patients with acute middle cerebral infarction of different stroke types [10].

The aim of this study is to examine, compare and discuss the results of acute ischemic stroke patients undergoing IV thrombolytic therapy with cardioembolism and large vessel atherosclerosis according to TOAST classification.

Materials and methods

The data of the patients who were admitted to the emergency department within the first 4.5 hours following the onset of symptoms, diagnosed with acute ischemic stroke and underwent IV r-tPA at Kütahya Evliya Çelebi Training and Research Hospital Neurology Department between May 2014 and September 2018 were evaluated retrospectively. Thrombolytic treatment decision was made according to AHA / ASA 2013 [11] and 2016 [12] guidelines. All patients were given an intravenous bolus of 10% of the total dose of 0.9 mg / kg (maximum 90 mg) of r-tpA (alteplase®) and the rest was administered as hourly infusion. Ischemic stroke risk factors, demographic and clinical features, neurological examination findings, results of hemogram and biochemistry tests, and symptom needle (SN) time were recorded from patient files. The patients' evaluation was based on the etiological classification of Acute Stroke Treatment [13] (TOAST) in Trial of Stroke Org 10172. Eighty-five patients with cardioembolic and large vessel atherosclerosis were included in the study. The computed brain tomography images of the patients were examined before and during IV r-tPA, or intracranial bleeding. The presence of hemorrhagic infarction with more than 30% of the infarct area accompanied by neurological deterioration, intracranial hemorrhages causing an increase of more than 4 points in NIHSS or death were called symptomatic intracerebral hemorrhage (sICH), while those detected incidentally in control imaging were called asymptomatic intracerebral hemorrhage (aICH) [14]. Intracranial bleeding occurring within the first 36 hours of treatment was considered r-tPA complication. The pre-post-treatment neurological disabilities of the patients were evaluated with the national Health Institutes of Health Stroke Scale (NIHSS) scores and the 3rd month neurological disabilities, with modified Rankin Scale **(**mRS**)** scores.

Early neurological improvement (ENI) was defined as a NIHSS score of 0 to 1 24 hours following thrombolytic therapy or an improvement in the NIHSS score of ≥8 points (14). Having mRS ≤2 at 3 months was considered a good functional result, and mRS >2, a poor one [15].

The study was approved by the Dumlupinar University of Local Ethics Committee (Date: 14/11/2018, Decision no: 2018/14-8).

Statistical analysis

Statistical analyses were performed using SPSS 24.0 (IBM Corp.; Armonk, NY, USA) program. Normally distributed variables were presented as mean (standard deviation), and non-normally distributed variables were presented as median (minimum-maximum). In the comparison between the independent groups, t-test was used for the parametric data and Mann-Whitney U test was used for the non-parametric data. The difference between the categorical data was evaluated by chi-square and Fisher's exact test. *P*-value <0.05 was considered statistically significant.

Results

Demographic and basic features of patients

The study included eighty-five patients with cardioembolic and large vessel atherosclerosis who were diagnosed with acute ischemic stroke and underwent IV-r tPA. Forty-eight were male (56.5%) and thirty-seven were female (43.5%) and their mean age was 70.32 (10.39) (range, 35-88) years.

Two groups were formed with fifty-one patients in the cardioembolic stroke (60%) group and thirty-four patients in the large vessel atherosclerosis (40%) group. Among vascular risk factors, smoking was more prevalent in the large vessel atherosclerosis group (P=0.03), while coronary artery disease (CAD) and atrial fibrillation (AF) were more common in the group with large vessel atherosclerosis (P<0.001). The two groups were similar in terms of age, gender, SN time, initial NIHSS score averages, glucose levels, systolic and diastolic blood pressure mean values. There was no significant difference in mean platelet volume (MPV) and platelet averages between the groups. Demographic and basic characteristics of the patients and the statistical comparison between them are presented in Table 1.

Table 1: Comparison of demographic and basic characteristics of patients with acute ischemic stroke receiving thrombolytic therapy

	Cardioembolism n=51 (%60)	Large vessel atherosclerosis n=34 (%40)	Total n=85	*P*-value
Age (year)	74 (35-88)	69.85 (9.97)	73 (35-88)	0.66
Gender, n (%)				
•Female	27 (52.9)	10 (29.4)	37 (43.5)	0.03*
Vascular risk factors,	n (%)	n (%)	n (%)	
•CAD+AF	40 (78.4)	7 (20.6)	47 (55.3)	<0.001*
•Hypertension	30 (58.8)	24 (70.6)	54 (63.5)	0.27
•Diabetes	19 (37.3)	15 (44.1)	34 (40)	0.52
•Hyperlipidemia	22 (43.1)	14 (41.2)	36 (42.4)	0.85
•Smoking	14 (27.5)	17 (50)	31 (36.5)	0.03*
SBP (mmHg)	146.76 (25.99)	152.35 (23.84)	149.00 (25.16)	0.31
DBP (mmHg)	80 (60-120)	82.50 (60-160)	80 (60-160)	0.91
Blood glucose level (mg/dL)	132 (78-347)	134.50 (93-345)	134 (78-347)	0.28
SN Duration (minute)	159.31 (54.90)	157.97 (53.55)	158.77 (60-270)	0.91
NIHSS (Before treatment)	14.76 (5.67)	12 (5-24)	13 (3-25)	0.17
MPV (fL)	9.14 (1.02)	9.12 (1.32)	9.13 (1.14)	0.95
Platelet (x10^3/mm^3)	243.37 (75.76)	238.02 (55.64)	241.23 (68.11)	0.72

* *P*<0.05, AF: Atrial fibrillation, DBP: Diastolic Blood Pressure, fL: Femtolitre, CAD: Coronary artery disease, Min.: Minimum, Max.: Maximum, NIHSS: The National Institutes of Health Stroke Scale score, MPV: Mean platelet volume, SD: Standard Deviation, SN: Symptom/needle, SBP: Systolic Blood Pressure.

Clinical and functional results

Clinically good functional results were obtained in forty-seven patients (55.3%) (mRS ≤2). Good functional results were obtained in 32 patients (62.7%) in the cardioembolic stroke group and in 15 patients (44.1%) in the atherothrombotic stroke group, the rates of which were similar (*P*=0.09).

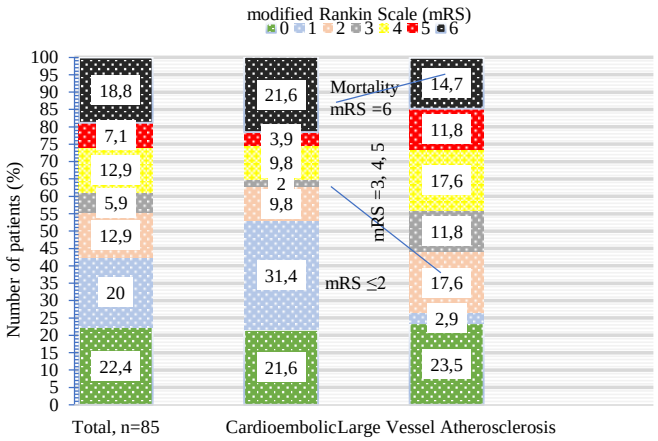
Early neurological improvement was detected in 26 (30.6%) patients. Among these, eighteen patients were (35.3%) in the cardioembolic stroke group and eight (23.5%) had large vessel atherosclerosis (*P*=0.88). Similarly, at the 24th hour after treatment, no significant difference was found between the mean scores of NIHSS (*P*=0.24). Asymptomatic intracerebral hemorrhage developed in 12 patients (14.1%). Although the cardioembolic group [10 patients (19.6%)] constituted the majority of asymptomatic bleeding, it was of no statistical significance (19.6% -5.9%, *P*=0.07). While symptomatic intracerebral hemorrhage was not observed in the atherothrombotic stroke group, symptomatic intracerebral bleeding was detected in 3 patients (5.9%) in the cardioembolic stroke group (*P*=0.27). Total mortality rate in this study was 18.8% (16 patients), and 21.6% (11 patients) of the patients who died were in the cardioembolic stroke group, while 14.7% (5 patients) had stroke due to large vessel atherosclerosis. There was no significant difference in mortality between the groups (*P*=0.42). Clinical and functional results of the patients are presented in Table 2 and mRS score distributions are given in Figure 1.

Table 2: Comparison of clinical and functional results in patients with cardioembolic and large-vessel atherosclerosis stroke

	Cardioembolic n=51, (%60)	Large vessel atherosclerosis n=34, (%40)	Total n=85	*P*-value
ENR, n (%)	18 (35.3)	8 (23.5)	26 (30.6)	0.24
NIHSS (24 hr after treatment)	10.09 (0-23)	8.5 (0-26)	8 (0-26)	0.88
aICH, n (%)	10 (19.6)	2 (5.9)	12 (14.1)	0.07
sICH, n (%)	3 (5.9)	-	3 (3.5)	0.27†
mRS (3rd month)≤2, n (%)	32 (62.7)	15 (44.1)	47 (55.3)	0.09
Mortality, n (%)	11 (21.6)	5 (14.7)	16 (18.8)	0.42

†: Fisher's Exact Test, aICH: Asymptomatic Intracerebral Hemorrhage, ENR: Early Neurological Recovery, Min: Minimum, Max: Maximum, mRS: Modified Ranking Scale, NIHSS: The National Institutes of Health Stroke Scale score, sICH: Symptomatic Intracerebral Hemorrhage.

Figure 1: Distribution of patients' mRS scores. There was no significant difference between mortality and functional outcomes (mRS ≤2) in stroke patients with cardioembolism and large vessel atherosclerosis (*P*>0.05).



Discussion

IV thrombolysis is the main treatment for acute ischemic stroke and effective in all stroke subtypes [3]. Different subtypes of ischemic stroke have different risk factors, clinical features, pathogenesis, and prognosis [16,17]. In earlier studies, it was investigated whether clinical results after thrombolysis differed from other stroke types in cardioembolic strokes, but contradictory results were obtained [7,18,19]. In this study, 3-month clinical and functional results were compared in patients with cardioembolic and large-vessel atherosclerosis following IV thrombolysis treatment, and no significant differences were observed.

Theoretically, cardioembolic thrombi are rich in fibrin and erythrocytes than atherosclerotic thrombi, which are more organized and richer in platelet. Thrombolytic treatment responses are expected to differ according to the structural composition of the thrombus, and thrombi of cardiac origin will be more prone to dissolution with intravenous alteplase. In this context, a study in which recanalization following IV thrombolysis was monitored with transcranial doppler showed that recanalization in patients with cardioembolic stroke was more frequent, faster and more complete than other stroke subtypes in patients with middle cerebral artery occlusion [6].

There are studies emphasizing that cardioembolic strokes are associated with poor results and high mortality [8,20]. In MRI-based studies of Schmitz et al. [19], earlier neurological recovery and better functional outcome (mRS: 0,1) were achieved following IV-tPA treatment in patients with cardioembolic stroke compared with stroke due to large vessel atherosclerosis. Similarly, in the study of Vaclavik et al. [14], compared to atherothrombotic strokes, the likelihood of symptomatic intracranial hemorrhage was low in cardioembolic strokes, and early neurological healing, increased 3-month good functional clinical outcome (mRS: 0,1), and indifferent mortality rates were observed. ENI is a strong determinant of positive functional results in 3 months in patients with acute ischemic stroke after thrombolytic therapy [21]. In the study of Fuentes et al., no significant difference was found between ENI and 3-month functional results in stroke subtypes, as in this study [22]. In accordance with the present study, no difference was found between the two groups in terms of ENI, 3-month good functional outcome, intracerebral hemorrhage and mortality.

Patients with cardioembolic stroke have a higher risk of hemorrhagic transformation [18,23,24]. Wang et al. [18] reported that this may decrease the benefit of thrombolytic therapy. In this study, symptomatic intracerebral hemorrhage was higher in patients with cardioembolic stroke after thrombolysis, and worse clinical results were obtained at 3 months follow-up compared to stroke patients with large vessel atherosclerosis. It has been reported that patients with AF have a higher risk and poor prognosis in terms of intracerebral bleeding following thrombolysis [25,26]. In this study, the rate of patients with AF and intracerebral bleeding rates were significantly higher in the cardioembolic stroke group. In a study investigating the frequency of hemorrhagic transformation in ischemic stroke and related factors, the size of AF and infarct area were independent risk factors, but no relationship was found between the 3rd month prognosis and hemorrhagic transformation [27]. In the report of Dang H et al., hemorrhagic transformation following the treatment was significantly higher in patients with AF undergoing IV thrombolysis, while no correlation was detected with prognosis [28]. Similarly, in a large-scale metanalysis study involving Chinese patients, Wen L., et al. stated that hemorrhagic transformation was significantly higher in patients with AF who underwent IV thrombolysis [29]. In our study, there was no significant difference between symptomatic and asymptomatic intracerebral bleeding rates and functional results between the two groups.

Limitations

The limitations of this study include its retrospective and single-center design, as only few patients with cardioembolic and atherothrombotic stroke were admitted. Therefore, etiologically, patients with cardioembolic stroke could not be compared with other stroke subtypes except for large vessel atherosclerotic strokes.

Conclusion

Thrombolytic therapy should be applied to all suitable acute ischemic stroke patients, regardless of the etiology. Sharing these results in terms of the spread of IV-r tPA in our country is valuable.

References

1. Ois A, Cuadrado-Godia E, Rodriguez-Campello A, Giralt-Steinhauer E, Jiménez-Conde J, Lopez-Cuiña M, et al. Relevance of stroke subtype in vascular risk prediction. Neurology. 2013;81:571-80.
2. Wei W, Li S, San F, Zhang S, Shen Q, Guo J, et al. Retrospective analysis of prognosis and risk factors of patients with stroke by TOAST. Medicine (Baltimore). 2018:97:e0412.
3. The National Institute of Neurological Disorder and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581-7.
4. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352:1245-51.
5. Timsit SG, Sacco RL, Mohr JP, Foulkes MA, Tatemichi TK, Wolf PA, et al. Brain infarction severity differs according to cardiac or arterial embolic source. Neurology. 1993;43:728-33.
6. Molina CA, Montaner J, Arenillas JF, Ribo M, Rubiera M, Sabín JA. Differential pattern of tissue plasminogen activator-induced proximal middle cerebral artery recanalization among stroke subtypes. Stroke. 2004;35:486-90.
7. Rocha S, Pires A, Gomes J, Rocha J, Sousa F, Pinho J, et al. Intravenous thrombolysis is more effective in ischemic cardioembolic strokes than in non-cardioembolic? Arq Neuro psiquiatr. 2011;69:905-9.
8. Nam HS, Lee KY, Kim YD, Choi HY, Cho HJ, Cha MJ, et al. Failure of complete recanalization is associated with poor outcome after cardioembolic stroke. Eur J Neurol. 2011;18:1171-8.
9. Kimura K, Iguchi Y, Shibazaki K, Iwanaga T, Yamashita S, Aoki J. IV t-PA therapy in acute stroke patients with atrial fibrillation. J Neurol Sci. 2009;276:6-8.
10. Güneş M. Relationship between blood pressure levels during thrombolytic therapy and functional outcomes in patients with middle cerebral artery infarction. J Surg Med. 2020;4:378-82.
11. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke. A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:870-947.
12. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, E Fugate JE, Grotta JC, et al. American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47:581-641.
13. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35-41.
14. Vaclavik D, Vilionskis A, Jatuzis D, Karlinski MA, Gdovinova Z, Kõrv J, et al. Clinical outcome of cardioembolic stroke treated by intravenous thrombolysis. Acta Neurol Scand. 2018;137:347-55.
15. Mustanoja S, Meretoja A, Putaala J, Viitanen V, Curtze S, Atula S, et al. Outcome by stroke etiology in patients receiving thrombolytic treatment: Descriptive subtype analysis. Stroke. 2011;42:102–6.
16. Tan YF, Zhan LX, Chen XH, Guo JJ, Qin C , En Xu E. Risk Factors, Clinical Features and Prognosis for Subtypes of Ischemic Stroke in a Chinese Population. Curr Med Sci. 2018;38:296-303.
17. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. Stroke. 2000;31:1062-8.
18. Wang XG, Zhang LQ, Liao XL, Pan YS, Shi YZ, Wang CJ, et al. Thrombolysis Implementation and Monitoring of acute ischemic Stroke in China (TIMS-China) Investigators. Unfavorable Outcome of Thrombolysis in Chinese Patients with Cardioembolic Stroke: a Prospective Cohort Study. CNS Neurosci Ther. 2015;21:657-61.
19. Schmitz ML, Simonsen CZ, Svendsen ML, Larsson H, Madsen MH, Mikkelsen IK, et al. Ischemic stroke subtype is associated with outcome in thrombolyzed patients. Acta Neurol Scand. 2017;135:176-82.
20. Boeckh-Behrens T, Kleine JF, Zimmer C, Neff F, Scheipl F, Pelisek J, et al. Thrombus Histology Suggests Cardioembolic Cause in Cryptogenic Stroke. Stroke. 2016;47:1864-71.
21. Yeo LL, Paliwal P, Teoh HL, Seet RC, Chan BPL, Wakerley B, et al. Early and continuous neurologic improvements after intravenous thrombolysis are strong predictors of favorable long-term outcomes in acute ischemic stroke. J Stroke Cerebrovasc Dis. 2013;22:e590-6.
22. Fuentes B, Martínez-Sánchez P, Alonso de Leciñana M, Egido J, Reig-Roselló G, Díaz-Otero F, et al. Madrid Stroke Network. Efficacy of intravenous thrombolysis according to stroke subtypes: the Madrid Stroke Network data. Eur J Neurol. 2012;19:1568-74.
23. Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, Lanari A, et al. Early hemorrhagic transformation of brain infarction: Rate, predictive factors, and influence on clinical outcome: Results of a prospective multicenter study. Stroke. 2008;39:2249–56.
24. Liu M, Pan Y, Zhou L, Wang Y. Predictors of post-thrombolysis symptomatic intracranial hemorrhage in Chinese patients with acute ischemic stroke. PLoSOne. 2017;12:e0184646.
25. Ge WQ, Chen J, Pan H, Chen F, Zhou CY. Analysis of Risk Factors Increased Hemorrhagic Transformation after Acute Ischemic Stroke.J Stroke Cerebrovasc Dis. 2018;27:3587-90.
26. Shon SH, Heo SH, Kim BJ, Choi HY, Kwon Y, Yi SH, et al. Predictors of Hemorrhage Volume after Intravenous Thrombolysis. J Stroke Cerebro vasc Dis. 2016;25:2543-8.
27. Tan S, Wang D, Liu M, Zhang S, Wu B, Liu B. Frequency and predictors of spontaneous hemorrhagic transformation in ischemic stroke and its association with prognosis. J Neurol. 2014;261:905-12.
28. Dang H, Ge WQ, Zhou CF, Zhou CY. The Correlation between Atrial Fibrillation and Prognosis and Hemorrhagic Transformation. Eur Neurol. 2019;82:9-14.
29. Wen L, Zhang S, Wan K, Zhang H, Zhang X. Risk factors of haemorrhagic transformation for acute ischaemic stroke in Chinese patients receiving intravenous thrombolysis: A meta-analysis. Medicine (Baltimore). 2020;99:e18995.

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(2):115-119.
DOI: 10.28982/josam.876062

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

Arthroereisis of the subtalar joint in the management of pediatric flexible flatfoot: A retrospective clinical study

Çağrı Neyişci, Yusuf Erdem, Ahmet Burak Bilekli

Gulhane Training and Research Hospital, Department of Orthopedics and Traumatology, Ankara, 06010, Turkey

ORCID ID of the author(s)
ÇN: 0000-0001-8481-7808
YE: 0000-0002-8685-2356
ABB: 0000-0002-6294-4838

Corresponding Author
Çağrı Neyişci
Department of Orthopedics and Traumatology, Gülhane Training and Research Hospital, Ankara, Turkey
E-mail: cagri_neyis@yahoo.com
drcagrineyisci@gmail.com

Ethics Committee Approval
Ethics committee approval was received for this study from Gülhane Scientific Research Ethics Committee (2021/65).
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 February 19

Abstract

Background/Aim: Management of flatfoot is still a challenge for orthopedic surgeons because it is a common and physiological process that usually requires observation and follow-up due to its asymptomatic nature in the pediatric population. The aim of this study was to investigate the radiological and pedobarographic results of symptomatic flexible flatfoot in pediatric patients who were treated by simultaneous gastrocnemius lengthening and arthroereisis of the subtalar joint.

Methods: This retrospective cohort study included 20 feet of 10 children (5 males, 5 females; mean age: 11.4 years; age range 9-14 years) who underwent simultaneous gastrocnemius lengthening and subtalar joint arthroereisis procedure for bilateral symptomatic flatfoot. The mean follow-up period was 24 months (range 11-32). All arthroereisis procedures were performed using a cannulated arthroereisis titanium implant. To assess the radiological results, calcaneal pitch angle and Meary's talus-first metatarsal angle on radiographs were measured preoperatively and at the final follow-up. Pedobarographic assessment was based on plantar heel and forefoot pressures preoperatively and at the final follow-up.

Results: The mean calcaneal pitch angle increased from 8° (0.93°) preoperatively to 16.5° (1.14°) postoperatively (P<0.001), while the mean Meary's talus-first metatarsal angle decreased from 7.5° (1.14°) preoperatively to 0.5° (0.51)° postoperatively (P<0.001). The mean heel peak pressure and forefoot peak pressure increased from 11.5 (1.14) N/cm^2 and 10.5 (1.14) N/cm^2 preoperatively to 17.5 (1.14) N/cm^2 and 15.5 (1.14) N/cm^2 postoperatively, respectively (P<0.001 for both variables). In addition, the pedobarographic assessment revealed that medially increased center of pressure moved to laterally increased center of pressure in all feet with an improvement in terms of forefoot and heel pressures. None of the patients experienced major intraoperative or postoperative complications.

Conclusion: Simultaneous gastrocnemius lengthening and arthroereisis of the subtalar joint seems an effective and safe surgical option for symptomatic flexible flatfoot in pediatric patients.

Keywords: Arthroereisis, Flatfoot, Gastrocnemius lengthening, Pediatric, Subtalar joint

How to cite: Neyişci Ç, Erdem Y, Bilekli AB. Arthroereisis of the subtalar joint in the management of pediatric flexible flatfoot: A retrospective clinical study. J Surg Med. 2021;5(2):115-119.

Introduction

Management of flatfoot is still a challenge for orthopedic surgeons because it is a common and generally physiological process that usually requires observation and follow-up due to its asymptomatic nature in the pediatric population [1]. Flexible flatfoot (FFF) is the most common form and the major abnormal biomechanical changes include valgus malalignment of the calcaneus, plantar deviation of the talus, and medial longitudinal arch collapse occurring during weight-bearing [1-3]. However, in symptomatic cases, this process can lead to subjective symptoms such as foot and ankle pain with postural difficulties [1]. Furthermore, additional equinus pathology (isolated gastrocnemius or gastro-soleus tightness) combined with FFF may aggregate pain along the medial side of the foot, heel, calf, knee, or low back during gait phases and make daily activities difficult, which sometimes extends to walking disability in children [2].

The main management of FFF requires physical and behavioral therapies, but surgical management is common [3-5]. Although there is still a controversy on the surgical indications and treatment modalities, surgical intervention is recommended when the child is complaining of excessive foot pain after 8 years of age [3]. The diagnosis is also based on parental warnings about child's unwillingness to walk or take part in athletic activities because of foot pain [4, 5]. Surgical management of symptomatic FFF includes diverse options: Soft tissue procedures (posterior tibial tendon transposition, Achilles/gastrocnemius lengthening, spring ligament repair), osteotomy and bony procedures (medializing calcaneal osteotomies, lateral column lengthening osteotomies), arthrodesis, and arthroereisis [5, 6]. The main goal of these procedures is to restore proper alignment between talus and calcaneus, and better results are obtained with osteotomies, bony procedures, and arthroereisis than with soft tissue procedures [7].

With increasing interest in foot and ankle sub-specialty and minimally invasive procedures, arthroereisis has become popular and widely accepted. However, the necessity of implant removal is still a negative aspect of the procedure, and most current studies focus on overcoming this problem by developing new bio-absorbable implants and evaluating their effects on correction [6, 8, 9]. There are few comparative studies investigating the biomechanical effects of this procedure on foot plantar pressures [10, 11].

The aim of this study is to investigate the alterations in foot biomechanics and plantar pressures utilizing pedobarographic and radiographic measurements in pediatric population who have undergone simultaneous gastrocnemius lengthening and arthroereisis procedure to treat symptomatic flatfoot with a tight heel cord.

Materials and methods

This retrospective study included 20 feet of 10 children (5 males, 5 females) who underwent bilateral gastrocnemius lengthening and simultaneous arthroereisis procedure for symptomatic flat feet between August 2016 and December 2018. Children between 9 and 14 years of age with idiopathic, flexible, symptomatic FFF (painful feet during standing and walking), and gastrocnemius/gastrosoleus tightness (positive Silverskiöld test) who had not responded to adaptive footwear, orthotics, or physiotherapy were included to our study. All patients were discharged on day 1 after operation with a short leg soft cast. Casts were removed 6 weeks after the operation, and the patients were encouraged to engage in full weight-bearing activities, as tolerated.

Exclusion criteria included post-traumatic, neurological or neuromuscular disorders, presence of joint hyperlaxity, foot synostosis, and clubfoot sequelae. Study protocol was approved by Gülhane Scientific Research Ethics Committee (2021/65) and conducted in accordance with the principles of the Declaration of Helsinki.

Physical examination

The diagnosis was based on clinical history and physical examination and documented by radiographs and pedobarographs. All patients were carefully examined preoperatively and at follow-up visits postoperatively by the same surgeon. Clinical diagnosis was based on increased hindfoot valgus position at rest and during tip-toe standing test. Postoperative clinical assessment also included the observations of parents regarding activities (physical domain assessing general activity limitations, assessing school and play participation restrictions, emotional domain assessing to what extent a child is bothered about their foot or ankle because of the appearance or the way people treat them, and wanting or not wanting to wear any shoes) of the children. Since clinical evaluation was not considered effective, scoring was not performed, and it was evaluated only if there was pain in daily and sports activities.

Radiographic assessment

The radiographic assessment included weight-bearing anteroposterior and lateral radiographs of the feet preoperatively and postoperatively at 6 weeks, 3 months, 6 months, 1 year, and 2 years. On radiographs, Meary's talar-first metatarsal angle and calcaneal pitch angle were measured (Figure 1). Additional computed tomography or magnetic resonance imaging studies were performed in patients when the aforementioned exclusion criteria were suspected.

Pedobarographic measurement

The pedobarographic assessment included plantar heel and forefoot (2-5 metatarsophalangeal joints and phalanges) pressures preoperatively and postoperatively at 6 weeks, 3 months, 6 months, 1 year, and 2 years. Footprint enlargement ratio (degree of plantar collapse) was evaluated using Viladot's classification [12] (Figure 2, 3).

Two masks of plantar foot pressures including heel and forefoot peak pressures were analyzed with the pedobarograph (footscan7®, RSscan International NV, Olen, Belgium) and were recorded as static and dynamic pressure data (Figure 4). Dynamic measurements were performed while the child was walking at natural speed.

Figure 1: a-f: (a) Preoperative, (b) anteroposterior, and (c) weight-bearing lateral radiographs of the flatfoot of a 10-year-old boy. Calcaneal pitch angle and Meary's angle were improved (d) postoperative, (e) anteroposterior, and (f) weight-bearing lateral radiographs of the foot after surgical correction

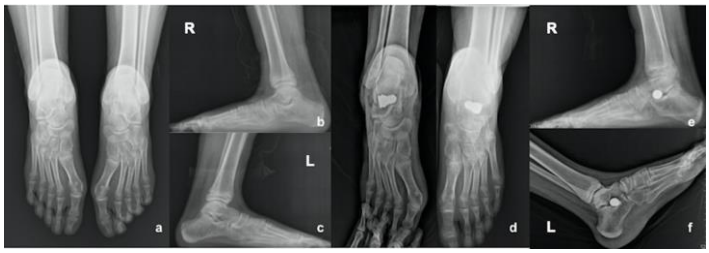


Figure 2: Footprint enlargement ratio according to Viladot [12]

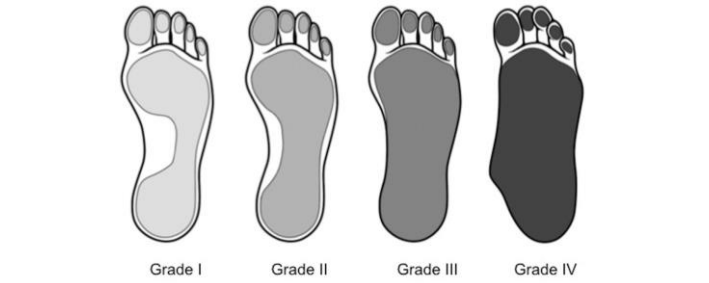


Figure 3: a, b. (a) Preoperative and (b) postoperative images of foot of a 10-year-old girl

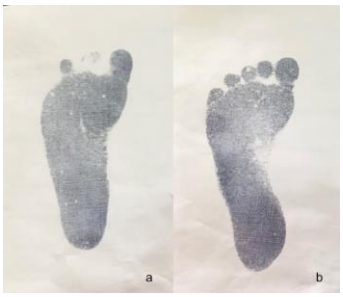
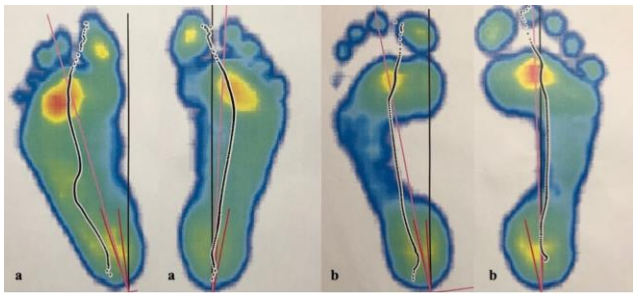


Figure 4: a, b. (a) Preoperatively printed out and (b) postoperative static and dynamic pedobarographic measurements of 12-year-old girl with symptomatic flatfoot. Loading of plantar foot shifted laterally after surgery



Surgical technique

All children were placed supine on the operating table under general anesthesia. A tourniquet was applied on the thigh for a bloodless and adequately exposed surgical field for the gastrocnemius lengthening procedure. The foot and the leg were prepared in usual sterile fashion, and local anesthetic was applied to the incision sites for postoperative pain control. After inflation of the tourniquet, a longitudinal 6-7 cm incision medial to the midline was performed at the middle of the calf. After subcutaneous dissection, Z-shaped incision at the aponeurosis of the gastrocnemius muscle was made. With controlled passive dorsiflexion of the foot, elongation of the gastrocnemius was obtained. After that, a 2-cm oblique skin incision was made over the tarsal sinus approximately 1-1.5 cm distal to the tip of the lateral malleolus. Blunt dissection to the location of the tarsal sinus was carried out, and the soft tissues within were transected to create a soft tissue pocket for the insertion of the guide wire and trial sizer. Inadequate soft tissue transection compromises proper placement as well as the size of trials. The guide wire in the tarsal sinus canal should be in the configuration of distal-lateral to proximal-medial (Figure 5). In-line cannulated trial sizers from small to large were inserted into the canal over the guide wire, and proper size was selected by evaluating talotarsal mechanism until reaching the optimal hindfoot valgus which was considered less than 5°. After fluoroscopic assessment, a proper size titanium cone-shaped implant was placed into the canal, and plain radiographs were obtained to evaluate the position of the implant (Figure 6). After wound irrigation, hemostasis, closure, and dressing, a short leg soft cast was applied with the ankle in neutral position.

Figure 5: a-c. (a) Anteroposterior and lateral views of the guide wire and screw placement into the sinus tarsi in direction of distal-lateral to proximal-medial, (b) Neutral position of the heel after proper size implantation of subtalar correction screw (not varus/valgus), and (c) Intraoperative fluoroscopic images of correct placement of guide wire and screw

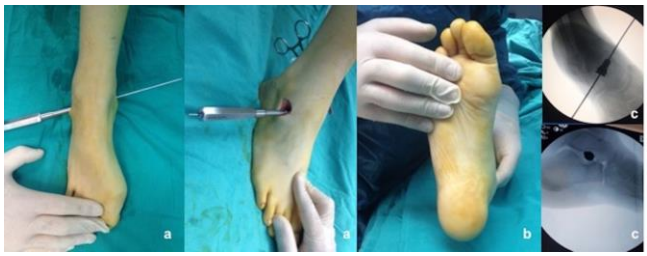


Figure 6: Cannulated arthroereisis titanium implant

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for Mac version 23.0 software (IBM SPSS Corp.; Armonk, NY, USA). Descriptive data were expressed in mean (SD), number, and frequency. Paired samples t test was used to compare preoperative and postoperative calcaneal pitch angle, Meary's angle, heel peak pressure, and forefoot peak pressures. The interim analysis was performed by an independent statistician blinded for the treatment allocation. A *P*-value of less than 0.05 was considered statistically significant.

Results

Among 10 patients (20 feet), there were 5 (50%) females and 5 (50%) males with a mean age of 11.4 (1.46) years. The mean follow-up period was 24 (range: 11-32 months) months. Applied implant diameters were between 7-10 mm. Patients' demographic data, radiological, and pedobarographic results are presented in Table 1. The mean preoperative calcaneal pitch angle of 8° (0.93°) increased to 16.5° (1.14°) postoperatively ($P<0.001$). In contrast, the mean preoperative Meary's angle of 7.5° (1.14°) decreased to 0.5° (0.51°) postoperatively ($P<0.001$).

The mean preoperative heel peak pressure of 11.5 (1.14) N/cm^2 increased to 17.5 (1.14) N/cm^2 postoperatively, and the preoperative forefoot peak pressure of 10.5 (1.14) N/cm^2 increased to 15.5 (1.14) N/cm^2 postoperatively ($P<0.001$ for both) (Table 2).

Table 1: Patients' demographic data, radiologic, and pedobarographic results

No	Gender (female/ male)	Age (year)	Screw diameter (mm)	Calcaneal pitch angle (degree)				Meary's angle (degree)				Heel peak pressure (N/cm^2)				Fore foot peak pressure (N/cm^2)			
				Right		Left		Right		Left		Right		Left		Right		Left	
				PO	PT	PO	PT	PO	PT	PO	PT	PO	PT	PO	PT	PO	PT	PO	PT
1	F	11	9	7	15	8	15	6	0	9	1	10	16	13	19	9	14	12	17
2	M	10	8	8	16	7	17	8	1	7	0	12	19	11	16	11	17	10	14
3	M	9	10	8	18	8	17	9	1	6	0	13	18	10	17	9	15	11	16
4	M	13	7	9	17	7	15	6	0	8	1	10	16	11	17	10	15	12	17
5	M	12	8	8	16	9.5	17	7	0	9	1	11	16	12	18	12	16	11	16
6	F	12	9	9	16	7	18	9	1	6	0	10	17	13	18	11	16	9	15
7	F	10	8	7	15	9.5	17	7	0	8	1	12	19	11	17	9	14	10	15
8	F	12	9	9	16	8	15	8	1	7	0	13	18	12	19	11	17	10	15
9	F	14	10	9.5	18	8	16	6	0	9	1	12	18	10	16	10	14	12	17
10	M	11	7	9	18	9.5	18	7	0	8	1	13	19	11	17	12	16	9	14

PO: preoperative, PT: postoperative

Table 2: Comparison of radiological and pedobarographic parameters

Parameter	Preoperative			Postoperative			*P*-value
	Min	Max	Mean (SD)	Min	Max	Mean (SD)	
Calcaneal pitch angle (degree)	7	9.5	8 (0.93)	15	18	16.5 (1.14)	<0.001
Meary's angle (degree)	6	9	7.5 (1.14)	0	1	0.5 (0.51)	<0.001
Heel peak pressure (N/cm^2)	10	13	11.5 (1.14)	16	19	17.5 (1.14)	<0.001
Fore foot peak pressure (N/cm^2)	9	12	10.5 (1.14)	14	17	15.5 (1.14)	<0.001

Min: Minimum, Max: Maximum, SD: Standard deviation, * paired samples t test

Clinically, children's ability to take part in athletic activities improved according to their parents' observations. Nine patients (18 feet) (90%) reported that their feet were significantly pain-free. In contrast, 1 patient (2 feet) (10%) reported minor discomfort since the implant had been inserted. In addition, their parents reported significant decrease of wear on the soles of their shoes.

Radiologically, Meary's angle improved within normal values, while the calcaneal pitch angle was within near-normal values.

Pedobarographically, medially increased center of pressure moved to laterally increased center of pressure in all feet with an improvement in terms of forefoot and heel pressures. Preoperatively, 10 feet were Viladot's grade 4 and 10 feet were Viladot's grade 3. Postoperatively, 18 feet improved to Viladot's grade 2, and 2 feet improved to Viladot's grade 3. The rate of footprint improvement is listed in Table 3.

Table 3: Degree of plantar collapse measured using Viladot's classification preoperatively and postoperatively (n=20 feet in 10 children)

Condition	Viladot's Classification				
	0	1	2	3	4
Preoperatively	0 (0%)	0 (0%)	0 (0%)	10 (50%)	10 (50%)
Postoperatively	0 (0%)	0 (0%)	18 (90%)	2 (10%)	0 (0%)

Full foot and ankle ROMs were recorded before and after surgery. None of the patients experienced major intraoperative or postoperative complications during follow-up; there was no infection, deep vein thrombosis, or implant-related problems. No patient was lost during follow-up. None of the implants were removed during the 24-month follow-up.

Discussion

In this study, we evaluated the alteration of the foot pressures and radiographic changes in the patients with symptomatic FFF and tight heel cord after simultaneous gastrocnemius lengthening and arthroereisis procedure.

Our results suggest that this procedure yields statistically significant improvement of the dynamic pedobarographic measurements including mean heel peak and mean forefoot peak pressures as well as the radiological measurements including calcaneal pitch and Meary's angle.

FFF is a common problem in children which usually does not require treatment [13]. Only 5% of the children with FFF have symptoms of plantar foot pain and muscle fatigue with increased physical activity owing to the dynamic functional changes at the lower extremities [14]. Regarding flatfoot biomechanics, the walking pressure mostly tends to distribute medially including medial arch, medial of the hindfoot, and first metatarsal head [15].

It was quite difficult to assess pedobarographic and radiological measurements immediately after cast removal at 6 weeks owing to the orientation in walking; however, the patients were orientated at follow-ups.

Pedobarographic evaluation shows that plantar pressure alterations at the foot is useful to determine abnormal walking patterns [14, 16]. In addition, the lack of radiation exposure of the children is another benefit of this evaluation. Normative data for dynamic plantar pressure measurements by pedobarographic technique was reported in several studies to define healthy feet in comparison to flatfoot deformity [17, 18]. Furthermore, numerous surgical corrective techniques have been introduced for symptomatic flatfoot [19]. Expected results with the corrective techniques may be explained as lateral shifting of foot pressures. In a dynamic pedobarographic study by Matheis et al., they reported significant changes in the medial to lateral shifting on forefoot and midfoot in terms of walking peak pressure and percentage of body weight [20]. In their comparative study of intraoperative plantar pressure evaluation by pedobarographic device, MacMahon et al. concluded that greater medial plantar pressures moved to the lateral side of the foot, especially forefoot, after corrective surgery [21]. Our study includes preoperative dynamic pedobarographic evaluation of foot, the forefoot, and heel peak pressures. Whereas higher peak pressures of the forefoot were localized on the first metatarsophalangeal joint and phalanx preoperatively, it was higher on second to fifth metatarsophalangeal joints postoperatively. In contrast, lower preoperative heel peak pressures during walking increased and were close to the normative data after surgical correction, which is consistent with literature.

With regards to corrective surgical techniques, arthroereisis stands out as a less invasive technique with the advantage of restricting the subtalar joint movement without any particular damage [19]. This periodically popularized technique has been nearly abandoned recently owing to implant-related complications and the necessity of implant removal which is considered as the most common complication [22]. In a recent study, Saxena et al. [23] reported an implant removal rate of 22.1% in 100 patients; however, the study population consists of patients older than 18 ye ars of age. It is also emphasized that an implant diameter of more than 11 mm would be a risk factor for implant removal. In our study, arthroereisis was applied to children under 14 years old, and the implant diameter was smaller than 11 mm for all cases, which is consistent with the literature. Furthermore, in weight-bearing radiographs, the mean calcaneal pitch angle increased to near-normal ranges, and Meary's angle had been corrected to the straight line between midline axis of the talus and first metatarsal rather than the convex downward position, all of which were significant. In contrast, arthroereisis procedure was performed with concomitant gastrocnemius lengthening for all cases in our study; addressing the underlying equinus deformity with gastrocnemius lengthening would provide better outcomes in children with FFF deformity. We concluded that the satisfying

changes on foot biomechanics were obtained with this combined procedure.

Numerous studies about arthroereisis procedure have evaluated the implant types, alteration of foot biomechanics, complications of implants, and walking patterns; however, there is no current data about the plantar pressure distribution in children after this procedure. The results of our study showed significant increases in both the heel and forefoot peak pressures, coinciding with the postoperative results of previous studies [15, 20].

Limitations

Nonetheless, there are some limitations to our study. First, there is no control group thus limiting the strength of the current analysis. Second, our cohort is a set of consecutive patient series in a highly specific patient group of a single surgeon in the first decade of his practice. Third, we have not used clinical outcome scores which may affect the power of study. Fourth, the study population is small owing to the low incidence of symptomatic FFF. A larger sample size might be better for detecting the prevalence of implant-related complications after this procedure. Finally, the mean follow-up period of this study is 24 months, which may be relatively short for a flatfoot series; therefore, further studies are needed to elucidate the long-term outcomes of this technique.

Conclusion

In conclusion, our study results suggest that arthroereisis procedure in combination with gastrocnemius lengthening in symptomatic FFF can yield promising short-term results if one remains faithful to the surgical technique of stabilizing the subtalar joint. However, we recommend large-scale and long-term, prospective, clinical studies to confirm the efficacy and safety of this technique.

References

1. Caravaggi P, Lullini G, Berti L, Giannini S, Leardini A. Functional evaluation of bilateral subtalar arthroereisis for the correction of flexible flatfoot in children: 1-year follow-up. Gait Posture. 2018 Jul;64:152-8.
2. Herring JA. Tachdjian's Pediatric Orthopaedics. 5th Edn. Elsevier, Philadelphia 2013.
3. Roth S, Sestan B, Tudor A, Ostojic Z, Sasso A, Durbesic A. Minimal invasive calcaneo-stop method for idiopathic flexible per planovalgus in children. Foot Ankle Int. 2007;28(9):991-5.
4. Mosca VS. Flexible flatfoot in children and adolescents. J Child Orthop. 2010 Apr;4(2):107-21.
5. Faldini C, Mazzotti A, Panciera A, Perna F, Stefanini N, Giannini S. Bioabsorbable implants for subtalar arthroereisis in pediatric flatfoot. Musculoskelet Surg. 2018 Apr;102(1):11-9.
6. Viladot Voegeli A, Fontecilla Cornejo N, Serrá Sandoval JA, Alvarez Goenaga F, Viladot Pericé R. Results of subtalar arthroereisis for posterior tibial tendon dysfunction stage IIA1. Based on 35 patients. Foot Ankle Surg. 2018 Feb;24(1):28-33.
7. Arangio GA, Salathe EP. A biomechanical analysis of posterior tibial tendon dysfunction, medial displacement calcaneal osteotomy and flexor digitorum longus transfer in adult acquired flat foot. Clin Biomech (Bristol, Avon). 2009 May;24(4):385-90.
8. Fernández de Retana P, Alvarez F, Viladot R. Subtalar arthroereisis in pediatric flatfoot reconstruction. Foot Ankle Clin. 2010 Jun;15(2):323-35.
9. Schon LC. Subtalar arthroereisis: a new exploration of an old concept. Foot Ankle Clin. 2007 Jun;12(2):329-39.
10. Wong DW, Wang Y, Chen TL, Leung AK, Zhang M. Biomechanical consequences of subtalar joint arthroereisis in treating posterior tibial tendon dysfunction: a theoretical analysis using finite element analysis. Comput Methods Biomech Biomed Engin. 2017 Nov;20(14):1525-32.
11. Hagen L, Pape JP, Kostakev M, Peterlein CD. Pedobarographic changes during first month after subtalar extra-articular screw arthroereisis (SESA) operation of juvenile flexible flatfoot. Arch Orthop Trauma Surg. 2019 Jul;140:313-20.
12. Jerosch J, Schunck J, Abdel-Aziz H. The stop screw technique-a simple and reliable method in treating flexible flatfoot in children. Foot Ankle Surg. 2009;15(4):174-8.
13. Sullivan JA. Pediatric flatfoot: evaluation and management. J Am Acad Orthop Surg. 1999 Jan;7(1):44-53.
14. Lin CJ, Lai KA, Kuan TS, Chou YL. Correlating factors and clinical significance of flexible flatfoot in preschool children. J Pediatr Orthop. 2001 May-Jun;21(3):378-82.
15. Ledoux WR, Hillstrom HJ. The distributed plantar vertical force of neutrally aligned and pes planus feet. Gait Posture. 2010;15:1-9.
16. Dziuba A, Szpala A. Foot kinematics in gait of children with cerebral palsy (CP). Acta Bioeng Biomech. 2008;10(4):3-6.
17. Alvarez C, De Vera M, Chhina H, Black A. Normative data for the dynamic pedobarographic profiles of children. Gait Posture. 2008 Aug;28(2):309-15.
18. Liu XC, Thometz JG, Tassone C, Barker B, Lyon R. Dynamic plantar pressure measurement for the normal subject: Free-mapping model for the analysis of pediatric foot deformities. J Pediatr Orthop. 2005 Jan-Feb;25(1):103-6.
19. Ford SE, Scannell BP. Pediatric Flatfoot: Pearls and Pitfalls. Foot Ankle Clin. 2017 Sep;22(3):643-56.
20. Matheis EA, Spratley EM, Hayes CW, Adelaar RS, Wayne JS. Plantar measurements to determine success of surgical correction of Stage IIb adult acquired flatfoot deformity. J Foot Ankle Surg. 2014 Sep-Oct;53(5):562-6.
21. MacMahon A, Hillstrom HJ, Do HT, Chan JY, Deland JT, Ellis SJ. In Vivo Plantar Pressures in Adult-Acquired Flatfoot Compared to Control Using an Intraoperative Pedobarographic Device. HSS J. 2017 Jul;13(2):136-45.
22. Ortiz CA, Wagner E, Wagner P. Arthroereisis: What Have We Learned? Foot Ankle Clin. 2018 Sep;23(3):415-34.
23. Saxena A, Via AG, Maffulli N, Chiu H. Subtalar Arthroereisis Implant Removal in Adults: A Prospective Study of 100 Patients. J Foot Ankle Surg. 2016 May-Jun;55(3):500-3.

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(2):120-123.
DOI: 10.28982/josam.862849

Research article

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

Corneal endothelial alterations in patients with diabetic macular edema

Gamze Uçan Gündüz [1], Hafize Gökben Ulutaş [2], Neslihan Parmak Yener [2], Özgür Yalçınbayır [1]

[1] Bursa Uludağ University, Faculty of Medicine, Department of Ophthalmology, Bursa, Turkey
[2] Health Sciences University, Yüksek İhtisas Training and Research Hospital, Ophthalmology Clinic, Bursa, Turkey

ORCID ID of the author(s)

GUG: 0000-0002-1686-5484
HGU: 0000-0002-7961-3664
NPY: 0000-0002-4253-7856
ÖY: 0000-0002-1219-8304

Corresponding Author
Gamze Uçan Gündüz
Uludağ Üniversitesi Tıp Fakültesi, Göz Hst. AD, Görükle, 16059, Bursa, Türkiye
E-mail: gamzeucan@gmail.com
gamzeug@uludag.edu.tr

Ethics Committee Approval
For this study, approval was obtained from Uludağ University Faculty of Medicine Clinical Research Ethics Committee (decision dated November 21, 2017 and numbered 2017-17 / 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 February 19

Abstract

Background/Aim: Diabetic macular edema (DME) is the main cause of visual loss in diabetic patients. Although it is known that diabetes mellitus could affect all corneal layers, there is no data about the morphological and quantitative changes of corneal endothelium in patients with DME. The aim of this study is to evaluate the corneal endothelial cell density (CD), morphology and central corneal thickness (CCT) in patients with DME.

Methods: This retrospective study included 47 diabetic patients (79 eyes) with DME, 48 diabetic patients (93 eyes) without DME, and 46 nondiabetic subjects (74 eyes). Diagnosis of DME was based on fundoscopy and optical coherence tomography imaging. The corneal endothelial structure and CCT were evaluated using non-contact specular microscopy. The endothelial CD (cells/mm^2), coefficient variation of cell area (CV), percentage of hexagonality (HEX) and CCT of the three subgroups were compared.

Results: The mean age of participants was 59.8 (8.3) years. There was no significant difference in terms of age between diabetic patients and control subjects (P=0.761). In the diabetic subgroups, HbA1c levels and the number of patients receiving insulin were similar (P=0.962, P=0.082, respectively), but the mean duration of diabetes was significantly longer in the DME subgroup than in the no-DME subgroup (P=0.015). Patients in the DME subgroup did not differ from the patients in the no-DME and control subgroups with regards to endothelial CD and CCT. However, there was a statistically significant decrease in HEX and increase in CV in patients with DME (P=0.012, P=0.012, respectively).

Conclusion: Patients with DME were found to have higher rates of polymegathism and polymorphism although there were no significant changes in corneal endothelial CD and CCT. These alterations may be the first signs of early corneal damage in patients with DME.

Keywords: Corneal endothelium, Diabetic macular edema, Polymegathism, Polymorphism, Specular microscopy

How to cite: Uçan Gündüz G, Ulutaş HG, Parmak Yener N, Yalçınbayır Ö. Corneal endothelial alterations in patients with diabetic macular edema. J Surg Med. 2021;5(2):120-123.

Introduction

Diabetic macular edema (DME) is the main cause of visual loss in diabetic patients, with an annual incidence of 2.19% [1]. DME can develop in any stage of either nonproliferative or proliferative diabetic retinopathy (DR) [2]. It results in macular thickening due to the failure of the blood-retinal barrier and fluid accumulation within the macula. Although vascular endothelial growth factor (VEGF) overexpression and inflammation are thought to be responsible for DME, the certain pathogenesis is still controversial. In experimental studies, VEGF receptors were expressed on the corneal endothelium [3]. Therefore, the altered expression of growth factors, including VEGF and inflammatory cytokines, may cause corneal endothelial changes in patients with DME [4].

Treatment options for DME include intravitreal injections of anti-VEGF or steroids and photocoagulation [5]. Patients with DME tend to have cataracts because of both chronic hyperglycemia and recurrent intravitreal injections, particularly steroids [6]. Therefore, they are likely to require cataract surgery in the near future. Rarely, pars plana vitrectomy may be required in cases of refractory DME. A healthy corneal endothelium with morphological and functional integrity is necessary for maintaining corneal transparency following intraocular surgeries, particularly after phacoemulsification. It is important to have information about endothelial cells to take intraoperative precautions to minimize the risk of endothelial failure.

Some recent studies have suggested that endothelial cell counts decreases and cell morphology changes in diabetic patients [7-9], while other data have indicated no change in corneal endothelial cell density (CD) [4, 10]. Few studies have examined the correlation between the severity of corneal endothelial changes and DR [11, 12]. However, to the best of the authors' knowledge, no study has evaluated the correlation between corneal endothelial changes and DME. The present study aimed to determine the changes in corneal endothelial CD, endothelial morphology and central corneal thickness (CCT) in patients with DME.

Materials and methods

The medical reports of patients with type II DM who attended the ophthalmology outpatient clinic between January 2016 and November 2017 were identified retrospectively. The diagnosis of type II DM was based on the patients' medical history. Demographic characteristics, most recent HbA1c levels, type of antidiabetic medication and duration of DM were recorded from the medical data. Diabetic patients with no or mild DR were included in the study. Patients with proliferative DR, glaucoma, corneal diseases and a history of previous intraocular surgery, intravitreal injection, argon laser photocoagulation and contact lens–wearing were excluded from the study. Since the corneal endothelium is affected by age, care was taken to ensure that the ages of the patients in the study groups were similar.

Diabetic patients were divided into two subgroups based on the presence of DME. The presence of DME and stages of DR were determined via a dilated fundus examination, optical coherence tomography (Optovue, iVue, USA) and fluorescein angiography. Patients with center-involving DME, which was defined as fovea-involving fluid on optical coherence tomography in association with the clinical diagnosis of diabetic maculopathy [13], were included in the DME subgroup. Diabetic patients with normal foveal configuration without any fluid on optical coherence tomography were included in the no-DME subgroup. The control group consisted of age-matched nondiabetic subjects who were admitted to the ophthalmology clinic for a routine examination. All subjects underwent a complete ophthalmologic examination, which included testing for best corrected visual acuity, slit lamp examination, intraocular pressure measurement with pneumotonometer and fundoscopy. This study was approved by the Ethics Committee of the Uludag University Faculty of Medicine on 21.11.2017 with the number of 2017-17/11 and conducted per the Declaration of Helsinki.

Corneal endothelial CD (cells/mm^2), coefficient variation of cell area (CV), the percentage of hexagonal cells (HEX) and CCT were analyzed automatically using a non-contact specular microscopy (NSP-9900, NonconRobo, Konan, Japan). Pictures were taken from the central cornea in a suitable head position while the patient was sitting. The measurements were obtained three times, and the mean was calculated.

The demographic characteristics, duration of DM, HbA1c levels, central macular thickness, corneal endothelial parameters, CCT and intraocular pressure of the three subgroups were then compared.

Statistical analysis

The Shapiro–Wilk test was used to decide the distribution of the data. The results were presented as mean (±standard deviation) or frequency and percentage. According to pilot study, using pooled standard deviation of CV (5.92), a power analysis indicated that a total sample of 46 people would be needed to detect effect size (d=0.27) with 80% power with alpha at 0.05, 2-sided significance level. Normally distributed data were compared with an independent sample *t*-test or one-way ANOVA. Kruskal–Wallis and Mann–Whitney U tests were used for non-normally distributed data. The Bonferroni test was used as a multiple comparison test. Categorical variables were compared using Pearson's chi-square test and Fisher's exact test between groups. A *P*-value of <0.05 was considered the significance level. Statistical analyses were performed with IBM SPSS ver.23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

Results

A total of 95 diabetic patients and 46 healthy subjects enrolled in the present study. The mean age was 59.8 (8.3) years. Seventy-five patients (53.2%) were female. Seventy-nine eyes of 47 diabetic patients had DME with a mean central macular thickness of 417.7 (115.7) μ. These were classified as the DME subgroup. Ninety-three eyes of 48 diabetic patients without DME were classified as the no-DME subgroup. Seventy-four eyes of 46 nondiabetic subjects were classified as a control group. There were no statistically significant differences between the three groups in terms of age and sex (Table 1).

In the diabetic subgroups, no patient had proliferative DR. The mean duration of DM was 12.6 (6.4) years, and the

mean HbA1c level was 8.8 (2.2) %. There were no differences between the diabetic groups in terms of HbA1c levels (P=0.962) and frequency of insulin usage (P=0.082), but the mean duration of DM was significantly longer in the DME subgroup than in the no-DME subgroup (P=0.015) (Table 1).

The endothelial CD was 2641.4 cells/mm^2 in the DME subgroup, 2648.6 cells/mm^2 in the no-DME subgroup, and 2690.6 cells/mm^2 in the control group (P=0.429) (Table 2). In the DME subgroup, the mean HEX was 43.3 (5.9), and it was significantly lower than the no-DME and control subgroups (P=0.012). Similarly, the mean CV was 45.1 (6.8) in the DME subgroup, which was significantly higher than in the no-DME and control subgroups (P=0.012). There were no significant differences between the three subgroups in terms of CCT and intraocular pressure (P=0.188, P=0.076, respectively) (Table 2).

Table 1: Demographic characteristics and clinical properties of patients

Parameters	DME group n=47 pts	No-DME group n=48 pts	Control group n=46 pts	*P*-value
Gender (F/M)	23 F / 24 M	27 F / 21 M	25 F / 21 M	0.761
Age in years, mean (SD)	61.32 (6.9)	59.54 (8.8)	58.5 (9.1)	0.242
Duration of DM, years, mean (SD)	14.2 (6.3)	11.0 (6.1)	-	0.015
HbA1c level, mean (SD)	8.8 (1.9)	8.8 (2.6)	-	0.962
Insulin usage (%)	35 (74.5)	27 (57.4)	-	0.082

DME: diabetic macular edema, DM: diabetes mellitus, pts: patients, F: female, M: male, SD: standard deviation

Table 2: Central macular thickness, corneal parameters and intraocular pressure of study eyes

Parameters	DME group n=79 eyes	No-DME group n=93 eyes	Control group n=74 eyes	*P*-value
CMT	417.7 (115.7)	252.0 (19.5)	256.0 (27.0)	<0.001
CD	2641.4 (238.0)	2648.6 (261.1)	2690.6 (256.6)	0.429
CV	45.1 (6.8)	42.2 (6.4)	42.6 (6.7)	0.012
HEX	43.3 (5.9)	46.3 (7.1)	45.6 (8.1)	0.012
CCT	541.8 (35.5)	551.0 (35.7)	549.5 (31.7)	0.188
IOP	17.7 (2.9)	18.0 (2.8)	17.0 (2.3)	0.076

Parameters are written as mean (standard deviation). DME: diabetic macular edema, CMT: central macular thickness, CD: cell density, CV: coefficient of variation, HEX: hexagonality, CCT: central corneal thickness, IOP: intraocular pressure

Discussion

Diabetes mellitus can affect all corneal layers, and several corneal disorders are present in more than 70% of diabetic patients [14]. It can also damage the corneal endothelium, which is the layer responsible for maintaining corneal transparency. However, data about the correlation between corneal endothelial changes and the severity of DR is limited. While most studies on this topic have found that the stage of DR is not correlated with corneal endothelial findings [9, 15, 16], only a few studies have reported that the number of endothelial cells is significantly lower in eyes with proliferative DR [11, 14, 17].

Diabetic macular edema can be considered a separate entity from DR because it occurs in isolation without other signs of microangiopathy in the peripheral retina [5]. In addition, it can accompany any stage of DR. To the best of our knowledge, no study has evaluated the morphological and quantitative changes of corneal endothelium in patients with DME.

The endothelial cells of retinal capillaries are joined to each other by tight junctions occurring the inner blood-retinal barrier to regulate retinal fluid level. In diabetes mellitus (DM), Muller cells and retinal endothelial cells produce several chemokines, such as VEGF, tumor necrosis factor α, interleukin 1β and matrix metalloproteinase, due to chronic inflammation and hyperglycemia. These inflammatory cytokines cause the tight junctions to break down, which, in turn, causes DME. Corneal endothelial cells also have tight junctions between them to maintain corneal dehydration and clarity. With a mechanism similar to retinal pathology, corneal endothelial junctions may break down, and paracellular permeability may increase through junctional alterations in eyes with DME [2, 18].

In the present study, the mean endothelial CD was 2641.4 cells/mm^2 in the DME subgroup. This was similar to the no-DME and control subgroups in this study. In the last 10 years, numerous studies have investigated endothelial CD alterations in diabetic patients by comparing them with healthy controls. Most of these studies have reported a decrease in the endothelial CD in diabetic patients, particularly in those with type I DM [19, 24]. However, similar to the present study, some studies did not find statistically significant differences in endothelial CD between diabetics and healthy controls. All these studies included patients with type II DM, as did our sample [10, 19, 20]. The reason that CD was more affected in type I than type II DM may be due to the younger onset and longer duration of disease in type I DM. In addition, in most studies, the duration of DM was correlated with a decrease in endothelial CD in diabetic patients [21, 22, 25].

Corneal endothelial cells have hexagonal shapes, usually with a mosaic pattern, and do not proliferate in vivo. Physiologically, the number of endothelial cells decreases with ageing, but ocular trauma and surgery cause endothelial cell loss more than usual. In this instance, the defective area is compensated via enlargement of residual cells. These alterations can be determined by specular microscopy as polymegathism (variability in cell size) and polymorphism (variability in cell shape) [26].

In the present study, patients with DME had higher rates of polymegathism [45.1 (6.8)] and polymorphism [43.3 (5.9)] than the no-DME and control subgroups. In most previous studies, polymegathism and polymorphism accompanied lower endothelial CD in diabetic patients compared to healthy individuals [22, 25, 27]. However, polymegathism and polymorphism could be a more sensitive precursor of endothelium under stress before the occurrence of a significant decrease in CD [28]. This may be because the endothelial CD will decrease by 1% if only one cell is lost in a cluster of 100 cells, which would be an insignificant decrease. However, if a six-sided cell is lost in the cluster of 100 cells, two (2%) or six (6%) adjacent cells will show significant morphological changes for repairing the defect [26]. Therefore, higher rates of polymegathism and polymorphism in eyes with DME may be explained as early diabetic corneal endothelial damage before significant changes in endothelial CD. Similarly, in a recent study, Leelawongtawun et al. [19] found that when diabetes progresses, hexagonal cells decreased at first (in > 1-year diabetics). This was followed by polymegathism (in > 2 years diabetics) before changes in endothelial CD occurred. However, higher rates of polymegathism and polymorphism could also be associated with diabetes duration, which was longer in patients with DME than in those without DME in the present study [14.2 (6.3) and 11.0 (6.1) years, respectively).

Another indicator of endothelial cell dysfunction is CCT. Endothelial cell Na/K ATPase and tight junctions are responsible for controlling the entrance of aqueous humour into the corneal stroma to maintain corneal dehydration. If endothelial cell loss occurs, the frequency of tight junctions

between cells decreases, allowing more aqueous humour to enter the corneal stroma. Consequently, CCT increases with the loss of corneal transparency [29]. Regarding CCT in the present study, there was no significant difference between subjects in the DME, no-DME, and control subgroups. This could be due to the similar density of endothelial cells in the three subgroups. This outcome was in concordance with those of El-Agamy et al. [9], and Choo et al. [16], while other authors have reported higher CCT in those with type 2 DM compared to nondiabetics [7, 10].

Only a few studies have compared the corneal endothelial changes that occur in diabetics and nondiabetics after cataract surgery. Recently, Sahu et al. [30] found that diabetic patients showed a significantly higher loss of corneal endothelial density after phacoemulsification than nondiabetic patients with similar nuclear grading and phaco energy used. They suggested that a more careful approach during phacoemulsification was required in diabetic patients, even in the presence of good glycemic control. It was, therefore, important to have information about the corneal endothelial integrity of diabetic patients prior to cataract surgery to reduce the risk of endothelial decompensation.

The strength of the present study was that patients were age-matched among three subgroups to eliminate possible age-related bias in corneal endothelium. No patient had a history of intraocular surgery, intravitreal injection or laser photocoagulation in order to avoid influencing the corneal endothelial parameters. Diabetic patients with and without DME had similar glycemic status regarding HbA1c levels. No patient had proliferative DR that could have had a probable effect on corneal endothelium and CCT, as suggested by several studies [12, 13].

Limitations

Limitations of the study include retrospective data collection, lack of multivariate study and different lengths of diabetes duration in patients with and without DME. Future prospective studies are required for confirming the corneal alterations in patients with DME.

Conclusion

This study suggested higher rates of polymegathism and polymorphism in patients with DME, although there were no significant changes in endothelial CD and CCT. These alterations may be the first signs of early corneal damage. Therefore, evaluation of corneal endothelium in patients with DME should be a part of routine examination prior to intraocular surgery. Extra care should be taken when treating patients with low endothelial reserve.

References

1. Romero-Aroca P, Baget-Bernaldiz M, Pareja-Rios A, Lopez-Galvez M, Navarro-Gil R, Verges R. Diabetic macular edema pathophysiology: vasogenic versus inflammatory. J Diabetes Res. 2016;2016:2156273. doi: 10.1155/2016/2156273.
2. Das A, McGuire PG, Rangasamy S. Diabetic macular edema: pathophysiology and novel therapeutic targets. Ophthalmol. 2015;122:1375-94.
3. Gan L, Fagerholm P, Palmblad J. Vascular endothelial growth factor (VEGF) and its receptor VEGFR-2 in the regulation of corneal neovascularization and wound healing. Acta Ophthalmol Scand. 2004;82:557–63.
4. Ljubimov AV. Diabetic complications in the cornea. Vision Res. 2017;139:138-52.
5. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, et al. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica. 2017;237:185-222.
6. Falavarjani KG, QD Nguyen. Adverse events and complications associated with intravitreal injection of anti-VEGF agents:a review of literature. Eye. 2013;27:787–94.
7. Galgauskas S, Laurinavičiūtė G, Norvydaitė D, Stech S, Ašoklis R. Changes in choroidal thickness and corneal parameters in diabetic eyes. Eur J Ophthalmol. 2016;26:163-7.
8. Calvo-Maroto AM, Cerviño A, Perez-Cambrodí RJ, García-Lázaro S, Sanchis-Gimeno JA. Quantitative corneal anatomy: evaluation of the effect of diabetes duration on the endothelial cell density and corneal thickness. Ophthalmic Physiol Opt. 2015;35:293-8.
9. El-Agamy A, Alsubaie S. Corneal endothelium and central corneal thickness changes in type 2 diabetes mellitus. Clin Ophthalmol. 2017;11:481-6.
10. Storr-Paulsen A, Singh A, Jeppesen H, Norregaard JC, Thulesen J. Corneal endothelial morphology and central thickness in patients with type II diabetes mellitus. Acta Ophthalmol. 2014;92:158-60.
11. Shenoy R, Khandekar R, Bialasiewicz A, Al Muniri A. Corneal endothelium in patients with diabetes mellitus: a historical cohort study. Eur J Ophthalmol. 2009;19:369-75.
12. Durukan I. Corneal endothelial changes in type 2 diabetes mellitus relative to diabetic retinopathy. Clin Exp Optom. 2020;103:474-8.
13. Itoh Y, Petkovsek D, Kaiser PK, Singh RP, Ehlers JP. Optical coherence tomography features in diabetic macular edema and the impact on anti-VEGF response. Ophthalmic Surg Lasers Imaging Retina. 2016;47:908-13.
14. Quadrado MJ, Popper M, Morgado AM. Diabetes and corneal cell densities in humans by in vivo confocal microscopy. Cornea. 2006;35:761-8.
15. Choo M, Prakash K, Samsudin A, Soong T, Ramli N, Kadir A. Corneal changes in type II diabetes mellitus in Malaysia. Int J Ophthalmol. 2010;3:234-6.
16. Matsuda M, Ohguro N, Ishimoto I, Fukuda M. Relationship of corneal endothelial morphology to diabetic retinopathy, duration of diabetes and glycemic control. Jpn J Ophthalmol. 1990;34:53-6.
17. Taşlı NG, Icel E, Karakurt Y, Ucak T, Ugurlu A, Yilmaz H, et al. The findings of corneal specular microscopy in patients with type-2 diabetes mellitus. BMC Ophthalmol. 2020;20:214.
18. Goldstein AS, Janson BJ, Skeie JM, Ling JJ, Greiner MA. The effects of diabetes mellitus on the corneal endothelium: A review. Surv Ophthalmol. 2020;65:438-50.
19. Leelawongtawun W, Suphachearaphan W, Kampitak K, Leelawongtawun R. A comparative study of corneal endothelial structure between diabetes and non-diabetes. J Med Assoc Thai. 2015;98:484-8.
20. Qu JH, Li L, Tian L, Zhang XY, Thomas R, Sun XG. Epithelial changes with corneal punctate epitheliopathy in type 2 diabetes mellitus and their correlation with time to healing. BMC Ophthalmol. 2018;18:1.
21. Urban B, Raczyńska D, Bakunowicz-Łazarczyk A, Raczyńska K, Krętowska M. Evaluation of corneal endothelium in children and adolescents with type 1 diabetes mellitus. Mediators Inflamm. 2013;2013:913754. doi: 10.1155/2013/913754.
22. Anbar M, Ammar H, Mahmoud RA. Corneal endothelial morphology in children with type 1 diabetes. J Diabetes Res. 2016;2016:7319047. doi: 10.1155/2016/7319047.
23. Szalai E, Deák E, Módis L Jr, Németh G, Berta A, Nagy A, et al. Early corneal cellular and nerve fiber pathology in young patients with type 1 diabetes mellitus identified using corneal confocal microscopy. Invest Ophthalmol Vis Sci. 2016;57:853-8.
24. Módis L Jr, Szalai E, Kertész K, Kemény-Beke A, Kettesy B, Berta A. Evaluation of the corneal endothelium in patients with diabetes mellitus type I and II. Histol Histopathol. 2010;25:1531-7.
25. Islam QU, Mehboob MA, Amin ZA. Comparison of corneal morphological characteristics between diabetic and non diabetic population. Pak J Med Sci. 2017;33:1307-11.
26. Benetz BA, Yee R, Bidros M, Lass J. Specular microscopy. In: Krachmer JH, Mannis MJ, Holland EJ, eds. Cornea: Fundamentals, Diagnosis and Management. 3rd ed. China, Mosby Elsevier; 2011. pp.177-203.
27. Leelawongtawun W, Surakiatchanukul B, Kampitak K, Leelawongtawun R. Study of corneal endothelial cells related to duration in diabetes. J Med Assoc Thai. 2016;99:182-8.
28. Yee RW, Matsuda M, Schultz RO, Edelhauser HF. Changes in the normal corneal endothelial cellular pattern as a function of age. Curr Eye Res. 1985;4:671-8.
29. Del Buey MA, Casas P, Caramello C, López N, de la Rica M, Subirón AB, et al. An update on corneal biomechanics and architecture in diabetes. J Ophthalmol. 2019;2019:7645352. doi: 10.1155/2019/7645352.
30. Sahu PK, Das GK, Agrawal S, Kumar S. Comparative evaluation of corneal endothelium in diabetic patients undergoing phacoemulsification. Middle East Afr J Ophthalmol. 2017;24:195-201.

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(2):124-127.
DOI: 10.28982/josam.834535

Research article

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

Antibiotic consumption in the hospital during COVID-19 pandemic, distribution of bacterial agents and antimicrobial resistance: A single-center study

Aziz Ahmad Hamidi [1], Şerife Yılmaz [2]

[1] Infectious Diseases and Clinical Microbiology Department, Maltepe University, Maltepe medical faculty, Istanbul, Turkey
[2] Karabuk University Training and Research Hospital, Microbiology Laboratory, Karabuk, Turkey

ORCID ID of the author(s)
AAH: 0000-0003-4108-0847
ŞY: 0000-0001-5310-3933

Corresponding Author
Şerife Yılmaz
Karabuk University Training and Research Hospital, Microbiology Laboratory, Karabuk, Turkey
E-mail: mdserifeyilmaz@gmail.com

Ethics Committee Approval
This study was approved by the Non-invasive Clinical Research Ethics Board of Karabük University (approval number: 2020/242). 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 February 19

Abstract

Background/Aim: In recent years, the consumption of broad-spectrum antibiotics used in hospitals and the number of multidrug-resistant pathogens are increasing. Coronavirus disease 2019 (COVID-19) pandemic could also affect consumption of antibiotics used in the treatment of hospital-acquired infections and cause a difference antibiotic resistance rate. There is no study on whether there was a change in this trend during the COVID-19 pandemic in Turkey. Our study was conducted to determine antibiotic consumption, the distribution of bacterial agents in culture samples and changes in their antimicrobial resistance rates in our hospital during the COVID-19 pandemic.

Methods: In this retrospective cohort study, January and February 2020 were defined as the pre-pandemic period (PPP), and March and April, as the pandemic period (PP). The bacterial agents isolated from blood, urine, and respiratory samples and the rates of antibiotic consumption during these periods were compared using statistical methods.

Results: A total of 3,384 samples were analyzed during the PPP and 2,170 samples, during the PP. While the total bacterial agents isolated in PPP was 469, this number was 394 in PP. The isolation of *Escherichia coli*, *Acinetobacter baumannii* complex was significantly lower in the PP ($P<0.001$; $P=0.008$, respectively). Conversely, the isolation of *Enterococcus* spp. was higher during the PP ($P<0.001$). In the PP, the consumption of piperacillin-tazobactam, teicoplanin, meropenem and fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin) were significantly higher ($P<0.001$; $P=0.016$; $P=0.016$; $P=0.02$; $P<0.001$; $P=0.018$, respectively) while that of cefazolin was significantly lower ($P<0.001$). Total antibiotic consumptions during the PPP and PP were 725.8 DDD / 1000 and 811.4 DDD / 1000 inpatient days, respectively ($P=0.002$).

Conclusions: Although bacterial agents isolated in PP were lower, antibiotics consumption was higher. The high positivity rate of *Enterococcus* spp. during the PP suggests that hand hygiene and contact isolation should be strictly observed, as this may be related to the inadequacy of hygiene practices.

Keywords: Covid-19, Culture, Infection, Antibiotic-resistance, Bacteria

How to cite: Hamidi AA, Yılmaz Ş. Antibiotic consumption in the hospital during COVID-19 pandemic and distribution of bacterial agents and antimicrobial resistance: A single-center study. J Surg Med. 2021;5(2):124-127.

Introduction

Antibiotic consumption has been increasing worldwide in recent years. The problem of antimicrobial resistance due to antibiotic consumption is one of the world's current problems that require urgent action. Consumption of carbapenem, polymyxin, and oxazolidinone antibiotics, used in the treatment of hospital-acquired infections caused by multidrug-resistant bacteria, is steadily increasing [1]. In addition, the rate of antimicrobial resistance development in bacteria is high [2, 3].

Coronavirus disease 2019 (COVID-19) appeared in Wuhan, China in December 2019 and caused a pandemic [4]. In Turkey, the first case was detected on March 11, 2020 and the number of cases continued to increase rapidly. On March 17, 2020, health authorities decided to defer elective surgeries, stop non-emergency hospitalizations, and minimize services offered at the outpatient clinics, so that healthcare services could be directed at the COVID-19 pandemic. In our center, which is a tertiary hospital, emergency surgeries and non-COVID-19 patient hospitalizations were continued in a separate department of the hospital while serving as a pandemic hospital.

Consumption of antibiotics used in the treatment of hospital-acquired infections may be affected, and there may be changes in the distribution of bacteria growing in culture and in the rates of antibiotic resistance during the COVID-19 pandemic. The present study was, therefore, conducted to compare antibiotic consumption and the distribution of bacteria growing in culture in our hospital before and during the COVID-19 pandemic.

Materials and methods

Our hospital, a tertiary university hospital, allocated 80% of its capacity for COVID-19 patients during the pandemic and 20% for emergency surgeries and emergency patient hospitalization. The hospital has 465 adult hospital beds and 52 adult intensive care beds. Non-COVID-19 patients were monitored in two separate services and a ten-bed intensive care unit while COVID-19 patients were followed up in eight services and in four ten-bed intensive care units. In the present study, blood, urine, bronchoalveolar lavage (BAL), sputum, and endotracheal aspirate (ETA) cultures analyzed in our hospital's microbiology laboratory between January 1, 2020 and April 30, 2020 were retrospectively evaluated. To prevent duplication, one sample from the same patient was included in the study according to urine, blood and respiratory samples. In this retrospective cohort study, the period between January 1 and February 29 was considered as the pre-COVID-19 pandemic period (PPP) while March 1 and April 30 was considered as the pandemic period (PP). Blood cultures were incubated for seven days in the automated blood culture system BACTEC FX 40 (Becton Dickinson, USA). The samples with growth signals were inoculated in 5% sheep blood agar, eosin methylene blue (EMB) agar, and chocolate agar and incubated at 37°C for 24–48 hours. Urine samples were inoculated in 5% sheep blood agar and EMB agar while BAL, sputum, and ETA samples were inoculated in 5% sheep blood agar, EMB agar, and chocolate agar and incubated at 37°C for 24–48 hours. Conventional methods and the Phoenix™ (Becton Diagnostics, USA) fully automated system were used to identify microorganisms with observed growth in their media. Antimicrobial susceptibility of active microorganisms was determined using Kirby–Bauer disk diffusion method, E-test (bioMérieux, France), and the Phoenix (Becton Diagnostics, USA) fully automated system, according to the European Committee on Antimicrobial Susceptibility Testing criteria. Carbapenem resistance in the group of *Enterobacteriaceae*, and vancomycin and teicoplanin resistance in the isolates of *Enterococcus* spp. were confirmed using the E-test stripes with gradient test method.

Bacteria that could be the causative agents of infection were classified as *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus* spp., and *Escherichia coli*. The strains of *Enterobacter* spp., *Serratia marcescens, Proteus* spp., and *Citrobacter* spp. were also classified as other gram-negative bacteria.

The amounts of antibiotics consumed were determined retrospectively at the hospital pharmacy between January 1 and April 30. Antibiotic consumption was calculated using the anatomical therapeutic chemical/defined daily dose (ATC/DDD) per 1000 inpatient days method determined by the World Health Organization. The amounts of antibiotics consumed and the antibiotic groups were compared between the PPP and PP.

Statistical analysis

Statistical Package for Social Sciences (SPSS) 15.0 (SPSS Inc.; Chicago, IL, USA) Windows program was used for statistical analysis of the data. Descriptive statistics were presented as mean, standard deviation, median, and minimum and maximum values, while chi-square test was used for categorical variables and Student's *t*-test was used for variables with normal distribution. Mann–Whitney U test was performed on continuous variables with non-normal distribution.

Results

During the two months before the COVID-19 pandemic, the total number of cultures requested at our hospital was 3,384, while this number dropped to 2,170 during the pandemic. The number of blood, urine and respiratory cultures requested during the PPP was 1051, 2174 and 159, respectively, which dropped to 956,1106 and 108, respectively, during PP. Among the cultures of blood, urine, and respiration (ETA, BAL, and sputum) samples studied, the most requested was urine culture, and the most frequently isolated agent was *E. coli* (Table 1). The positivity rates in different types of culture samples during the PPP and PP were also examined. In urine and blood cultures, the positivity rate of the causative agents during the PP was significantly higher than in the PPP ($P<0.001$; $P=0.012$ respectively). However, there was no significant difference between the PPP and PP in terms of the positivity rate of the causative agents in the respiratory samples (Table 2).

Table 1: Distribution of causative bacteria in urine, respiratory and blood cultures before and during COVID-19 pandemic periods (n)

Sample type	Date	The numbers of isolated agents							Total culture
		Escherichia coli	*Klebsiella spp.*	*Pseudomonas aeruginosa*	*Acinetobacter baumannii* complex	Other gram negative bacteria	*Staphylococcus aureus*	*Enterococcus spp.*	
Urine	PPP*	206	55	16	-	25	-	27	2174
	PP**	135	44	8	-	15	-	41	1106
ETA-BAL-SPUTUM	PPP	2	16	12	14	6	5	-	159
	PP	4	10	17	4	2	5	-	108
Blood	PPP	14	17	6	5	7	12	24	1051
	PP	6	40	1	5	4	16	37	956
Total	PPP	222	88	34	19	38	17	51	3384
	PP	145	94	26	9	21	21	78	2170

*: Pre-pandemic period, **: Pandemic period

Table 2: Comparison of the numbers of causative agents in pre-pandemic and pandemic periods according to the sample types

Sample type	Pre-pandemic period (%)		Pandemic period (%)		*P*-value
	Positive	Negative	Positive	Negative	
Blood culture	8.1	91.9	11.4	88.6	0.012
ETA-BAL-SPUTUM culture	34.6	65.4	38.9	61.1	0.474
Urine culture	15.1	84.9	22.0	78.0	<0.001

The isolation of *E. coli*, *Acinetobacter baumannii* complex, and other gram-negative bacilli were significantly lower in the PP than in the PPP ($P<0.001$; $P=0.008$; $P=0.002$, respectively). However, *Enterococcus* spp. isolation rate was significantly higher during the PP than in the PPP ($P<0.001$). In other causative agents, there was no significant difference in terms of the isolation rates in both periods ($P>0.05$). Although there was a decrease in extended spectrum beta lactamases and carbapenem resistance in gram-negative bacteria, methicillin resistance in staphylococci, and vancomycin resistance in enterococci in the PP, there was no statistically significant difference between both periods ($P>0.05$) (Table 3).

In our hospital, 5941 (18330 patient days) and 3144 (11789 patient days) patients were hospitalized during the PPP and PP, respectively. When assessed according to the defined daily dose per 1000 inpatient days (DDD/1000 inpatient days), the total consumption of antibiotics was 725.8 DDD/1000 inpatient days in the PPP, and 811.4 DDD/1000 inpatient days during the PP ($P=0.002$). The amount of antibiotics consumed showed that the consumption of cefazolin and colistin was lower ($P<0.001$; $P=0.034$), while meropenem, piperacillin-tazobactam, teicoplanin, and fluroquinolone (ciprofloxacin, levofloxacin, and moxifloxacin) consumption was significantly higher ($P<0.001$; $P=0.016$; $P=0.016$; $P=0.02$; $P<0.001$; $P=0.018$, respectively) in the PP. The consumption of other antibiotics was similar in the two periods. The most consumed antibiotics in our hospital during the period covered in the present study were ceftriaxone, cefazolin, and meropenem (Table 4).

Table 3: Comparison of isolated bacteria and resistance rate in pre-pandemic and pandemic periods

Bacteria and resistance rate*	Pre-pandemic period	Pandemic period	*P*-value
Escherichia coli (n)	222	145	<0.001
- **ESBL (%)	40.5	35.2	
- Carbapenem resistance (%)	7.2	6.2	
Klebsiella spp. (n)	88	94	0.893
- ESBL (%)	68.2	64.9	
- Carbapenem resistance (%)	23.9	18.1	
Pseudomonas aeruginosa (n)	34	26	0.144
- Carbapenem resistance (%)	47.1	34.6	
Acinetobacter baumannii complex (n)	19	9	0.008
- Carbapenem resistance (%)	100	100	
Staphylococcus aureus (n)	17	21	0.359
- Methicillin resistance	17.6	14.3	
Enterococcus spp. (n)	51	78	<0.001
- Vancomycin resistance	2.0	1.3	
Other gram negative bacteria (n)	38	21	0.002
Total	469	394	<0.001

*: There was no significant difference between the two periods in terms of resistance rates, **: Extended spectrum beta-lactamases

Table 4: Antibiotic consumption in pre-pandemic and pandemic periods

Antibiotic lists	Pre-pandemic period *DDD/1000 inpatient-days	Pandemic period DDD/1000 inpatient-days	*P*-value
Colistin	11.7	5.4	**0.034
Imipenem	7.3	6.5	0.695
Ertapenem	6.6	10.4	0.303
Meropenem	65.1	86.4	0.016
Ceftriaxone	199.6	224.6	0.086
Ceftazidime	4.1	3.7	0.690
Cefazolin	148.7	101.9	**<0.001
Ampicillin sulbactam	50.7	43.4	0.243
Piperacillin tazobactam	35.5	63.6	<0.001
Vancomycin	36.5	35.6	0.869
Teicoplanin	5.2	11.6	0.016
Tigecycline	6.7	4.0	0.201
Intravenous Fosfomycin	5.7	6.0	0.657
Ciprofloxacin	33.5	49.1	0.02
Levofloxacin	25.6	53.7	<0.001
Moxifloxacin	43.6	60.0	0.018
Clarithromycin	33.8	34.3	0.863
Amikacin	9.0	11.6	0.355

*DDD: Defined daily dose, ** Significantly lower in the pandemic period

Discussion

In this study, although the number of cultures requested at our hospital laboratory were lower during the PP, the rate of the causative agents isolated in blood and urine cultures were significantly higher. The positivity rate of blood culture varies from 5%–10% in the literature. Positivity rate decreases as a result of performing blood cultures from inappropriate patients at inappropriate times and in non-sterile conditions. Additionally, false positives are also detected as a result of contaminations [5-7]. In our study, the positivity rate in blood culture in the PP (11.4%) was significantly higher compared to that of the PPP (8.1%). When performing blood culture during the PP, paying more attention to sterile conditions and obtaining cultures when really needed can be effective in identifying correct rates. We believe that the increase in the positivity rates of urine culture was because the majority of outpatient clinics were closed in the PP and the samples were usually requested for inpatients.

The present study shows that *A. baumannii* strains, which are important nosocomial agents during the PPP, was significantly lower in the PP. *A. baumannii* is a gram-negative coccobacilli that cause a wide range of hospital-acquired infections in the respiratory tract, urinary system, soft tissues, and wounds. The most important infections caused by *A. baumannii* are ventilator-associated pneumonia and catheter-related bloodstream infection, which have high mortality rates. It has an important role among the causative agents of multidrug-resistant hospital-acquired infections in Turkey [8-10]. While the positivity rate of this bacterium reduced in our hospital during the PP, it was observed that the positivity rate of *K. pneumoniae*, another causative agent of nosocomial infection, insignificantly increased. There was a significant decrease in the detection of *E. coli*, which is probably because it is the most common causative

agent of community-acquired urinary tract infections and that most outpatient clinics were closed.

Another agent with a significant increase in positivity in the PP compared to the PPP was enterococci. Enterococci cause bloodstream and urinary tract infections that often develop in hospital settings, and these bacteria have recently gained increasing importance due to vancomycin resistance [11-13]. In our study, *S. aureus*, one of the other important gram-positive bacteria, also increased, albeit insignificantly, in positivity. In order to limit the spread of gram-positive infections within hospitals, healthcare workers have to comply with the preventive measures of hand hygiene and isolation. In addition, the use of some antiseptics, such as chlorhexidine bath, has been found useful in patient care [14, 15]. We believe that healthcare workers used gloves more often than usual and reduced hand hygiene compliance during the PP. We also believe that using double-layered gloves complicates the hand hygiene compliance. Considering that 80% of the cases hospitalized during the PP were COVID-19, it was thought that 80% of the reproductive agents could indicate secondary bacterial infections developed in COVID-19 cases. Likewise, 80% of the antibiotics consumed in the hospital during the PP may be due to the secondary bacterial infections. In a multicenter study conducted in Turkey, antibiotic consumption was 674.5 DDD/1000 inpatient-days in hospitalized patients [16]. In another multicenter study in Switzerland, antibiotic consumption in hospitalized patients was 46.1 - 54.0 DDD / 100 patient bed-days [17]. In our study, the total consumption of antibiotics was 725.8 DDD/1000 inpatient-days in the PPP, and 811.4 DDD/1000 inpatient-days in the PP. Our data was similar to Turkey-wide data. Teicoplanin and piperacillin-tazobactam used against gram-positive bacteria were consumed in greater quantities during the PP, which we believe may also be associated with increased positivity rate of *Enterococcus* spp. and *S. aureus*. In addition, fluoroquinolone consumption increased during the PP in our hospital. Clinical and radiological findings of patients with SARS, Hantavirus, and other viral pneumonia are similar to atypical pneumonia [18]. Hospitalization and monitoring of atypical pneumonia cases with suspected COVID-19 by administering fluoroquinolones therapy during the PP may be an important reason for this finding. The use of antibiotics is the primary factor in the development of bacterial resistance. Common and extensive use of antibiotics leads to the selection of multidrug-resistant bacteria [19, 20]. In study previously conducted by Guclu et al. [16] it was found that at least one antibiotic was used in one of every two patients hospitalized. Additionally, in the said study, carbapenems, cephalosporins, and quinolones were the most used antibiotics in hospitals. Similarly, the consumption of meropenem, cefazolin and ceftriaxone were highest in the present study. The consumption of cefazolin was significantly lower during the PP. Cefazolin is mostly used as a surgical prophylaxis. Since routine surgery was not performed in PP, cefazolin consumption was low in this period. Also, colistin, which is used in *Acinetobacter* infections, is lower in PP because *Acinetobacter* spp. was lower in the same period. Although insignificant, there was a reduction of the resistance rates in gram-negative bacteria during the PP.

One of the limitations of our study is its monocentric design that covers only a brief period i.e., the months in which the pandemic was highly intense in our province. The other limitation is the lack of enough clinical and demographic features about patients. In fact, it has not been determined how much of the evaluated cultures and consumed antibiotics belonged to COVID-19 patients.

Conclusions

The present study showed that the positivity rates of *A. baumannii* and *E. coli* was lower in the blood, urinary, and respiratory tract cultures while *Enterococcus* spp. was significantly higher during the PP. Since the increase of enterococci, which are among the gram-positive bacteria, may be associated with non-adherence to hand hygiene, it is necessary to pay more attention to hand hygiene during the PP. We believe that the increasing detection of causative agents in contrast to the decreasing number of urine and blood culture positivity rates may be associated with unnecessary culture requests during the PPP. Another important result of the study was the high consumption of fluoroquinolones, piperacillin tazobactam, meropenem and teicoplanin in PP compared to PPP. Although fewer pathogens were detected in the PP compared to the PPP, the total antibiotic consumption was higher. This indicates the excess of secondary bacterial infection in COVID-19 cases or the habit of physicians to use antibiotics. This issue needs to be clarified with further and multi-center studies.

References

1. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018;115(15):E3463-70.
2. Isler B, Keske Ş, Aksoy M, Azap ÖK, Yılmaz M, Yavuz SŞ, et al. Antibiotic overconsumption and resistance in Turkey. Clin Microbiol Infect. 2019;25(6):651-3.
3. Soyletir G, Altinkanat G, Gur D, Altun B, Tunger A, Aydemir S, et al. Results from the Survey of Antibiotic Resistance (SOAR) 2011-13 in Turkey. J Antimicrob Chemother. 2016;71 Suppl 1(Suppl 1):i71-83.
4. Zengin S, Avcı S, Yılmaz S. Clinical and basic cardiovascular features of patients with COVID-19 admitted to a tertiary care center in Turkey. J Surg Med. 2020;4(5):367-70.
5. Roth A, Wiklund AE, Pålsson AS, Melandar EZ, Wullt M, Cronqvist, et al. Reducing blood culture contamination by a simple informational intervention. J Clin Microbiol. 2010;48(12):4552-8.
6. Linsenmeyer K, Gupta K, Strymish JM, Dhanani M, Brecher SM, Breu AC. Culture if spikes? Indications and yield of blood cultures in hospitalized medical patients. J Hosp Med. 2016;11(5):336-40.
7. Shapiro NI, Wolfe RE, Wright SB, Moore R, Bates DW. Who needs a blood culture? A prospectively derived and validated prediction rule. J Emerg Med. 2008;35(3):255-64.
8. Antunes LC, Visca P, Towner KJ. Acinetobacter baumannii: evolution of a global pathogen. Pathog Dis. 2014;71(3):292-301.
9. Dijkshoorn L, Nemec A, Seifert H. An increasing threat in hospitals: multidrug-resistant Acinetobacter baumannii. Nat Rev Microbiol. 2007;5(12):939-51.
10. Boral B, Unaldi Ö, Ergin A, Durmaz R, Eser ÖK; Acinetobacter Study Group. A prospective multicenter study on the evaluation of antimicrobial resistance and molecular epidemiology of multidrug-resistant Acinetobacter baumannii infections in intensive care units with clinical and environmental features. Ann Clin Microbiol Antimicrob. 2019;18(1):19.
11. Kilbas I, Ciftci IH. Antimicrobial resistance of Enterococcus isolates in Turkey: A meta-analysis of current studies. J Glob Antimicrob Resist. 2018;12:26-30.
12. Remschmidt C, Schröder C, Behnke M, Gastmeier P, Geffers C, Kramer TS. Continuous increase of vancomycin resistance in enterococci causing nosocomial infections in Germany - 10 years of surveillance. Antimicrob Resist Infect Control. 2018;7:54.
13. Barros M, Martinelli R, Rocha H. Enterococcal urinary tract infections in a university hospital: clinical studies. Braz J Infect Dis. 2009;13(4):294-6.
14. Siegel JD, Rhinehart E, Jackson M, Chiarello L; Health Care Infection Control Practices Advisory Committee. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Care Settings. Am J Infect Control. 2007;35(10 Suppl 2):65-164.
15. Climo MW, Yokoe DS, Warren DK, Perl TM, Bolon M, Herwaldt LA, et al. Effect of daily chlorhexidine bathing on hospital-acquired infection. N Engl J Med 2013;368(6):533-42.
16. Guclu E, Ogutlu A, Karabay O, Demirdal T, Erayman I, Hosoglu S, et al. Antibiotic consumption in Turkish hospitals; a multi-centre point prevalence study. J Chemother. 2017;29(1):19-24.
17. Plüss-Suard C, Pannatier A, Kronenberg A, Mühlemann K, Zanetti G. Hospital antibiotic consumption in Switzerland: comparison of a multicultural country with Europe. J Hosp Infect. 2011;79(2):166-71.
18. Cunha BA. The atypical pneumonias: clinical diagnosis and importance. Clin Microbiol Infect. 2006;12 Suppl 3:12-24.
19. Olesen SW, Barnett ML, MacFadden DR, Brownstein JS, Diaz S, Lipstich M, et al. The distribution of antibiotic use and its association with antibiotic resistance. Elife. 2018;7:e39435.
20. Harbarth S, Samore MH. Antimicrobial resistance determinants and future control. Emerg Infect Dis. 2005;11(6):794-801.

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(2):128-131.
DOI: 10.28982/josam.877434

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

Comparison of end-effector and exoskeleton devices with robot-assisted gait training in patients with stroke

Aylin Sarı

Department of Physical Medicine and Rehabilitation, Istanbul Erenkoy Physical Treatment and Rehabilitation Hospital, Istanbul, Turkey

ORCID ID of the author(s)
AS: 0000-0002-0391-2940

Abstract

Background/Aim: Loss of gait is the key problem after stroke. Robotic rehabilitation devices, which constitute the new treatment alternatives for stroke, can be divided into two groups on the basis of their design, the exoskeletons and end-effectors. This study aims to investigate the effects of gait training with two different types of robot on rehabilitation outcomes in patients with stroke.

Methods: Twenty-four patients treated for stroke between December 2015 and December 2018 were included in the study. They were randomly divided into two groups for rehabilitation with either the exoskeleton or the end-effector. They attended the robotic rehabilitation programme for five days a week for six weeks, with each session lasting for 40 minutes. They were evaluated in terms of motor stage, ambulation, walking speed and walking capacity at the start and end of the programme.

Results: According to baseline evaluations, there were higher scores in the endpoint evaluations for motor stage, ambulation, 6-minute walking test and lower scores in the endpoint evaluations for 10-meter walking test ($P<0.001$ for all). There was no difference between the two groups in terms of motor phase, ambulation, 6-minute walking or 10-meter walking scores ($P>0.05$ for all).

Conclusion: In patients with stroke, improvements were observed following robot-assisted gait training. No superiority was observed between the end-effector device with the exoskeleton device.

Keywords: Robot-assisted gait training, Stroke, End-effector robot, Exoskeleton robot

Corresponding Author
Aylin Sarı
Erenkoy Physical Treatment and Rehabilitation Hospital Semsettin Gunaltay Avenue Sultan Street No 14 Kadikoy, Istanbul, Turkey
E-mail: mdaylinsari@gmail.com

Ethics Committee Approval
Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee (28.05.15 / 22)
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 February 19

How to cite: Sarı A. Comparison of end-effector and exoskeleton devices with robot-assisted gait training in patients with stroke. J Surg Med. 2021;5(2):128-131.

Introduction

Stroke is the third most common cause of death in the world and a long-term cause of severe disability in adults [1]. It is critical for stroke patients to regain their walking ability in order to cope with their daily life activities and improve their quality of life [2]. One fifth of patients with stroke become wheelchair dependent. In those who do not lose their walking ability, gait speed and capacity are diminished [3]. Gait training is therefore very important in the rehabilitation of stroke patients.

Robot-assisted gait training (RAGT) is an innovative form of rehabilitation that has been increasingly applied in recent years. Robotic systems aim to give the patient maximum benefit from the rehabilitation process by performing high-dose, high-intensity and task-specific movements with the extremities [4].

The support and guidance of the robot enables a patient who could not perform the movement to move independently. According to their mechanical properties and design basis, these robots are divided into two groups, the end-effectors and the exoskeletons [2–5].

The end-effector system works by applying mechanical force from the last connection of the kinematic chain. Since the hip and knee joints are free in the end-effector system, the patient is actively involved in the walking training.

Exoskeleton systems can be either fixed or mobile. Their axes are aligned with the patient's anatomic axes. They provide direct control of the joints and have the ability to activate each part either separately or together by connecting to the extremities from many places [3–5].

The literature contains few clinical studies comparing the two different types of RAGT devices with comparable groups of patients. This study was therefore conducted to compare the results of treatment with the two different types of robotic systems in stroke patients.

Materials and methods

This prospective randomized clinical study was conducted between December 2015 and December 2018 at a Physical Medicine and Rehabilitation Clinic of a Physical Therapy and Rehabilitation Hospital, and a Physical Therapy Center.

The study was performed with 24 patients who were referred with hemiparesis following a first stroke. They were included in the rehabilitation program provided they met the study criteria as described below. Permission was obtained from the hospital management for the study, which was conducted per the “Helsinki Declaration.” Fatih Sultan Mehmet Education and Research Hospital Ethics Committee approved the protocol (Decision no: 2015/22).

Inclusion criteria were being over the age of 18 years, having had a stroke for the first time, requiring treatment due to the stroke, and having gait loss after stroke (functional ambulation category < 4). Exclusion criteria included presence of spasticity in the lower limbs, contractures of the lower limbs, weighing more than 300 pounds (135 kg), cognitive deficits, cardiac disease, traumatic stroke, epilepsy and problems with fitting the patient's body with orthosis of robots.

We used power analysis to determine sample size, which was 12 individuals in each group with a power of 80% at α=0.05. Twenty-four patients who met the inclusion criteria were randomly divided into two groups, and we used the simple randomization method. We enumerated the patients according to their application order, and those with odd numbers in the end-effector group and those with even numbers in the exoskeleton group.

The patients were evaluated at the beginning and at the end of treatment.

End-effector (Lokohelp) consists of an electromechanical device fixed parallel to the walking direction with a harness suspension assembly that supports the body weight as the patient walks on a treadmill. The device provides both passive and active assistance to the foot movement to enable the patient to use the feet as the last link in the kinematic chain. In this device, the knee and hip joints are actively controlled by the patient. The ankles are fixed in a pair of boots attached to the device. The bottom of the boot is rounded (a rocker base) to facilitate the pushing phase of the walk (Figure 1, Lokohelp).

Exoskeleton (Lokomat) is an exoskeletal type of robotic walking device consisting of a harness carrying the body weight, a walking orthosis with brackets holding the legs at three points, a treadmill and a visual feedback support monitor (Figure 2, Lokomat).

Figure 1: Lokohelp

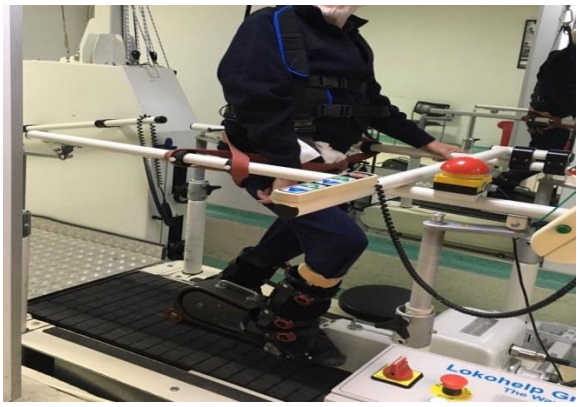
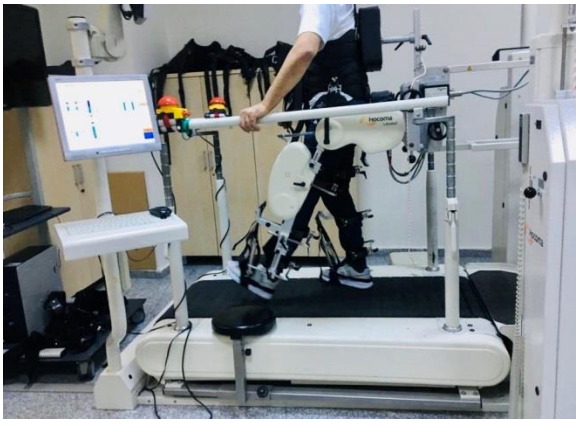


Figure 2: Lokomat



In addition to conventional rehabilitation treatment six days a week, patients in the study attended robotic therapy five days a week for six weeks. The sessions lasted for 40 minutes. In the first session with both devices, the body weight support (BWS) was initiated at fifty percent and then adjusted to the patient's tolerance.

Patients were assessed on a 10-meter walking test, a 6-minute walking test, the Brunnstrom motor staging, and the Functional ambulation category (FAC) at baseline and again at the end of the program. These tests included walking velocity, walking capacity, motor level and ambulation level.

Statistical analysis

The statistical analysis for this study was performed with the Number Cruncher Statistical System (NCSS) 2007 Statistical Software package (Utah, USA). In addition to the descriptive statistics (mean, standard deviation), the distribution of the variables was examined with the Shapiro-Wilk normality test, and the input of variables with a normal distribution was evaluated. The paired t-test was used for output comparisons, the independent t-test for intergroup comparisons, the Wilcoxon test for input-output comparisons of variables that did not show a normal distribution, the Mann Whitney U test for intergroup comparisons, and other quantitative data. The chi-square test was used for a comparison of the qualitative data. The results were evaluated at the significance level of $P<0.05$.

Results

The demographic data for the patients and the descriptive data related to their strokes are shown in Table 1. The rehabilitation results of the Exoskeleton and End-Effector groups are shown in Table 2.

Table 1: Demographic and stroke-related descriptive data

		Exoskeleton group		End-Effector group		*P*-value
Age		62 (11.56)		59.38 (10.11)		0.407
		n	%	n	%	
Sex	Male	4	33.33	5	41.67	0.551
	Female	8	66.67	7	58.33	
Marital status	Married	7	58.33	9	75.00	0.167
	Not married	2	16.66	0	0.0	
	Widow/Divorced	3	25.00	3	25.00	
Time since stroke (days)		110.17 (42.99)		111.21 (42.73)		0.933
Aetiology	Ischemic	8	66.67	8	66.67	1
	Haemorrhage	4	33.33	4	33.33	
Risk Factors	Hypertension	10	83.33	8	66.67	0.086
	Age	5	41.67	5	41.67	1
	Cardiac Disease	8	66.67	7	58.33	0.755
	Hyperlipidaemia	3	25.00	4	33.33	0.525
	Diabetes Mellitus	3	25.00	3	25.00	1
	Smoking	1	8.33	2	16.67	0.383
Hemiplegic side	Left	7	58.33	6	50.00	0.773
	Right	5	41.77	6	50.00	
Dominant Hand	Right	12	100.00	11	91.67	0.551
	Left	0	0.00	1	8.33	

Table 2: Rehabilitation results of the Exoskeleton and End-Effector Groups

		Exoskeleton group	End-Effector group	*P*-value†
Brunnstrom	Baseline	2.21(1.14)	2.25(1.15)	0.900
Motor Assessment	Endpoint	2.5(0.98)	2.75(1.33)	0.461
-Upper Extremity	*P*-value‡	0.016	<0.001	
Brunnstrom	Baseline	2.13(1.42)	2.00(1.18)	0.742
Motor Assessment	Endpoint	2.38(1.35)	2.38(1.28)	0.999
-Hand	*P*-value‡	0.011	0.009	
Brunnstrom	Baseline	2.58(1.06)	2.83(0.82)	0.365
Motor Assessment	Endpoint	3.42(0.88)	3.58(0.78)	0.490
-Lower Extremity	*P*-value‡	<0.001	<0.001	
Functional	Baseline	0.75(1.03)	1.08(0.83)	0.224
Ambulation Category	Endpoint	2.38(1.14)	2.42(0.93)	0.890
	P-value‡	<0.001	<0.001	
6-minute walking test	Baseline	21.92(42.48)	28.04(30.30)	0.568
(meter)	Endpoint	90.17(90.29)	81.50(75.43)	0.720
	P-value‡	<0.001	0.001	
10-meter walking test	Baseline	0.060(0.117)	0.078(0.084)	0.545
(m/s)	Endpoint	0.225(0.250)	0.225(0.210)	0.993
	P-value‡	<0.001	0.001	

‡ Wilcoxon Signed-Rank Test, † Mann Whitney U Test

No significant difference was observed between the Brunnstrom upper extremity, hand and lower extremity baseline and endpoint scores of the Exoskeleton and End-Effector groups ($P>0.05$). The Brunnstrom upper extremity, hand, and lower extremity endpoint scores for both the Exoskeleton group and the End-Effector group were significantly higher than the Brunnstrom upper extremity, hand, and lower extremity baseline scores ($P<0.05$ for all).

The FAC baseline and endpoint averages of the Exoskeleton and End-Effector groups were similar ($P>0.05$), while the FAC endpoint averages for the Exoskeleton and End-Effector groups were significantly higher than the FAC baseline averages ($P<0.001$).

No statistically significant difference was observed between the 6-minute walking test baseline and endpoint averages of the Exoskeleton and End-Effector groups ($P>0.05$). The 6-minute walking test endpoint averages for both the Exoskeleton and End-Effector groups were significantly higher than the 6-minute walking test baseline averages ($P<0.001$).

The 10-meter walking test baseline and endpoint averages of the Exoskeleton and End-Effector groups ($P>0.05$) were similar, while 10-meter walking test endpoint averages for both the Exoskeleton and End-Effector groups were significantly higher than the 10-meter walking test baseline averages ($P<0.001$).

Discussion

Gait recovery is a particularly crucial factor in the independence of the individual after stroke. There are many rehabilitation approaches to gait recovery. Treadmill based RAGT is one such approach [6]. With this treatment, rehabilitation robots of either the end-effector or exoskeleton type can be used. There are findings regarding the contribution of each device to walking capacity, walking velocity, and ambulation in stroke patients. This study was conducted to compare the rehabilitation results in stroke patients when using two distinct types of RAGT device in addition to conventional treatment.

Twenty-four stroke patients were recruited for the study. Both treatments were well tolerated by all patients and proved to be safe. We obtained complete adherence to the protocol as all subjects completed the training sessions without any dropouts. No adverse events were observed.

According to the study results, both groups of patients benefited from the RAGT. It has already been confirmed that treadmill based RAGT is beneficial in the treatment of walking impairment in patients with stroke, improving motor stage, walking velocity, walking capacity and ambulation level [3, 6–7].

When Mehrholz et al. [8] compared two different devices, they showed that there was no significant difference between the two devices in any parameter except walking speed. This important review states that the end-effector devices contribute more to walking speed. However, the fact that most of the patients included in the analysis of the end-effector group were taken from the same study was criticized in the review.

In the review by Bruni et al., the end-effector (Gait Trainer) was more effective than conventional treatment. No difference was found between the control group and the group using the exoskeleton (Lokomat) [9].

Ours is the first study to compare the rehabilitation results of two different treadmill based RAGTs. The study by

Goffredo et al. compared a larger number of different groups. In that study, a treadmill-based end-effector (GE-O system), an over-ground exoskeleton (Ekso™) and conventional treatment were compared. There was no difference between the treadmill-based end-effector and the over-ground exoskeleton, but these two treatments were superior to the conventional treatment alone [10].

Although some studies indicate that conventional treatment is superior to treadmill based RAGT [11], the American Heart Association / American Stroke Association Guidelines describe Class IIb evidence that supports using mechanically assisted walking with body weight support for patients who are non-ambulatory after stroke [12].

Limitations

The main limitation of this was the small number of patients in each group. Another limitation was that training details were selected based on clinical experience.

Conclusion

The biggest advantage of robot-assisted walking support is that it reduces the workload for the therapists and increases the number, duration, and intensity of a patient's sessions. Treadmill based RAGT provides additional benefits to conventional treatment as shown in many areas of improvement, such as motivation, active participation in treatment, improved timing and coordination of motor activity and perception of walking. In patients with stroke, both exoskeleton and end-effector RAGT devices are useful, and neither is superior to the other.

Acknowledgement

The author would like to thank Pendik Physical Therapy Center and Prof. Dr. Bekir Durmuş for supporting the use of Lokomat.

References

1. Adamson J, Beswıck A, Ebrahım S. Is Stroke The Most Common Cause Of Disability? J Stroke Cerebrovasc Dis. 2004;13(4):171-7.
2. Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, et al. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PLoS One. 2014 Feb 4;9(2):e87987.
3. Mehrholz J, Thomas S, Werner C, Kugler J, Pohl M, Elsner B. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2017;May 10:5(5):CD006185.
4. Johnson MJ, Feng X, Johnson LM, Winters JM. Potential of a suite of robot/computer-assisted motivating systems for personalized, home-based, stroke rehabilitation. J Neuroeng Rehabil. 2007;4(1):6.
5. Dzahir MAM, Yamamoto S. Recent trends in lower-limb robotic rehabilitation orthosis: Control scheme and strategy for pneumatic muscle actuated gait trainers. Robotics.2014;3.2:120-48.
6. Veerbeek JM, van Wegen E, van Peppen, Hendriks E, Rietberg M, Kwakkel G. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PloS One. 2014 Feb 4;9(2):e87987. doi: 10.1371/journal.pone.0087987.
7. Molteni F, Gasperini G, Cannaviello G, Guanziroli E. Exoskeleton and end-effector robots for upper and lower limbs rehabilitation: Narrative review. PM&R,2018;10(9):174-88.
8. Mehrholz J, Pohl M. Electromechanical-assisted gait training after stroke: a systematic review comparing end-effector and exoskeleton devices. J Rehabil Med. 2012;44(3):193-9.
9. Bruni MF, Melegari C, De Cola MC, Bramanti A, Bramanti P, Calabrò RS. What does best evidence tell us about robotic gait rehabilitation in stroke patients: a systematic review and meta-analysis. J Clin Neurosci. 2018; 48: 11-17.
10. Goffredo M, Lacovelli C, Russo E, Pournajaf S, Di Blasi C, Galafate, D, et al. Stroke Gait Rehabilitation: A Comparison of End-Effector, Overground Exoskeleton, and Conventional Gait Training. Applied Sciences. 2019;9(13):2627.
11. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell DD, Kahn J H, et al. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23.1:5-13.
12. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47(6):e98-169.

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(2):132-134.
DOI: 10.28982/josam.823728

Research article

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

Do embryo transfer catheters affect pregnancy success?

Elif Ganime Aygün [1], Talat Umut Kutlu Dilek [2]

[1] Acibadem Atakent University Hospital of Obstetrics and Gynecology IVF Center, Istanbul, Turkey
[2] Mehmet Ali Aydınlar Acıbadem University Faculty of Medicine Department of Perinatology, Istanbul, Turkey

ORCID ID of the author(s)
EGA: 0000-0003-3737-7250
TUKD: 0000-0003-4297-3081

Corresponding Author
Elif Ganime Aygün
Acıbadem Üniversitesi Atakent Hastanesi Kadın Hastalıkları Doğum Kliniği ve Tüp Bebek Merkezi, Halkalı Merkez Mah. Turgut Özal Bulvarı No:16, Küçükçekmece, İstanbul, Türkiye
E-mail: gynelifaygun@gmail.com

Ethics Committee Approval
Acıbadem Mehmet Ali Aydınlar University Atakent Hospital ethic committee (date: 12.09.2019, number: ATADEK-2019-14/63). 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 February 19

Abstract

Background/Aim: In-vitro fertilization-embryo transfer requires meticulous technique. To minimize endometrial trauma and perform the procedure as delicately as possible, various catheters are used for embryo transfer. In this study, we aimed to determine whether pregnancy rate is affected by the softness of those catheters. A standard catheter is not preferred in clinics. We wanted to see how pregnancy success would be affected if we made the catheter a constant variable.
Methods: A retrospective cohort study was conducted with the participation of 149 patients in Acibadem University Atakent Hospital IVF Unit. We used Wallace (Smith Medical) semi-rigid catheters and Labotect (Labor-Technik-Göttingen) flexible catheters (divided into two groups). Patients between 28-35 years of age, with infertility without known causes or who had mild male factors and received Gn-RH antagonist treatment protocol were included in this study. Patients with azoospermic partners, tubal factors and severe ovarian failure were excluded.
Results: There were no statistically significant differences between the patients who got pregnant and those who did not in terms of age, basal FSH, duration of infertility, antral follicle count and endometrial thickness before transfer. The pregnancy rates after transfer in the semi-rigid (Group 1) and soft catheter (Group 2) groups were 43,5% and 56,5%, respectively (P=0.108).
Conclusions: In our study, the pregnancy rates were higher in transfers performed with a soft catheter. Soft catheter positively affects pregnancy success. However, it is difficult to say that this alone affects pregnancy success.

Keywords: Catheter, Embryo transfer, Pregnancy rate, Assisted reproductive medicine

How to cite: Aygün EG, Dilek TUK. Do embryo transfer catheters affect pregnancy success? J Surg Med. 2021;5(2):132-134.

Introduction

In-vitro fertilization-embryo transfer (IVF-ET) broke new ground in reproductive medicine, following its first use in 1978. Regarding the IVF-ET process, the most exciting part with the highest expectation is embryo transfer. In practice, embryo transfer is the stage that requires working most tactfully and meticulously [1].

To minimize endometrial trauma and perform the procedure as delicately as possible, various catheters are used for embryo transfer with ultrasonography. During the transfer, the main purpose is not contacting the uterine fundus, so a contraction is not triggered, and the endometrium is not damaged while advancing the catheter [2]. Although embryo transfer is considered the most critical process, the quality of the embryo, endometrial receptivity, and embryo transfer technique all play significant roles in pregnancy success [3]. In the first years of IVF treatments, the zygote was transferred into the fallopian tubes. Live birth occurred in 1983, following the transfer of fertilized sperm and oocyte to the fallopian tube [4]. In 1986, the first zygote from sperm and oocyte were transferred to the fallopian tube after in vitro fertilization. These methods were performed under laparoscopic observation by passing through the cervical canal with the aid of a modified catheter [5]. Although these methods have a more natural course, there are risks associated with anesthesia and laparoscopy [6].

A study evaluated the effects of soft, very soft, and rigid catheters in terms of their effects on the endometrium during a sham embryo transfer. The evaluation was made hysteroscopically, and soft and very soft catheters were observed to cause less trauma [7]. Further studies with catheters have also reported that flexible catheters cause less endometrial trauma [8,9]. For this reason, the ideal embryo transfer is that which reaches the uterine cavity causing the least physical trauma in the endocervix and endometrium. A meta-analysis comparing pregnancy rates between soft and hard catheters revealed a slight difference in clinical pregnancy rates [10].

Despite this meta-analysis result, the dexterity of the operator cannot be neglected. In a study, it was argued that not the softness of the catheter, but the application technique was associated with procedure success, and softer catheters were not superior to others for this reason [11, 12]. The catheter, which is not included in the treatment protocol for a successful procedure, is the most independent variable of IVF programs [13, 14].

In our study, we aimed to compare clinical pregnancy rates in a series of patients with no anatomical factors that would affect procedure success, enough ovarian reserve, and mild male factors, with regards to two diverse types of catheters, used by a single operator.

Materials and methods

The patients who visited Acıbadem Mehmet Ali Aydınlar University Atakent Hospital IVF Clinic (12.09.2019 ethic committee number: ATADEK-2019-14/63) were reviewed according to the below-mentioned inclusion and exclusion criteria, and their consents were obtained. A total of 149 cases were included in the study, which was conducted in accordance with the Helsinki declaration principles. Patients between 28-35 years of age with unknown infertility and mild male factors (except azoospermia) were included in the study. Patients whose partners were diagnosed with azoospermia, those with poor ovarian reserve and tubal factors were excluded. Antagonist protocol was administered to the patients participating in the study. The semi-rigid catheter was used in 74 cases and the soft catheter, in 75 cases. All transfers were made after fresh treatment cycles using 5th day embryos. Clinical pregnancy was considered the primary outcome and defined as the observation of a gestational sac along with the yolk sac or double decidual sac finding in transvaginal ultrasonography.

Embryo transfer technique

With the patient in lithotomy position, the perineum, vulva, and vagina were cleaned with saline solution, after which a sterile cover was placed. The collum was monitored with the speculum and the vagina and collum were cleaned with EBSS (Earle's balanced salt solution, Sigma Aldrich). Then, the cervical mucus was cleaned with cotton tips and the outer sheath of the catheter was brought up to the internal os level under ultrasonographic guidance, and the embryo was delivered to the mid-cavitary region through the inner catheter.

Statistical analysis

Statistical analyses were performed with MedCalc 12.3 (MedCalc Software bvba). FSH levels, antral follicle count, infertility duration, pre-transfer endometrial thickness and clinical pregnancy rates were compared in both groups. Non-normally distributed data were presented as medians and compared with the Mann-Whitney U test. $P<0.05$ was considered statistically significant.

Results

The 5th day embryos were transferred in fresh treatment cycles to 74 patients (divided into two groups) using a semi-rigid catheter (group 1) and to 75 patients, with a soft catheter (group 2). There were no statistically significant differences between the patients who got pregnant and those who did not in terms of age, basal FSH, duration of infertility, antral follicle count and endometrial thickness before the transfer (Table 1). The pregnancy rates after transfer with the semi-rigid (group 1) and soft catheter (group 2) groups were 43.5% and 56.5%, respectively ($P=0.108$) (Table 2).

Table 1: The classification of cases according to clinical pregnancy

	Clinically pregnant (n=97)	Clinically non-pregnant (n=52)	*P*-value*
Age	32 (28-35)	31 (28-35)	0.31
Basal FSH (mIU/ml)	5,5 (3-8)	5 (4-9)	0.95
Duration of Infertility (Years)	3 (1-9)	3 (1,5-25)	0.46
Antral Follicle Count	9 (5-15)	10 (6-15)	0.062
Pre-transfer endometrial thickness (mm)	10 (7-14)	9 (8-14)	0.38

* $P<0.05$ is considered statistically significant.

Table 2: Comparison of pregnancy outcomes in terms of used catheter type

Catheter type	Clinical pregnancy achieved n (%)	Clinical pregnancy not achieved n (%)	*P*-value
Wallace (Group 1)	43 (43.5)	31 (56.5)	0.108
Labotect (Group 2)	54 (56.5)	21 (43.5)	
Total	97 (65.1)	52 (34.9)	

Discussion

The last stage of the IVF-ET process is embryo transfer. The use of a technique that will result in minimal tissue manipulation and endometrial trauma increases the chance of

success. There is evidence in the literature that the usage of soft transfer catheters results in higher pregnancy rates compared to rigid ones [8, 10].

Although it is known that many factors affect pregnancy rate, the catheter that will damage the endometrium the least is preferred. Cook and Wallace catheters were compared, and no difference was observed between pregnancy rates [15, 16].

Apart from the choice of catheter, it has been reported that ultrasound-guided embryo transfer does not cause a difference or adverse effect, but these studies were biased due to their retrospective design. A study by Drakeley [17] reported no difference between groups.

Although the patient's age, embryo quality, hormone profile, and treatment protocol have been standardized in all conducted studies, 9% report no additional information about the experience of the operator who made the transfer. This can lead to serious bias because experience is an important parameter in this process. Steps such as the clinical procedure, recommended treatment protocol and technique are important in terms of standardization of the transfer procedure. Experience and protocol standardization are vital to conduct more qualified studies with better results and increase the success of in vitro fertilization treatment.

In our clinic, we do not use rigid catheters unless we encounter problems with passing through the cervix. Therefore, we wanted to compare the two catheters (semi-rigid and soft) we use most in our clinic and evaluate pregnancy rates. Although there were no statistically significant differences, the clinical pregnancy percentage was higher in soft catheters compared to semi-rigid ones. The standardization of embryo quality, the day of transfer, reason of infertility, and age, all of which may affect clinical pregnancy rates, is the main strength of our study, while its retrospective design and sparse number of cases constitute its main limitations. Although factors such as physician experience, embryo quality, endometrium quality and preparation, and transfer technique are particularly important, preference of a catheter which causes the least trauma is a crucial factor in embryo transfer, which is the last step of in vitro fertilization.

Limitation

The standardization of embryo quality, the day of transfer, reason of infertility, and age, all of which may affect clinical pregnancy rates, is the main strength of our study, while its retrospective design and small number of cases constitute its main limitations.

Acknowledgements

I would like to thank our IVF Coordinator Nurse Ece Nur Büyükçolak for her contribution in gathering the study data.

References

1. Sallam HN. Embryo transfer: factors involved in optimizing the success. Curr Opin Obstet Gynecol. 2005;17:289-98.
2. Buckett WM. A review and meta-analysis of prospective trials comparing different catheters used for embryo transfer. Fertil Steril. 2006;85:728-34.
3. Montag M, Toth B, Strowitzki T. New approaches to embryo selection. Reproductive Biomedicine Online. 2019;27:539-46.
4. Tesarik J, Pilka L, Dvorak M, Travnik P. Oocyte recovery, in vitro insemination and transfer into the oviduct after its microsurgical repair at a single laparotomy. Fertil Steril. 1983;39:472–5.
5. Devroey P, Braeckmans P, Smitz J, Van Waesberghe, L, Wisanto A, Van Steirteghem A, et al. Pregnancy after trans laparoscopic zygote intrafallopian transfer in a patient with sperm antibodies. Lancet. 1986;1:1329.
6. Society for Assisted Reproductive Technology, American Society for Reproductive Medicine. Assisted reproductive technology in the United States: 2001 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology registry. Fertil Steril. 2007;87:1253–66.
7. Poncelet C, Sifer C, Hequet D, Porcher R, Wolf JP, Uzan M, et al. Hysteroscopic evaluation of endocervical and endometrial lesions observed after different procedures of embryo transfer: A prospective comparative study. Eur J Obstet Gynecol Reprod Biol. 2009;147:183–6.
8. Ruhlmann C, Gnocchi DC, Cattaneo AR, Molina LG, Rivadeneira LR, Tessari L, et al. Embryo Transfer Catheters: Softer is Easier. JBRA Assist Reprod. 2015;19:204-9.
9. Omidi M, Halvaei I, Mangoli E, Khalili MA, Razi MH. The effect of embryo catheter loading technique on the live birth rate. Clin Exp Reprod Med. 2015;42:175-80.
10. Abou-Setta AM, Al-Inany HG, Mansour RT, Serour GI, Aboulghar MA. Soft versus firm embryo transfer catheters for assisted reproduction: A systematic review and meta-analysis. Hum Reprod. 2005;20:3114–21.
11. Yao Z, Vansteelandt S, Van Der Elst J, Coetsier T, Dhont M, De Sutter P. The efficacy of the embryo transfer catheter in IVF and ICSI is operator-dependent: A randomized clinical trial. Hum Reprod. 2009;24:880–7.
12. Hearns-Stokes RM, Miller BT, Scott L, Creuss D, Chakraborty PK, Segars JH. Pregnancy rates after embryo transfer depend on the provider at embryo transfer. Fertil Steril. 2000;74:80–6.
13. Kovacs GT. What factors are important for successful embryo transfer after in-vitro fertilization? Hum Reprod. 1999;14:590–2.
14. Salha OH, Lamb VK, Balen AH. A postal survey of embryo transfer practice in the UK. Hum Reprod. 2001;16:686–90.
15. Rhodes TL, Higdon HL 3rd, Boone WR. Comparison of pregnancy rates for two embryo-transfer catheters. Fertil Steril. 2007; 87:411-6.
16. McIlveen M, Lok FD, Pritchard J, Lashen H. Modern embryo transfer catheters and pregnancy outcome: a prospective randomized trial. Fertil Steril. 2005;84:996.
17. Drakeley A, Jorgensen A, Sklavounos J, Aust T, Gazvani R, Williamson P, et al. A randomized controlled clinical trial of 2295 ultrasound-guided embryo transfers. Hum Reprod. 2008;23:1101–6.

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(2):135-139.
DOI: 10.28982/josam.757190

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

Comparison of high aortic arch and other arterial cannulation types in ascending aortic pathologies

Cihan Yücel [1], Nihan Kayalar [1], Serkan Ketenciler [1], Vedat Erentuğ [2]

[1] Department of Cardiovascular Surgery, Okmeydani Research and Training Hospital, Istanbul, Turkey
[2] Department of Cardiovascular Surgery, Mehmet Akif Ersoy Research and Training Hospital, Istanbul, Turkey

ORCID ID of the author(s)
CY: 0000-0002-1941-0873
NY: 0000-0002-1220-7071
SK: 0000-0003-1528-6788
VE: 0000-0002-9686-8933

Corresponding Author
Cihan Yücel
Okmeydanı Eğitim ve Araştırma Hastanesi, Kalp ve Damar Cerrahisi Kliniği, Kaptanpaşa Mahallesi, Darülaceze Caddesi No: 25, 34384, Okmeydanı, Şişli, İstanbul, Türkiye
E-mail: cihanyucell@hotmail.com

Ethics Committee Approval
Bağcılar Training and Research Hospital ethics committee approval was obtained with the number 2012/38.
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 article was presented as an oral presentation at the 13th Turkish Cardiovascular Surgery Congress (30 October-2 November 2014 / Antalya / Turkey).

Published
2021 February 19

Abstract

Background/Aim: Various cannulation techniques are used for different aortic pathologies during aortic surgery. High aortic arch cannulation is an easy technique which does not require a second incision. The aim of this study is to compare high aortic arch cannulation with other arterial cannulation techniques and assess its safety and risks profile.

Methods: This retrospective study included sixty consecutive patients (23 female and 37 male) who underwent elective surgery for ascending aortic aneurysm between July 2011 and June 2014. Patients were divided into Group 1 (aortic arch cannulation) and Group 2 (femoral artery, axillary artery, innominate artery cannulations) according to the location of arterial cannulation. Preoperative, operative, and postoperative data of patients with or without arch cannulation were compared.

Results: Ascending aorta was replaced with a graft in all patients. High aortic arch cannulation was performed in thirty-eight patients (63.3%) while the cannulation site was axillary artery in 9 (15%), femoral artery in 8 (13.3%) and innominate artery in 5 (8.3%) patients. There were no differences between the two groups in terms of preoperative demographic factors, concomitant cardiac pathologies, additional surgical procedures, and intraoperative parameters ($P>0.05$). Moreover, there was no difference between postoperative complications with the one exception of complications related to the cannulation site which was significantly more frequent in cannulation techniques other than arch cannulation ($P=0.04$). We observed no complications related to the cannulation site in patients with arch cannulation.

Conclusion: Our study showed that high aortic arch cannulation in patients with ascending aortic aneurysms is an easy, fast, and safe technique with low complication rates. It can be the technique of first choice for those with ascending aortic aneurysms limited to ascending aorta with no place for cannulation, cross clamp and anastomosis but still can be repaired with single cross-clamping without total circulatory arrest.

Keywords: Cannulation, Aortic arch, Ascending aorta

How to cite: Yücel C, Kayalar N, Ketenciler S, Erentuğ V. Comparison of high aortic arch and other arterial cannulation types in ascending aortic pathologies. J Surg Med. 2021;5(2):135-139.

Introduction

The arterial cannulation site for cardiopulmonary bypass is determined in accordance with the type of operation and the quality of aortic wall. The usual site for arterial cannulation is the ascending aorta in most cardiac operations [1] and intrapericardial aorta is used due to its relative resistance to tear and dissection. Although this technique is easy, safe and does not require an extra incision [2], peripheral arterial cannulation may be necessary in emergency cases, redo surgeries, aortic surgeries, minimal invasive and robotic surgeries and in cases where central cannulation is not possible. In patients with aortic aneurysms, calcification and atherosclerosis found proximal to innominate artery, arch cannulation may be an alternative to peripheral cannulation in selected cases.

In the current study, we evaluated the safety and indications for aortic arch cannulation in patients undergoing surgery for proximal aortic aneurysms.

Materials and methods

A total of sixty consecutive patients, who presented to our hospital between July 2011 and June 2014 and underwent elective operations due to ascending aortic aneurysm were included in the study. After obtaining the approval of the local ethical committee of Bagcilar Training and Research Hospital (02.07.2012/38), the patients were informed thoroughly, after which they were asked to sign the informed consent forms, so their approvals were obtained.

Only patients operated for aortic aneurysms were included in the study. Those who underwent surgery for aortic dissection, patients who required arch cannulation during other cardiac operations due to reasons such as ascending aortic calcification or reoperation were excluded to create a homogenous group.

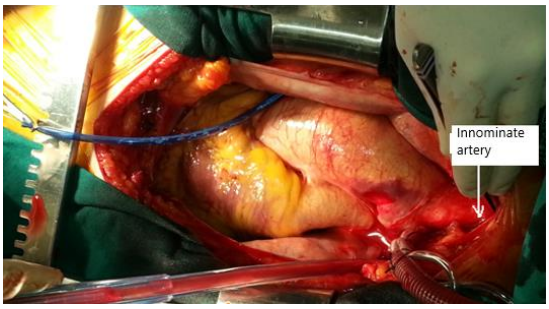
All patients underwent an evaluation with thorax CT angiography before the operation and patients aged 40 years and above underwent coronary angiography. Demographic characteristics of the cases and routine biochemical examinations before and after the surgery were recorded. In addition, ejection fraction was noted. Data about the surgical procedure, parameters of the early postoperative period, mortalities and morbidities were recorded.

Patients were divided into two groups according to the location of arterial cannulation. They were defined as Group 1 (aortic arch cannulation) and Group 2 (femoral artery, axillary artery, innominate artery cannulations). Results were evaluated through statistical analysis and advantages and disadvantages of aortic arch arterial cannulation to other cannulation types of cannulation were assessed.

Surgical technique

After general anesthesia and intubation, standard median sternotomy was performed, and cardiopulmonary bypass (CPB) was instituted by cannulating either the aortic arch or one of the other sites. The site of arterial cannulation (axillary, innominate and femoral arteries, or aortic arch) was determined according to the extension of the aortic pathology. For patients who would undergo hemi-arcus or aortic arch replacement, antegrade cerebral perfusion was planned during total circulatory arrest, and axillary cannulation was performed in all these patients. In those patients with the extension of ascending aortic aneurysm to the proximal of innominate artery, where there is no space for both aortic clamp and cannulation, we performed arch cannulation and no circulatory arrest (Figure 1). The aortic clamp was placed below innominate artery and angled to cover part of the arch by the extent of the aneurysm.

Figure 1: Arch cannulation



Statistical analysis

Preoperative, perioperative, and postoperative data of the patients were saved on a Microsoft Excel 2003® database. Statistical analyses were performed using SPSS 16.0 for Windows R (SPSS Inc., Chicago, III) software. In addition to descriptive statistical methods (mean (standard deviation) for continuous variables, percentages for categorical variables), data were evaluated using independent t-test for comparing binary groups, and chi-square and Fisher reliability tests for the comparison of qualitative data. The level of significance was $P<0.05$.

Results

Preoperative data

The mean age of all patients was 62.15 (11.09) years and most were male (61.7%). The most frequent concomitant disease was hypertension (66.7%).

In forty patients (66.6%), there was only ascending aortic aneurysm, six patients (10%) had ascending aortic and hemi-arcus aneurysms, two (3.3%) had ascending aorta and aortic arch aneurysms, and twelve patients (20%) had ascending aorta and aortic root aneurysms. Thirty-eight patients (63.3%) with aortic arch cannulation were included in Group 1 while the remaining twenty-two patients (36.7%) with femoral artery, axillary artery or innominate artery cannulations were included in Group 2. Both groups were compared, and no differences were observed in terms of preoperative comorbid diseases (Table 1).

Table 1: Preoperative data

	Group 1	Group 2	*P*-value
Age (year)	62.7 (10.8)	61.1(11.7)	0.61
EF (%)	55.2 (8.5)	57.2(5.9)	0.32
Preop creatinine	0.9 (0.2)	0.9(0.2)	0.69
NYHA	2.05 (0.56)	2.09(0.52)	0.79
Sex, n (%)			
Male	23 (60.5%)	14 (63.6%)	0.81
Female	15 (39.5%)	8 (36.4%)	
BMI (kg/m2)	28.1 (4.6)	27.5(4.2)	0.61
Hypertension, n (%)	24 (63.2%)	16(72.7%)	0.44
CVD, n (%)	2 (5.3%)	1 (4.5%)	1.00
Carotid stenosis, n (%)	0	2 (9.1%)	0.13
COPD, n (%)	7 (18.4%)	5 (22.7%)	0.74
Diabetes Mellitus, n (%)	12 (31.6%)	4 (18.2%)	0.25
CRF, n (%)	5 (13.2%)	3 (13.6%)	1.00
Smoker, n (%)	18 (47.4%)	9 (40.9%)	0.62
Hypercholesterolemia, n(%)	18 (47.4%)	9 (40.9%)	0.62
PAD, n (%)	0	1 (4.5%)	0.36
Myocardial infarction	4 (10.5%)	1 (4.5%)	0.64

EF: Ejection fraction, BMI: body mass index, CVD: cerebro vascular disease, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, PAD: peripheral arterial disease, NYHA: New York Heart Association.

Operative data

The surgical procedure differed according to the extension of the aneurysm and the presence of additional diseases. Concomitant procedures included coronary artery bypass grafting in thirty patients (50 %), aortic valve replacement in thirty-two patients (53.3 %) and mitral repair in one patient (1.7 %). There was no difference between the two groups in terms of concomitant diseases and procedure. Concomitant diseases and the procedures performed are presented in Table 2.

Table 2: Additional cardiac diseases and operation procedures

	n	%
Coronary artery disease	30	50%
Aortic stenosis	9	15%
Aortic regurgitation	23	38.3%
Mitral regurgitation	3	5%
Reoperation	2	3.3%
AAR	12	20%
AAR+CABG	13	21.6%
AAR+AVR	9	15%
AAR+AVR+CABG	7	11.7%
Bentall	5	8.3%
Bentall+CABG	4	6.7%
AAR+Hemiarch	2	3.3%
AAR+Hemiarch+CABG	2	3.3%
Bentall+MC+CABG	1	1.7%
Bentall+Hemiarch+CABG	1	1.7%
Bentall+Hemiarch	1	1.7%
AAR+Arch+CABG	1	1.7%
Bentall+MVR+ DVTA +Ablation	1	1.7%
Bentall+ mitral ring annuloplasty	1	1.7%
AAR+Arch+AVR+CABG	1	1.7%
AAR+AVR+MVR	1	1.7%

AAR: Ascending Aorta Replacement, AVR: Aortic Valve Replacement, CABG: Coronary Artery Bypass Grafting, MC: Mitral Commissurotomy, MVR: Mitral Valve Replacement, DVTA: DeVega tricuspid annuloplasty

Innominate artery cannulation was performed in 9 (15%) patients and axillary artery cannulation with a side graft was performed in 5 (8.3%). Aortic arch cannulation was the preferred cannulation site in thirty-eight patients (63.3%). We performed femoral artery cannulations in eight patients (13.3%) by placing the cannula directly into the artery. The mean durations of cross-clamp and total perfusion were 106.5(46.7) and 151.83(72.7) minutes, respectively. There was no difference in terms of cross-clamp (P=0.768) and perfusion durations (P=0.311) between two patient groups.

Postoperative data

No difference was observed between the two groups in terms of durations of stay in the intensive care (P=0.163) and in the hospital (P=0.504). The amount of postoperative drainage was insignificantly higher in the arch cannulation group (P=0.433), and the need for erythrocyte suspension (unit) transfusion similar between the two groups (P=0.454) (Table 3).

Renal dysfunction was a frequent complication after the operation which occurred in sixteen patients (26.7%), four of which required temporary hemodialysis (Table 4). A total of six patients required re-exploration for postoperative bleeding and four of these patients had symptoms of cardiac tamponade. All these patients were in the aortic arch cannulation group; however, bleeding was not related to the aortic arch cannulation site in any of these patients.

Table 3: Comparison of postoperative parameters and complications

	Group 1	Group 2	P-value
ICU stay (day)	5.08(3.80)	7.23(7.23)	0.16
Hospital stay (day)	11.82(13.02)	14.14(12.65)	0.50
Total bleeding (cc)	877.63(547.1)	769.55(440.96)	0.43
ICU Erythrocyte suspension (unit)	1.84(1.48)	2.18(1.99)	0.45
ICU Fresh frozen plasma (unit)	1.89(2.44)	2.77(2.56)	0.19
ICU Whole blood (unit)	1.05(1.50)	1.00(0.81)	0.88
Complications	0	3 (13.6%)	0.04
Cardiac tamponade	3(7.9%)	1 (4.5%)	1.00
Respiratory failure	7(18.4%)	5 (22.7%)	0.74
Bleeding revision	6(15.8%)	0	0.07
Renal failure	10(26.3%)	6 (27.3%)	0.93
Dialysis	2 (5.3 %)	2 (9.1%)	0.61
Stroke	1(2.6%)	1 (4.5%)	1.00
Mortality	4 (10.5%)	2 (9.1%)	1.00

ICU: Intensive care unit

Table 4: Postoperative complications

	n (%)
Renal failure	16 (26.7%)
Postop dialysis	4 (6.7%)
Respiratory failure	12(20.0%)
Re-intubation	6 (10.0%)
Bleeding revision	6(10.0%)
Cardiac tamponade	4 (6.7%)
Pleural Effusion	4 (6.7%)
Pneumothorax	3 (5.0%)
Cerebral emboli	2(3.3%)

Complications related to the site of cannulation were brachial plexus injury in one patient (1.7%), axillary artery dissection in one patient (1.7%) and axillary artery laceration in one patient. In the latter two patients, the cannulated artery was repaired with a PTFE graft. There were no infections at the site of the cannulation in any patients. Thrombosis and distal embolism were not observed in the cannulated arteries and no ischemia developed in the extremities. No complications were seen in any of the patients with arch cannulation such as aortic dissection or aortic laceration that required treatment. In terms of postoperative complications, a significant difference was detected only in complications related to the site of the cannulation (P=0.04).

Mortality rate was 5.0% with 3 patients (P=1.00) (Table 3). One of these as were lost due to sepsis and two died of multiorgan failure within 30 days of operation.

Discussion

Different cannulation techniques can be used in different aortic pathologies and each technique has both advantages and disadvantages. In the presence of an ascending aortic aneurysm, arterial cannulation may be performed through high aortic arch, femoral artery, axillary artery, or innominate artery. The aortic arch cannulation technique that we use in ascending aortic aneurysms has several advantages compared to other techniques such as ease of access in many cases, no requirement for a second incision and more options for the size of the cannula to be used [3, 4].

Femoral cannulation is associated with various complications including tearing, dissection and delayed stenosis of the artery and infection, embolism, and ischemia of the extremities [5, 6]. One of the most severe complications of femoral arterial cannulation is the arterial dissection, which could cause retroperitoneal bleeding or retrograde extension to the proximal aorta. The incidence of this complication is low and was reported as between 0.02% and 1.3% [7, 8]. However, once developed, this may result in severe morbidity and mortality.

Another significant complication associated with femoral artery cannulation is the increased risk of stroke with retrograde flow. In comprehensive studies where femoral

cannulation was used, the stroke rate was between 0-11% [9]. On the other hand, Strauch et al. [10] reported the incidence of stroke as 4.6% in 284 ascending and aortic arch replacement cases where antegrade flow was provided through axillary cannulation. We did not observe any of these complications in patients who underwent femoral artery cannulation in our patient group. This is mainly because femoral artery cannulation was performed only in eight patients (13.3%) and these patients were selected after careful examination of CT angiograms for calcifications of the aorta and peripheral arterial disease.

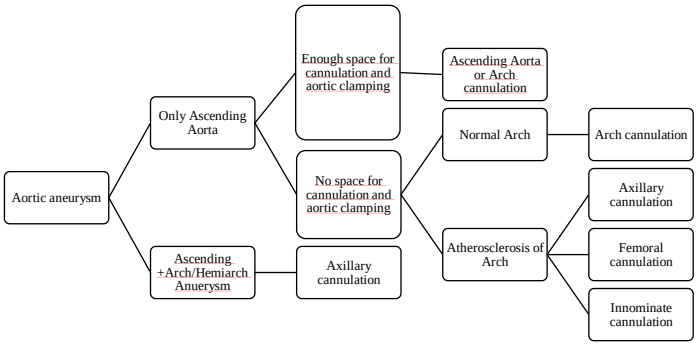
Axillary artery cannulation has certain advantages to femoral artery such as the low probability of atherosclerosis, good collateral flow, reduced risk of ischemic and embolic cerebral events and less frequent complications related to the cannulation site. Injuries in the nerves of the arm and axillary artery thrombosis have been reported as important complications of this technique [11]. One of our patients experienced injuries in the nerves of the arm and one patient experienced axillary artery thrombosis. It is believed that certain complications related to the axillary artery cannulation could be reduced by using a side graft and the data in the literature supports that. In their study on 399 axillary artery cannulations, Sabik et al. [12] found the cannulation-related morbidity as 7% in the direct group and 2% in the side graft group and suggested that axillary cannulation should be performed with a side graft. Svensson et al. [13] found that the risk of stroke was reduced only in the axillary artery cannulations with a side graft in their study on 1336 cases, in which hypothermic circulatory arrest was used. We performed axillary artery cannulation with a side graft in all patients and observed complications related to the cannulation site in 2 patients. These complications were related to the traction of the artery during mobilization.

The cannulation of the aortic arch has the advantages of axillary cannulation such as antegrade cerebral flow and minimal risk of cerebral embolism while avoiding its complications. It is noteworthy that no complications were observed regarding the site of the aortic arch cannulation in our study. We can consider aortic arch cannulation a significant alternative due to the ease of application and negligible risk of complications, particularly for patients who do not require total circulatory arrest and do not have sufficient space for both cross clamping and anastomosis in the ascending aorta. By using aortic arch cannulation in these patients, both a second incision and the complications of femoral and axillary artery cannulations can be avoided. Even though the axillary artery is an appropriate choice in these patients, exploration is difficult in patients with obesity and chest deformities, and it requires a second incision.

In addition to these significant advantages, aortic arch cannulation also has certain disadvantages. Aortic dissection or tearing are especially important complications and since cannulation cannot be performed on the intrapericardial aorta, they may be expected to occur at higher rates. However, we have never experienced that with our patients. We believe that a meticulous surgical technique, optimization of the arterial pressure during the placement of the cannula and using pledgetted suture for purse stitches in selected patients could prevent these complications to a great extent. We prefer the use of pledgetted stitches particularly in the elderly patients and those with thin aortic walls and in redo cases. Other complications are similar to that of the ascending aorta cannulation and include intramural placement, dislocation of atheroembolism, air embolism, continued bleeding around the cannula or after the removal of the cannula, and abnormal cerebral perfusion. Theoretically, the risk of the malperfusion of aortic branches is higher compared to the other types of cannulation. However, careful placement of cannula with attention to the direction of its tip prevents this complication. We observed cerebrovascular complication in one patient with axillary cannulation and one patient with arch cannulation which was not related to displacement of cannula.

Our study showed that the aortic arch cannulation is a safe procedure and is an alternative to axillary artery cannulation in selected patients. We developed an algorithm for the selection of cannulation site in patients with ascending aortic aneurysms as shown in Figure 2. Aortic arch cannulation should be considered primarily in patients with aneurysms without insufficient space for both aortic cannulation and anastomosis and normal arch.

Figure 2: Cannulation algorithm



Limitations

This was a single-institution retrospective study, not a randomized trial. Nevertheless, we consider that the aim of this study was accomplished since we demonstrated the safety of a cannulation technique that is usually avoided due to concerns for complications. We also set a clear algorithm for choice of cannulation site. This study cohort was relatively small and future studies with higher patient numbers may help to provide a better insight for probable complications and comparison with other cannulation techniques.

Conclusions

Aortic arch cannulation is an easy, quick, and reliable technique with low complication rates in patients with ascending aortic aneurysms. It can be considered as the first choice in cases where the aneurysm is limited to the ascending aorta but there is insufficient space for cannulation, cross clamping, and anastomosis. The careful placement of an aortic clamp may prevent the use of circulatory arrest in many cases. This technique also avoids a second incision and complications related to axillary and femoral cannulations.

References

1. McAlpine WA, Selman MW, Kawakami T. Routine use of aortic cannulation in open heart operations. Am J Surg. 1967;114:831–4.
2. Davidson KG. Cannulation for cardiopulmonary bypass. In: Taylor KM ed. Cardiopulmonary bypass: principles and management . Baltimore: Williams &Wilkins, 1987.pp.55–89.
3. Salerno TA, Lince DP, White DN, Lynn R, Charrette EJP. Arch versus femoral artery perfusion during cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1978;78:681–4.
4. Merin O, Silberman S, Brauner R, Munk Y, Shapira N, Falkowski G, et al. Femoro-femoral bypass for repeat open-heart surgery. Perfusion 1998;13:455–9.
5. Hendrickson SC, Glower DD. A method for perfusion of the leg during cardiopulmonary bypass via femoral cannulation. Ann Thorac Surg. 1998;65:1807–8.

6. Greason KL, Hemp JR, Maxwell JM, Fetter JE, Moreno-Cabral RJ. Prevention of distal leg ischemia during cardiopulmonary support via femoral cannulation. Ann Thorac Surg. 1995;60:209–10.
7. Bigutay AM, Garamella JJ, Danyluk M, Remucal HC. Retrograde aortic dissection occurring during cardiopulmonary bypass. JAMA. 1976;236:465–8.
8. Jones TW, Vetto RR, Winterscheid LC, Dıllard DH, Merendıno KA. Arterial complications incident to cannulation in open-heart surgery. Ann Surg. 1960;152:969–74.
9. Svensson LG, Crawford ES, Hess KR, Coselli JS, Raskin S, Shenaq SA, et al. Deep hypothermia with circulatory arrest. Determinants of stroke and early mortality in 656 patients. J Thorac Cardiovasc Surg. 1993;106:19-28.
10. Strauch JT, Spielvogel D, Lauten A, Lansman SL, McMurtry K, Bodian CA, et al. Axillary artery cannulation: routine use in ascending aorta and aortic arch replacement. Ann Thorac Surg. 2004;78:103-8.
11. Bichell DP, Balaguer JM, Aranki SF, Couper GS, Adams DH, Rizzo RJ, et al. Axilloaxillary cardiopulmonary bypass: A practical alternative to femorofemoral bypass. Ann Thorac Surg. 1997;64:702–5.
12. Sabik JF, Nemeh H, Lytle BW, Blackstone EH, Gillinov AM, Rajeswaran J, et al. Cannulation of the axillary artery with a side graft reduces morbidity. Ann Thorac Surg. 2004;77:1315-20.
13. Kucuker SA, Ozatik MA, Saritas A, Tasdemir O. Arch repair with unilateral antegrade cerebral perfusion. Eur J Cardiothorac Surg. 2005;27:638-43.

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(2):140-143.
DOI: 10.28982/josam.833593

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

Assessment of serum TWEAK levels in patients with familial Mediterranean fever

Gökhan Yavuzbilge [1], Muhammed Okuyucu [2], Yeşim Civil [3], Serkan Günaydın [1], Bahattin Avcı [3]

[1] Department of Rheumatology, Medical Faculty, Ondokuz Mayis University, Samsun, Turkey
[2] Department of Internal Medicine, Medical Faculty, Ondokuz Mayis University, Samsun, Turkey
[3] Department of Biochemistry, Medical Faculty, Ondokuz Mayis University, Samsun, Turkey

ORCID ID of the author(s)

GY: 0000-0002-8879-8859
MO: 0000-0002-6026-2024
YC: 0000-0002-9662-244X
SG: 0000-0002-1131-2531
BA: 0000-0001-6471-6495

Corresponding Author
Gokhan Yavuzbilge
Ondokuz Mayis University, Medical Faculty, Department of Rheumatology, Korfez Mahallesi, Ondokuz Mayis University, 55270, Atakum, Samsun, Turkey
E-mail: gokhany_89@hotmail.com

Ethics Committee Approval
The study protocol was approved by Ondokuz Mayis University ethics committee (OMU-KAEK, 1.11.2020, approval no. 2020/669). 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 February 19

Abstract

Background/Aim: Mediterranean fever is an autoinflammatory disease characterized by recurrent attacks. Tumor necrosis factor (TNF) - like weak inducer of apoptosis (TWEAK) is a member of the TNF ligand family, and it has been reported to contribute significantly to the initiation of many inflammatory and immunological processes. In previous studies, an increasing amount of evidence has implicated the participation of TWEAK / Fn14 pathway in the pathogenesis of rheumatic inflammatory diseases that include rheumatoid arthritis, systemic lupus erythematosus and Behçet's disease. The aim of this study was to investigate the serum TWEAK levels of patients with Familial Mediterranean fever (FMF) and its possible relationship with inflammatory markers and disease activity.

Methods: Our study included 20 patients with FMF and 19 healthy volunteers. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) were measured, and PRAS disease severity score was determined in patients with FMF. Also, the FMF attack period was questioned. Serum TWEAK levels were measured with available commercial Enzyme Linked Immunosorbent Assay kits.

Results: There was no significant difference in terms of age and gender between the FMF group and the healthy control group ($P>0.05$, for all). ESR, CRP and serum TWEAK levels were significantly higher in patients with FMF ($P<0.001$ for all). PRAS score in FMF patients was 3.4. Serum TWEAK level was not correlated with ESR (r=-0.042, $P=0.0801$), CRP (r=-0.017 $P=0.921$), or PRAS score (r=0.247, $P=0.149$). The ESR and CRP levels of patients in FMF attack period were significantly higher compared to attack free period ($P<0.001$ for both) whereas there was no significant difference in serum TWEAK levels ($P=0.686$).

Conclusions: Serum TWEAK levels are increased in FMF disease with attacks. However, this increase is not associated with increased ESR and CRP during FMF attacks. These results indicate that the TWEAK / Fn14 pathway plays a role in earlier stages where the inflammatory pathways have not differentiated yet. Serum TWEAK levels appear to be more successful in reflecting a lower degree of inflammation compared to ESR and CRP.

Keywords: TWEAK, Familial Mediterranean fever, Inflammation, Biomarker

How to cite: Yavuzbilge G, Okuyucu M, Civil Y, Günaydın S, Avcı B. Assessment of serum TWEAK levels in patients with familial Mediterranean fever. J Surg Med. 2021;5(2):140-143.

Introduction

Familial Mediterranean fever (FMF) is the most common autoinflammatory disorder in the world [1, 2]. It is an autosomal recessive disease that is caused by the MEFV (MEditerranean FeVer) gene and manifests itself as recurrent attacks of fever and short-lived inflammation in the serosal membranes, joints and skin [1, 3]. It is more common among Turks, Arabs, Sephardic Jews and Armenians living in the Mediterranean region [1]. Like other autoinflammatory diseases, it is characterized by abnormalities in the innate immune system.

Before the discovery of the MEFV gene, it was commonly known that FMF attacks were caused by an increase in polymorphonuclear leukocytes in serosal membranes, joints and some areas of the skin. After the discovery of the MEFV gene, research focused on the potential role of pyrin protein in FMF. Pyrin, released from neutrophils and monocytes, has a significant role in the initiation of inflammation and the activation of potent pyrogenic cytokine interleukin (IL) -1ß [4, 5]. It is involved in the activation of caspase-1 which is a structural part of the inflammasome complex and the release of active IL-1. Pyrin activity occurs at the level of the cytoskeletal assembly [6, 7]. In FMF patients, specific microtubule assembly inhibitors prevent pyrin-mediated caspase-1 activation and secretion of IL-1 in peripheral blood mononuclear cells.

Tumor necrosis factor (TNF) - like weak inducer of apoptosis (TWEAK) is a member of the TNF ligand family and first synthesized as a 249 amino acid transmembrane protein [8]. Although it was initially defined as an apoptosis stimulant [9], it was shown in later studies that it is involved in many inflammatory and immunological processes [10, 11]. TWEAK binds to its only known receptor, fibroblast growth factor-inducible 14 (Fn14), and increased TWEAK levels due to inflammation stimulate the release of cytokines such as TNF- α, IL-1, IL-6, granulocyte-colony stimulating factor (G-CSF), and interferon-γ monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP-1α), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) [12-14]. The main source of soluble TWEAK in inflammatory tissue is macrophages / monocytes [15]. These data show that the TWEAK / Fn14 pathway makes significant contributions to inflammation in tissues and indicates that excessive or persistent upregulation of this pathway contributes significantly to the pathogenesis of some rheumatic inflammatory and infective diseases [16-20].

Behçet's disease is also considered an autoinflammatory disease and common in our country [21]. The fact that anti-TNF treatments are useful in the treatment of Behçet's disease and the results of a previous study suggest that the TWEAK pathway also plays a role in the pathogenesis of Behçet's disease [22]. From this point of view, in this study, we aimed to investigate the serum TWEAK levels and its possible relationship with disease activity in FMF.

Materials and methods

Healthy and patient volunteers

Patients with FMF (n=40) and healthy volunteers (n=38) who visited our rheumatology outpatient clinic between May 1-31, 2020 were included in our study. The study protocol was approved by the local ethics committee. FMF diagnosis was made on the basis of the Tel-Hashomer or Livneh diagnostic criteria [23]. The disease severity score was determined with the PRAS score in FMF patients. Gender, age, anamnesis, physical examination findings, laboratory data, comorbidities, and smoking history were recorded for all participants. Individuals with active infection, a diagnosis of malignancy, chronic lung, kidney or liver disease, and heart failure were excluded from the study.

Laboratory analysis

Serums obtained by centrifuging blood samples (Shimadzu UV160A, S.No: 28006648, Japan) at 3000 rpm for 10 minutes were stored at -80ºC. On the day of analysis, samples were dissolved at room temperature. All analysis was performed according to the manufacturer's instructions. Samples showing high concentration were diluted and measured twice.

TWEAK concentrations in serum were measured using the commercially available Enzyme Linked Immunosorbent Assay (ELISA) kit (Human Tumour Necrosis Factor Related Weak Inducer of Apoptosis, Cat. No. E1820Hu, Bioassay Technology Laboratory, Shangai, China). Enzymatic reactions were measured in an automatic microplate photometer. TWEAK levels were determined by comparing the optical density of the samples with the standard curve. The mean within-test and within-test percentage coefficients of variation for TWEAK were <10% and <8%, respectively. When determining serum TWEAK levels, all ELISA kit studies were carried out in accordance with the manufacturer's instructions. The expected values of the test were 10-4000 mg / L.

Statistical analysis

A sample size of 35 persons per group was calculated based on a power of 85% and a P value of 0.05 (G*power 3.1). The Statistical Package for the Social Sciences (SPSS 11.0, Chicago, IL, USA) was used for the statistical analysis of all data. The results were expressed with mean (standard deviation (SD)). One-way analysis of variance (ANOVA) followed by Tukey's post hoc test were used to determine the statistical differences among the groups. The categorical variables were compared with the chi-square test. The Pearson correlation coefficient was used for correlation analysis. Analysis of covariance (ANCOVA) was also used in order to modify the variables for age, gender, and BMI. Values of $P<0.05$ were considered statistically significant.

Results

The demographic and laboratory data of FMF patients and healthy volunteers are summarized in Table 1.

Table 1: Demographics and laboratory data in the study groups

	Healthy Controls (n:38)	FMF (n:40)	*P*-value
Age (years)	32.5 (10.71)	31.85 (10.64)	0.857
Gender (F/M)	21/17	20/20	0.762
BMI (kg/m^2)	23.5 (3.4)	24.7 (5.2)	0.072
ESR (mm/h)	3.38 (1.01)	29.8 (17.7)	<0.001
CRP (mg/l)	3.5 (0.8)	5.6 (7.5)	<0.001
TWEAK (ng/ml)	55 (52)	1313 (756)	<0.001

FMF: Familial Mediterranean fever BMI: Body mass index, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, TWEAK: Tumor necrosis factor-like weak inducer of apoptosis

There was no significant difference between the two groups in terms of age and gender. ESR, CRP and serum

TWEAK levels were significantly higher in the FMF patients (P<0.001).

It was determined that gender, obesity, hypertension, atherosclerosis, diabetes mellitus and smoking had no effect on serum TWEAK levels in FMF group (for all P> 0.05).

PRAS score in FMF patients was 7.6 (2.3). There was no correlation between age (r=-0.128, P=0.430), ESR (r=-0.042, P=0.0801), CRP (r=-0.017 P=0.921), PRAS (r=0.247, P=0.149) score and serum TWEAK levels. The ESR (59.9 (25.6) & 24.9 (15.6), P<0.001) and CRP (47.2 (23.1) & 2.6 (2.6), P<0.001) levels of patients in FMF attack period were significantly higher compared to the attack free period while there was no significant difference in serum TWEAK levels (1303 (817) & 1351 (845) ng/ml, P=0.686).

Discussion

In this study, it was investigated whether the TWEAK/Fn 14 pathway was also activated in FMF disease since it had a significant role in the etiopathogenesis of some rheumatic inflammatory diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and Behçet's disease. Serum TWEAK levels were significantly higher in FMF patients compared to healthy volunteers. However, serum TWEAK levels were not associated with ESR, CRP and disease severity score in FMF patients. Moreover, serum TWEAK levels were similar during the attack and attack-free period.

In a study conducted to investigate the possible role of the TWEAK / Fn14 pathway in the pathogenesis of RA, it was found that the expression and serum levels of TWEAK increased in the synovial tissue, synovial fluid and serum of patients with RA [24]. In an experimental model of RA, anti-tweak monoclonal antibodies were observed to provide significant reductions in disease inflammation, joint inflammation, angiogenesis, cartilage and bone loss [25]. There was significant decrease in serum TWEAK levels and inflammatory markers at the end of the 1st month due to anti-TWEAK monoclonal antibodies in a phase 1 study conducted in RA [26]. To best of our knowledge, our study is the first investigating the serum TWEAK levels in FMF patients. The TWEAK / Fn14 pathway, which has been shown to make significant contributions to the pathogenesis of an inflammatory disease such as RA, appears to be activated in FMF.

TWEAK is a pluripotent and multifunctional cytokine that belongs to the TNF superfamily. In previous studies, it has been revealed the TWEAK / Fn14 pathway has an effective role in many different processes such as inflammation, chemotaxis, proliferation of inflammatory cells, differentiation, apoptosis and angiogenesis [27-29].

It is interesting that the TWEAK / Fn14 pathway is activated in many diseases with different etiopathogenesis such as SLE, Behçet's disease, inflammatory bowel disease, and multiple sclerosis [30, 31]. In our study, the high serum TWEAK levels in FMF patients compared with the healthy control group suggests that the TWEAK / Fn14 pathway is also activated in FMF. However, there was no correlation between ESR, CRP and serum TWEAK levels and there was no significant difference in serum TWEAK levels of patients in FMF attack period comparing to that obtained during attack-free period. The fact that the TWEAK / Fn14 pathway is activated in diseases with different cytokine release patterns and does not show a significant correlation with disease activity in FMF suggests that the TWEAK / Fn14 pathway can be involved in a more common and preliminary stage in which inflammatory cascades have not differentiated yet. Another possibility is the presence of minimal inflammation in FMF even during the attack-free period. According to the results of the study conducted by Kehribar et al. [20], the detection of high serum TWEAK levels despite normal ESR and CRP values in patients with asymptomatic COVID-19 infection supports our view.

Limitations

The main limitations of this study are its cross-sectional design and small sample size. The results might be different if we had more patients for comparing the serum TWEAK levels during the attack and attack-free periods. In addition, if the control group consisted of patients with an inflammatory disease instead of healthy volunteers, some other inflammatory cytokines could be evaluated and their relationship with different cytokine release patterns could be demonstrated. However, we think that our study is important since it is the first study investigating serum TWEAK levels in FMF.

Conclusions

In conclusion, serum TWEAK levels are increased in FMF disease with attacks. However, this increase is not associated with increased ESR and CRP during FMF attacks. Although different cytokine release patterns are demonstrated in previous studies, it has also been shown that the TWEAK / Fn14 pathway is activated in many diseases. When the previous studies and the results of this study are combined, it can be suggested that the TWEAK / Fn14 pathway plays a role in the earlier stages where the inflammatory cascades are not differentiated yet. Serum TWEAK levels appear to be more successful in reflecting a lower degree of inflammation compared to ESR and CRP.

References

1. Rigante D. A developing portrait of hereditary periodic fevers in childhood. Expert Opinion on Orphan Drugs. 2018;6(1):47-55.
2. Kehribar DY, Özgen M.The importance of Mediterranean fever gene in familial Mediterranean fever. Eur J Rheumatol. 2020;7:173-6
3. Kehribar DY, Özgen M. Efficacy of anti-interleukin-1 treatment in colchicine-resistant arthritis in patients with familial Mediterranean fever. Eur J Rheumatol. 2020 Sep 18. doi: 10.5152/eurjrheum.2020.20126
4. Abderrazak A, Syrovets T, Couchie D, El Hadri K, Friguet B, Simmet T, et al. NLRP3 inflammasome: from a danger signal sensor to a regulatory node of oxidative stress and inflammatory diseases. Redox Biol. 2015;4:296-307. doi: 10.1016/j.redox.2015.01.008
5. The French FMF Consortium. A candidate gene for familial mediterranean fever.Nat Genet. 1997;17(1):25-31. doi: 10.1038/ng0997-25
6. Franchi L, Eigenbröd T, Munoz-Planillo R, Nurez G. The inflammasome; a caspase-1- activation platform that regulates immune response and disease pathogenesis. Nat Immunol. 2009;10(3):241-7. doi: 10.1038/ni.1703.
7. Papin S, Cuenin S, Agostini L, Martinon F, Werner S, Beer H-D, et al. The SPRY domain of pyrin, mutated in familial Mediterranean fever patients, interacts with inflammasome components and inhibits proIL-1 beta processing. Cell Death Differ. 2007;14(8):1457-66. doi: 10.1038/sj.cdd.4402142.
8. Roos C, Wicovsky A, Müller N, Salzmann S, Rosenthal T, Kalthoff H, et al. Soluble and transmembrane TNF-like weak inducer of apoptosis differentially activate the classical and noncanonical NF-kappa B pathway. J Immun. 2010;3:1593-695.
9. Chicheportiche Y, Bourdon PR, Xu H, Hsu YM, Scott H, Hession C, et al. TWEAK, a new secreted ligand in the tumor necrosis factor family that weakly induces apoptosis. J Biol Chem. 1997;272:32401-10.
10. Xia Y, Herlitz LC, Gindea S, Wen J, Pawar RD, Misharin A, et al. Deficiency of fibroblast growth factor-inducible 14 (Fn14) preserves the filtration barrier and ameliorates lupus nephritis. J Am Soc Nephrol. 2015;5:1053-70.
11. Xia WY, Stock A, Michaelson JS, Burkly LC, Gulinello M, Putterman C, et al. Neuropsychiatric disease in murine lupus is dependent on the TWEAK/Fn14 pathway. J Autoimmun. 2013;43:44-54.
12. Winkles JA. The TWEAK-Fn14 cytokine-receptor axis: discovery, biology and therapeutic targeting. Nat Rev Drug Discov. 2008;7:411-25.
13. Zimmermann M, Koreck A, Meyer N, Basinski T, Meiler F, Simone B, et al. TNF-like weak inducer of apoptosis (TWEAK) and TNF-α cooperate in the induction of keratinocyte apoptosis. J Allergy Clin Immunol. 2011;1:200-7.

14.Burkly LC, Michaelson JS, Hahm K, Jakubowski A, Zheng TS. TWEAKing tissue remodeling by a multifunctional cytokine: role of TWEAK/Fn14 pathway in health and disease. Cytokine. 2007;40:1-16.
15.Madrigal-Matute J, Fernandez-Laso V, Sastre C, Llamas-Granda P, Egido J, Ventura MJL, et al. TWEAK/Fn14 interaction promotes oxidative stress through NADPH oxidase activation in macrophages. Cardiovasc Res. 2015;1:139-47.
16.Wisniacki N, Amaravadi L, Galluppi GR, Zheng TS, Zhang R, Kong J, Burkly LC. Safety, tolerability, pharmacokinetics, and pharmacodynamics of anti-TWEAK monoclonal antibody in patients with rheumatoid arthritis. Clin Ther. 2013;35:1137-49.
17.Sun F, Teng J, Yu P, Li W, Chang J, Xu H. Involvement of TWEAK and the NF-κB signaling pathway in lupus nephritis. Exp Ther Med. 2018;15:2611-9.
18.Panezai J, Ali A, Ghaffar A, Benchimol D, Altamash M, Klinge B, et al. Upregulation of circulating inflammatory biomarkers under the influence of periodontal disease in rheumatoid arthritis patients. Cytokine 2020;131:155117.
19.Chen J, Jia F, Ren K, Luo M, Min X, Wang P, et al. Inhibition of suppressor of cytokine signaling 1 mediates the profibrotic effect of TWEAK/Fn14 signaling on kidney cells. Cell Signal. 2020;71:109615.
20.Kehribar DY, Cihangiroğlu M, Sehmen E, Avci B, Çapraz M, Boran M, et al. The assessment of the serum levels of TWEAK and prostaglandin F2alpha in COVID - 19. Turk J Med Sci. 2020 Sep 27. doi: 10.3906/sag-2006-96.
21.Kehribar DY, Özgen M. Clinical Features of Patients with Vascular Involvement in Behçet's Disease Tepecik Eğit. ve Araşt. Hast. Dergisi. 2020;30(2):122-6.
22.Kehribar DY, Ozgen M. Infliximab treatment in refractory vascular Behcet's disease: A single-center experience. Vascular. 2020;28(6):829-33.
23.Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997; 40: 1879-85.
24.Van Kuijk AW, Wijbrandts CA, Vinkenoog M, Zheng TS, Reedquist KA, Tak PP. TWEAK and its receptor Fn14 in the synovium of patients with rheumatoid arthritis compared to psoriatic arthritis and its response to TNF blockade. Ann Rheum Dis. 2009;69:301-4.
25.Kamata K, Kmaijo S, Nakajima A, Koyanagi A, Kurosawa H, Yagita H, et al. Involvement of TNF-like WEAK inducer of apoptosis in the pathogenesis of collagen-induced arthritis. J Immunol. 2006;177:6433-9.
26.Wisniacki N, Amaravadi L, Galluppi GR, Zheng TS, Zhang R, Kong J, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of anti-TWEAK monoclonal antibody in patients with rheumatoid arthritis. Clin Ther. 2013;35:1137-49.
27.Reyes-Martinez F, Pérez-Navarro M, Rodriguez-Matias A, Virgilia Soto-Abraham V, Gutierrez-Reyes G, Medina-Avila Z, et al. Assessment of urinary TWEAK levels in Mexican patients with untreated lupus nephritis: an exploratory study. Nefrologia. 2018;38:152-60.
28.Choe JY, Kim SK. Serum TWEAK as a biomarker for disease activity of systemic lupus erythematosus. Inflamm Res. 2016;65:479-88.
29.Schwartz N, Michaelson JS, Putterman C. Lipocalin-2, TWEAK, and other cytokines as urinary biomarkers for lupus nephritis. Ann N Y Acad Sci. 2007;1109:265-74.
30.Maarouf A, Stephan D, Ranjeva MP, Ranjeva JP, Pelletier J, Audoin B, et al. High levels of serum soluble TWEAK are associated with neuroinflammation during multiple sclerosis. J Transl Med. 2019;17:51.
31.Grimstad T, Skoie IM, Doerner J, Isaksen K, Karlsen L, Aabakken L, et al. TWEAK is not elevated in patients with newly diagnosed inflammatory bowel disease. J Gastroenterol. 2017;52:420-4.

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(2):144-148.
DOI: 10.28982/josam.831592

Research article

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

Protective effect of resveratrol on the kidney in rats under immunosuppression with tacrolimus

Hüseyin Özden [1], Muhammed Gömeç [2], Yaşar Şahin [3], Gökhan Karaca [4], Huri Bulut [5], Asuman Kilitçi [6]

[1] Ahi Evran University, Faculty of Medicine Department of General Surgery, Kırşehir, Turkey
[2] Cumhuriyet University, Faculty of Medicine Department of General Surgery, Sivas, Turkey
[3] Kırıkkale University, Faculty of Veterinary Medicine Department of Pharmacology And Toxicology, Kırıkkale, Turkey
[4] Yüksek İhtisas Hospital, Department of General Surgery, Kırıkkale, Turkey
[5] Bezmialem Vakif University Faculty of Medicine Department of Biochemistry, Istanbul, Turkey
[6] Ahi Evran University Faculty of Medicine Department of Pathology, Kırşehir, Turkey

ORCID ID of the author(s)

HÖ: 0000-0002-2786-3805
MG: 0000-0002-9127-3201
YŞ: 0000-0001-5936-4210
GK: 0000-0002-5107-5999
HB: 0000-0003-2706-9625
AK: 0000-0002-5489-2222

Corresponding Author
Hüseyin Özden
Ahi Evran University, Faculty of Medicine, Department of General Surgery, Kirsehir, Turkey
E-mail: huseyinozden@ahievran.edu.tr

Ethics Committee Approval
Written approval was obtained from the Local Ethics Committee of the Kırıkkale University on September 2, 2020 with the meeting number 2020/04, decision number 21.

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 February 19

Abstract

Background/Aim: Tacrolimus is a commonly used agent for immunosuppression in organ transplantation with known nephrotoxic effects. We think that kidney-sparing therapy should be added to current treatment protocols. We aimed to observe the protective effect of resveratrol (RSV) against the adverse effects of tacrolimus (TAC) on rat kidneys.

Methods: Twenty-four rats were randomly divided into the following three groups of eight rats each: Control, TAC, and RSV. The control group was not treated in any way. Tacrolimus was administered to the TAC group. In addition to tacrolimus use, resveratrol was administered to the RSV group. At the end of the experiment, one kidney was used for histopathological examination and the other, for biochemical examination. Results were analyzed statistically.

Results: IL-1β, IL-6, TNF-Alpha levels in the control group were significantly lower than those in TAC and RSV groups (IL-1; $P<0.001$, $P<0.001$, IL-6; $P<0.001$ $P=0.002$, TNF-Alpha; $P<0.001$, $P<0.001$), and those in the RSV group were significantly lower than those in the TAC group (IL-1: $P=0.032$, IL-6: $P=0.001$ TNF-Alpha: $P=0.026$). TAS levels of the control group were significantly higher than those of the TAC group ($P=0.030$). TOS and OSI levels of the control group were significantly lower than those of the TAC and RSV groups (TOS: $P=0.002$, $P=0.012$, OSI: $P=0.001$, $P=0.004$). In histopathological evaluation, the TAC group showed the highest levels of fibrosis. The differences between the control and TAC groups and the TAC and RSV groups were statistically significant ($P=0.003$, $P=0.003$).

Conclusion: Resveratrol has a protective effect against the adverse effects of tacrolimus on the kidney, which may be because of its anti-inflammatory and antioxidant properties.

Keywords: Anti-inflammatory, Antioxidant, Immunosuppression, Resveratrol, Tacrolimus

How to cite: Özden H, Gömeç M, Şahin Y, Karaca G, Bulut H, Kilitçi A. Protective effect of resveratrol on the kidney in rats under immunosuppression with tacrolimus. J Surg Med. 2021;5(2):144-148.

Introduction

It has been more than 60 years since the first human kidney transplantation. Over the years, it had a multidisciplinary nature [1]. Organ transplantation is one of the most complex and challenging areas of modern medicine today. It is a medical procedure in which an organ is removed from the donor and placed in the body of a recipient. After the organ is placed in the recipient's body, a complex process begins. The organ will survive healthily if the body accepts the organ. However, transplant rejection occurs when the immune system suppresses and rejects it. In this case, the transplanted organ may need to be removed. This bears high morbidity and mortality for the recipient.

For the organ transplantation to result in a healthy way, the immune system of the recipient body is suppressed. Suppression of the immune system prevents an excessive immune reaction and gives the new organ a chance to survive.

Transplant rejection is believed to develop through the activation of alloimmune responses mediated by effector CD4 + T cells [2]. Available studies show that the Th1 and Th17 cells, subsets of T cells, exhibit the highest activation [3].

Experiences have taught us that we need to use the right immunosuppressive drugs if we want to perform successful organ transplantation. Today, one of the most effective drugs used for this purpose is tacrolimus (TAC or FK506), which is a calcineurin inhibitor. It is a macrolide lactone isolated from streptomyces tsukubaensis [4].

TAC was first approved in the United States for use in liver transplantation. It was used in other organ transplants with the recognition of its effectiveness over time [4]. While the success of TAC in immunosuppression cannot be ignored, the need for individual dose adjustment due to the narrow therapeutic range has brought difficulties. Some studies report the nephrotoxic effect of TAC, however, it is a controversial topic in the literature [5]. Also, various studies that TAC was ineffective on Th17 [6].

In one study, combining TAC with a medical therapy that could have a modulatory effect on Th17 was suggested, and successful results were obtained with RSV [7]. Another study reported positive results about the effect of resveratrol in diabetic nephropathy. Resveratrol is a natural polyphenol compound [8].

In the present study, we aimed to examine the protective effect of resveratrol therapy on the kidney by combining it with tacrolimus.

Materials and methods

Written approval was obtained from the Local Ethics Committee of the Kırıkkale University on September 2, 2020 with the meeting number 2020/04, decision number 21.

A total of 24 Wistar albino male rats weighing 220-260 g were randomly divided into the following three groups with eight rats in each group: Control, TAC, and RSV. All animals were kept in collective cages at a controlled temperature (24°C) in daylight and dark conditions and had ad libitum access to water and food. The control group was not subject to any procedures. The TAC group was administered 0.5mg/kg tacrolimus (Prograf; Astellas Pharma Inc., Tokyo, Japan) perorally through oral gavage from day 7 to day 28. In addition to the procedure in the TAC group, 10 mg/kg of resveratrol (Interpharma Praha, Tokyo, Japan) was administered from day 1 to day 28 through oral gavage in the RSV group. On day 28, all animals were anesthetized with 8 mg/kg of ketamine intramuscularly and operated. Blood samples were obtained before the procedure. Laparotomy was performed with a 2 cm midline incision. Both kidneys were removed and submerged in isotonic NaCl solution. One kidney was used for histopathological examination and the other kidney, for biochemical examination. At the end of the experiment, all animals were sacrificed by decapitation (cervical dislocation).

Tissue homogenization and total protein assay

For this study, kidney samples were collected from twenty-four rats. Tissues samples were stored at -80°C until the experiments, and homogenized with PBS (Phosphate Buffer Saline, pH: 7.4) with a homogenizer (Fast prep-24, MP Biomedical, USA). The total amount of protein was measured by the Bradford method (Thermo scientific Pierce BCA) in all tissue samples with the spectrophotometer (Thermo Scientific Multiskan FC, 2011-06, USA).

Commercial kits

Rat IL-1β (Interleukin 1 Beta) ELISA Kit, Elabscience, Catalog No: E-EL-R0012, USA)

Rat IL-6 (Interleukin 6) ELISA Kit, Elabscience, Catalog No: E-EL-R0015, USA)

Rat TNF-Alpha ELISA Kit, Elabscience, Catalog No: E-EL-R0019, USA)

TAS (Total antioxidant status) Kit, Rel Assay Diagnostics, Turkey)

TOS (Total oxidant status) Kit, Rel Assay Diagnostics, Turkey)

ELISA analysis

Samples were thawed and Tumor Necrosis Factor α (TNF- α) ELISA kit (Elabscience, Catalog No: E-EL-R0019), Interleukin 1-β (IL-1 β) ELISA kit (Elabscience, Catalog No: E-EL-R0012) and Interleukin- 6 (IL-6) ELISA Kit (Elabscience, Catalog No: E-EL-R0015) were used for the quantitative measurement of TNF-α, IL-1 β and IL-6 in tissue homogenates. Samples and standards were added to appropriate wells which were pre-coated with Anti-Human monoclonal antibody before incubation. Biotin was added to all wells and combined with Streptavidin-HRP to form immune complex. Then, they were incubated and washed to remove the uncombined enzyme. Chromogen Solution A, B were added for the color of the liquid to change to blue, which later changed to yellow because of the acid. Optical density was read on a standard automated plate reader at 450 nm (Thermo Scientific Microplate Reader). The detection range of kits were between 78.13-5000 pg/mL for TNF-α, 31.25-2000 pg/ml for IL-1 β and 12.5-800 pg/mL for IL-6.

TAS and TOS measurement

Total Antioxidant Status (TAS) levels were measured spectrophotometrically using commercial kits (Rel Assay, Turkey). Assaying was performed at Thermo Scientific Microplate Reader, USA. Antioxidants in the sample reduce the dark blue-green colored ABTS radical to colorless ABTS form. The change of absorbance at 660 nm is related with the total

antioxidant level of the sample. Total antioxidant activities were expressed in mmol Trolox Equiv/L.

Total Oxidant Status (TOS) levels were measured by the spectrophotometric method using commercial kits (Rel Assay, Turkey). Assaying was performed at Thermo Scientific Microplate Reader, USA. Oxidants present in the sample oxidize the ferrous ion chelator complex to ferric ion. The oxidation reaction is prolonged by enhancer molecules, which are abundantly present in the reaction medium. The ferric ion makes a color complex with chromogen in an acidic medium. The color intensity is related to the total amount of oxidant molecules present in the sample. Results are expressed in terms of μm H202 Equiv/L.

Macroscopic assessment

The excised kidney specimens were fixed in 10% neutral buffered formalin. All specimens were excised parallel to the longitudinal body axis and followed up for 1 night for histopathological examination.

Histopathologic assessment

After the tissues were embedded in paraffin blocks, four-micrometer sections were obtained and stained with hematoxylin and eosin (H&E) after deparaffinization and rehydration. Masson's trichrome staining and PAS (Periodic Acid Schiff's) histochemical staining were performed to better assess renal fibrosis, protein material accumulation, and glomerulosclerosis. Histopathological specimens were assessed using a light microscope by an experienced pathologist who was unaware of the experimental groups (Olympus CX41 microscope) (Olympus, Tokyo, Japan). A minimum of ten fields were examined for each slide and evaluated in terms of the severity of the changes.

Histopathologic scoring was made according to the highest field. Categories were determined by semi-quantitative analysis (0: None, 1: Minimal, 2: Mild, 3: Moderate, 4: Severe) and parameters were scored accordingly. The following parameters were used to decide the degree of tubular damage, glomerular damage, and interstitial damage: Tubular dilation (TD), proteinaceous material accumulation (PMA) in tubules, tubular epithelial cell change (ECC), glomerular damage (fibrosis, atrophy, thrombosis), interstitial fibrosis (IF), interstitial congestion/hemorrhage (IC/H), interstitial mononuclear inflammatory cell infiltration (ICI).

Statistical analysis

Statistical Analysis Statistical Package for Social Sciences version 21.0 software for Windows (IBM SPSS Statistics for Windows, Version 21.0 Armonk, NY: IBM Corp., USA) was used for the statistical analysis of the study. Assumption of normality was tested by Shapiro-Wilk tests. The normally distributed data were compared with one-way ANOVA, followed by a Tukey correction test (post hoc). Non-normally distributed data were analyzed with the Kruskal-Wallis test, followed by Games-Havell correction test. *P*-value <0.05 was considered significant.

Results

IL-1β, IL-6, TNF-Alpha levels in the control group were significantly lower than those in TAC and RSV groups (IL-1: $P<0.001$, $P<0.001$, IL-6: $P<0.001$, $P=0.002$, TNF-Alpha: $P<0.001$, $P<0.001$), and those in the RSV group were significantly lower than those in the TAC group (IL-1: $P=0.032$, IL-6: $P=0.001$ TNF-Alpha: $P=0.026$) (Table 1).

TAS levels of the control group were significantly higher than those of the TAC group ($P=0.030$, while TAS values were similar between the control-RSV group and TAC-RSV group ($P=0.063$, $P=0.359$). TOS and OSI levels of the control group were significantly lower than those of the TAC and RSV groups (TOS: $P=0.002$, $P=0.012$, OSI: $P=0.001$, $P=0.004$), while those of the TAC and RSV groups were similar ($P=0.757$). OSI was significantly lower in the control group compared to the TAC and RSV groups ($P=0.001$, $P=0.004$), but similar between the TAC and RSV groups ($P=0.884$) (Table 2).

Table 1: The results of IL-1, IL6 and TNF alfa levels

Group	IL1 Mean (SD)	IL6 Mean (SD)	TNF Alfa Mean (SD)
1	35.8 (9.6)	50.3 (9.4)	117.9 (29.2)
2	447.9 (128.6)	285.7 (59.0)	2009.7 (565.5)
3	291.0 (78.3)	142.9 (48.4)	1258.6 (428.9)
		P-value	
Group 1 vs. Group 2	<0.001	<0.001	<0.001
Group 1 vs. Group 3	<0.001	0.002	<0.001
Group 2 vs. Group 3	0.032	0.001	0.026

Table 2: The results of TAS, TOS and OSI levels

Group	TAS Mean (SD)	TOS Mean (SD)	OSI Mean (SD)
1	1.0 (0.1)	8.2 (0.4)	7.8 (0.5)
2	0.8 (0.1)	9.3 (0.4)	10.3 (1.5)
3	0.9 (0.1)	9.1 (0.6)	10.8 (1.4)
		P-value	
Group 1 vs. Group 2	0.030	0.002	0.001
Group 1 vs. Group 3	0.065	0.012	0.004
Group 2 vs. Group 3	0.359	0.757	0.884

Histopathological findings are presented in Table 3. Dilation, proteinaceous material accumulation (PMA), epithelial cell abnormalities (ECA) were analyzed to assess tubular damage, fibrosis/atrophy/thrombosis (FAT) was used to assess the degree of glomerular damage, and lymphoplasmacytic cellular inflammatory infiltration (CII), vascular congestion/hemorrhage (VCH), and fibrosis were used to determine the degree of interstitial damage. There was no difference between the groups, except interstitial fibrosis. The TAC group showed the highest levels in interstitial fibrosis. There was a significant difference between the control and TAC groups ($P=0.003$) and the TAC and RSV groups ($P=0.003$) (Figure 1, 2). There was no difference between the control and RSV groups ($P=1.00$).

Table 3: The results of the histopathological analysis

Group	TD Mean (SD)	pmA Mean (SD)	ECC Mean (SD)	ICI Mean (SD)	IC/H Mean (SD)	IF Mean (SD)
1	0.12	0.25	0.75	0.50	1.87	0.62
2	0.12	0.00	0.62	0.87	1.87	1.37
3	0.37	0.12	0.25	0.87	1.00	0.62
				P-value		
Group 1 vs. Group 2	1.000	0.442	0.798	0.234	0.959	0.030
Group 1 vs. Group 3	0.442	0.721	0.195	0.234	0.050	1.000
Group 2 vs. Group 3	0.442	0.721	0.234	1.000	0.083	0.030

Figure 1: Interstitial fibrosis in a large area in the kidney section of a rat in the tacrolimus group (Score: 2) (H&E, x100).

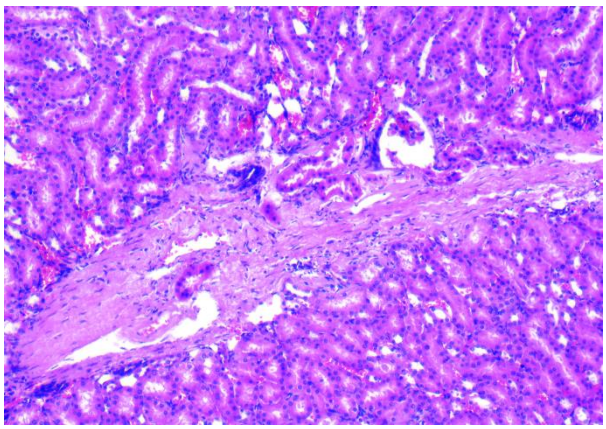
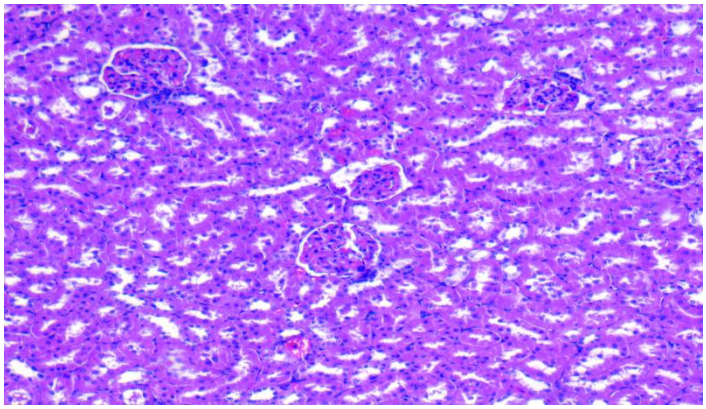


Figure 2: Normal histological appearance without fibrosis in the kidney section of a rat belonging to the resveratrol group (Score: 0) (H&E, x100).



Discussion

Organ transplantation involves obtaining an organ from a living human or cadaver and transferring it to a recipient's body. The donor and recipient may be at the same location, or organs may be transported from a donor's site to another location. The operation is quite risky, complex, and exhausting. Financial loss and disappointment are common. Modern medicine continues to develop to get better results from such an extensive process.

Organ transplantation is a multifaceted medical procedure. Various conditions must be met, and many obstacles must be overcome to execute successful organ transplantation. A multidisciplinary hospital with private and intensive care services is required, enabling the participation of all relevant branch physicians in the treatment of the patient when necessary. An immunological balance is vital for the patient. The higher the tissue compatibility, the more successful results can be obtained. For this reason, patients wait for a suitable donor for years. In some countries, it is a religiously controversial issue, on which restrictions have been imposed. It is regulated through legal processes by ethical committee decisions and regulations. Even if one overcomes these obstacles and manages to undergo organ transplantation, the immune system may reject the transplanted tissue. Therefore, any kind of study and research on the performance of organ transplantation in the safest way bears great value. In particular, suppression of immunity and protection of tissue are priorities.

Molecules on the transplanted organ, perceived as foreign by the host, are called allo-antigens. Antibodies and T cells formed in the host are alloreactive. Major Histocompatibility Complex (MHC) is responsible for the introduction of allo-antigens to host T cells. The compatibility of MHC molecules between the donor and recipient is essential for successful transplantation. Each individual's CD4 and CD8 T cells are selected to recognize the peptides presented by their MHC molecules during the transformation into mature cells in the thymus. CD4 and CD8 are transformed separately through thymic antigen-presenting cells. CD4 T-cells are called T helper (Th) cell and CD8 T-cells are called cytotoxic T lymphocytes (CTL). This way, T cells recognize their own specific MHC.

Transplant rejection can be classified as hyperacute, acute, or chronic. Hyperacute rejection is usually mediated by memory-infused antibodies during pregnancy or blood transfusions. Rejection may occur within minutes. Acute rejection is mainly evoked by T cells, and antibodies are less effective. It manifests with vascular and parenchymal damage. It is either caused by a direct cytotoxic T-cell attack on graft cells or damage through secreted inflammatory cytokines. The CD4+T cell (Th) play the most active role in this process. Immunosuppressive therapies used today aim to prevent or repress T cell-mediated rejection [9]. Chronic rejection is associated with progressive proliferation.

Popular immunosuppressive drugs developed to prevent acute rejection include tacrolimus, cyclosporine, and mycophenolate mofetil. They can be used alone or in combination to prevent graft rejection [10]. TAC is a highly effective immunosuppressive but also safer and better tolerated than others. However, in their study, Millis et al. [11] found that TAC has side effects such as neurotoxicity, nephrotoxicity, hepatotoxicity, glucose intolerance, gastrointestinal toxicity, post-transplant lymphoproliferative disorder, and infections. Another study emphasized that the use of TAC triggered the production of reactive oxygen species (ROS) and created oxidative stress [12].

While tacrolimus use has become popular in organ transplantation, its nephrotoxic effects were figured out over time, and medical treatment procedures are needed for prevention. Metabolites of tacrolimus are thought to be responsible for renal pathologies. It is difficult to determine accurate dosage since the minimum effective dose within the therapeutic range cannot be measured at the cell or tissue level. In our experimental study, we applied an equal dose of TAC in rats with equal weight and the same gene lineage. The dose we administered was determined on the basis of previous studies [13]. We obtained significant differences in laboratory tests and microscopic examination between the TAC group and the control group. Inflammation markers such as IL-1, IL-6, and TNF-alpha were significantly higher in the TAC group. Among the oxidative stress markers of TAS, TOS, and OSI, TAS was significantly lower, while TOS and OSI were significantly higher. In addition, the microscopic examination revealed that the TAC group exhibited the highest levels of interstitial fibrosis, which showed tacrolimus nephrotoxicity.

The use of tacrolimus may have nephrotoxic effects. Probable causes should be first ruled out in case of renal impairment. If no cause is found, a TAC dose adjustment may be required, or the immunosuppressive procedure may be changed. Hydration provides an effective treatment for kidney protection. Many drug modalities may be preferred in a normal transplant

follow-up. In the present study, we aimed to investigate the effect of resveratrol, which had antioxidant and anti-inflammatory properties.

Resveratrol (trans-3,4 ', 5- trihydroxystilbene) is a type of polyphenol called phytoalexin, and it is a plant-derived compound as a defense mechanism against diseases. It is found in peanuts and red wine. It can now be easily supplied and used as a food supplement [14].

A study reported that a drug called kojokon in China and Japan is the same drug that we call resveratrol [15]. We believe that this historical drug should be included in studies. In the literature, many studies have been conducted with resveratrol with successful outcomes. Available studies have mostly investigated its anti-inflammatory and antioxidant properties against malignancy, cardiovascular diseases, ischemia, toxicity, inflammation, and tissue injury [16-21].

Dolezelova et al. [22] performed a preliminary study and reported the minimum effective dose of resveratrol in rats as 10 mg/kg, which we administered. In the present study, no rat died due to resveratrol use. Inflammatory markers such as IL-1, IL-6, and TNF alpha were significantly lower in the RSV group compared to the TAC group. Oxidative markers such as TAL, TOS, and OSI revealed no significant difference although TAS was higher, and TOS was lower. In addition, histopathological examination revealed that interstitial fibrosis in the RSV group was lower than that in the TAC group. These results showed that the nephrotoxic effect of TAC regressed with the use of resveratrol.

Limitations

The small number of rats in our study constitutes a limit. Further studies with more sample size are needed.

Conclusion

We determined the nephrotoxic effects of TAC metabolites in the experimental animal model under immunosuppression with tacrolimus. Nephrotoxicity decreased with the use of RSV combined with TAC. We think that these positive effects are mostly due to the anti-inflammatory and antioxidant properties of RSV.

References

1. Daniel A, Rainer O, Uwe H, Ondrej V, Licia P, Christophe M, et al. Recent advances in kidney transplantation: a viewpoint from the Descartes advisory board. Nephrol Dial Transplant. 2018 Oct 1;33(10):1699-707. doi: 10.1093/ndt/gfx365.
2. Calvo-Turrubiartes M, Romano-Moreno S, García-Hernández M, Chevaile-Ramos JA, Layseca-Espinosa E, González-Amaro R, et al. Quantitative analysis of regulatory T cells in kidney graft recipients: a relationship with calcineurin inhibitor level. Transpl Immunol. 2009 May;21(1):43-9. doi: 10.1016/j.trim.2009.02.002.
3. Loong CC, Lin CY, Lui WY. Expression of interleukin-17 as a predictive parameter in acute renal allograft rejection. Transplant Proc. 2000 Nov;32(7):1773. doi: 10.1016/s0041-1345(00)01382-8.
4. David IP. Sourcing a chemical succession for cyclosporin from parasites and human pathogens. Drug Discov Today. 2005 May 15;10(10):688-91. doi: 10.1016/S1359-6446(05)03395-7.
5. Meng Y, Mouze L, Wei Z, Yingzi M. Pharmacokinetics, pharmacodynamics and pharmacogenetics of tacrolimus in kidney transplantation. Curr Drug Metab. 2018;19(6):513-522. doi: 10.2174/1389200219666180129151948.
6. Byung HC, Kyoung WK, Bo MK, Shang GP, Sun WL, Bum SC, et al. Dysregulation of Th17 cells during the early post-transplant period in patients under calcineurin inhibitor based immunosuppression. PLoS One. 2012;7(7):e42011. doi: 10.1371/journal.pone.0042011.
7. Anne LW, Joseph AB, Ole V. mTOR: more targets of resveratrol?. Expert Rev Mol Med. 2013 Sep 23;15:e10. doi: 10.1017/erm.2013.11.
8. Tomasz S, Katarzyna S. Resveratrol and diabetes: from animal to human studies. Biochim Biophys Acta. 2015 Jun;1852(6):1145-54. doi: 10.1016/j.bbadis.2014.10.013.
9. Lynn DC, R Neal S, Robert BC. Kidney transplantation: mechanisms of rejection and acceptance. Annu Rev Pathol. 2008;3:189-220. doi: 10.1146/annurev. pathmechdis.3.121806.151508.
10. Manuel RP, Marta GM, Douglas T, Brian RD, Emmanuel T, Kurinchi SG. Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis. Cochrane Database Syst Rev. 2017 Mar 31;3(3):CD011639. doi: 10.1002/14651858.CD011639.pub2.
11. Millis JM, Woodle ES, Piper JB, Bruce DS, Newell KA, Seaman DS, et al. Tacrolimus for primary treatment of steroid-resistant hepatic allograft rejection. Transplantation. 1996 May 15;61(9):1365-9. doi: 10.1097/00007890-199605150-00014.
12. Shang GP, Sun WL, Kyoung CD, Long J, Seong BH, Yu FZ. Combined treatment of tacrolimus and everolimus increases oxidative stress by pharmacological interactions. Transplantation. 2014 Jul 15;98(1):22-8. doi: 10.1097/TP.0000000000000146.
13. Akbulut S, Dogan Z, Baskiran A, Elbe H, Turkoz Y. Effect of a honey and arginine-glutamine-hydroxymethylbutyrate mixture on the healing of colon anastomosis in rats immunosuppressed with tacrolimus. Biotech Histochem. 2019 Oct;94(7):514-21. doi: 10.1080/10520295.2019.1601257
14. Belgaied J-E. Resveratrol content of Tunisian wines. Journal of Wine Research. 2001; 12:47-52
15. Savouret JF, Quesne M. Resveratrol and cancer: a review. Biomed Pharmacother. 2002 Mar;56(2):84-7. doi: 10.1016/s0753-3322(01)00158-5.
16. Amiot MJ, Riva C, Vinet A. Effects of dietary polyphenols on metabolic syndrome features in humans: a systematic review. Obes Rev. 2016 Jul;17(7):573-86. doi: 10.1111/obr.12409.
17. Rodica PB, Andrew Y. Resveratrol and malignancies. Curr Pharmacol Rep. 2015; Aug;1(4):266-71. doi: 10.1007/s40495-015-0030-1
18. Chibuike CU, Vanu RR, Rotimi EA, Peter JHJ. Potential of resveratrol in anticancer and anti-inflammatory therapy. Nutr Rev. 2008 Aug;66(8):445-54. doi: 10.1111/j.1753-4887.2008.00076.x.
19. Sara H, Karen LT, Steen BP, Hendrik V, Jacob G, Henning G. Effects of resveratrol in experimental and clinical non-alcoholic fatty liver disease. World J Hepatol. 2014 Apr 27;6(4):188-98. doi: 10.4254/wjh.v6.i4.188.
20. Alessandra F, Mariangela DG, Vincenzo Z. Antioxidant dietary approach in treatment of fatty liver: new insights and updates. World J Gastroenterol. 2017 Jun 21;23(23):4146-57. doi: 10.3748/wjg.v23.i23.4146.
21. Zakaria MMH, Hajipour B, Estakhri R, Saleh BM. Anti-oxidative effect of resveratrol on aluminum induced toxicity in rat cerebral tissue. Bratisl Lek Listy. 2017;118(5):269-72. doi: 10.4149/BLL_2017_053.
22. Eva D, Alena P, Jolana C, Alejandro C, Lucie H, Milos H, et al. Resveratrol modifies biliary secretion of cholephilic compounds in sham-operated and cholestatic rats. World J Gastroenterol. 2017 Nov 21;23(43):7678-92. doi: 10.3748/wjg.v23.i43.7678.

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(2):149-152.
DOI: 10.28982/josam.740090

Research article

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

Comparison of laboratory parameters between children with and without febrile convulsion

Hilal Aydın [1], İbrahim Hakan Bucak [2], Mehmet Turgut [2]

[1] Balıkesir University, Faculty of Medicine, Department of Child Health and Diseases, Department of Child Neurology, Balikesir, Turkey
[2] Adiyaman University, School of Medicine, Department of Child Health and Diseases, Adiyaman, Turkey

ORCID ID of the author(s)

HA: 0000-0002-2448-1270
İHB: 0000-0002-3074-6327
MT: 0000-0002-2155-8113

Corresponding Author
Hilal Aydın
Balıkesir Üniversitesi, Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Nöroloji Bölümü, Balıkesir, Türkiye
E-mail: drhilalaydin@gmail.com

Ethics Committee Approval
The study was approved by the Ethics and Research Committee of Adiyaman University (approval number 2019/1-20).
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
It was presented as an oral presentation at the 4th Spring Pediatrics Days (02.03.2018, Adana, Turkey).

Published
2021 February 19

Abstract

Background/Aim: Febrile convulsion is the most common central nervous system disease of childhood. The etiology of febrile convulsion is not fully brightened. In this study, we aimed to evaluate the relationship between hemogram, biochemical and hormonal parameters and febrile convulsion, and the roles of laboratory parameters in its etiopathogenesis.
Methods: A total of fifty-four patients diagnosed with febrile convulsion in the pediatric neurology outpatient clinic of a tertiary hospital from October 2017 to December 2018 were included in this retrospective cohort study. Age, sex, age of first convulsion, type of convulsion and laboratory parameters of the patients were recorded. ILAE classification system was used for the diagnosis of febrile convulsion. Febrile convulsion patients were included in the study group, while the control group was randomly selected from patients between 6 months and 6 years of age who visited general pediatric outpatient clinic.
Results: A total of 54 patients (30 males, 24 females) in the study group and 82 patients (53 males, 29 females) in the control group were included in the study (P=0.288). The mean ages of the patients in the study and control groups were 30.31 (14.64) months and 32.32 (19.70) months, respectively (P=0.524). Mean platelet volume (MPV), platelet count, 25-OH D3, vitamin B12 and phosphorus values were significantly lower in the study group (P<0.001, P=0.013, P=0.017, P=0.020).
Conclusion: MPV, platelet count, 25 OH D3, vitamin B12 lower levels may be risk factors for febrile convulsion. Studies related to the etiopathogenesis of febrile convulsion are necessary to enlighten the subject and laboratory results will be the guide in this sense.

Keywords: Febrile convulsion, Laboratory parameters, Children, Seizure

How to cite: Aydın H, Bucak İH, Turgut M. Comparison of laboratory parameters between children with and without febrile convulsion. J Surg Med. 2021;5(2):149-152.

Introduction

Febrile convulsions (FC) are seizures usually accompanied by febrile diseases other than central nervous system (CNS) infections, which do not meet other acute symptomatic convulsion criteria, seen in children between 1 month and 6 years of age without any history of neonatal or afebrile convulsions [1, 2]. The prevalence of FC varies between 2-8% [3]. Although the pathogenesis of FC is not well known, there are studies reporting increased levels of interferon-α and neuron-specific enolase, decreased thyroid-stimulating hormone values, prolactin, growth hormone and cortisol, central thermoregulation disorders, delayed maturation of CNS, increased excitatory amino acids, and iron deficiency anemia [4]. The purpose of this study was to compare the laboratory parameters among children with and without FC.

Materials and methods

A total of fifty-four patients diagnosed with FC in the pediatric neurology outpatient clinic of a tertiary hospital from October 2017 to December 2018 were included in the study. The data were obtained retrospectively by scanning the patient files. Age, sex, age of first convulsion, type of convulsion and laboratory parameters of the patients were recorded. ILAE classification system was used for the diagnosis of FC. Adiyaman University Ethics Committee approved the study with number 2019/1-20.

Febrile convulsion was diagnosed with the following criteria: Patients within the age range of 1 month to 6 years, convulsions accompanied with fever, absence of any infections in the CNS and electrolyte imbalance, metabolic disorder, intoxication, trauma, and pathological neurological findings (mental motor retardation, cerebral palsy) that may cause convulsions. Cases were evaluated as simple and complex FC according to FC classification. Convulsions lasting more than fifteen minutes, with focal features and/or recurrence within 24 hours were interpreted as complex FC and others were considered simple FC. FC patients were included in the study group. Patients diagnosed with febrile convulsion using antiepileptic drugs were not included in the study. The control group was randomly selected from the patients who visited the general pediatric outpatient clinic between 6 months and 6 years of age with a diagnosis code of Z00.1: Encounter for routine child health examination, and who had not previously been diagnosed with FC.

Demographic data (age, sex) and laboratory results [hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), red cell distribution width (RDW), mean platelet volume (MPV), neutrophil/lymphocyte ratio, 25-OH D3, parathormone (PTH), iron, serum iron binding capacity, ferritin, calcium, phosphorus, vitamin B12, folate] were recorded. The ratios of neutrophil and lymphocyte count were calculated from hemogram parameters. Vitamin B12 values below 250 pg/ml were defined as vitamin B12 deficiency.

Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 23.0 was used for statistical analysis in the evaluation of data obtained in this study. Independent Sample T test was used for normal distribution parameters and Mann-Whitney U test was used for non-normal distribution parameters. Chi-square test was used to evaluate categorical variables. A *P*-value <0.05 was considered statistically significant.

Results

A total of fifty-four patients (30 males, 24 females) in the study group and eighty-two patients (53 males, 29 females) in the control group were included in the study. The mean age of the patients in study and control groups were 30.31 (14.64) months and 32.32 (19.70) months, respectively. There was no significant difference among the study and control groups in terms of age and gender (*P*=0.524, *P*=0.288) (Table 1).

Of the fifty-four patients in study group, 28 (51.80%) had simple FC and 26 (48.20%) had complex FC. A total of 7 (13%) patients had a single episode of FC while 47 (87%) patients had two or more episodes. Among forty-seven patients had two or more FC episodes, 17 (36.20%) had two episodes of FC, and 30 (63.80%) had three or more episodes of FC.

The Hb, Hct, MCV, MCH, RDW, Neutrophil/Lymphocyte ratio, PTH levels, iron, iron binding capacity, ferritin, calcium and folic acid values of the control and study groups were similar (*P*>0.05) (Tables 1 and 2). MPV, platelet count, 25-OH D3, vitamin B12 and phosphorus levels were significantly lower in the study group (Tables 1 and 2).

Table 1: Distribution and comparison of laboratory parameters between groups

	Study group n (%)	Control group n (%)	
Gender			Total
Male	30 (22.10)	53 (38.90)	83 (61)
Female	24 (17.63)	29 (21.37)	53 (39)
Total	54 (39.73)	82 (60.27)	136 (100)
	Mean (SD)	Mean (SD)	*P*-value
Age (month)	30.31 (14.64)	32.32 (19.70)	0.524
WBC (/mm3)	9.54 (2.08)	10.17 (3.15)	0.196
N/L	0.89 (0.54)	0.82 (0.63)	0.539
Hemoglobin (gr/dl)	11.87 (1.06)	11.84 (1.44)	0.900
Hct %	36.12 (2.82)	35.98 (3.8)	0.816
MCV (fL)	74.47 (5.72)	74.43 (6.71)	0.973
MPV (fL)	6.52 (0.77)	7.52 (1.52)	<0.001*
Platelet (103/µL)	312.5 (93.27)	364.56 (134.55)	0.013*
Lymphocytes	4.64 (1.45)	5.28 (2.33)	0.073
Neutrophil	3.62 (1.54)	3.68 (1.98)	0.876

* Mann-Whitney U test, WBC: White Blood Cell, Hct: Hematocrit, MCV: Mean Corpuscular Volume, MPV: Mean Platelet Volume

Table 2: Comparison of other laboratory parameters in study group and control group

	Study group Mean (SD)	Control group Mean (SD)	*P*-value
Iron (mg/dl)	39 (51)	54 (35)	0.380
Iron binding capacity (ug/dL)	261 (117)	328 (100)	0.100
Ferritin (ml/ng)	22 (18)	17 (12)	0.214
Folate (ng/ml)	12 (8)	10 (9)	0.365
PTH (pg/mL)	26 (18)	15 (10)	0.641
Calcium (mg/dL)	9.57 (0.55)	10 (0.45)	0.660
25 OH D3 (ng/mL)	22 (12)	31 (17)	0.017
Vitamin B12 (pg/ml)	316 (205)	419 (208)	0.039
Phosphorus (mg/dL)	4.86 (0.51)	5.60 (0.83)	0.020

PTH: Parathormone

Discussion

Febrile convulsion is defined as that which occurs during a febrile disease in patients without a history of central nervous system infection, metabolic disorder, or afebrile seizure. The age range varies between 6-60 months and peaks at 18 months [2]. FCs are classified into two groups as simple and complex. Seizures that are generalized from the onset, last for less than 15 minutes and do not recur within 24 hours are defined as simple FC while convulsions with at least one focus at the

onset, last longer than 15 minutes and recur within 24 hours are defined as complex FC [3].

The pathogenesis of FC is not fully known. In the studies conducted, increased levels of interferon-α and neuron-specific enolase, decreased thyroid-stimulating hormone values, prolactin, growth hormone and cortisol, central thermoregulation disorders, delayed maturation of CNS, increased excitatory amino acids, and iron deficiency anemia were detected in children with FC. However, their role in the pathogenesis of FC remains controversial [4]. In the literature, low serum iron levels in iron deficiency have been shown to lower the seizure threshold and lead to febrile convulsions [5]. Sadeghzadeh et al. [6] have shown that anemia is not common in patients diagnosed with FC; however, iron deficiency was observed more frequently in these patients. Contrarily, some studies have reported that iron deficiency is less common in patients diagnosed with FC and that iron deficiency has a protective effect against seizures [7,8]. In the literature, a systemic review and meta-analysis conducted on 2416 FC patients and 2387 healthy individuals in 2017 showed that iron deficiency increases the risk of FD [9]. In their study evaluating 323 patients, Waheed et al. [10] stated that iron deficiency anemia was not common in patients diagnosed with FC and had no role in its pathogenesis. In our study, no statistically significant difference was detected among the study and control groups in term of hemoglobin, serum iron, iron binding capacity and ferritin levels.

Mean platelet volume (MPV) is a laboratory finding that is routinely measured on whole blood count and reflects the average volume of circulating platelets. Inflammatory, infectious and allergic conditions stimulate the bone marrow, leading to increased platelet production and the introduction of larger platelets into the bloodstream. In this case, increase in platelet count and MPV were observed. The increase in MPV occurs before the increase in platelet count [11]. In recent years, the importance of MPV has been investigated in many studies and it has been shown that it reflects platelet functions much better than platelet count [12-14]. MPV is directly associated with platelet function and activation. Increased MPV is an indication that platelets are activated. In the literature, it was shown that MPV was significantly higher among healthy individuals when compared with the FC group [15]. In our study, platelet count and MPV values were also significantly higher in the control group, in line with the literature.

The neutrophil/lymphocyte ratio (N/L) is calculated by neutrophil and lymphocyte counts in whole blood count and considered an indicator of subclinical inflammation. It is the subject of many studies today [16, 17]. Liu et al. [18] reported that N/L ratio was significantly higher in patients with FC compared with the control group. In our study, N/L ratios of the study and control groups were similar. The most common causes of febrile convulsions are viral infections; N/L was thought to be low due to increased lymphocyte ratio in viral infections.

Vitamin B12 is an important vitamin in humans, especially for the central nervous system. In children, vitamin B12 deficiency can develop due to decreased intake, abnormal absorption, dysfunctional transport of vitamin B12 and congenital defects in the metabolism. Low vitamin B12 level plays a role in the occurrence and recurrence of convulsions [19]. Osifo et al. [20] found that serum vitamin B12 levels were lower in patients with FC compared to healthy group and febrile group without seizures. Vitamin B12 levels were significantly lower in our study group compared to the control group, which suggests that low vitamin B12 levels may act a part in the etiopathogenesis of FC.

Vitamin D deficiency is an important public health problem in children [21, 22]. It is thought to be associated with diabetes and oncologic, cardiovascular, autoimmune, and central nervous system diseases [23]. Vitamin D deficiency is common in patients with epilepsy and febrile convulsion [24, 25]. In a case report, a child with recurrent febrile convulsion had rickets due to vitamin D deficiency and another study reported that there were cases of hypocalcemic seizures due to vitamin D deficiency [26, 27]. In our study, vitamin D and phosphorus levels were significantly lower in study group, while PTH and calcium levels were similar. Even though there was a statistically significant difference in phosphorus levels among the groups, the mean phosphorus level of the study group was within normal laboratory range.

Osifo et al. [20] investigated the relationship among serum folic acid values and seizure formation in thirty-two febrile children aged 8 months to 5 years. The authors reported that serum folic acid values in children with FC were significantly higher than those in seizure-free children. Folic acid plays a significant role in cerebral mitochondrial function and nucleic acid synthesis [28]. In addition, a decrease in the oxidative enzyme activity in the brain, seen in folic acid deficiency, has been reported to cause seizure activity [29]. Contrary to the literature data, no statistically significant difference was found among the groups in terms of mean folic acid level. We think that further studies evaluating the relationship between FC and folic acid level are needed.

Limitation

The retrospective design and the inclusion of small number of patients with febrile convulsions constitute the limitations of this study.

Conclusion

MPV, platelet count, 25 OH D3, vitamin B12 lower levels may be a risk factor for the development of febrile convulsion. It is shown that studies related to the etiopathogenesis of febrile convulsion are necessary to enlighten the subject and laboratory results will be the guide in this sense.

References

1. National Institutes of Health Consensus Statement. Febrile seizures: Long term management in children with fever associated seizures. Pediatrics. 1980;66:1009-112.
2. Commission on epidemiology and prognosis. International League Against Epilepsy: Guidelines for epidemiologic studies on epilepsy. Epilepsia. 1993;34:592-6. doi: 10.1111/j.1528-1157.1993.tb00433.x.
3. Paul SP, Rogers E, Wilkinson R, Paul B. Management of febrile convulsion in children. Emerg Nurse. 2015;23:18–25. doi: 10.7748/en.23.2.18.e1431.
4. Chung S. Febrile seizures. Korean J Pediatr. 2014;57:384–95. doi: 10.3345/kjp.2014.57.9.384.
5. Naveed-ur-Rehman, Billoo AG. Association between iron deficiency anemia and febrile seizures. Journal of the College of Physicians and Surgeons Pakistan. 2005;15(6):338-40. doi: 06.2005/jcpsp.338340.
6. Sadeghzadeh M, Asl PK, Mahboubi E. Iron Status and Febrile Seizure-A Case Control Study in Children Less Than 3 Years. Iranian Journal of Child. 2012 Autumn;6(4):27–31. PMID:24665277.
7. Kobrinsky NL, Yager JY, Cheang MS, Yatscoff RW, Tenenbein M. Does iron deficiency raise the seizure threshold? Journal of Child Neurology. 1995;10(2):105-9. doi: 10.1177%2F088307389501000207.
8. Derakhshanfar H, Abaskhanian A, Alimohammadi H, ModanlooKordi M. Association between iron deficiency anemia and febrile seizure in children. Medicinski Glasnik. 2012;9(2):239-242. PMID:22926357.
9. Kwak BO, Kim K, Kim SN, Lee R. Relationship between iron deficiency anemia and febrile seizures in children: A systematic review and metaanalysis. Seizure. 2017;52:27-34. doi: 10.1016/j.seizure.2017.09.009

10. Waheed N, Butt MA. Iron status: is there a role in febrile seizures? J Ayub Med Coll Abbottabad. 2012;24(3-4):128-30. PMID:24669632.
11. Andrews RK, Berndt MC. Platelet physiology and thrombosis. Thromb Res. 2004;114:447-53. doi: 10.1016/j.thromres.2004.07.020.
12. Özkan EA, Khosroshahi HE, Serin Hİ, Ozdemir ZT, Kılıc M, Ekim M. The evaluation of carotid intima-media thickness and mean platelet volume values and correlation with cardiac functions in obese children. Int J Clin Exp Med. 2015;15;8:22557-63.
13. Zdrojewski Z, Raszeja-Specht A, Kustosz J, Skibowska A. Evaluation of factors influencing platelet aggregation in patients with chronic glomerulonephritis. Przegl Lek. 1996;53:434-8. PMID:8754409.
14. Tajarernmuang P, Phrommintikul A, Limsukon A, Pothirat C, Chittawatanarat K. The role of mean platelet volume as a predictor of mortality in critically ill patients: a systematic review and metaanalysis. Crit Care Res Pract. 2016;2016:4370834. doi: 10.1155/2016/4370834.
15. Bath PM. Butterworth RJ. Platelet size: measurement, physiology and vascular disease. Blood Coagulation and Fibrinolysis. 1996;7(2):157-61. PMID:8735807.
16. Goksugur SB, Kabakus N, Bekdas M, Demircioglu F. Neutrophil-to-lymphocyte ratio and red blood cell distribution width is a practical predictor for differentiation of febrile seizure types. Eur Rev Med Pharmacol Sci. 2014;18:3380–5. PMID:25491611.
17. Yigit, Y, Yılmaz S, Akdoğan A, Halhallı HC, Ozbek AE, Gencer EG. The role of neutrophil-lymphocyte ratio and red blood cell distribution width in the classification of febrile seizures. Eur Rev Med Pharmacol Sci. 2017;21:554–9. PMID:28239812.
18. Liu Z, Li X, Zhang M, Huang X, Bai J, Pan Z, et. al. The role of Mean Platelet Volume/ platelet count Ratio and Neutrophil to Lymphocyte Ratio on the risk of Febrile Seizure. Scientific Reports. 2018;8:15123. doi: 10.1038%2Fs41598-018-33373-3"10.1038/s41598-018-33373-3.
19. Bak M, Çakar S, Ünalp A. Neurological manifestations of vitamin B12 deficiency in 15 infants. Journal of Pediatric Neurology. 2009;07(03):275-8. doi: 10.3233/JPN-2009-0313.
20. Osifo BO, Lukanmbi FA, Familusi JB.Cerebrospinal fluid folate and cobalamin levels in febrile convulsion. Journal of the Neurological Sciences. 1985;68.2-3:185-90. doi: 10.1016/0022-510X(85)90099-1.
21. Mahmoodzadeh H, Nasimfar A, Sadeghi E, Macooie A, Gazavi A, Rasouli J, et al. Study of Vitamin D Level in Children with Non-specific Musculoskeletal Pain. International Journal of Pediatrics. 2017;5(3):4533-40. doi: 10.22038/ijp.2016.20988.1756.
22. Qader E, Alkhateeb N. Vitamin D Status in Children with Iron Deficiency and/or Anemia. International Journal of Pediatrics. 2016;4(9):3571-7. doi: 10.22038/ijp.2016.7482.
23. Whiting SJ, Clavo MS, Stephensen CB. Current understanding of vitamin D metabolism, nutritional status, and rule in disease prevention. In:Coulston AM, Boushey C (eds). Nutrition in the prevention and treatment of disease. Sandiego, CA: Academic Press, 2008; 807-32.
24. Fong CY, Kong AN, Poh BK, Mohamed AR, Khoo TB, Ng RL, et al. Vitamin D deficiency and it`s risk factors in Malaysian children with epilepsy. Epilepsia. 2016;57(8):1271-9. doi: 10.1111/epi.13443.
25. Singh V, Sharma P, Dewan D. Association of vitamin D levels with simple febrile seizures in under five children: a case control study. Int J Contemp Pediatr. 2019;6(2):365-68. doi.org/10.18203/2349-3291.ijcp20190019.
26. Hoecker CC, Kanegaye JT. Recurrent febrile seizures, unusual presentation of nutritional rickets. J of Emerg Med. 2002;23(4):367-70. doi: 10.1016/S0736-4679(02)00570-X.
27. Mantadakis E, Deftereos S, Tsouvala E, Thomaidis S, Chatzimichael A. Seizures as initial manifestation of vitamin D-deficiency rickets in a 5-month-old exclusively breastfed infant. Pediatr Neonatol. 2012;53(6):384-6. doi: 10.1016/j.pedneo.2012.08.004.
28. Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ. Mitochondrial function and toxicity: role of B vitamins on the one-carbon transfer pathways. Chemico Biological Interactions. 2006;163:113-32. doi: 10.1016/j.cbi.2006.05.010.
29. Hallacogl B, Sassaroli A, Fantini S, Troen AM. Cerebral perfusion and oxygenation are impaired by folate deficiency in rat: absolute measurements with noninvasive near-infrared spectroscopy. J Cereb Blood Flow Metab. 2011;31:1482-92. doi: 10.1038%2Fjcbfm.2011.13.

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(2):153-157.
DOI: 10.28982/josam.843719

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

Analysis of pediatricians' knowledge about autism

Şenay Kılınçel [1], Fikriye Baki [2]

[1] Sakarya Child and Adolescent Psychiatry Institute, Sakarya, Turkey
[2] Department of Pediatry, Behçet Uz Training and Research Hospital, Izmir, Turkey

ORCID ID of the author(s)
ŞK: 0000-0001-5298-0264
FB: 0000-0002-3021-9471

Corresponding Author
Şenay Kılınçel
Sakarya Child and Adolescent Psychiatry Institute, Sakarya, Turkey
E-mail: senaykilincel@gmail.com

Ethics Committee Approval
Approval was obtained from Sakarya University non-interventional studies ethics committee on 20.10.2020 (no. 71522473/050.01.04/551). 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 February 19

Abstract

Background/Aim: In autism spectrum disorders (ASD), early diagnosis is important for treatment, and pediatricians are health professionals who are likely to encounter ASD at the earliest stages. In this study, we aimed to examine the information sources of pediatricians, their current knowledge about autism and the affecting factors.

Methods: The study was conducted as an online cross-sectional self-report questionnaire and the data of 145 pediatricians were analyzed. The sociodemographic information form created by the researchers and the Healthcare Professionals' Knowledge of Childhood Autism Questionnaire-Turkish Version were filled by the participants. Correct response rates were divided into quantile values and under 3rd Quartile (Q3) was considered "insufficient information." Logistic regression analysis was used for descriptive data and factors affecting the level of knowledge.

Results: Of 145 participants, 59.3% completed Child and Adolescent Psychiatry (CAP) internship during their medical education, 60.7% completed CAP rotation, and 49.7% attended training or meetings related to autism. The highest rate of correct answers in autism knowledge evaluation questionnaire was on "Information on social interaction," while the lowest rate of correct answers was on "Information on neurodevelopmental diseases." For the total correct answer rates, the Q3 and Q1 values were 68.1% and 89.5%, respectively. According to the logistic regression model, being single (Mean: 3.60) and not having an MCS rotation (Mean: 8.49) predicted a score below Q3.

Conclusions: Our research shows that in this disorder, where early diagnosis is of foremost importance, pediatricians who regularly monitor children have a high level of knowledge about recognizing autistic symptoms; however, there are some deficiencies in answering questions that will resolve the concerns of families about autism. For this reason, pediatricians who examine a child at least 3-4 times a year need pediatric psychiatry training that will give them specific skills in diagnosing and making recommendations, as well as initiating interventions. Another option is being more involved in departments that will enable them to gain experience in autism.

Keywords: Autism, Child psychiatry, Pediatrician

How to cite: Kılınçel Ş, Baki F. Analysis of pediatricians' knowledge about autism. J Surg Med. 2021;5(2):153-157.

Introduction

The evaluation of children with autism spectrum disorder (ASD) is a data collection process performed to determine the problems experienced by the child, and the interventions required to eliminate such problems [1]. It further aims to find the strengths and weaknesses of the child and any accompanying developmental or mental disabilities, assess the family's needs, and identify resources to meet them [2].

Screening evaluations are made among preschool children to identify and become aware of those with inadequate social adjustment and those at increased risk of experiencing inadequate social adjustment. Diagnostic evaluation aids in deciding the cause of a disease more intensely compared to screening. In Turkey, the evaluation and diagnosis process in the medical, psycho-social, and educational fields are used to individually analyze the developmental weaknesses and strengths, and interests of children with autism and other special needs. Early diagnosis of all neurodevelopmental disorders is of foremost importance in terms of early initiation of special-education programs. The literature review has shown that a reliable diagnosis for children with autism can be established at about 30 months of age, and autism-related screenings can be performed at 18 months at the earliest [3].

Children's developmental problems are first noticed by the parents. They start to seek service on the matters they are concerned about or in areas where their children have weaknesses [4]. In a study involving 42 parents from Italy, parents' perspectives towards the diagnosis of autism were evaluated and 71% of the parents, who participated in the study, stated that they first recognized the autism symptoms of their children at the age of two whereas the remaining one-third stated that they noticed symptoms when their children were aged three to four years. Only one mother said she noticed that her child had symptoms from birth. In the study, all parents stated that their children had difficulties in four areas in total: Language, social relationship, behavior, and motor skills. Most parents consulted experts when they realized these symptoms to clarify their child's situation or obtain information about the process. Only two parents did not want their child's situation to be clarified. Half of the mothers were observed to request a diagnostic evaluation and further examination for their child's condition, without guidance by any specialist whereas other families acted in line with the suggestions of teachers or other professionals. In the study, 50% of the parents obtained detailed information about special education centers and various application programs after their children were diagnosed [5]. In another study investigating the experiences of mothers of children diagnosed with ASD, mothers expressed their opinions specifically on three issues during the evaluation process and mentioned their initial concerns about the development and behavior of their children. The parents' concerns were mostly caused by uncertainties and continued in the second pregnancy. However, mothers said that they shared these concerns about their children with their doctors or family physicians, but they did not refer them to a physician specializing in diagnosing and treating children with ASD. Many parents expressed that they felt lonely in deciding where to go to receive services and which educational services would be more appropriate for their children. Parents further stated that they needed to be informed and supported about interventions and practices for their children diagnosed with ASD [6].

Families start a search after realizing the different behaviors of their children. It is a known fact that the sooner children diagnosed with autism are intervened, the more successful the results. There are no reliable biomarkers or specialized laboratory tests to diagnose autism and clinical observation is still the gold standard for diagnosis [7], making the knowledge and experience of doctors about autism especially important. In the American Academy of Pediatrics (AAP) Autism Guidelines of 2006-2007, the importance of including routine autism screening in pediatric applications is underlined [8].

In a study on the role of pediatricians in the evaluation of children with autism, in which parents' opinions were sought, how pediatricians' approaches to the concerns of parents affected the evaluation process and parents' views on the importance of interaction between parents and pediatricians were investigated. The interviews revealed that the relationship between parents and pediatricians was multifaceted or complex and would make a significant contribution to early or late diagnosis of ASD [9].

Pediatricians and family physicians are often the first healthcare professionals to encounter children with symptoms associated with developmental disorders such as autism. In other words, pediatricians are the first individuals with whom the parents share their concerns about their child's development. Therefore, the attitudes of pediatricians have a prominent place in the early diagnosis and treatment of a severe and chronic problem with a lifelong impact such as autism [10]. Unfortunately, the diagnosis and treatment of developmental problems are not clearly included in the education of pediatricians. Moreover, since the department of pediatric mental health and diseases is not present in all medical faculties located in Turkey, the education of medical faculty students regarding pediatric psychiatry remains insufficient. Only some of the students of the faculties with the department of pediatric mental health and diseases receive relatively adequate pediatric psychiatry training. As a result, some of the physicians graduate without learning about autism, which progresses with severe developmental problems when not diagnosed in the initial period by a pediatric psychiatrist [11]. Therefore, it is believed that pediatricians do not have adequate information about autism symptoms and do not know which strategies to use in their treatment and how to guide children, particularly those with severe autism symptoms [12].

This study aimed to examine pediatricians' sources of information on autism and their current knowledge.

Materials and methods

This study was designed as a cross-sectional self-report questionnaire-based internet study and conducted between 21–28 October 2020. The population of the study consisted of pediatricians. The data were collected using Google Forms questionnaires (Google, California, USA) sent to the smartphones of volunteer physicians, who were reached from hospital databases and research groups. A total of 151 physicians answered the questionnaire, 145 of which (96.0%) completed it.

Sociodemographic data

This form was created by the researchers. It includes questions about pediatricians' age, sex, marital status, professional experience, and possible sources of information about autism.

Knowledge about Childhood Autism among Health Workers questionnaire (KCAHW) - Turkish version

This questionnaire, which was developed by Bakare et al. [13], consists of 19 questions about the four domains of autism. The first domain consists of eight items and concerns the impairment in social interaction observed in children with autism. The second domain consists of a single item, symptoms related to communication and language development. The third domain consists of four items indicating the obsessive and compulsive, repeating, and stereotypical symptoms observed in autism. The fourth domain consists of six items and questions whether autism is a neurodevelopmental disorder, examines possible comorbid conditions, and explores the ages at which it occurs. The possible total score that can be received from the questionnaire ranges from 0 to 19. Each item is answered as "yes," "no," or "I don't know." Correct answers receive 1 point, and the other answers receive 0. The last item questions the age of onset of autism and is scored as zero for neonatal age or infancy, and one for childhood. It is completed within 10 minutes on average. Özgür et al. [14] conducted the Turkish validity and reliability study of the scale.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 software. Results were expressed as mean (standard deviation), median (minimum-maximum), and number (%) for ease of understanding. Visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov, Shapiro-Wilk tests) methods were used to determine whether the variables followed a normal distribution. In regression analysis, the total of confirmatory answers was divided into quartiles. Logistic regression analysis was performed with retrospective elimination method to predict the group considered unsuccessful (below Q3). A *P*-value of <0.05 was considered statistically significant.

Results

The data of 145 participants were analyzed in the study. The mean age was 35.4 years. Of the participants, 79.3% were females and 70.3% were married. Table 1 shows the sociodemographic variables.

Table 1: Sociodemographic variables

Study parameter		Mean (SD) (n=145)
Age		35.4 (6.1)
Sex	Male	20.7% (n=30)
	Female	79.3% (n=115)
Marital Status	Single	29.7% (n=43)
	Married	70.3% (n=102)
Professional Experience	0–5 years	53.8% (n=78)
	6–10 years	23.4% (n=34)
	11–20 years	17.9% (n=26)
	>20 years	4.8% (n=7)

Among all, 59.3% of the participants completed a child and adolescent psychiatry (CAP) internship during their medical education, 60.7% completed a CAP rotation and 49.7% attended trainings or meetings in this field. Sources of information about ASD are presented in Table 2.

Table 2: Sources of information about ASD

Study Parameter		(n=145)
Did you complete a child and adolescent psychiatry internship during your medical education?	Yes	59.3% (n=86)
	No	40.7% (n=59)
Did you attend a child and adolescent psychiatry rotation during your residency	Yes	60.7% (n=88)
	No	39.3% (n=57)
Did you attend a training or meeting on autism spectrum disorder?	Yes	49.7% (n=72)
	No	50.3% (n=73)

The results of the KCAHW questionnaire showed that the questions about social interaction (8 questions) were mostly answered correctly while the questions about neurodevelopmental disorders (6 questions) were given the most wrong answers. Table 3 shows the results of the KCAHW questionnaire.

When the rate of answering each question was examined, the most correctly answered questions were those related to social interaction, and the questions related to "mental retardation accompanying autism", "epilepsy accompanying autism" and "autism onset" were answered wrongly the most. Table 4 shows the correct answer rates for the questions.

Table 3: The results of the KCAHW questionnaire

Study parameter	Rates of correct answers (%)	Score Median (min-max)
Information on social interaction (8 questions)	89.3	7 (4–8)
Information on language and communication problems (1 question)	85.5	1 (0–1)
Information on repeating or restricted interest symptoms (4 questions)	82.2	4 (0–4)
Information on neurodevelopmental disorders (6 questions)	58.7	4 (0–5)
Total (19 questions)	77.7	15 (9–19)

Table 4: Rates of correctly answered questing (%)

Question	Rates of correct answering (%)	n
Marked impairment in non-verbal behaviors during social interaction.	99.3	144
Failure to develop peer relationships appropriate for developmental age.	98.6	143
Lack of social and emotional reciprocity.	97.6	142
Loss of interest in the environment and surroundings.	97.2	141
Stereotypical or repetitive movements.	97.2	141
Persistent preoccupation with parts of objects.	91.7	133
The child can appear as if deaf or dumb.	87.6	127
Delay or total lack of development of spoken language.	85.5	124
A social smile is usually absent in a child with autism.	83.4	121
Lack of spontaneous will to share enjoyment, interest, or activities with other people.	80.0	116
Autism is a childhood schizophrenia.	79.3	115
There may be abnormal eating habits.	72.4	105
Staring into open space and not focusing on anything specific.	70.4	102
Autism is a neurodevelopmental disorder.	68.3	99
Autism is an autoimmune condition.	67.6	98
Love for regimented routine activities.	66.9	97
Autism may be accompanied by mental retardation.	49.7	72
Autism may be accompanied by epilepsy.	42.1	61
The onset of autism is usually in childhood.	42.1	61

For the total correct answer rates, the Q3 and Q1 values were 68.1% and 89.5%, respectively. Accordingly, logistic regression analysis using the backward-elimination method performed with sociodemographic and education-related data to determine the factors affecting scoring below Q3 showed that the model was significant (X: 39.053, *P*=0.001) and explained 39.1% of the group in the fourth step. According to the remaining variables in the fourth step, being single (OR: 3.60) and not performing a CAP rotation (OR: 8.49) predicted scores below Q3 (sensitivity 53.8%, specificity: 99.2%). Table 5 summarizes the logistic regression model.

Table 5: Logistic regression model to determine the factors that affect scoring below Q3

Study parameter	χ^2	R^2	B	SE	*P*-value	OR	95% CI
Model	39.053	0.391					
Being single			1.281	0.607	0.035	3.600	1.100–111.834
Not attending a CAP rotation			2.139	1.147	0.042	8.491	1.012–80.429

In the first step, age, sex, marital status, professional experience, and sources of information are added. The fourth step is shown. SE: Standard error, OR: Odds Ratio, CI: Confidence interval

Discussion

The present study included a total of 145 pediatricians. The mean age of the sample was 35.4 years, and most participants were females.

The rate of correct answers to the questions about the core symptoms of autism (e.g., language and communication problems, social interaction, repeating symptoms, and limited area of interest) was high, while questions about neurodevelopmental diseases (causes of illness or concomitant illnesses) were mostly answered wrongly. Similar to the results of our study, a study conducted in the United States reported that 82% of pediatricians performed routine screening in children with developmental retardations and that 50% of children undergoing screening were evaluated with the Denver-II developmental test. However, the authors suggested that although there were many scanning and diagnostic tools developed for young children with ASD, there was still a delay in the early diagnosis [15]. In a study conducted by interviewing parents, pediatricians' approach towards parents' anxieties and concerns was reported to affect the diagnostic process and the interaction between parents and pediatricians was of immense importance. The authors reported that parents' negative experiences with pediatricians negatively affected their approach to the issue and that even if not intentionally, it increased the parent's sense of denial or rejection, causing a delay in the diagnosis. On the other hand, all parents stated that they trusted their pediatricians for the accuracy of the information about the health and development of their children and that they would like to be informed not only about ASD, but also on the causes of ASD and its treatment [9]. In another study published in 2011, interviews were made with the parents of children with ASD and parents reported that pediatricians did not want to talk to them about autism. In parallel with this result, mothers stated that they shared their concerns about the development and behavior of their children with their pediatricians, but their pediatricians did not refer them to a specialist. They further stated that their pediatricians provided information related to various health problems seen in early childhood, irritability, retardation in motor development, and sensory sensitivity [6]. In a study investigating the opinions and experiences of physicians, pediatricians stated that they did not feel comfortable when they established a diagnosis without consulting a specialist experienced in autism [16]. All these findings suggest that pediatricians are successful in identifying problems in children, but they lack information, which has been previously suggested but now begins to lose their validity, regarding the issues specific to autism, matters of concern to families, or issues related to the causes of autism. In fact, along with pediatricians, physicians working in other branches dealing with autism have difficulties in keeping up with the latest information about autism. In a study investigating the adaptation of French psychiatrists to changes made to the Diagnostic and Statistical Manual of Mental Disorders (DSM) classification system and diagnostic criteria, psychiatrists resisted adaptation to the relevant changes but were willing to acquire information sources for the new system and receive training on this subject [10].

A remarkable finding of the present study was that pediatricians' knowledge about the core symptoms of autism was mostly accurate. In a study from Turkey published in 2010, it was reported that more than 60% of pediatricians informed the parents of children with autism and pervasive developmental disorder (PDD) that their children's development was normal, and only 4% of the children were referred to a child psychiatry clinic due to symptoms of autism or PDD although they were followed regularly by pediatricians, between four to twenty-four times in the past year [11]. Although the rates of pediatricians referring their patients to a specialist were not investigated in the present study, this finding suggests that the knowledge of pediatricians about autism in Turkey has gradually increased within the last decade.

The further analyses performed in the present study have shown that being single and not receiving CAP rotation during residency predict that pediatricians' knowledge of autism is inadequate. In a study investigating the experiences and opinions of pediatricians involved in the diagnosis process of children with ASD, diagnosing a child was very difficult due to several reasons. Physicians stated that one of these reasons was that they did not receive sufficient training on ASD in medical faculties and during their residency. Secondly, they stated that they did not have sufficient time and opportunity to attend in-service training or meetings to obtain information about the diagnosis of children with ASD [16]. In another study from Turkey, specialists mentioned that they were having difficulties due to problems such as insufficiency of the duration for the diagnosis, lack of biological marker in the diagnosis, lack of following the neuro-motor development of the child, insufficiency of the special education services for the children with autism, the commercialization of the foundations giving education services in autism, and lack of informing the parents about autism [17]. Although several standards were introduced in the USA in 2001 for early recognition of developmental problems, no decrease was observed in the age of diagnosis in 2006, bringing up the issue that physicians could not receive sufficient information on this subject during their medical education [11]. The present study has shown that gaining experience in autism during a specific education on child health is more important.

This study has several limitations. First, although the knowledge of pediatricians on autism was measured, no information could be obtained about referring patients, making recommendations, and interventions performed. There is a need for further studies evaluating these parameters together.

Limitations

Our sampling strategy could be biased due to the hospital databases and research groups in which the questionnaire was posted. The sample was not fully representative, because most physicians were recruited from secondary and tertiary hospitals. The second limitation is our sample size, which limits the generalization of the results to all

countries. Further research in this area should address these issues and clarify these factors**.**

Conclusion

The results of this study have shown that pediatricians, who regularly monitor children, have a high level of knowledge about recognizing the symptoms of autism, a disorder in which early diagnosis is of great importance, whereas they have some deficiencies in answering questions that will eliminate families' concerns about autism. Therefore, pediatricians who see the child at least three to four times a year need pediatric psychiatry training that will ensure them to gain specific skills in diagnosing, making recommendations and initiating interventions outside of their specialization. The other option is being more involved in departments that will enable them to gain experience in autism.

References

1. Yıldırım AA, Çetinkol Y, Esnafoğlu E, Çalgın MK. Association of Borna disease virus with autism spectrum disorder in Turkish children. J Surg Med. 2020;4(11):986-9.
2. Baird G, Cass H, Slonims V. Diagnosis of autism. Br Med J. 2003;327:488-93.
3. Cuvo AJ. Training children with autism and pervasive developmental disorders to comply with healthcare procedures: Theory and research. International handbook of autism and pervasive developmental disorders: Springer, 2011,381-95.
4. Woods JJ, Wetherby AM. Early Identification of and Intervention for Infants and Toddlers Who Are at Risk for Autism Spectrum Disorder. Lang Speech Hear Serv Sch. 2003;34:180-93.
5. Molteni P, Maggiolini S. Parents' Perspectives Towards the Diagnosis of Autism: An Italian Case Study Research. Journal of Child and Family Studies. 2015;24:1088-96.
6. McCaffrey E. The maternal experience in the diagnosis of autism spectrum disorder: Chestnut Hill College; 2011.
7. Smith T, McAdam D, Napolitano D. Autism spectrum disorders: Applied behavior analysis, evidence, and practice. J Appl Behav Anal. 2007:1-29.
8. Council on children with disabilities, section on developmental-behavioral pediatrics, Bright Futures Steering Committee, Medical Home Initiatives For Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: An algorithm for developmental surveillance and screening. Pediatrics. 2006;118:405-20.
9. Sudhinaraset A, Kuo A. Parents' perspectives on the role of pediatricians in autism diagnosis. J Autism Dev Disord. 2013;43:747-8.
10. Chamak B, Bonniau B. Changes in the diagnosis of autism: how parents and professionals act and react in France. Cult Med Psychiatry. 2013;37:405-26.
11. Erden G, Akçakin M, Doğan DG, Ertem İÖ. Çocuk hekimleri ve otizm: Tanıda zorluklar. Türkiye Klinikleri Pediatri Dergisi. 2010;19:9-15.
12. Lancaster BM. Assessment and treatment of autism. Indian J Pediatr. 2005;72:45-52.
13. Bakare MO, Ebigbo PO, Agomoh AO, Menkiti NC. Knowledge about childhood autism among health workers (KCAHW) questionnaire: description, reliability, and internal consistency. Clin Pract Epidemiol Ment Health. 2008;4:17.
14. Gürbüz Özgür B, Aksu H, Eser E. Validity and reliability of the Turkish version of the knowledge about childhood autism among health workers questionnaire. Psychiatr Clin Psychopharmacol. 2019;29:765-73.
15. Dosreis S, Weiner CL. Autism spectrum disorder screening and management practices among general pediatric providers. J Dev Behav. 2006;27:88-94.
16. Finke EH, Drager KDR, Ash S. Pediatricians' perspectives on identification and diagnosis of autism spectrum disorders. Early Child Res Q. 2010;8:254-68.
17. Karaaslan D. Examination of the opinions of families and specialist doctors involved in the diagnosis of medical diagnosis of children with autism. Postgraduate Thesis, Marmara University, Istanbul, 2015. (Turkish).

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(2):158-162.
DOI: 10.28982/josam.867770

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

The relationship between corrected QT interval and neutrophil to lymphocyte ratio in patients with acute coronary syndrome

Saadet Demirtas İnci, Mehmet Erat

University of Health Sciences, Diskapi Education and Research Hospital, Department of Cardiology, Ankara, Turkey

ORCID ID of the author(s)
SD: 0000-0003-2900-2926
ME: 0000-0002-0952-5263

Corresponding Author
Saadet Demirtas İnci
Ziraat Mah. Sehit Omer Halisdemir Cad. No:20 Diskapi, Ankara, Turkey
E-mail: saadet_demirtas@yahoo.com

Ethics Committee Approval
The study protocol was made with the approval of Diskapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee with the number 11.01.2021 / 102/19.
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 February 19

Abstract

Background/Aim: In recent years, prolonged corrected QT (QTc) interval is thought to be an independent risk factor in patients with Acute Coronary Syndrome (ACS). Our aim in this study is to determine whether there is a relationship between the Neutrophil/Lymphocyte Ratio (NLR), which is a new inflammatory parameter, and prolonged QTc corrected (QTc) interval in patients with ACS.
Methods: In a retrospective cohort study, 649 patients with ACS were enrolled from January 2017 to July 2019, out of which ninety-two patients died during follow-up. Patients were divided into two groups according to the prolonged QTc interval (QTc ≥450 msec). The relationship between QTc interval prolongation and NLR was evaluated. The primary endpoint was early all-cause death.
Results: Thirty-one of 135 patients (22.9% *P*=0.002) with QTc interval prolongation and 61 of 514 patients without QTc prolongation (11.8% *P*=0.002) died. Prolonged QTc interval was positively correlated with NLR (r=0.20, *P*=0.001). Both NLR (OR: 1,016; 95% CI: 1.004–1.028; *P*=0.01) and QTc interval (OR: 1.016; 95% CI: 1.004–1.028; *P*=0.006) independently predicted early mortality. In the ROC curve analysis, the AUC value of QTc interval to predict in-hospital mortality was 0.680 (95% CI: 0.597-0.763; *P*=0.001), with a sensitivity of 35%, a specificity of 82% and an optimum cut-off value of ≥450 msec. The AUC value of NLR to predict in-hospital mortality was 0.711 (95% CI: 0.653-0.769; *P*<0.001), with a sensitivity of 64%, a specificity of 68% and an optimum cut-off value of ≥3.9.
Conclusion: In this study, we showed that prolonged QTc interval was positively associated with NLR, which is an indicator of systemic inflammation in patients with ACS, for the first time. Also, QTc interval prolongation and increased NLR were independent predictors of early mortality.

Keywords: Systemic inflammation, Early mortality, Electrocardiography

How to cite: İnci SD, Erat M. The relationship between corrected QT interval and neutrophil to lymphocyte ratio in patients with acute coronary syndrome. J Surg Med. 2021;5(2):158-162.

Introduction

Acute Coronary Syndromes (ACS) are among the most important causes of morbidity and mortality worldwide, especially in developed countries [1]. The heart rate-corrected QT interval predisposes patients with ACS to serious ventricular arrhythmias and is considered an indicator of arrhythmic risk. It also represents the action potential duration of depolarization and repolarization of the ventricle [2, 3]. The reason for prolongation in the QTc interval can be congenital or acquired, and include structural heart diseases, bradyarrhythmias, endocrine diseases, liver diseases, nervous system traumas, some infections such as HIV infection, hunger, hypothermia, drugs, and toxins [3].

In acute coronary events, inflammatory cells play an essential role in the initiation, progression, and rupture of atherosclerotic plaques. Neutrophil/Lymphocyte Ratio (NLR) has been evaluated in many cardiovascular diseases as a new inflammatory biomarker, especially in patients with ACS. The predictive effect of adverse cardiac events was reported in previous studies [4, 5]. It has been stated recently that systemic inflammation may cause prolongation of the QTc interval. To the best of our knowledge, no studies examine the relationship between the QTc interval and NLR, one of the new inflammatory parameters. We aimed to investigate the relationship between prolonged QTc interval and NLR and early hospital mortality in patients with ACS.

Materials and methods

We retrospectively collected demographic and clinical data of patients with ACS who were admitted to the Coronary Intensive Care Unit (CICU) between January 2017 and July 2019. A total of 700 ACS patients were included in the study, and fifty-one were excluded due to lack of data [Electrocardiography (ECG) or laboratory data]. Finally, 649 patients were evaluated, including 365 (56.2%) patients with ST-elevation myocardial infarction (MI), 220 (33.8%) patients with non-ST-elevation MI, and 64 (9.8%) patients with unstable angina. The AMI diagnostic criteria are based on the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force [6]. Diagnostic criteria for MI are as follows: (a) Electrocardiographic changes (ST-segment depression or 1 mm ST-segment elevation in 2 standard leads or two adjacent precordial leads, development of new left bundle branch block), (b) angina pectoris or angina equivalent symptoms, (c) specific cardiac biomarker elevations in troponin-I (>99th percentile of normal value), and (d) new marks of viable myocardial loss or regional wall motion defect on imaging methods [7]. Patients with STEMI were characterized by typical chest pain lasting >30 minutes at rest and met the above criteria on ECG with positive cardiac markers. Patients identified as NSTEMI had positive cardiac enzymes with typical chest pain symptoms but no ST-segment elevation in ECG. Unstable angina was defined as the occurrence of one or more angina episodes at rest in the last 48 hours or a progressive worsening of chest pain with normal cardiac biomarker values and no ST-segment elevation criteria in ECG. Coronary angiograpy was performed to all study patients and primary angioplasty of the culprit lesion was performed according to standard techniques. The treatment of all patients was arranged by the current guideline recommendations, and antiaggregant, angiotensin-converting enzyme inhibitors, beta-blockers and statin treatment were initiated within the first 24 hours after hospitalization in patients without contraindications.

Hypertension (HT) was defined as repeated blood pressure measurements with systolic blood pressure higher than 140 mmHg and diastolic blood pressure higher than 90 mmHg or previously using antihypertensive drugs. Diabetes mellitus (DM) was defined as fasting blood glucose levels above 126 mg/dL or above 200 mg/dL at any given time, using blood glucose-lowering medication or hemoglobin (Hb) A1c levels greater than 6.5%.

Patients with various ECG features such as atrial fibrillation, left or right bundle branch block or paced rhythm, complete atrioventricular block, incomplete or unreadable ECG printout, unreadable QT intervals, left ventricular (LV) hypertrophy, those with advanced heart valvular disease, history of cardiomyopathy, history of congenital heart disease, or implantable heart defibrillators, antidepressant, antipsychotic, and antiarrhythmic use, and patients with severe electrolyte disturbances were excluded from the study. Follow up was performed for all patients during their hospital stay and for one month after discharge. All-cause death was the primary endpoint, observed within 30 days of release from the hospital.

Traditional cardiovascular risk factors such as age, gender, HT, DM, hyperlipidemia, smoking and biochemical parameters such as glucose, creatinine, low-density lipoprotein (LDL) cholesterol, triglycerides, troponin I, and highly sensitive-C Reactive Protein (hs-CRP) were recorded. Transthoracic echocardiography was performed in all patients following standard images and techniques.

White blood cell (WBC) and differential counts (Beckman Coulter Inc., Hialeah, Florida, USA) were measured from blood samples (filled into tubes with standardized EDTA: Ethylenediamine tetraacetic acid) obtained at the time of admission to the Emergency Department (ED). Total neutrophil and lymphocyte counts were found, and NLR was automatically calculated with the statistical program used.

Our study adhered to the Helsinki Declaration principles. The study protocol was approved by Diskapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee with the number 11.01.2021/ 102/19.

Assessment of ECG

In all patients, 12-lead ECG recordings were taken in the supine position using a new generation ECG system (Cardiofax V model 9320, Nihon Kohden, Tokyo, Japan) with a paper speed of 25 mm/sec and a voltage of 10 mm/mV. After the patients were admitted to the CICU, the first ECG (or the first ECG before admission to the ED) was examined. ECG data was collected by two researchers who did not know of the patients' clinical statuses. The QT interval in ECG was measured as the time elapsed from the beginning of the QRS wave to where the T wave returned to its starting point on ECG [8]. The QTc interval was measured using the Bazett formula on the entire standard 12-lead ECG. We accepted the cut-off point defining the QTc interval extension as 450 msec [9]. Therefore, we divided our patients into two groups according to the QTc interval: Patients

without a prolonged QTc interval: <450 msec, and those with a long QTc interval: ≥450 msec

Statistical analysis

SPPS 25 (IBM Corp. Published 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) statistical package program was used to evaluate the data. Variables were calculated as mean (standard deviation) and percentage and frequency values. Shapiro Wilk and Levene tests were used for assessing the variables for normality and variance homogeneity preconditions. Independent 2-group t-test (Student's t-test) was used to compare the two groups' analysis, and Mann Whitney-U test was used if the prerequisites were not met. Chi-Square and Fisher's exact tests were used for categorical data. The relationship between two continuous variables was evaluated with Pearson's Correlation Coefficient and Spearman's Correlation Coefficient. Binary logistic regression analysis was used to evaluate the significance of the data on mortality and adjusted odd ratios (OR) at 95% confidence intervals (CI). Receiver operating characteristic (ROC) curve analysis was performed for the cut-off values in the variables' responses. The area under the curve (AUC) was calculated such that sensitivity and selectivity were maximum. Values of $P<0.05$ and $P<0.01$ were considered significant.

Results

The study population consisted of 649 patients with ACS, and 68% of which were males (n=469). The ages of the patients ranged between 28-98 years, with a mean of 60.67 (13.03) years. Table 1 shows the overall characteristics of all patients included in this study. Also, baseline characteristics of patients divided according to QTc interval prolongation are presented in Table 1. In the group with prolonged QTc interval, age, the number of diabetic patients and the number of patients with pre-existing coronary artery disease (CAD), and NLR ($P=0.02$) were higher, while Hb and LV ejection fraction (LVEF) were significantly lower.

Table 1: Baseline characteristics of patients

Variables	All patients (n=649)	No QTc prolonged (n=514)	QTc prolonged (n=135)	*P*-value
Age, (years)	60.67 (13.03)	59.93 (12.79)	63.46 (13.60)	0.005
BMI, (kg/m^2)	27.52 (4.50)	27.42 (4.54)	27.96 (4.35)	0.490
Gender, men, n (%)	469 (68)	372 (72.3)	97 (71.8)	0.914
HT, n (%)	314 (45)	239 (46.4)	75 (55.5)	0.065
DM, n (%)	189 (27)	140 (27.2)	49 (36.2)	0.043
Smoker, n (%)	326 (47)	271 (52.7)	55 (40.7)	0.008
Previous CAD, n (%)	201 (29)	148 (28.7)	54 (40.0)	0.008
HR, (beats/min)	76.19 (15.09)	75.98 (15.41)	76.99 (13.84)	0.492
SBP, (mmHg)	134.4 (26.52)	134.0 (26.43)	135.92 (26.91)	0.457
DBP, (mmHg)	78.53 (16.54)	78.52 (17.07)	78.60 (14.39)	0.961
Glucose,(mg/dL)	141.5 (64.1)	140.47 (64.47)	145.59 (63.15)	0.411
Creatinine,(mg/dL)	1.22 (0.91)	1.19 (0.80)	1.34 (1.25)	0.098
Sodium, (mEq/L)	136.8 (2.8)	136.76 (2.82)	137.03 (2.93)	0.336
Potassium, (mEq/L)	4.1 (0.48)	4.10 (0.46)	4.07 (0.54)	0.515
ALT, (mg/dL)	67.9 (101.2)	66.09 (103.28)	75.22 (93.05)	0.353
LDL-C, (mg/dL)	128.4 (34.9)	128.81 (35.02)	127.05 (34.96)	0.609
Triglycerides, (mg/dL)	154.43 (96.52)	158.97 (99.82)	137.24 (80.91)	0.023
Hb, (g/dL)	14.2 (2.0)	14.37 (2.03)	13.70 (2.07)	0.001
Platelet, (10^9/µL)	250.7 (73.7)	249.05 (72.47)	257.01 (78.40)	0.265
WBC, (10^9/µL)	11.02 (3.7)	11.0 (3.75)	11.08 (3.78)	0.825
Neutrophile, (10^9/µL)	7.49 (3.39)	7.35 (3.54)	8.00 (3.55)	0.053
Lymphocyte, (10^9/µL)	2.57 (1.49)	2.73 (1.88)	2.36 (1.39)	0.015
Hs-CRP, (mg/L)	30.66 (50.14)	30.37 (51.99)	31.83 (42.17)	0.800
Troponin T, (ng/mL)	7.35 (20.8)	7.29 (20.97)	7.57 (20.21)	0.887
EF (%)	48.18 (9.43)	48.60 (9.40)	46.57 (9.41)	0.030
QT interval, (msec)	386.30 (40.56)	376.46 (35.83)	424.07 (35.24)	0.001
QTc interval,(msec)	421.97 (34.02)	409.40 (24.44)	469.62 (20.31)	0.001
NLR	4.11 (3.77)	3.93 (3.75)	4.76 (3.78)	0.026

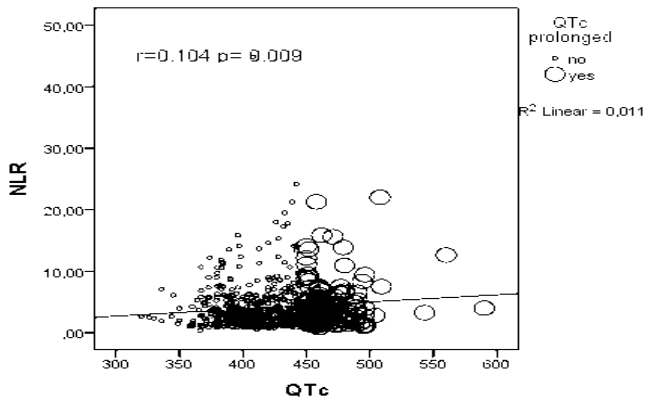
BMI: body mass index, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, ALT: Alanine aminotransferase, LDL-C: low density lipoprotein cholesterol, Hb: Hemoglobin, EF: ejection fraction, WBC: White blood cell, Hs-CRP: highly sensitive C-reactive protein, QTc: corrected QT, NLR: Neutrophile / lymphocyte ratio

Pearson's and Spearman's Correlation analysis was performed for the factors associated with the QTc interval prolongation. In correlation analysis, QTc interval prolongation significantly positively correlated with age and NLR and negatively correlated with Hb and LVEF (Table 2). The correlation between QTc interval prolongation and NLR is shown in Figure 1.

Table 2: Factors correlated with the QTc interval

Variables	QTc interval	
	r	*P*-value
Age, years	0.176	<0.001
EF, (%)	0.097	0.016
Hb, (g/dL)	-0.153	<0.001
Lymphocyte, (10^9/µL)	-0.061	0.120
NLR	0.104	0.009

Figure 1: Correlation of QTc interval with NLR



A total of 92 (14.1%) patients died during follow-up. When patients were grouped in terms of mortality, risk factors such as age, DM, HT, and CAD history were higher in the mortality group (Table 3). Also, there was a significant difference in heart rate, LVEF, creatinine, and Hb in the mortality group. The QTc interval and NLR values were significantly higher ($P<0.001$) in the mortality group (Table 3). Independent variables affecting mortality were age, LVEF, Hb, creatinine, QTc interval, and NLR in binary logistic regression analysis (Table 4). In the ROC curve analysis, the AUC value of QTc interval to predict early hospital mortality was 0.680 (95% CI: 0.597-0.763; $P=0.001$), with a sensitivity of 35%, a specificity of 82% and an optimum cut-off value of ≥450 msec. The AUC value of NLR to predict early hospital mortality was 0.711 (95% CI: 0.653-0.769; $P<0.001$), with a sensitivity of 64%; a specificity of 68% and an optimum cut-off value of ≥3.9 (Figure 2).

Table 3: Comparison of the clinical features of the patients according to early mortality

Variables	Mortality (+) (n=92)	Mortality (-) (n=557)	*P*-value
Age, years	72.47 (11.84)	58.71 (12.78)	<0.001
Men, n (%)	61 (66)	408 (73)	0.169
BMI, kg/m^2	28.10 (5.52)	27.42 (4.32)	0.439
HT, n (%)	63 (68)	251 (45)	<0.001
DM, n (%)	45 (49)	144 (26)	<0.001
Smoker, n (%)	24 (26)	303 (54)	<0.001
Previous CAD, n (%)	41 (45)	160 (29)	0.008
HR(beats/min)	81.87 (15.94)	75.25 (14.25)	<0.001
SBP (mmHg)	134.49 (23.90)	134.39 (26.93)	0.973
EF, (%)	44.83 (10.38)	48.69 (9.19)	0.001
Hb, (g/dL)	12.61 (2.07)	14.49 (1.93)	<0.001
Glucose, (mg/dL)	151.72 (66.7)	139.89 (63.67)	0.105
Creatinine, (mg/dL)	1.54 (1.05)	1.17 (0.88)	0.001
Hs-Troponin, (ng/mL)	8.24 (16.98)	7.20 (21.37)	0.661
WBC, (10^9/µL)	11.36 (4.59)	10.96 (3.62)	0.352
QTc interval, (msec)	434.48 (43.23)	419.86 (31.81)	<0.001
NLR	6.74 (6.14)	3.66 (2.99)	<0.001

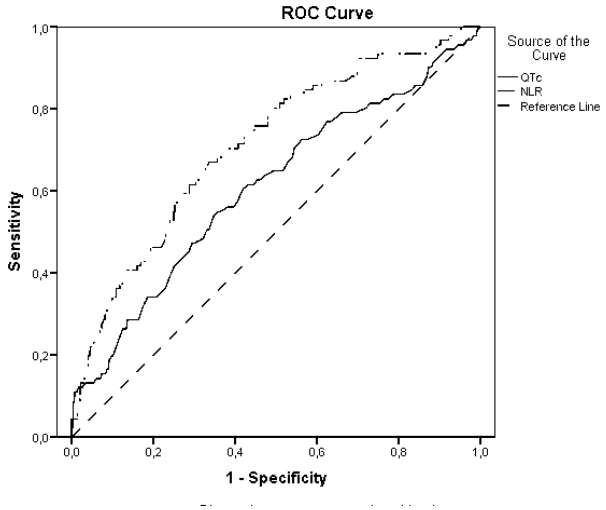
BMI: body mass index, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, HR: heart rate, SBP: systolic blood pressure, EF: ejection fraction, Hb: hemoglobin, WBC: White blood cell, QTc: corrected QT, NLR: Neutrophile / lymphocyte ratio

Table 4: Different variables affecting early mortality in binary logistic regression analysis

Variables	OR	95% CI	*P*-value
NLR	1.080	1.007-1.157	0.031
QTc interval, (msec)	1.011	1.003-1.020	0.009
EF, (%)	0.959	0.930-0.989	0.007
Hb, (g/dL)	0.764	0.651-0.896	0.001
Age, years	1.078	1.049-1.108	<0.001
Creatinine, (mg/dL)	0.942	0.735-1.207	0.637

OR: Odds ratio, CI: Confidence interval, QTc: corrected QT, NLR: Neutrophile / lymphocyte ratio, EF: ejection fraction, Hb: hemoglobin

Figure 2: Receiver operating characteristic curve analysis; NLR (AUC: 0.711, CI: 0.653-0.769; *P*=0.001), QTc (AUC: 0.608, CI 0.542-0.675; *P*<0.001)



Discussion

This study examines the relationship between NLR and QTc interval calculated during admission to CICU in patients with ACS. Our main finding was that NLR was significantly higher in the group with prolonged QTc interval; a significant positive correlation was found between these two parameters. Other inflammatory parameters such as WBC, neutrophil count, and hs-CRP were not significantly different between the groups. Lymphocyte count was lower in the QTc prolonged group, but no correlation was found between lymphocyte count and QTc prolongation.

Inflammation plays a vital role in all stages from the initial phase of atherosclerotic plaque to the development of clinical complications such as ACS [10]. Studies have reported that WBC and its subtypes indicate systemic inflammation and have a vital role in regulating the atherosclerotic process's inflammatory response [11, 12]. In acute coronary events, because of the decrease or interruption of the coronary vessel flow, leukocytes accumulate in the infarction area and regulate the response of the inflammation. Neutrophils are thought to be the first to accumulate [13]. They have several functions such as regulating and enhancing the inflammatory process by increasing their numbers in this region and causing the release of various mediators such as prothrombotic, proteolytic enzymes and oxidant substances, while lymphocytes decrease in number because of glucocorticoids secreted due to increased stress response [13, 14]. NLR represents a combination of neutrophils and lymphocytes, which are components of two independent inflammatory reactions. NLR is one of the new, easy and straight-forward inflammatory markers which has been used frequently in recent years. In one study, NLR was predictive of adverse outcomes in 34,000 ACS patients undergoing coronary revascularization and various other cardiovascular diseases [15, 16]. Also, it has been stated in previous studies that inflammation is associated with various types of cardiac arrhythmias [17, 18].

Significant prolongation of the QTc interval poses a significant risk for life-threatening ventricular arrhythmias such as Torsade de pointes [19]. In addition to congenital QT prolongation, many acquired diseases or conditions, such as ischemic heart disease, left ventricular hypertrophy, heart failure, Takotsubo cardiomyopathy, complete atrioventricular block or any bradyarrhythmia, inflammatory rheumatic heart disease (myocarditis, Chagas disease, rheumatic heart disease) or systemic inflammatory diseases (rheumatoid arthritis, connective tissue diseases), end-stage liver disease, endocrine disorders, cerebrovascular diseases, hypokalaemia, hypocalcemia, hypomagnesemia, drugs or toxins may cause QT prolongation [3-20]. Recent studies show that inflammation and immunity may be important determinants of prolonged QTc [3, 21, 22]. Systemic inflammation is thought to play a role in the pathogenesis of QTc prolongation in some non-inflammatory heart diseases. In patients with HT [23], Chang et al. reported that CRP level was associated with QTc and independently predicted prolonged QTc. Similarly, in another study, a significant relationship was reported between QTc duration and CRP level in patients with CAD [24]. There was no significant difference in WBC, neutrophil count, and hs-CRP between the groups in our study, but prolonged QTc group had a lower lymphocyte count. Still, there was no correlation between lymphocyte count and QTc prolongation. A significant positive correlation was found between QTc prolongation and NLR. Both parameters were predictors of early mortality. However, to the best of our knowledge, there are no studies examining the relationship between the QTc interval and NLR.

Limitations

Our study has numerous limitations. This is a single-center retrospective study, and the number of patients is not large due to the exclusion criteria. Unfortunately, the follow-up time was short (up to 30 days after discharge from the hospital), and long-term follow-up data are not available. Likewise, other inflammatory parameters, such as IL-1β, IL-6, and TNF-α, were not evaluated in our study.

Conclusions

It has been reported that prolonged QTc interval in patients with acute coronary syndrome is an early sign of acute ischemia. In these patients, prolonged QTc interval is considered a marker for adverse events, particularly arrhythmia [18, 25]. Systemic inflammation has a major place in the pathophysiology of many heart diseases and may prolong the QTc interval [23-24]. In this study, we found that NLR, a new inflammatory marker, was significantly higher in the group with prolonged QTc interval in patients with ACS, a significant positive correlation existed between these two parameters. Additionally, these two parameters were independent predictors of early mortality. Inflammation alone cannot explain QTc prolongation in patients with ACS, but it may be a synergistically contributing factor. More comprehensive prospective studies are needed to better evaluate this.

References

1. Smith JN, Negrelli JM, Manek MB, Hawes EM, Viera AJ. Diagnosis and Management of Acute Coronary Syndrome: An Evidence-Based Update. The Journal of the American Board of Family Medicine. 2015;28(2):283-93.
2. Jiménez-Candil J, Diego M, Cruz González IC, Matas J M G, Martín F, Pabón P, et al: Relationship between the QTc interval at hospital admission and the severity of the underlying ischaemia in low and intermediate risk people studied for acute chest pain. Int J Cardiol. 2008;126:84–9.

3. Lazzerini PE, Capecchi PL, Laghi-Pasini F. Long QT syndrome: an emerging role for inflammation and immunity. Front Cardiovasc Med 2015;2:26. doi: 10.3389/fcvm.2015.00026.
4. Fiechter M, Ghadri JR, Jaguszewski M, Siddique A, Vogt S, Haller RB, et al. Effect of inflammation on adverse cardiovascular events in patients with acute coronary syndrome. J Cardiovasc Med (Hagerstown). 2013;14(11):807-14.
5. Choi DH, Kobayashi Y, Nishi T, Kim HK, Ki YJ, Kim SS, et al. Combination of mean platelet volume and neutrophil to lymphocyte ratio predicts long-term major adverse cardiovascular events after percutaneous coronary intervention. Angiology. 2019;70:345–51.
6. Thygesen K, Alpert JS, Harvey D, Jaffe AS, Apple FS, Galvani M, et al. White on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the redefinition of myocardial infarction. Universal definition of myocardial infarction. Eur Heart J. 2007;28:2525–38.
7. Hamm C, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. E SC Guidelines for the management of acute coronary syndromes in patients presenting without ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2999–3054.
8. Savonitto S, Ardissino D, Granger CB, Morando G, Prando MD, Mafrici A, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. JAMA.1999;281:707.
9. Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, et al: AHA/ACC/HRS recommendations for the standardization and interpretation of the electrocadiogram part IV: The ST segment, T and U waves, and the QT interval. A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009;53:982–91.
10. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105:1135–43.
11. Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, et al; Intermountain Heart Collaborative Study Group. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol. 2005;45(10):1638-43.
12. Gurm HS, Bhatt DL, Lincoff AM, Tcheng JE, Kereiakes DJ, Kleiman NS, et al. Impact of preprocedural white blood cell count on long term mortality after percutaneous coronary intervention: insights from the EPIC, EPILOG, and EPISTENT trials. Heart. 2003;89(10):1200-4.
13. Oncel RC, Ucar M, Karakas MS, Akdemir B, Yanikoglu A, Gulcan AR, et al. Relation of neutrophil-to-lymphocyte ratio with GRACE risk score to in-hospital cardiac events in patients with ST-segment elevated myocardial infarction. Clin Appl Thromb Hemost. 2015;21(4):383-8.
14. Soylu K, Gedikli O, Dagasan G, Aydin E, Aksan G, Nar G, et al. Neutrophil-to-lymphocyte ratio predicts coronary artery lesion complexity and mortality after non-ST-segment elevation acute coronary syndrome. Rev Port Cardiol. 2015;34(7-8):465-71.
15. Guasti L, Dentali F, Castiglioni L, Maroni L, Marino F, Squizzato A, et al. Neutrophils and clinicaloutcomes in patients with acute coronary syndromes and/or cardiacrevascularisation. A systematic review on more than 34,000 subjects. Thromb Haemost. 2011;106:591–9.
16. Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiryet G, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013;11:55–9. doi: 10.1586/erc.12.159.
17. Kucuk U, Arslan M. Assessment of the white blood cell subtypes ratio in patients with supraventricular tachycardia: Retrospective cohort study. J Surg Med. 2019;3(4):297-9.
18. Lewek J, Kaczmarek K, Cygankiewicz I, Wranicz JK, Ptaszynski P. Inflammation and arrhythmias: potential mechanisms and clinical implications. Expert Rev Cardiovasc Ther. 2014;12(9):1077-85.
19. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation. 2010;121:1047–60.
20. Kenigsberg DN, Santaya K, Khanal S, Kowalski M, Krishnan SC. Prolongation of the QTc interval is seen uniformly during early transmural isquemia. J Am Coll Cardiol. 2007;49:1299-305.
21. Kim E, Joo SJ, Kim J, Ahn JC, Kim JH, Kimm K, et al. Association between C-reactive protein and QTc interval in middle-aged men and Women. European Journal of Epidemiology. 2006;21:653–9.
22. Lazzerini PE, Laghi-Pasini F, Bertolozzi I, Morozzi G, Lorenzini S, Simpatico A, et al. Systemic inflammation as a novel QT-prolonging risk factor in patients with torsades de pointes. Heart. 2017;0:1–9. doi: 10.1136/heartjnl-2016-311079.
23. Chang KT, Shu HS, Chu CY, Lee WH, Hsu PC, Su HM, et al. Association between C-reactive protein, corrected QT interval and presence of QT prolongation in hypertensive patients. Kaohsiung J Med Sci. 2014;30:310–5. doi: 10.1016/j.kjms.2014.02.012.
24. Yue W, Schneider A, Rückerl R, Koenig W, Marder V, Wang S, et al. Relationship between electrocardiographic and biochemical variables in coronary artery disease. Int J Cardiol. 2007;119:185–91. doi: 10.1016/j.ijcard.2006.07.129.
25. Nowinski K, Jensen S, Lundshl G, Bergfeldt L. Changes in ventricular repolarization during percutaneous transluminal coronary angioplasty in humans assessed by QT interval, QT dispersion and T vector loop morphology. J Intern Med. 2000;248:126–36.[i]

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.

i

J Surg Med. 2021;5(2):163-167.
DOI: 10.28982/josam.850739

Research article

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

Inflammatory prognostic index score as a new parameter predicting overall survival in renal cell carcinoma

Ahmet Dirican [1], Ferhat Ekinci [2], Atike Pınar Erdoğan [2], Gamze Göksel Öztürk [2]

[1] Department of Medical Oncology, Izmir University of Economics, Medicalpark Hospital, Izmir, Turkey
[2] Celal Bayar University, Department of Medical Oncology, Manisa, Turkey

ORCID ID of the author(s)

AD: 0000-0001-6992-9289
FE: 0000-0002-9317-942X
APE: 0000-0003-4859-7574
GGÖ: 0000-0002-7991-0036

Corresponding Author
Ahmet Dirican
Department of Medical Oncology, Izmir University of Economics, Medicalpark Hospital, Yeni Girne Bulvarı, 1825. Sk. No:12, 35575 Karşıyaka, Izmir, Turkey
E-mail: ahmetdirican@yahoo.com

Ethics Committee Approval
The study protocol was approved by Manisa Celal Bayar University Ethics Committee (11.01.2021/ 102/19).
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 February 19

Abstract

Background/Aim: The importance of prognostic markers in the treatment and follow-up of metastatic renal cell carcinoma is gradually increasing. Currently used markers do not meet the exact needs in this regard. In this study, we evaluated the predictive and prognostic values of inflammatory prognostic index (IPI) scoring in metastatic Renal cell carcinoma (RCC) patients. In IPI scoring, we used four biochemical parameters related to inflammation, including albumin, CRP, neutrophils, and lymphocytes.
Methods: Medical records of fifty-seven patients with RCC treated in Celal Bayar University Medical Faculty Hospital Medical Oncology Clinic between February 2012 and April 2019 were retrospectively reviewed. The IPI was calculated as C-reactive protein × NLR (neutrophil/lymphocyte ratio)/serum albumin. Univariate and multivariate analyses were performed to assess the prognostic value of relevant factors.
Results: The cut-off value for IPI in predicting mortality was 1.03 according to ROC curve analysis. Median OS of the patients with IPI ≥1.03 was 8 months (95 %Cl 3-10.9). The relationship between overall survival and IPI score was remarkable. According to this analysis, comorbidity, metastasis to the lung, liver, lymph nodes, bone, the number of metastatic sites (one metastatic area), high NLR, high IPI were also significantly associated with OS (P<0.05 for each). In multivariate analyses, IPI was an independent prognostic factor in RCC. Patients with high IPI (>1.03) had an increased mortality risk compared to those with low IPI (<1.03) (HR: 8.5; 95 %CI, 2.303-31.42; P<0.001). Comorbidity, lung metastasis, lymph nodes and bone metastasis, high NLR, IMDC risk also independently predicted worse OS in RCC.
Conclusion= The relationship between many inflammatory markers, such as NLR and RCC, and overall survival was proven earlier, while the relationship with IPI is discussed for the first time. We would like to discuss the findings we obtained in our study in the light of other analyses in the literature investigating the relationship between other inflammation markers and RCC. IPI may be an easily accessible and independent prognostic index for RCC patients, and useful for clinical practice.

Keywords: Renal cell carcinoma, IPI scoring, Overall survival, Neutrophil/lymphocyte ratio, Inflammation mediators, C-reactive protein, Albumin

How to cite: Dirican A, Ekinci F, Erdoğan AP, Öztürk GG. Inflammatory prognostic index score as a new parameter predicting overall survival in renal cell carcinoma. J Surg Med. 2021;5(2):163-167.

Introduction

Renal cell carcinoma (RCC) is the most common renal malignancy, and most originate from the renal parenchyma. Due to the lack of routine screening tests and late manifestation, it is often diagnosed at advanced stages. Most patients remain asymptomatic until later stages of the disease [1-3]. Therefore, as with most cancers, RCC misses the chance of surgery, which is the main curative treatment. In stage I RCC patients, the five-year disease-specific survival is about 80-95%, while in stage IV patients this rate is less than 10%, and the average overall survival is 10-15 months [3, 4].

The disease recurrence or metastasis in cancer depends on the complex relationship between the tumor and the inflammatory response established with the host [5]. In fact, the existence of this relationship was shown by Virchow for the first time in the 19th century. He observed leukocytes in the tumoral tissue and that cancer was more frequent in chronic inflammation sites [6]. However, the central role of inflammation in tumor formation was revealed more prominently with the research conducted in the last 15 years [7, 8]. Inflammation mediators are important components of the tumor microenvironment, especially in some cancers, and m inflammatory changes may occur before or after oncogenic changes. Inflammatory microenvironment in the tumor engages in angiogenesis or metastasis [8]. Some oncogenes are also mediated, and the tumor environment is rearranged [9, 10]. Hypoxia and lacking nutrients lead to necrotic cell death within the tumor nucleus. This leads to the release of proinflammatory cytokines from the tissue [10, 11]. DNA damage and genomic instability can be induced indirectly because of the mediators produced in case of inflammation [6, 12, 13]. DNA mismatch can also cause inactivation and suppression of repair genes, causing mutagenic effects. That and similar other mechanisms explain the relationship of inflammation and oncogenic mutations [6, 14]. T and NK cells activated because of tumorigenicity have anti tumoral properties with cytotoxic effect. In the tumor tissue developed due to inflammation, the pro-tumorigenic structure is induced by the triggering of the inflammatory cells, while the anti-tumorigenic effect continues with the cellular immune elements. Despite this dual mechanism, the net effect is often tumor growth and progression [15].

The most common indicators of inflammatory response in cancer patients are a number of biochemical or hematological markers [16]. The most used are C-reactive protein, white cell, neutrophil and platelet count, and low albumin [17, 18]. These values have many uses, such as calculating neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (TLR), Glasgow Prognostic Score (using C-reactive protein and albumin) for prediction of disease recurrence, prognosis, and response to treatment [19]. In a study published by Dirican et al. [20], non-small cell lung cancer (NSCLC) patients' survival was predicted by inflammatory prognostic index (IPI) using the level of C-reactive protein, NLR and Serum Albumin. In the light of this data, we think that there is a need for simple and accessible markers that can both predict postoperative recurrence in RCC and consequently establish a relationship with survival. For this reason, the main purpose of our study is to analyze the predictive and prognostic value of IPI in metastatic RCC patients in addition to other markers currently used.

Materials and methods

Medical records of patients with RCC treated in Celal Bayar University Medical Faculty Hospital Medical Oncology Clinic between February 2012 and April 2019 were retrospectively reviewed. Of these patients, those in the metastatic stage and those with sufficient follow-up data were included in the study as a retrospective cohort. Clinicopathologic variables such as age, gender, performance status (PS), treatments, histopathology type, localization of metastasis, Comorbidity, International Metastatic RCC Database Consortium (IMDC) risk classification were recorded by an electronic medical record system. Patients' performance statuses were noted based on the Karnofsky performance status scores. A total of 57 RCC patients were reviewed. Patients histologically diagnosed as RCC and staged according to the TNM criteria were included. Only metastatic patients were analyzed. The initial treatment modalities included operation, chemotherapy, targeted therapy, immunotherapy, and best supportive care. Other factors that could shorten survival were not excluded from the study to prevent bias (co-morbidity etc.). Patients who were under metastatic RCC treatment for a brief time and had to quit due to side effects or progression were included in the study. This study was approved by Manisa Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee with the decision number 20.478.486 dated 27/11/2019.

Laboratory data collection

Neutrophil, lymphocyte, hemoglobin level and biochemical parameters such as serum albumin, calcium level and CRP were recorded. IPI was calculated with the following formula: CRP × NLR / serum albumin.

Statistical analysis

A Kaplan-Meier analysis with log-rank test was performed to determine cumulative survival curves. Univariate and multivariate analyses for survival difference were performed using the Cox proportional hazards model and were expressed as hazard ratios (HRs) and 95% CIs. Overall survival (OS) was calculated from the metastasis diagnosis of the patient to either the date of death from any cause or the date of the last follow-up. Progression free survival (PFS) was calculated as the interval between the diagnosis and the progression of the disease, recurrence, or death from any cause. Categorical variables were presented as the number of patients and percentages and compared using Chi-square or Fisher's exact test with odds ratio (OR), within a 95% confidence interval (CI). Receiver Operating Characteristics (ROC) curve analysis was used to determine the cut-off value for NLR and IPI. Tumor response was assessed according to response evaluation criteria in solid tumors (RECIST). Statistical analyses were performed using SPSS 18.0 software (SPSS Inc. Chicago, IL). All statistical assessments were two-sided and a *P*-value of 0.05 was considered statistically significant.

Results

Patient characteristics

A total of fifty-seven mRCC patients were evaluated retrospectively. Among all, 71.9% (41) were male, and 28.1 % (16) were female. The median age was 57 (range 21-78) years. Patients with at least one metastatic lesion were included in the study. Three patients (13%) had metastasis at diagnosis. Other clinical and pathological features are shown in Table 1. Patients were grouped according to IMDC risk classification. The favorable, intermediate, and poor risk groups had 7 (12.3%), 35 (61.4%) and 15 (26.3%) patients, respectively.

Table 1: Patient characteristics

No of patients	57
Median age (range)	57 (21-78)
	No (%)
Male	41 (71.9)
Female	16 (28.1)
Histological type	
Clear cell	38 (66.7)
Non-clear cell	18 (31.6)
Localization of metastasis	
Lung	39 (68.4)
Liver	22 (38.6)
Brain	5 (8.8)
Bone	18 (31.6)
Lymph nodes	43 (75.4)
Other	21 (36.8)
Number site of metastasis	
1	13 (22.8)
2	20 (35.1)
≥3	24 (42.1)
IMDC	
Favorable	7 (12.3)
Intermediate	35 (61,4)
Poor	15 (26.3)
Therapy	
First line	47 (82.5)
Second line	24 (42.1)
At least three lines	15 (26.3)
Comorbidity	
At least one	31 (54.4)

Treatment

Of the patients, 82.5% (47) received first-line treatment, 42.1% (24) received second-line treatment, and 26.3% (15) received third-line treatment. The treatments received by the patients were interferon (n=12), sunitinib (n=33), pazopanib (n=9), axitinib (n=12), everolimus (n=9), and nivolumab (n=7). These are all the standard treatments our patients receive.

Survival analysis

The NLR cut off value was 2.77. The median OS of 36 (63.2%) patients was 52 months (95% CI 15.3-88.6) with NLR <2.77 and median OS of 21 (36.8%) patients was 8 months (95% CI 3.4-12.5) with NLR ≥2.77 (Figure 1). The cut off value for IPI was 1.03. The median OS of 19 (33.3 %) patients was NR (not reached) with IPI <1.03 and median OS of 38 (66.7%) patients was 8 months (95% CI. 3-10.9) with IPI ≥1.03 (Figure 2). The median OS of 7 (12.3%) patients in the favorable risk group, 35 patients (61.4%) in the intermediate risk group and 15 patients (26.3%) in the poor risk group were 49 months, 41 months, and 2 months, respectively (P=0.022). Comorbidity, lung metastasis, liver metastasis, lymph node metastasis, bone metastasis, number of metastatic sites (one metastatic area), high NLR, high IPI were also significantly associated with OS. However, OS did not differ in terms of age (P=0.797), gender (P=0.671), brain metastasis (P=0.575) and the number of metastatic sites (P=0.066 for two metastatic sites and P=0.136 for ≥3 metastatic sites). In multivariate analyses, IPI was an independent prognostic factor in RCC. Patients with high IPI (>1.03) had increased mortality risk compared with those with low IPI (<1.03) (HR, 8.5; 95% CI, 2.303-31.42; P<0.001). Comorbidity, lung, lymph node and bone metastasis, high NLR, IMDC risk also independently predicted worse OS in RCC. All multivariate survival analyses are presented in Table 2.

Figure 1: Overall survival curves comparing patients with RCC with a high NLR vs low NLR

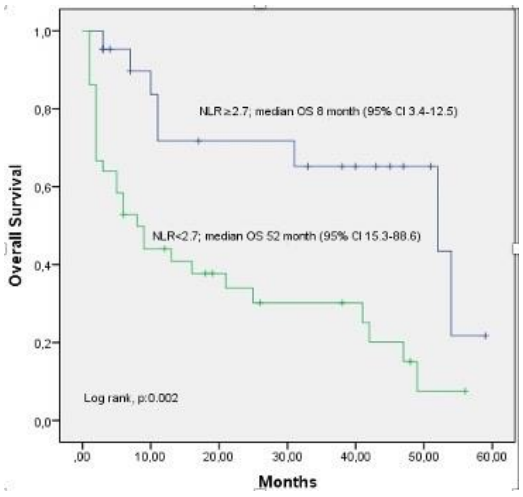


Figure 2: Overall survival curves comparing patients with RCC with a high IPI vs low IPI

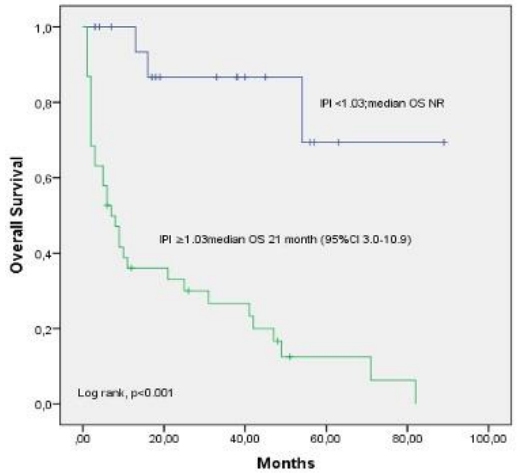


Table 2: Results of univariate and multivariate Cox's proportional hazard models in terms of OS

Characteristics	Univariate Analysis OS HR (95%CI)	*P*-value	Multivariate Analysis OS HR (95%CI)	*P*-value
Age	1.018 (0.951-1.068)	0.797		
Sex	1.23 (0.469-3.241)	0.671		
Comorbidity	4.63 (1.720-12.495)	0.002	3.13 (1279-7.700)	0.013
Lung metastasis	3.42 (1.087-10.809)	0.035	4.31 (1.492-12.485	0.007
Liver metastasis	3.98 (1.306-12.155)	0.015	1.25 (0.466-3.350)	0.658
Lymph nodes metastasis	0,16 (0.041-0.673)	0.012	0.120 (0.056-0.762)	0.018
Bone metastasis	0,19 (0.062-0.623)	0.006	0.28 (0.053-0.872)	0.028
Brain metastasis	0,600 (0.106-3.404)	0.575		
Other metastases	1.78 (0.648-4.893)	0.263		
Number of metastatic sites				0.055
(one metastatic site,		0.002		0.125
two metastatic sites and	0.23 (0.052-1.100)	0.066	0.33 (0.081-1.357)	0.679
≥3 metastatic sites)	3.08 (0.702-13.581)	0.136	1.33 (0.338-5.289)	
High NLR	3.601 (1.263-10.287)	0.017	3.39 (1.207-9.550)	0.021
High IPI	10.0 (2.596-38.523)	0.001	8.501(2.303-31.42)	0.001
IMDC risk				0.037
(good risk,		0.018		0.019
intermediate risk and	12.23 (1.350-110.86)	0.026	5.26 (1.671-41.361)	0.014
poor risk)	25.06 (2.582-243.21)	0.005	14.96(1.552-144.013)	

NLR: Neutrophil/lymphocyte ratio, IMDC: International Metastatic RCC Database Consortium

Discussion

The main purpose of our study was to analyze the predictive and prognostic value of IPI in metastatic RCC patients. In IPI scoring, we used four biochemical parameters related to inflammation, including albumin, CRP, neutrophils, and lymphocytes. The relationship of overall survival in RCC and NLR has been previously proven, while its relationship with

IPI is discussed for the first time. We would like to discuss the findings we obtained considering the relationship between other inflammation markers and RCC.

The most recent meta-analysis was performed by Shen et al. in 2019 to investigate the prognostic value of neutrophil count in pretreatment metastatic renal cell carcinoma. In a total of thirteen studies, 3021 patients were included. An elevated pretreatment neutrophil count resulted in worse OS (HR: 2.17, 95% CI 1.68–2.79, P<0.001) and PFS (HR: 1.78, 95% CI 0.91–3.49, P<0.001). In view of the heterogeneity of the studies in this publication, it seems reasonable to consider the neutrophil count a common marker of inflammation [21]. The high neutrophil count was the basis of the proportional formula in our study. However, it was confirmed with other inflammation parameters [22,23]. We found that high NLR (≥2.77) and high IPI (>1.03) were associated with decreased median OS. There are data proving that some of the neutrophil-related factors may induce genetic mutations in tumors or may secrete factors that promote tumor cell proliferation. Although the mechanism is not fully explained, neutrophils play a significant role in physiological angiogenesis, which may explain its key role in tumorigenesis [5,6,22]. There are studies showing that neutrophils have a prominent role in tumorigenesis, tumor cell proliferation and metastasis [6]. This makes it a key marker in the investigation of the relationship between inflammation and prognosis.

In a recent meta-analysis, which included twenty-four studies by Nunno et al., the relationship between NLR and both metastatic and localized RCC was investigated. A total of 10034 patients were included. A higher NLR was significantly associated with poor OS with a pooled HR of 1.57 (95% CI: 1.27–1.94) and 2.05 (95% CI: 1.74–2.41) in localized (n=1933) and metastatic (n=2318) patients, respectively. The same significance applies to PFS. Higher NLR resulted in worse PFS with a pooled HR of 1.69 (95% CI: 1.42–2.01) with a high level of heterogeneity. Higher NLR resulted in worse PFS with a pooled HR of 1.69 (95% CI: 1.42-2.01) in both localized (n=2656) and metastatic disease (n=1847). There are comparable results in our study in which high NLR is associated with poor survival rates. However, other parameters of inflammation were not included in this analysis. Although patient heterogeneity has been a problem in designing a meta-analysis, the substantial number of patients is an important advantage in this study [11]. In our study, the NLR cut-off value was 2.77. The short survival time in cases with high NLR and longer OS in those with low NLR were similar the study results in the literature [4,24].

CRP is a good indicator of inflammation because it is sensitive and responds more rapidly to changes in clinical status. Albumin is a negative acute phase reactant and a negative prognostic factor in cancer patients [4]. Using these two markers alone can predict prognosis in renal cell carcinoma. However, this index was an independent prognostic factor in many tumors, including kidney cancer [25]. In the study published in 2019 by T. Tsujino et al., C-reactive protein-albumin ratio (CAR) was studied as a prognostic factor in renal cell carcinoma. In that study, data obtained from studies involving 699 patients were analyzed. Five-year OS rates for patients in low and high CAR groups were 92.1% and 61.4%, respectively, illustrating a significant prognosis difference in terms of CAR among RCC patients (OS: P<0.001, in log-rank test). However, non-metastatic patients who underwent nephrectomy were included in this study. Similar results were observed in 72 patients who were subsequently metastatic. Two important aspects of this study are that it was conducted with two important parameters of inflammation that we use in IPI scoring and an elevated CAR was associated with shorter survival, and an independent predictor for OS [25].

In 2017, a study by Ishihara et al. investigated the role of systemic inflammatory markers including CRP, NLR and platelet/lymphocyte ratio (PLR) in predicting survival among sixty-three patients with metastatic renal cell carcinoma receiving second-line molecular-targeted therapy (mTT). The cut-off values of CRP, NLR and PLR were 0.48, 2.53 and 183, respectively. In patients with high CRP, NLR and PLR values, PFS and OS were significantly lower than those with low values. The major contribution of this study to the literature is that it is the first study to show that pre-treatment NLR and PLR values are closely related and patients with high CRP, NLR, and PLR values have shorter PFS and OS with second-line mTT after first-line TKI failure in mRCC [26]. In a study published in 2017 by Sekar et al, a new preoperative inflammatory marker prognostic score was studied in patients with localized and metastatic RCC. They suggested that a combination of specific inflammatory markers, called the RCC Inflammatory Score (RISK), can be a rigorous prognostic indicator of OS in RCC. Markers included in the scoring were CRP, albumin, erythrocyte sedimentation rate (ESR), corrected calcium and aspartate transaminase to alanine transaminase (AST/ALT) ratio. A total of 391 localized or metastatic patients who underwent nephrectomy were examined. Each patient was given a total RISK score of 0 to 10 based on the sum of 0, 1 or 2 individual biomarker scores (baseline risk (RISK 0), low risk (RISK 1-3), intermediate risk (RISK 4-6), and high risk (RISK 7-10). Median survival among the high-risk group was 7.2 months (95% CI: 4.9-11.4), which was 14.5 months (95% CI: 10.1-21.5) among the intermediate risk group (P=0.008). However, median survival was not reached among the low-risk and baseline groups. An importance of this study for us is that a template has been developed to include all three parameters used in IPI scoring. On the other hand, NLR was proven as a marker of inflammation at RCC [27]. Dirican et al. [20] published a study showing the prognostic value of the combination of NLR, CRP and albumin formulated as an IPI score in NSCLC patients. This study remains the only publication in the literature on IPI. They found that high IPI (≥15) was an indicator of poor OS, leading to 3.47-fold increase in the mortality risk (P<0.001). This encouraged us to study the same parameter in RCC, where more diverse inflammation markers were needed. The significant relationship between IPI and survival results also led us to conduct this study. The median OS of 19 (33.3%) patients was NS (not significant) with IPI <1.03 and median OS of 38 (66.7%) patients was 8 months (95% CI. 3-10.9) with IPI ≥2.77. In multivariate analyses, IPI was an independent prognostic factor in RCC. Patients with high IPI (>1.03) had increased risk of death compared with those with low IPI (<1.03) (HR, 8.5; 95% CI, 2.303-31.42; P<0.001). Comorbidity, lung, lymph nodes and bone metastasis, high NLR, IMDC risk also

independently predicted worse OS in RCC. We did not have the opportunity to compare these factors in RCC because there were no similar studies. However, in all the above-mentioned studies, the strong association of markers used in IPI scoring with survival was already proven [21, 24-27].

Limitations

The major limitations of our study are its retrospective design and that it cannot be performed with large patient series.

Conclusion

We think that IPI we developed will prove helpful because it is cheap and easy to use in routine clinical practice. Nowadays, prognosis has become especially important in the treatment decision of metastatic RCC and the search for new prognostic criteria increases the importance of our study. Studies evaluating this parameter in stage, locally advanced and metastatic stages may be needed. We believe that our study deserves attention as it is the first in the RCC literature.

References

1. Peinemann F, Unverzagt S, Hadjinicolaou AV, Moldenhauer I. Immunotherapy for metastatic renal cell carcinoma: A systematic review. J Evid Based Med. 2019 Nov;12(4):253-62. doi: 10.1111/jebm.12362.
2. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, et al. Renal Hücreli Karsinomun Epidemiyolojisi. Eur Urol. 2019;75(1):74-84. doi: 10.1016/j.eururo.2018.08.036
3. Jonasch E, Gao J, Rathmell WK. Renal cell carcinoma. BMJ. 2014;75(1):74-84. doi: 10.1016/j.eururo.2018.08.036.
4. Dirican A, Kucukzeybek Y, Erten C, Somali I, Demir L, Can A, et al. Prognostic and predictive value of hematologic parameters in patients with metastatic renal cell carcinoma: second line sunitinib treatment following IFN-alpha. Asian Pac J Cancer Prev. 2013;14(3):2101-5.
5. Roxburgh S, McMillan C. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncology. 2010;6(1):149-63.
6. Grivennikov SI, Greten R, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883-99.
7. Karin M. Nuclear factor-κB in cancer development and progression. Nature. 2006;441(7092):431-6.
8. Mantovani A, Allavena P, Sica A, Balkwill, F. Cancer-related inflammation. Nature. 2008;454(7203):436-44.
9. Soucek L, Lawlor ER, Soto D, Shchors K, Swigart LB, Evan GI, et al. Mast cells are required for angiogenesis and macroscopic expansion of Myc-induced pancreatic islet tumors. Nature Medicine. 2007;13(10):1211-8.
10. Sparmann A, Bar-Sagi D. Ras-induced interleukin-8 expression plays a critical role in tumor growth and angiogenesis. Cancer Cell. 2004;6(5):447-58.
11. Vakkila J, Lotze MT. Inflammation and necrosis promote tumour growth. Nature Reviews Immunology. 2004;4(8):641-8.
12. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A.Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 2009;30(7):1073-81.
13. Hussain SP, Hofseth LJ, Harris C.Radical causes of cancer. Nature Reviews Cancer. 2003;3(4):276-85.
14. Okazaki IM, Kotani A, Honjo T. Role of AID in tumorigenesis. Advances in Immunology. 2007;94:245-73.
15. Bui JD, Schreiber RD. Cancer immunosurveillance, immunoediting and inflammation= independent or interdependent processes? Current opinion in immunology. 2007;19(2):203-8.
16. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. New England journal of medicine. 1999;340(6):448-54.
17. Morley JE, Thomas DR, Wilson G. Cachexia: pathophysiology and clinical relevance. The American Journal of Clinical Nutrition. 2006;83(4):735-43.
18. Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. The American Journal of Clinical Nutrition. 2006;83(6):1345-50.
19. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Current Opinion in Clinical Nutrition & Metabolic Care. 2009;12(3):223-6.
20. Dirican N, Dirican A, Anar C, Atalay S, Ozturk O, Bircan A, et al. A new inflammatory prognostic index, based on C-reactive protein, the neutrophil to lymphocyte ratio and serum albumin is useful for predicting prognosis in non-small cell lung cancer cases. Asian Pacific journal of cancer prevention= APJCP. 2016;17(12):5101.
21. Shen J, Chen Z, Fan M, Lu H, Zhuang Q, He X. Prognostic value of pretreatment neutrophil count in metastatic renal cell carcinoma: a systematic review and meta-analysis. Cancer Management and Research. 2019;10(11):5365-74.
22. Tazzyman S, Lewis CE, Murdoch C. Neutrophils: key mediators of tumour angiogenesis. International Journal of Experimental Pathology. 2009;90(3):222-31.
23. Dirkx AE, Egbrink M.G, Wagstaff J, Griffioen AW. Monocyte/macrophage infiltration in tumors: modulators of angiogenesis. Journal of Leukocyte Biology. 2006;80(6):1183-96.
24. Nunno , Mollica V, Gatto L, Santoni M, Cosmai L, Porta C, Massari, F. Prognostic impact of neutrophil-to-lymphocyte ratio in renal cell carcinoma: a systematic review and meta-analysis. Immunotherapy. 2009;11(7):631-43.
25. Tsujino T, Komura K, Hashimoto T, Muraoka R, Satake N, Matsunaga T, et al. C-reactive protein-albumin ratio as a prognostic factor in renal cell carcinoma–A data from multi-institutional study in Japan. In Urologic Oncology: Seminars and Original Investigations. 2019;37(11):812.e1-812.e8.
26. Ishihara H, Kondo T, Yoshida K, Omae K, Takagi T, Iizuka J, et al. Effect of systemic inflammation on survival in patients with metastatic renal cell carcinoma receiving second-line molecular-targeted therapy. Clinical Genitourinary Cancer. 2017;15(4):495-501.
27. Sekar RR, Patil D, Baum Y, Pearl J, Bausum A, Bilen MA, et al. A novel preoperative inflammatory marker prognostic score in patients with localized and metastatic renal cell carcinoma. Asian Journal of Urology. 2017;4(4):230-8.

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(2):168-173.
DOI: 10.28982/josam.859368

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

Could eosinophil chemotactic factor (CCL11) be a useful biomarker of Covid-19?

Muzaffer Katar

Tokat Gaziosmanpasa University, Faculty of Medicine, Medical Biochemistry Department, Tokat, Turkey

ORCID ID of the author(s)
MK: 0000-0002-6296-2390

Corresponding Author
Muzaffer Katar
Kaleardı Mahallesi Muhittin Fisunoğlu Caddesi Ali Şevki EREK Yerleşkesi Tıp Fakültesi-Merkez, Tokat, Turkey
E-mail: drkatar@hotmail.com
muzaffer.katar@gop.edu.tr

Ethics Committee Approval
The study was approved by Tokat Gaziosmanpasa University Medical Faculty Clinical Research Ethics Committee on 25 June 2020 with the number 20-KAEK-165.
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 February 19

Abstract

Background/Aim: Differentiating COVID-19 positive patients from negative ones with similar symptoms and predicting the course of disease are major problems in COVID-19. For this purpose, we investigated the performance of Eosinophil Chemotactic Factor (CCL11) in COVID-19 and compared complete blood count parameters and indexes.
Methods: In this retrospective case-control study, ECF/CCL11 values, as well as the clinical, laboratory and radiological data of thirty patients who were diagnosed with Covid-19 between 15 March-15 June 2020 were compared with those of thirty healthy controls.
Results: Both patients and controls included 10 (33.30%) females and 20 (66.60%) males with a mean age of 57.2 (15.46) and 60.07 (20.59) years, respectively. Eosinophil counts of the patients on admission (EO1) were significantly lower than those of the controls and one-week later EO2 levels (P<0.001, P=0.004 respectively). EO1, NE1, NE2, PLT2/LYM2, LYM1/CRP1 and LYM2/CRP2 were the most predictive indexes. ECF values of the patients one week after admission (ECF2) were significantly lower than that of controls and admission levels (P=0.046, P=0.011 respectively). ECF2 values differentiated Covid19 negative individuals from patients with 46.70% sensitivity, 93.30% specificity at a cutoff value of ≤45.00 pg/mL. In ROC analysis of ECF2, AUC was 0.702 (P=0.045; 95% CI: 0.875-0.636).
Conclusions: Tracking ECF with CBC subsets and indexes may be helpful in the early prediction of severity, diagnosis, and follow up of critical COVID-19 patients in the course of the disease.

Keywords: Covid-19, ECF, CCL11, Diagnosis, Neutropenia, Lymphopenia

How to cite: Katar M. Could eosinophil chemotactic factor (CCL11) be a useful biomarker of Covid-19? J Surg Med. 2021;5(2):168-173.

Introduction

In early December 2019, cases of pneumonia of unknown origin appeared in Wuhan, China. A novel coronavirus was identified using metagenomic analyses from Bronchoalveolar lavage fluids at the Wuhan Virology Institute [1]. The United States Center for Disease Control and Prevention (CDC) named it 2019 novel coronavirus (2019-nCov). In infected patients, Covid-19 can cause a variety of symptoms, including fever, dry cough, shortness of breath, fatigue, lymphopenia, and eosinopenia. In more severe cases, infections that cause viral pneumonia can lead to acute respiratory syndrome (SARS) and even death [2].

Various chemokines and cytokines play roles in the proliferation of eosinophils and regulate their movement from bone marrow to tissues [3]. After allergen exposure, IL-5 is required for the migration of eosinophils from the bone marrow to the lung [4]. On allergen challenge, large amounts of IL-5 are produced by T helper 2 (Th2) lymphocytes [5]. Eosinophil migration is induced through IL-5 or CCL11 production by Type 2 native lymphoid cells (ILC2s) [6]. In recruitment of eosinophils into the tissue, chemokines CCL11 (eotaxin-1) and CCL24 (eotaxin-2) take the main part [7]. Eotaxin-1 selectively acts on the C-C motif receptor 3 (CCR3) [8]. CCL11 is involved in inflammatory conditions including allergic eosinophilia such as asthma and atopic dermatitis [9]. However, other eosinophil accumulation influencers in the lung have not yet been fully elucidated.

In recent studies, eosinophil counts in severe Covid-19 patients decreased significantly and the severity of the disease was associated with the level of eosinopenia. We also thought that this decrease in eosinophils might be related to Eosinophil Chemotactic Factor (ECF) / CCL11. Molecular (rt-PCR) or radiological diagnosis of patients with Covid-19 and those with similar symptoms takes too long, and these two groups are often confused. There is a need for simple and accessible laboratory biomarkers for the effective diagnosis of Covid-19 patients, and the prediction of disease course. For this purpose, we investigated the performance of ECF/CCL11 in Covid-19.

We aimed to find simple and accessible laboratory biomarkers to distinguish suspected COVID-19 patients from individuals exhibiting similar symptoms who are negative for the disease and predict the course. For this purpose, we investigated the diagnostic performance of ECF/CCL11, which is a major factor in the migration of eosinophils to tissues in Covid-19 patients with CBC subsets and indexes.

Materials and methods

After the Ministry of Health, Tokat Gaziosmanpasa University Medical Faculty Clinical Researches Ethical Committee also approved the study on 25 June 2020 with the number 20-KAEK-165. This retrospective case-control study conformed to the Helsinki Declaration principles. Due to the retrospective nature of the study, we did not obtain informed consent forms from the participants. Although the gold standard of diagnosis in Covid-19 is reverse transcriptase polymerase chain reaction (RT-PCR), we also included patients diagnosed with other methods, such as serologic tests or computerized tomography (CT). Based on power analysis, the inclusion of twenty-seven patients in the study planned in a single sample order yielded 80% power, 5% margin of error and an effect size of 0.50. Our patient group included thirty randomly chosen Covid-19 patients diagnosed with any of those diagnostic methods between 15 March and 15 June 2020, who were compared with thirty randomly chosen age and gender-matched healthy controls. All demographic and laboratory data of patients and controls were gathered by the same researchers. We did not know their eosinophil levels or ECF(CCL11) levels until all specimens were collected and assayed at one session by the same researcher. Considering all these conditions, we do not have any concerns of bias. Patients who underwent by-pass operation within the last month, those with a history of metabolic, malignant, and rheumatic diseases and pregnant women were excluded from the control group.

Data collection

All data of the patients were obtained retrospectively from archived medical file materials. The collected data includes demographic information, clinical medical history, concomitant diseases, signs and symptoms, laboratory findings and radiological imaging findings. The data of the hospitalization day of the patient was considered the admission day data. The data obtained at the end of one week after hospitalization was noted as the "first week data". Radiological images were classified as atypical, intermediate, and typical appearance according their compatibility with Covid-19.

Determination of serum ECF / CCL11 levels

The samples for measuring serum ECP levels were obtained from samples sent to the central laboratory for routine biochemical tests. No other samples were obtained from the patients for the purpose of study and no data were used except hospital and laboratory data. Serum ECF / CCL11 levels of the controls and Covid-19 patients at the time and first week of admission were measured with the Elabscience Co. 14780 commercial kit (Memorial Drive, Suite 216, Houston, Texas, USA) using the Enzyme Linked Immuno-Sorbent Assay (ELISA) method as per the kit package insert.

Statistical analysis

Descriptive analyses yield information about the features of the study groups. The data of continuous variables are presented as mean (standard deviation), and data on categorical variables are given as n (%). When comparing the means of quantitative variables between groups, the significance test of the difference between two means was used for the normally distributed variables, and the Mann Whitney U test was used for non-normally distributed variables. For intra-group comparison, the significance test of the difference between the two partners was used for the normally distributed variables, while Wilcoxon test was used for the non-normally distributed variables. Chi-square test was used to evaluate whether there was a relationship between qualitative variables. Paired t test was used to evaluate relations between quantitative variables. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic performance of ECP in Covid-19 disease. P values of less than 0.05 were considered statistically significant. Ready-made statistics software was used for calculations (SPSS 22.0 Chicago, IL, USA).

Results

Both our patient and control groups with mean ages of 57.2 (15.46) and 60.07 (20.59) years, respectively, consisted of 10 (33.30%) females and 20 (66.60%) males. PCR tests of 20 (66.60%) patients were positive, while those of 4 (13.30%) patients was negative. Serologic tests were positive in 24 (80%) patients. While the result of 24 (92.30%) patients who underwent computed tomography (CT) imaging were compatible with the disease, 2 (6.70%) were evaluated as negative. On admission, 22 (73.30%), 22 (73.30%), 10 (33.30%) and 24 (80.00%) of the patients had fever, coughing, dyspnea, and fatigue, respectively. Twenty-six (86.70%) patients had mild-moderate and 4 (13.30%) had severe disease. Mid-treatment, 22 (73.30%) were in mild-moderate and 8 (26.70%) were in severe condition. After a week of treatment, 24 (80.00%) were in mild-moderate and 6 (20.00%) were in severe condition. Four (13.30%), 2 (6.70%), 6 (20.00%), 2 (6.70%) and 2 (6.70%) of the patients had chronic lung disease, Diabetes Mellitus, hypertension, cardiovascular disease, and malignant comorbidities, respectively. While 3 (10.00%) of the patients lost their lives during the treatment process, 27 (90.00%) patients recovered and were discharged. The qualitative variable distributions according to the groups are shown in Table 1.

Table 1: Distribution of qualitative variables of patient group

Variables		n(%)
Gender	Female	10(33.3)
	Male	20(66.7)
Discharge	Discharged	27(90.0)
	Passed Away	3(10.0)
Chronical Lung Disease (CLD)	None	0(86.7)
	Present	4(13.3)
Diabetes Mellitus (DM)	None	28(93.3)
	Present	2(6.7)
Hypertension (HT)	None	0(80.0)
	Present	6(20.0)
Cardio-Vascular Disease (CVD)	None	28(93.3)
	Present	2(6.7)
Malignancy	None	28(93.3)
	Present	2(6.7)
Serological Test Positivity	Negative	6(20.0)
	Positive	24(80.0)
Polymerase Chain Reaction (PCR)	Negative	4(13.3)
	positive	20(66.6)
Computed Tomography (CT)	Incompatible	2(6.7)
	Compatible	24(92.3)
Clinical Condition (Admission)	Mild-Moderate	26(86.7)
	Critical-Severe	4(13.3)
Clinical Condition (Mid-Treatment)	Mild-Moderate	22(73.3)
	Critical-Severe	8(26.7)
Clinical Condition (After a week)	Mild-Moderate	24(80)
	Critical-Severe	6(20)
Fever	None	8(26.7)
	Present	22(73.3)
Dyspnea	None	20(66.6)
	Present	10(33.3)
Coughing	None	8(26.7)
	Present	22(73.3)
Malaise	None	6(20.0)
	Present	24(80.0)

Data were expressed in numbers and percentages. Pearson's chi-square test was used.

Laboratory findings

In our study, the eosinophil counts (EO1) of the patients at the time of admission were significantly lower than that of the controls (P<0.001). There was a significant increase in eosinophil levels (EO2) one week after admission compared to the admission levels (EO1) (P=0.004). A reliable demonstrator of eosinopenia, mean ratio of neutrophil to eosinophil on admission (NEU/EO1) was significantly higher than that measured one week later (NEU/EO2) (P=0.041). White Blood Cell (WBC1) counts of Covid-19 patients on admission were significantly lower than that of controls (P=0.007). Neutrophil (NEU1) counts on admission and one week later (NEU2) were significantly lower than those of controls (P=0.009, P=0.041, respectively). Lymphocyte (LYM1) counts on admission and one week later (LYM2) were significantly lower than those of controls and admission levels were significantly lower than those obtained one week later (P=0.001, P=0.033, and P=0.022, respectively). Monocyte counts on admission (MO1) and one week later (MO2) were significantly lower than those of controls (P=0.010 and P=0.049 respectively). Basophil counts on admission (BAS1) and one week later (BAS2) were significantly lower than those of controls (P<0.001 and P<0.001 respectively). Platelet counts on admission (PLT1) were significantly lower than those of controls and one week later (P=0.006 and P=0.001, respectively). EO1% was significantly lower than EO2% (P=0.041). PLT2/LYM2 ratios were significantly higher than controls and admission PLT1/LYM1 ratios (P=0.026 and P=0.020, respectively). Ferritin levels on admission were significantly higher than controls and lower than one week later (P=0.033 and P=0.011, respectively). Hs-CRP levels on admission were significantly higher than that of controls (P=0.048). The AUCs of EO1, NE1, NE2, PLT2/LYM2, LYM1/CRP1 and LYM2/CRP2 were 0.856, 0.778, 0.719, 0.738, 0.747 and 0.702 respectively, with cut-off values of 0.04, 3.32, 3.21, 144.59, 1.99 and 7.84, respectively. The sensitivity and specificity of EO1, NE1, NE2, PLT2/LYM2, LYM1/CRP1 and LYM2/CRP2 were 66.70% and 93.30%, 53.30% and 93.30%, 46.70% and 93.30%, 80.10% and 80.50%, 100.00% and 66.70, and 100.00% and 53.30%, respectively. The distribution of quantitative variables according to groups is shown in Table 2.

ECF2 values of the patients one week after admission were significantly lower than that of controls (P=0.046). The ECF2 values of the patients after one week also decreased significantly compared to the ECF1 values of admission (P=0.011). The distribution of quantitative variables according to the groups is shown in Table 2. In Figure 1, ROC analysis results of ECF2, EO1, NE1 and NE2 are presented.

Figure 1: ROC curves of selected variables

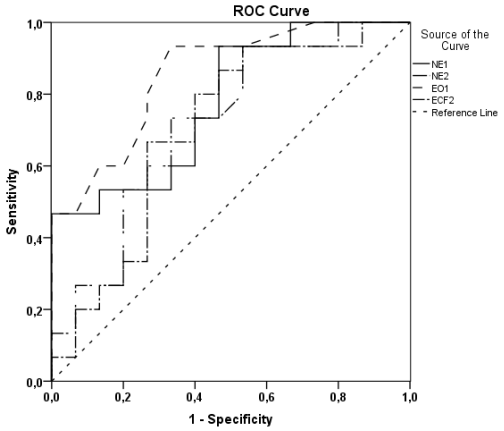


Table 2: Distribution of quantitative variables by groups

Variables	Groups				*P*-value$_1$
	Control		Patient		
	Mean (SD)	Median[Q3-Q1]	Mean (SD)	Median[Q3-Q1]	
Age	60.07 (20.59)	66[42-75]	57.2 (15.46)	59[46-69]	0.670
ECF1(pg / mL)	225.22 (205.47)	157.22[83.89-315]	145.96 (108.75)	143.89[61.67-155.56]	0.305*
ECF2(pg / mL)	225.22 (205.47)	157.22[83.89-315]	99.14 (112.01)	70.00 [18.89-126]	0.046*
P-value $_2$		0.999**		0.011**	
EO1(x10^3/µL)	0.16 (0.14)	0.09[0.06-0.24]	0.04 (0.03)	0.04[0.02-0.07]	<0.001*
EO2(x10^3/µL)	0.16 (0.14)	0.09[0.06-0.24]	0.15 (0.1)	0.12[0.06-0.21]	0.935*
P-value $_2$		0.999**		0.004**	
NE1/E01	84.98 (81.99)	69.33[22.87-104.14]	123.48 (86.10)	96[51.44-178]	0.174
NE2/EO2	84.98 (81.99)	69.33[22.87-104.14]	60.81 (70.74)	24.67[17.15-77.08]	0.285
P-value $_2$		0.999**		0.041**	
WBC1(x10^3/mL)	11.09 (7.89)	9.22[6.55-13.43]	5.05 (1.24)	5.07[4.02-6.12]	0.007
WBC2(x10^3/mL)	11.09 (7.89)	9.22[6.55-13.43]	6.81 (3.20)	5.95[4.28-7.6]	0.062
P-value $_2$	0.999		0.059		
NE1(x10^3/µL)	8.15 (7.64)	4.97[3.43-11.48]	3.55 (1.15)	3.32[2.47-4.63]	0.009*
NE2(x10^3/µL)	8.15 (7.64)	4.97[3.43-11.48]	4.84 (3.48)	3.43[2.63-4.92]	0.041*
P-value $_2$		0.999**		0.394**	
LYM1(x10^3/µL)	2.07 (0.95)	1.92[1.32-2.88]	1.08 (0.52)	0.87[0.65-1.39]	0.001
LYM2(x10^3/µL)	2.07 (0.95)	1.92[1.32-2.88]	1.39 (0.69)	1.56[0.74-1.85]	0.033
P-value $_2$	0.999		0.022		
MO1(x10^3/µL)	0.63 (0.38)	0.51[0.38-0.87]	0.35 (0.10)	0.33[0.27-0.4]	0.010
MO2(x10^3/µL)	0.63 (0.38)	0.51[0.38-0.87]	0.41 (0.16)	0.38[0.26-0.49]	0.049
P-value $_2$	0.999		0.096		
BAS1(x10^3/µL)	0.08 (0.05)	0.08[0.04-0.1]	0.03 (0.02)	0.03[0.02-0.04]	<0.001*
BAS2(x10^3/µL)	0.08 (0.05)	0.08[0.04-0.1]	0.03 (0.02)	0.03[0.02-0.04]	<0.001*
P-value $_2$	0.999			0.859**	
PLT1	233.8 (82.11)	193.8[179.9-280]	160.74 (47.34)	169.6[127.2-186.7]	0.006
PLT2	233.8 (82.11)	193.8[179.9-280]	261.51 (100.87)	253.9[210.7-332.4]	0.416
P-value $_2$	0.999		0.001		
EO1 %	1.69 (1.45)	1.04[0.67-2.62]	1.01 (0.73)	0.96[0.52-1.14]	0.113
EO2 %	1.69 (1.45)	1.04[0.67-2.62]	2.27 (1.59)	2.61[0.63-3.81]	0.307
P-value $_2$		0.999**		0.041**	
NEU1 %	66.97 (16.57)	63.94[52.08-82.71]	69.68 (10.24)	72.1[61.68-73.6]	0.594
NEU2 %	66.97 (16.57)	63.94[52.08-82.71]	66.12 (14.61)	66.09[54.79-68.93]	0.882
P-value $_2$	0.999		0.226		
LYM1 %	24.3 (14.31)	23.46[9.5-37.27]	21.59 (9.03)	20[17.47-30.88]	0.540
LYM2 %	24.3 (14.31)	23.46[9.5-37.27]	24.51 (12.57)	26.27[17.4-34.18]	0.967
P-value $_2$	0.999		0.273		
MPV1	8.8 (0.63)	8.7[8.3-9.4]	8.88 (0.62)	9[8.4-9.3]	0.727
MPV2	8.8 (0.63)	8.7[8.3-9.4]	8.95 (0.97)	8.8[8.3-9.4]	0.626
P-value $_2$	0.999		0.822		
NE/LYM1	5.89 (6.85)	2.74[1.4-8.7]	4.18 (2.85)	3.45[1.87-4.23]	0.653*
NE/LYM2	5.89 (6.85)	2.74[1.4-8.7]	7.27 (11.26)	2.53[1.6-4]	0.999*
P-value $_2$		0.999**		0.570**	
NMR1	14.70 (14.16)	12.43[6.43-16.06]	10.17 (3.52)	9.87[7.2-12.7]	0.443*
NMR2	14.94 (14.95)	11.3[6.76-15.75]	12.48 (8.07)	9.8[7-13.67]	0.787*
P-value $_2$		0.510**		0.281**	
LMR1	4.16 (2.78)	3.58[1.79-5.9]	3.01 (1.32)	2.9[2.05-3.48]	0.389*
LMR2	4.14 (2.68)	3.51[1.81-5.36]	3.88 (2.17)	3.64[1.74-6.05]	0.983*
P-value $_2$		0.778**		0.211**	
LYM/CRP1	17.25 (33.75)	9.21[0.39-16.63]	0.80 (0.65)	0.69[0.13-1.53]	0.021*
LYM/CRP2	17.25 (33.75)	9.21[0.39-16.63]	1.78 (2.22)	1.02[0.6-2.2]	0.061*
P-value $_2$		0.999**		0.031**	
PLT/LYM1	153.81 (141.41)	111.48[76.65-142.88]	183.75 (112.61)	149.3[97.85-213.45]	0.106*
PLT/LYM2	153.81(141.41)	111.48[76.65-142.88]	253.68 (186.74	205.14[144.59-312.19]	0.026*
P-value $_2$		0.999**		0.020*	
Glucose1(g/dl)	157.81 (93.05)	121.3[101.9-133.3]	168.33 (170.62)	122.35[103.4-156.7]	0.864
Glucose2(g/dl)	135.22 (51.06)	119.2[99.4-133.3]	130.35 (38.89)	116.5[99.75-156.7]	0.773
P-value $_2$	0.303		0.342		
Creattinine1(mg/dl)	0.84 (0.19)	0.85[0.75-0.93]	6.73 (25.72)	0.98[0.9-1.11]	0.479
Creattinine2(mg/dl)	0.82 (0.18)	0.85[0.75-0.93]	5.13 (18.33)	0.95[0.84-1.06]	0.467
P-value $_2$	0.043		0.827		
Troponin-I1	11.52 (6.20)	9.9[8.09-10.22]	105.67 (337.62)	15[4.86-23.95]	0.510
Troponin-I2	12.7 (6.46)	10.13[8.09-19.77]	18.55 (16.24)	13.69[4.29-29.05]	0.379
P-value $_2$			0.355		
D-dimer1(µg/L)	0.38 (0.39)	0.21[0.08-0.77]	0.47 (0.34)	0.33[0.2-0.79]	0.614
D-dimer2(µg/L)	0.38 (0.39)	0.21[0.08-0.77]	1.04 (1.09)	0.66[0.2-1.56]	0.176
P-value $_2$		0.999**		0.407**	
Ferritine1(ng/mL)	95.44 (92.93)	72.41[35.83-155.05]	596.75 (411.68)	491.25[303.1-876.9]	0.033
Ferritine2(ng/mL)	95.44 (92.93)	72.41[35.83-155.05]	624.5 (490.91)	508.5[286.95-838.35]	0.055
P-value $_2$		0.999**		0.011**	
Fibringn1(mg/dL)	274.5 (47.38)	274.5[241-308]	348.2 (124.87)	326.5[274-500]	0.444
Fibringn2(mg/dL)	274.5 (47.38)	274.5[241-308]	392.9 (121.36)	395[332-500]	0.217
P-value $_2$	0.999		0.169		
hs-CRP1(mg/L)	24.24 (43.00)	3.06[1.89-41.8]	65.81 (64.99)	43.15[15.64-96.6]	0.048
hs-CRP2(mg/L)	24.24 (43.00)	3.06[1.89-41.8]	57.77 (96.02)	29.06[11.96-51.45]	0.227
P-value $_2$		0.999**		0.078**	

Data were presented as mean (standard deviation) or median. quartile 1-quartile 3. *P*-value 1: *: Mann Whitney U test was used. For others. the significance test of the difference between the two means was used. *P*-value 2: **: Wilcoxon test for others the difference between two spouses. ECF: Eosinophil Chemotactic Factor, EO: Eosinophil, NE: Neutrophil, LYM: Lymphocyte, MO: Monocyte, BAS: Basophil, WBC: White Blood Cell, PLT: Platelet. Annex '1' at the end of parameters refers to 'value at admission' while '2' refers to 'one week after'.

Discussion

In the present study, the mean ages of both groups were 57.20 (15.46) and 60.07 (20.59) years, respectively, showing that hospitalized Covid-19 patients were over 40 years of age. With aging, the body's defenses decrease due to deterioration of immune and physiological functions. They had fever (73.30%), dyspnea (33.30%), cough (91.70%) and fatigue (80.00%). Patients who have these symptoms should take isolation measures and begin medical treatment to protect themselves and those around. Our patients had various comorbidities such as chronic lung disease, Diabetes Mellitus, hypertension, cardiovascular disease, and malignant diseases (13.30%, 6.70%, 20.00%, 6.60%, and 6.60%, respectively). Elderly patients had more underlying diseases, all of which increase the severity of the disease and hospitalization rates.

In line with the existing literature, in our study, patients had eosinopenia at the time of presentation, which improved significantly after one week. Three (20.00%) patients who died had eosinopenia both at the time of admission and one week later. Since the absolute eosinophil counts may vary between different laboratories, we preferred to calculate the NE/EO ratio instead of the absolute eosinophil count to achieve standardization. In the patient group, the NE2/EO2 ratios were significantly lower than those of NE1/EO1.

Since the beginning of the Covid-19 pandemic, eosinopenia or low eosinophil levels (<0.01x109 /L) were observed in most hospitalized patients in all patient series, which was associated with the severity of the disease. Eosinopenia was seen in 79% of PCR-confirmed SARS-Cov2 positive patients (n=52) and 36.00% of SARS-Cov2 negative patients [10].

Liu et al. [11] reported that eosinopenia at admission of patients mostly improved upon discharge, and this indicated improved clinical condition. Li et al. [12] conducted a retrospective case control study on 989 patients who applied to the fever clinic in Wuhan, China. Eosinopenia alone distinguished Covid-19 patients and controls with similar symptoms with 74.70% sensitivity and 68.70% specificity, and an Area Under Curve of 0.717 in ROC analysis. In our study, EO, NE1 and NE2 were highly capable of distinguishing Covid-19 negative patients with Covid-19 like symptoms.

Lymphopenia is also common in Covid-19, and blood eosinophil counts are positively correlated with lymphocyte levels in severe and mild coronavirus cases [13]. In our study, after one week of admission, lymphocyte levels recovered with treatment and LYM2 levels were significantly higher than LYM1. EO2 was positively and moderately correlated with LYM2, showing that eosinopenia and lymphopenia are comparable.

NE1, NE2, PLR2, LCRPR1 and LCRPR2 were the most predictive CBC subsets and indexes showing Covid-19 is an inflammatory condition. Ferritin levels on admission were significantly higher than that of controls and lower than one week later, showing recovery of inflammatory condition after one week of treatment.

In our study, patients had significantly higher Hs-CRP levels than controls on admission, in line with the laboratory findings of most inflammatory conditions.

Recently, researchers attempted to explain the role of eosinophils in inflammatory reactions and the mechanisms regulating their increased production and accumulation in various tissues. Until now, several factors with eosinophil chemotactic properties have been shown using different in vitro methods. However, sufficient comparative data on their strength, specificity, and ability to attract leukocytes are not available. Eosinophils are invoked into the lungs in response to infection with pneumo-pathogens and are associated with both pathophysiological sequelae of infection and accelerated virus clearance.

In the eosinophilic airway guinea pig hypersensitivity model, the main eosinophil chemotactic factor released into the lung was eotaxin [14]. Eotaxin plays a prominent role in eosinophil recruitment in various inflammatory diseases. Eotaxins are the C-C subfamily of eosinophil chemotactic proteins. CCL11 (eotaxin-1), CCL24 (eotaxin-2), and CCL26 (eotaxin-3) are three family members of eotaxins in humans [15].

Although most Covid-19 patients show very mild, self-limiting respiratory tract infection, severe patients show clinical symptoms such as severe eosinopenia, lymphopenia, generalized pneumonia, cytokine storm and multi-organ failure [16].

Although eosinopenia's pathophysiology in Covid-19 is not yet clear, it is multifactorial. Eosinophil outflow inhibition, eosinopoiesis blockage in the bone marrow, low production of chemokines, and stimulation of eosinophil apoptosis in acute infection are some of the causes of eosinopenia [17, 18]. Considering all these data in Covid-19 disease, there appears to be a disorder in immune response.

In the evaluation of the suspected patient with Covid-19 like symptoms, simple, fast, and accessible biochemical markers are needed to quickly distinguish the patients from negative ones and initiate empirical treatment, or to prioritize PCR or CT.

Due to high rates of eosinopenia seen in Covid-19, it is necessary to investigate the effect and diagnostic performance of CCL11, which contributes to eosinophil chemotaxis in Covid-19 patients. However, our study is the first one in this regard. We came upon studies investigating the CCL11, which is specific for eosinophils in Covid-19 disease, during the disease process.

We found that ECF2 values differentiated Covid19 negative individuals with Covid-19 like symptoms from positive patients. Tracking ECF with CBC subsets and CBC indexes may be helpful in the early prediction of severity of the disease, and the follow up of critical COVID-19 patients.

Limitations

Its retrospective, single center design and small number of hospitalized patients constitute the major limitations of our study, which needs validation with larger population-based cohorts.

Conclusions

Neutropenia, lymphopenia, and eosinopenia are seen in Covid-19. Lymphopenia and eosinopenia were positively correlated. Eosinopenia at admission is more severe compared to one week later, which is associated with good outcome. Elderly individuals with chronic diseases are more susceptible to COVID-19 and have a high likelihood of developing severe and critically severe infection. Levels of WBC, lymphocytes, neutrophils, CRP, NLR, PLR, troponin-I, and creatinine are

important indicators for severity grading in COVID-19. We can concur that EO, NE, CRP, LYM/CRP and PLT/LYM can be used as biomarkers to distinguish COVID-19 patients from healthy individuals and predict the severity of the disease. In addition, ECF / CCL11, a specific chemokine for eosinophils, may be an accessible and rapid biomarker with CBC subsets and indexes in the screening of Covid-19 patients, differentiating Covid-19 positive patients from negative ones and tracking the severity of the disease.

Acknowledgements

We thank our hospital's laboratory staff and data management department and Prof. Dr. Yunus Bulut for his advisory contribution.

References

1. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3.
2. Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. Jama. 2020;323(8):707-8.
3. Erickson MA, Morofuji Y, Owen JB, Banks WA. Rapid transport of CCL11 across the blood-brain barrier: regional variation and importance of blood cells. Journal of Pharmacology and Experimental Therapeutics. 2014;349(3):497-507.
4. Rothenberg ME, Hogan SP. The eosinophil. Annual review of immunology. 2006;24.
5. Nakayama T, Hirahara K, Onodera A, Endo Y, Hosokawa H, Shinoda K, et al. Th2 cells in health and disease. Annual review of immunology. 2017;35:53-84.
6. Lambrecht BN, Hammad H. The immunology of asthma. Nature immunology. 2015;16(1):45-56.
7. Blanchard C, Rothenberg ME. Biology of the eosinophil. Advances in immunology. 2009;101:81-121.
8. Kitaura M, Nakajima T, Imai T, Harada S, Combadiere C, Tiffany HL, et al. Molecular cloning of human eotaxin, an eosinophil-selective CC chemokine, and identification of a specific eosinophil eotaxin receptor, CC chemokine receptor 3. Journal of Biological Chemistry. 1996;271(13):7725-30.
9. Rankin SM, Conroy DM, Williams TJ. Eotaxin and eosinophil recruitment: implications for human disease. Molecular medicine today. 2000;6(1):20-7.
10. Du Y, Tu L. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan. A Retrospective Observational Study. 2020;201(11):1372-9. doi: 10.1164/rccm.202003-0543OC. PubMed PMID: 32242738.
11. Yao X, Zeng Y, Tong Y, Tang X, Yin Z. Determination and analysis of blood eosinophil in 200 severe acute respiratory syndrome patients. Lab Med. 2004;5(19):444-5.
12. Li Q, Ding X, Xia G, Chen H-G, Chen F, Geng Z, et al. Eosinopenia and elevated C-reactive protein facilitate triage of COVID-19 patients in fever clinic: a retrospective case-control study. E Clinical Medicine. 2020:100375.
13. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. Journal of Allergy and Clinical Immunology. 2020.
14. Jose P, Griffiths-Johnson D, Collins P, Walsh D, Moqbel R, Totty N, et al. Eotaxin: a potent eosinophil chemoattractant cytokine detected in a guinea pig model of allergic airways inflammation. The Journal of experimental medicine. 1994;179(3):881-7.
15. Van Coillie E, Van Damme J, Opdenakker G. The MCP/eotaxin subfamily of CC chemokines. Cytokine & growth factor reviews. 1999;10(1):61-86.
16. Riggioni C, Comberiati P, Giovannini M, Agache I, Akdis M, Alves-Correia M, et al. A compendium answering 150 questions on COVID-19 and SARS-CoV-2. Allergy. 2020:10-111.
17. Bass DA. Behavior of eosinophil leukocytes in acute inflammation. II. Eosinophil dynamics during acute inflammation. The Journal of clinical investigation. 1975;56(4):870-9.
18. Hassani M, Leijte G, Bruse N, Kox M, Pickkers P, Vrisekoop N, et al. Differentiation and activation of eosinophils in the human bone marrow during experimental human endotoxemia. Journal of Leukocyte Biology. 2020.

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(2):174-178.
DOI: 10.28982/josam.754698

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

Relationship between frontal QRS-T angle and coronary slow flow phenomenon

Sinan Cemgil Özbek

Department of Cardiology, Ahi Evran University Training and Research Hospital, Kirsehir, Turkey

ORCID ID of the author(s)
SCÖ: 0000-0001-9056-8350

Abstract

Background/Aim: Coronary slow flow phenomenon (CSFP) is termed as slow passage of contrast dye to distal portion of the coronary arteries, and can provoke angina pectoris, serious arrhythmias, or even sudden death. Previous reports suggested that frontal QRS-T angle (fQRSTa), measured by surface ECG may associate with ventricular arrhythmias and cardiac death. In this study, we aimed to assess the relationship between fQRSTa and CSFP.

Methods: In this case-control study, we retrospectively included 76 patients with CSFP [85.5% male; mean age 58.4 (9.2) years] and 50 patients with normal coronary flow (control group) [86.6% male; mean age 56.5 (10.1) years] between July 2017 and March 2019. CSFP was identified by TIMI frame count (TFC) method. Demographic, clinical and ECG characteristics were obtained from hospital records.

Results: The groups were similar concerning co-morbid cardiac conditions. Mean QTc interval and median fQRSTa were significantly greater in CSFP group compared with the controls [416.2 (34.5) vs 401 (36.3), P=0.020 and 51° (11° to 132°) vs 27° (4° to 92°), P<0.001; respectively].

Conclusion: The findings may suggest a possible distortion in cardiac electrical micropathways and indicate an increased likelihood of arrhythmia.

Keywords: Coronary slow flow phenomenon, Frontal QRS-T angle, Arrhythmia

Corresponding Author
Sinan Cemgil Özbek
Ahi Evran University, Training and Research Hospital, Department of Cardiology Kervansaray Mah. 2019. Sok. No:1, Post code: 40100, Kirsehir, Turkey
E-mail: ozbeksc@gmail.com

Ethics Committee Approval
Kırşehir Ahi Evran University Medical Faculty Clinical Research Ethics Committee approved the study design on 14/05/2019 with the decision number 2019-09 / 101
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 February 19

How to cite: Özbek SC. Relationship between frontal QRS-T angle and coronary slow flow phenomenon. J Surg Med. 2021;5(2):174-178.

Introduction

Coronary slow flow phenomenon (CSFP) is characterized by slow transmission of contrast dye towards distal vessel portions without overt stenosis in the epicardial coronary arteries [1]. Whereas the precise mechanism with which CSFP remains incompletely understood, its incidence was reported to between 1-5.5% in different studies [2-4]. Furthermore, the theme of CSFP was reported to associate with the de ventricular tachyarrhytmias, sudden cardiac death, atrial fibrillation, angina pectoris, acute coronary syndromes [5-7].

Previous evidence concerning the effect of CSFP on electrocardiographic (ECG) indices showed that the P wave dispersion and the parameters of ventricular repolarization, such as Tpeak-to-Tend interval (Tp-e), QT dispersion (QTd), T wave, Jpoint-to-Twave interval, and Tp-e/QT and Tp-e/QTc ratios, were significantly greater in patients with CSFP than the subjects with normal coronary flow [6, 8-10]. In addition, these parameters are known to associate with the atrial and ventricular tachyarrhythmia generation.

More recently, much attention has been devoted to the spatial QRS-T angle, a parameter that implies the angle between the directions of ventricular repolarization and depolarization vectors, since wider angles have been reported to indicate the risk of ventricular arrhythmias, sudden arrhythmic death, cardiovascular death and overall death in acute coronary events, heart failure and even in general population [11-14]. Since most physicians are not acquainted with the spatial QRS-T angle due to its lack of wide availability, frontal QRS-T angle (fQRSTa) is more appealing because it is readily available from a surface ECG and has a significantly well correlation with the spatial QRS-T angle [12].

In light of the afore-mentioned premises, we intended to assess the relationship between fQRSTa with CSFP in a comparable manner with normal epicardial flow.

Materials and methods

Study patients and design

This was a retrospectively designed study. Hospital database was scanned for coronary angiographies performed between July 2017 and March 2019, and a total of 76 patients who underwent coronary angiography that revealed CSFP in at least one of the main coronary arteries in the absence of overt stenosis or myocardial bridge were included. In addition, 50 sex- and age-matched patients whose angiography depicted normal coronary vessels with no CSFP were enrolled to comprise the control group. The reason for angiography in all patients was the presence of anginal chest pain or symptoms regarded as angina equivalent with positive non-invasive stress tests (treadmill test or myocardial perfusion scintigraphy). Demographic and clinical characteristics of the patients were also obtained from the hospital database. Exclusion criteria were as follows: Coronary stenosis, moderate-to-severe valvular heart disease, history of acute coronary syndrome, hearth rhythm other than normal sinus rhythm, bundle branch block, dilated or hypertrophic cardiomyopathy, history of myocarditis, malignancy, chronic obstructive pulmonary disease, severe kidney and liver dysfunction. All participants included in the study underwent a comprehensive echocardiographic evaluation using Vivid S5 (GE Vingmed Ultrason AS, Horten, Norway). Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's rule. The body-mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as BMI >30 kg/m^2.

Kırşehir Ahi Evran University Medical Faculty Clinical Research Ethics Committee approved our study design on 14/05/2019 with the decision number 2019-09 / 101, and our study follows the rules of the Declaration of Helsinki.

Coronary angiography

Using the standard Judkins technique, coronary angiography was performed in each patient via Siemens Artis Zee (Siemens Medical Solution, Erlangen, Germany) either through the transfemoral or transradial routes. Assessment of the cineangiographic views recorded at 15 frames/sec was fulfilled using Axiom (Siemens Medical Solution, Erlangen, Germany) workstation by two independent and experienced cardiologists blinded to the study.

CSFP was diagnosed according to Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) method proposed by Gibson et al [15]. In brief, the total number of the cine-frames for contrast dye to reach the distal end of each major epicardial coronary artery, namely the left anterior descending artery (LAD), the left circumflex artery (Cx), and the right coronary artery (RCA) were identified with cine frame counters [15]. The distal ends were defined as distal bifurcation of LAD, distal bifurcation of Cx or obtus marginalis, whichever was longer, and the first branch of posterolateral artery of RCA [6,8,15,16]. Since LAD follows a longer course compared with Cx and RCA, a correction was made by dividing the total frame counts calculated for LAD by 1.7 to obtain the corrected TFC (cTFC) for LAD [15]. As previously described by Gibson et al. [15], the normal values of cTFC for LAD, Cx and RCA are 21.1 (1.5), 22.2 (4.1), and 20.4 (3.0), respectively. Mean TFC was computed as the sum of the respective TFCs for LAD, LCx and RCA divided by 3. Since the standardized rate for filming for these normal values was 30 frames/sec [15], we multiplied the TFCs we counted by 2. Calculation of TFCs was fulfilled by two blinded and independent cardiologists, and any disagreement occurring between these two cardiologists was resolved by a third independent and blinded cardiologist. Patients with TFC greater than these normal values were considered to have CSFP.

Electrocardiography

The 12-lead ECG was recorded (MAC 2000, GE medical systems, Milwaukee, WI, USA) at a paper speed of 50 mm/s and 10mm / mV amplitude. All ECGs were scanned and transferred to a computer and then used with x400 magnification by software. All intervals were measured from Lead 2 [17]. The QT intervals were corrected using Bazett's formula [18]. The mean of the three consecutive beats was calculated. These intervals were measured by two cardiologists blinded to the study data. Respective intra- and interobserver coefficients of variations were 3.2% and 4.8%.

The P wave, QRS complex and T wave angles were obtained from the intrinsic reports provided by the ECG device [19-21]. To compute the fQRSTa, absolute difference was taken between the QRS and T wave angles to obtain values between 0

and 180°. If the value exceeded 180°, it was subtracted from 360°.

Statistical analysis

All analyses were conducted using the SPSS 18.0 (SPSS Inc, Chicago, USA). Categorical variables were given as percentage, while continuous variables were presented as mean ± standard deviation and median. The normality of the distribution was tested using the Kolmogorov-Smirnov test. Student's t test was used to compare variables with normal distribution and Mann-Whitney U test was used to compare variables with non-normal distribution. The relationship between fQRSTa and TFC was analyzed with bivariate linear correlation analysis. Univariate and multivariate logistic regression analysis was performed to determine the risk factors predicting the presence of CSFP. A *P*-value of <0.05 was considered statistically significant.

Results

This study enrolled a total of 126 patients, of which 76 had CSFP (CSFP group) [85.5% male; mean age: 58.4 (9.2) years] and 50 had normal flow (control group) [86.6% male; mean age: 56.5 (10.1) years]. Demographic and clinical characteristics were presented Table 1. Two groups were similar concerning age, gender, and co-morbid factors such as family history of coronary artery disease, hypertension (HT), diabetes mellitus (DM), dyslipidemia, obesity, and smoking habit (*P*>0.05). There were no significant differences regarding LVEF between the groups.

Table 1: Demographic and clinical characteristics of the study population

	CSFP group (n=76)	Control group (n=50)	*P*-value
Age, years	58.4 (9.2)	56.5 (10.1)	0.275
Gender, male, %	85.5	86.6	0.868
Cardiac risk factors, %			
Family history of CAD	27.6	28.0	0.957
Hypertension	76.3	74.0	0.768
Diabetes mellitus	28.9	18.0	0.169
Dyslipidemia	64.4	52.0	0.162
Obesity (BMI >30 kg/m2)	19.7	20.0	0.967
Smoking history	34.1	31.3	0.744
Systolic BP, mm Hg	147.1 (25.6)	142.3 (30.1)	0.341
Diastolic BP, mm Hg	87.121 (5.2)	85.1 (14.4)	0.458
Heart rate, beats per min	81.8 (13.2)	79.2 (16.3)	0.336
LVEF, %	62.5 (4.9)	63.0 (3.8)	0.542
LA diameter, mm	37.6 (3.4)	36.9 (3.7)	0.277
LVEDD, mm	46.3 (3.3)	45.8 (2.4)	0.358
LVESD, mm	28.5 (3.1)	27.7 (2.9)	0.148
IVST, mm	10.5 (1.1)	10.7 (1.2)	0.337
PWT, mm	8.9 (1.1)	8.8 (1.0)	0.605
LVMI, g/m^2	81.4 (13.0)	80.5 (12.7)	0.701

Data are given as number (percentage) for categorical variables and mean (standard deviation) for continuous variables, BMI: body-mass index, BP: blood pressure, CAD: coronary artery disease, IVST: interventricular septal thickness, LA: left atrium, LVEF: left ventricular ejection fraction, LVEDD: left ventricle end-diastolic pressure, LVESD: left ventricle end-systolic pressure, LVMI: left ventricle mass-index, PWT: posterior left ventricle wall thickness

Angiographic data of the groups were given in Table 2. In the CSFP group, respective distributions based on the number of the vessels involved were as follows: 1-vessel involvement, 38.1%; 2-vessel involvement, 30.3%; and, 3-vessel involvement, 30.2%. Most of the patients in CSFP group had single vessel involvement. More specifically, LAD was the predominantly involved vessel (68.2%) in CSFP group, followed by RCA (64.2%) and LCx (56.9%). Compared with the controls, the patients in CSFP group possessed significantly higher cTFC for LAD [44.7 (11.3) vs 20.5 (4.4), *P*<0.001], higher TFC for Cx [42.1 (9.4) vs 19.3 (4.9), *P*<0.001], and higher TFC for RCA [40.8 (8.5) vs 20.2 (4.7), *P*<0.001]. Moreover, mean TFC was significantly higher in the CSFP group compared with the control group [43.93 (9.56) vs 20.0 (4.1), *P*<0.001].

ECG variables of the groups were also provided in Table 2. Both groups were similar with regards to mean heart rate, PR interval, QRS interval, and QRS complex axis (p>0.05 for all). On the other hand, mean QTc interval was longer, albeit with weak statistical significance, in the CSFP group compared with that of controls [416.2 (34.5) vs 401 (36.3), *P*=0.020]. Although median T-wave axis seemed greater than that of control group, this difference did not reach the level of statistical significance [47° (-73 to 135) vs 41° (-65 to 121), *P*=0.128]. However, CSFP group displayed a significant increase in median fQRSTa compared with the control group [51° (11 to 132) vs 27° (4 to 92), *P*<0.001].

Table 2: Comparison of the baseline electrocardiographic and angiographic characteristics of the study population

	CSFP group (n=76)	Control group (n=50)	*P*-value
Heart rate (beats/min)	71.4 (10.2)	69.5 (12.3)	0.346
PR interval (msec)	141.0 (23.2)	138.4 (19.8)	0.520
QRS interval (msec)	96.71 (1.2)	94.4 (10.1)	0.248
QTc interval (msec)	416.2 (34.5)	401(36.3)	0.020
QRS axis (°)	34 (-80 to 120)	23 (-53 to 80)	0.838
T-wave axis (°)	47 (-73 to 135)	41 (-65 to 121)	0.313
QRS-T angle (°)	51 (11 to 132)	27 (4 to 92)	<0.001
Arterial involvement			
LAD, %	68.2	-	
LCx, %	56.9	-	
RCA, %	64.2	-	
Vessel involvement			
1-vessel, %	38.1	-	
2-vessel, %	30.3	-	
3-vessel, %	30.2	-	
TIMI frame counts			
Corrected LAD	44.7 (11.3)	20.5 (4.4)	<0.001
LCx	42.1 (9.4)	19.3 (4.9)	<0.001
RCA	40.8 (8.5)	20.2 (4.7)	<0.001
Mean TIMI frame count	43.93 (9.56)	20.0 (4.1)	<0.001

Data are given as number (percentage) for categorical variables and mean (standard deviation) or median (IQR) for continuous variables. CSFP: coronary slow flow phenomenon, LAD: left anterior descending artery, LCx: left circumflex artery, RCA: right coronary artery, TIMI: thrombolysis in myocardial infarction

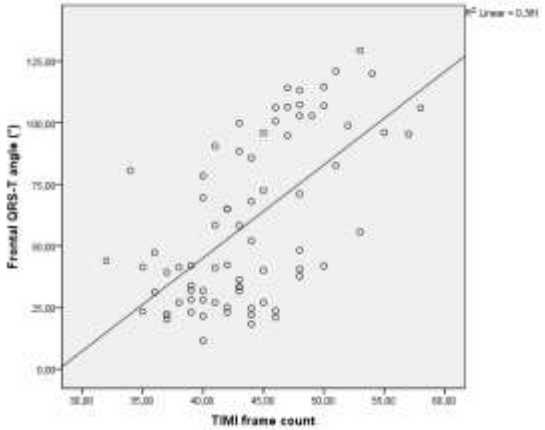
Pearson correlation analysis in SCFP group revealed significant correlation between the TIMI frame count and fQRSTa. (r=0.618, *P*<0.001) (Figure 1).

In the multivariate logistic regression model, frontal fQRSTa, together with smoking and DM, remained independently associated with CSFP (Table 3).

Table 3: Logistic regression model showing the variables associated with coronary slow flow phenomenon

	OR with 95% CI	*P*-value	OR with 95% CI	*P*-value
Age	1.02 (0.96–1.04)	0.851		
Male gender	1.45 (0.720- 3.02)	0.315		
Smoking	1.79 (1.13-2.90)	0.010	1.51 (1.10-2.21)	0.018
Heart rate	0.82 (0.79-1.03)	0.576		
Hypertension	1.08 (0.94-1.29)	0.124		
Diabetes mellitus	1.649 (1.07-2.52)	0.022	1.34 (1.01-2.01)	0.038
QRS-T angle	1.09 (1.02-1.17)	0.016	1.04 (1.01-1.06)	0.023

Figure 1: Pearson correlation analysis in SCFP group, between the TIMI frame count and fQRSTa



Discussion

The present study may contribute to the current literature with its main findings as follows: 1) Patients with CSFP were characterized with greater fQRSTa than the control subjects in the setting of angiographically-depicted normal coronary vasculature; 2) fQRSTa was significantly correlated with TFC and 3) Multivariate logistic regression analysis revealed significant and independent association of CSFP with fQRSTa, smoking and DM.

CSFP has a preponderance in smoking males [22]. The true pathophysiological mechanism underlying CSFP is yet to be completely resolved. However, a variety of hypotheses were proposed in this regard, including endothelial damage incurred by low plasma nitric oxide and high asymmetric dimethyl arginine concentrations [23,24]. Furthermore, histopathological examinations by Mosseri et al. [25] and Mangieri et al. [26] on ventricular biopsy specimens demonstrated presence of microvascular resistance against blood flow because of myointimal proliferation, fibromuscular hyperplasia, endothelial thickening and disruption in patients with CSFP. Accordingly, Pakdemir et al. [27] disclosed diffuse atherosclerosis in the coronary vasculature by means of intravascular ultrasound and fractional flow reserve.

There are a number of studies conducted with specific ECG markers for the anticipation of sudden death in patients with CSFP. Recent evidence suggested that some ECG parameters of ventricular repolarization such as Tp-e interval, QTd, and Tp-e/QT and Tp-e/QTc ratios were increased in the setting of CSFP [8-10]. Additionally, Yilmaz et al. [28] demonstrated a significant association between CSFP and QRS fragmentation. On the other hand, reports concerning the status of corrected QT interval (QTc) are conflicting. Sucu et al. [8] and Atak et al. [29] reported similar QTc interval between patients exhibiting CSFP and those with normal flow, whereas Karaman et al. [10] and Sezgin et al. [30] demonstrated a significant escalation in mean QTc in CSFP patients compared with those of normal coronary flow. However, Atak et al. [29] further reported an increase in the dispersion of QTc (QTcd) in their study despite similar maximum-QTc intervals. It has been well recognized from the previous studies that prolongation in QTc confers an increased risk of sudden cardiac death, and ventricular tachycardia and fibrillation [31]. In our study, mean QTc was greater in CSFP group compared with the controls, which is compatible with the findings of Karaman et al. and Sezgin et al. fQRSTa is a relatively novel ECG index utilized in the risk assessment of cardiac and overall deaths. It provides much more useful in risk stratification either QRS axis or T-wave axis alone [32]; however, there is no certain reference range for a normal fQRSTa owing to its variability by age and gender. In healthy persons possessing normal cardiac structure, fQRSTa is expected to be narrow. On the other hand, wider fQRSTa point out to more heterogeneity and distortion in the delicate balance between ventricular depolarization and repolarization, which translates into the presence of such cardiac fabric that is relatively more susceptible to ventricular arrhythmias [33-35]. Although the ultimate mechanism with which ventricular arrhythmias generate in the setting of CSFP remains unexplained due to scanty of relevant studies, deterioration in the aforementioned ventricular repolarization indices, namely QTcd, Tp-e, Tp-e/QT and Tp-e/QTc, were proposed as probable etiologies [10,29]. In this regard, significant widening of fQRSTa in our study may further contribute to the struggles to explain the arrhythmic mechanisms in CSFP.

Despite the definitive role of fQRSTa in the cardiac and overall mortality-risk stratification in a variety of conditions, the number of the studies regarding its potential role in diagnostic purposes is quite limited. Tanriverdi et al. [19] reported a significantly greater fQRSTa [47 (29.7°)] in non-dipper HT patients compared with those of dipping pattern [26.7 (19.6°)]. In addition, fQRSTa independently associated with the presence of non-dipping pattern. In another study, Gungor et al. [36] assessed fQRSTa in 307 patients in which angiography depicted normal coronary vasculature, and found that fQRSTa was independently associated with larger left main coronary artery caliper and presence of HT. Median fQRSTa in their study was 38°. In our study, we revealed a wider median fQRSTa 51° (11 to 132) in CSFP patients as compared with the patients with angiographically normal coronary flow [37.2 (26.5°)] in a cohort of 126 patients with apparent cardiac risk factors, and also demonstrated a significant and positive association between fQRSTa and CSFP. Not only are our findings consistent with findings of Gungor et al. but also extend their findings. Kuyumcu et al. [37] reported a significantly wider fQRSTa [69 (51°)] in SCFP patients compared with those of normal coronary artery patients [46 (36°)]. In contrast to our study, they found a significantly negative correlation (r= - 0.496) between TFC and fQRSTa. Also, the mean TFC was larger in normal coronary artery [32 (6)] patients than in SCFP patients [14 (4)]. In this study, the negative correlation between TFC and fQRSTa may be due to TFC being smaller in SCF patients than normal coronary artery patients.

Co-existence of prolonged QTc interval and wider fQRSTa in the present study is plausible, and attributable to distortion in the cardiac conduction patterns at microscopic level. Our premise is that myocardial ischemia due to widespread atherosclerosis and microscopic medial hypertrophy and fibrosis in the setting of CSFP serve as a main pathophysiological mechanism with which imbalance between ventricular depolarization and repolarization occurs.

Limitations

This study should be interpreted together with some limitations. The relatively small number of patients might have abated the statistical power of the study. Hence, our findings should be confirmed with future large-scale investigations. Secondly, prospective follow-up of the patients was not exercised so as to reveal possible arrhythmic or anginal complications in CSFP group. As a future perspective, studies with larger patient recruitment can be useful in search of association between fQRSTa and the frequency and severity of angina episodes in CSFP patients.

Conclusions

Subjects with CSF tend to be characterized with wider fQRSTa. Furthermore, fQRSTa is correlated with TFC, and independently associated with CSFP. Our findings may signify a possible distortion in the micropathways of ventricular electrical

activities, and hence an increase in the likelihood of arrhythmia generation. However, future large-scale and prospective studies may be able to establish such a relationship.

References

1. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries--a new angiographic finding. Am Heart J. 1972;84(1):66-71. doi:10.1016/0002-8703(72)90307-9
2. Beltrame JF, Limaye SB, Horowitz JD. The coronary slow flow phenomenon--a new coronary microvascular disorder. Cardiology. 2002;97(4):197-202. doi:10.1159/000063121
3. Diver DJ, Bier JD, Ferreira PE, Sharaf BL, McCabe C, Thompson B, et al. Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-IIIA Trial). Am J Cardiol. 1994;74(6):531-7. doi:10.1016/0002-9149(94)90739-0
4. Hawkins BM, Stavrakis S, Rousan TA, Abu-Fadel M, Schechter E. Coronary slow flow--prevalence and clinical correlations. Circulation journal : official journal of the Japanese Circulation Society. 2012;76(4):936-42. doi:10.1253/circj.CJ-11-0959
5. Wozakowska-Kaplon B, Niedziela J, Krzyzak P, Stec S. Clinical manifestations of slow coronary flow from acute coronary syndrome to serious arrhythmias. Cardiol J. 2009;16(5):462-8.
6. Suner A, Cetin M. The effect of trimetazidine on ventricular repolarization indexes and left ventricular diastolic function in patients with coronary slow flow. Coronary artery disease. 2016;27(5):398-404. doi:10.1097/MCA.0000000000000373
7. Amasyali B, Turhan H, Kose S, Celik T, Iyisoy A, Kursaklioglu H, Isik E. Aborted sudden cardiac death in a 20-year-old man with slow coronary flow. Int J Cardiol. 2006;109(3):427-9. doi: 10.1016/j.ijcard.2005.06.044
8. Sucu M, Ucaman B, Ozer O, Altas Y, Polat E. Novel Ventricular Repolarization Indices in Patients with Coronary Slow Flow. Journal of atrial fibrillation. 2016;9(3):1446. doi: 10.4022/jafib.1446
9. Eshraghi A, Hoseinjani E, Jalalyazdi M, Vojdanparast M, Jafarzadeh-Esfehani R. QT interval and P wave dispersion in slow coronary flow phenomenon. ARYA atherosclerosis. 2018;14(5):212-7. doi: 10.22122/arya.v14i5.1599
10. Karaman K, Altunkas F, Cetin M, Karayakali M, Arisoy A, Akar I et al. New markers for ventricular repolarization in coronary slow flow: Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio. Ann Noninvasive Electrocardiol. 2015;20(4):338-44. doi:10.1111/anec.12203
11. Aro AL, Huikuri HV, Tikkanen JT, Junttila MJ, Rissanen HA, Reunanen A, Anttonen O. QRS-T angle as a predictor of sudden cardiac death in a middle-aged general population. Europace: European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2012;14(6):872-6. doi:10.1093/europace/eur393
12. Zhang ZM, Prineas RJ, Case D, Soliman EZ, Rautaharju PM. Comparison of the prognostic significance of the electrocardiographic QRS/T angles in predicting incident coronary heart disease and total mortality (from the atherosclerosis risk in communities study). Am J Cardiol. 2007;100(5):844-9. doi: 10.1016/j.amjcard.2007.03.104
13. May O, Graversen CB, Johansen MO, Arildsen H. The prognostic value of the frontal QRS-T angle is comparable to cardiovascular autonomic neuropathy regarding long-term mortality in people with diabetes. A population based study. Diabetes research and clinical practice. 2018;142:264-8. doi:10.1016/j.diabres.2018.05.018
14. Oehler A, Feldman T, Henrikson CA, Tereshchenko LG. QRS-T angle: a review. Ann Noninvasive Electrocardiol. 2014;19(6):534-42. doi:10.1111/anec.12206
15. Gibson CM, Cannon CP, Daley WL, Dodge JT, Jr., Alexander B, Jr., Marble SJ, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation. 1996;93(5):879-88. doi: 10.1161/01.CIR.93.5.879
16. Sanghvi S, Mathur R, Baroopal A, Kumar A. Clinical, demographic, risk factor and angiographic profile of coronary slow flow phenomenon: A single centre experience. Indian Heart J. 2018;70 Suppl 3:S290-s4. doi:10.1016/j.ihj.2018.06.001
17. Castro-Torres Y, Carmona-Puerta R, Katholi RE. Ventricular repolarization markers for predicting malignant arrhythmias in clinical practice. World J Clin Cases. 2015;3(8):705-20. doi: 10.12998/wjcc.v3.i8.705
18. Bazett H. An analysis of the time relations of electrocardiograms. Heart 7:353-370. 1920.
19. Tanriverdi Z, Unal B, Eyuboglu M, Bingol Tanriverdi T, Nurdag A, Demirbag R. The importance of frontal QRS-T angle for predicting non-dipper status in hypertensive patients without left ventricular hypertrophy. Clin Exp Hypertens. 2018;40(4):318-23. doi:10.1080/10641963.2017.1377214
20. Kurisu S, Nitta K, Sumimoto Y, Ikenaga H, Ishibashi K, Fukuda Y, Kihara Y. Effects of deep inspiration on QRS axis, T-wave axis and frontal QRS-T angle in the routine electrocardiogram. Heart Vessels. 2019. doi:10.1007/s00380-019-01380-7
21. Lazzeroni D, Bini M, Camaiora U, Castiglioni P, Moderato L, Ugolotti PT, et al. Prognostic value of frontal QRS-T angle in patients undergoing myocardial revascularization or cardiac valve surgery. J Electrocardiol. 2018;51(6):967-72. doi: 10.1016/j.jelectrocard.2018.08.028
22. Goel PK, Gupta SK, Agarwal A, Kapoor A. Slow coronary flow: a distinct angiographic subgroup in syndrome X. Angiology. 2001;52(8):507-14. doi:10.1177/000331970105200801
23. Selcuk MT, Selcuk H, Temizhan A, Maden O, Ulupinar H, Baysal E, et al.. Asymmetric dimethylarginine plasma concentrations and L-arginine/asymmetric dimethylarginine ratio in patients with slow coronary flow. Coronary artery disease. 2007;18(7):545-51. doi: 10.1097/MCA.0b013e3282eff1c6
24. Sezgin N, Barutcu I, Sezgin AT, Gullu H, Turkmen M, Esen AM, Karakaya O. Plasma nitric oxide level and its role in slow coronary flow phenomenon. International heart journal. 2005;46(3):373-82. doi:10.1536/ihj.46.373
25. Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histologic evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. Circulation. 1986;74(5):964-72. doi: 10.1161/01.CIR.74.5.964
26. Mangieri E, Macchiarelli G, Ciavolella M, Barilla F, Avella A, Martinotti A, et al. Slow coronary flow: clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. Cathet Cardiovasc Diagn. 1996;37(4):375-81. doi:10.1002/(SICI)1097-0304(199604)37:4<375::AID-CCD7>3.0.CO;2-8
27. Pekdemir H, Cin VG, Cicek D, Camsari A, Akkus N, Doven O, Parmaksiz HT. Slow coronary flow may be a sign of diffuse atherosclerosis. Contribution of FFR and IVUS. Acta cardiologica. 2004;59(2):127-33.
28. Yilmaz H, Gungor B, Kemaloglu T, Sayar N, Erer B, Yilmaz M, et al. The presence of fragmented QRS on 12-lead ECG in patients with coronary slow flow. Kardiol Pol. 2014;72(1):14-9. doi:10.5603/KP.2013.0181
29. Atak R, Turhan H, Sezgin AT, Yetkin O, Senen K, Ileri M, et al. Effects of slow coronary artery flow on QT interval duration and dispersion. Ann Noninvasive Electrocardiol. 2003;8(2):107-11. doi:10.1046/j.1542-474X.2003.08203.x
30. Sezgin AT, Barutcu I, Ozdemir R, Gullu H, Topal E, Esen AM, et al. Effect of slow coronary flow on electrocardiographic parameters reflecting ventricular heterogeneity. Angiology. 2007;58(3):289-94. doi:10.1177/0003319707302486
31. Li G, Zhang L. The role of mexiletine in the management of long QT syndrome. J Electrocardiol. 2018;51(6):1061-5. doi: 10.1016/j.jelectrocard.2018.08.035
32. Chua KC, Teodorescu C, Reinier K, Uy-Evanado A, Aro AL, Nair SG, et al. Wide QRS-T Angle on the 12-Lead ECG as a Predictor of Sudden Death Beyond the LV Ejection Fraction. J Cardiovasc Electrophysiol. 2016;27(7):833-9. doi:10.1111/jce.12989
33. Scherptong RW, Henkens IR, Man SC, Le Cessie S, Vliegen HW, Draisma HH, et al. Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. J Electrocardiol. 2008;41(6):648-55. doi: 10.1016/j.jelectrocard.2008.07.006
34. Draisma HH, Schalij MJ, van der Wall EE, Swenne CA. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart rhythm. 2006;3(9):1092-9. doi: 10.1016/j.hrthm.2006.05.025
35. Saya S, Hennebry TA, Lozano P, Lazzara R, Schechter E. Coronary slow flow phenomenon and risk for sudden cardiac death due to ventricular arrhythmias: a case report and review of literature. Clin Cardiol. 2008;31(8):352-5. doi:10.1002/clc.20266
36. Gungor M, Celik M, Yalcinkaya E, Polat AT, Yuksel UC, Yildirim E, et al. The Value of Frontal Planar QRS-T Angle in Patients without Angiographically Apparent Atherosclerosis. Medical principles and practice : international journal of the Kuwait University, Health Science Centre. 2017;26(2):125-31. doi:10.1159/000453267
37. Kuyumcu M. S., Özbay M. B., Özen Y.,Yayla Ç. Evaluation of frontal plane QRS-T angle in patients with slow coronary flow. Scandinavian Cardiovascular Journal. 2019 29:1-6. doi:10.1080/14017431.2019.1682655.

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(2):179-182.
DOI: 10.28982/josam.857193

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

Depression prevalence among diabetic patients and comparison of demographics and complications

Arzu Cennet Işık, Seydahmet Akın

Department of Internal Medicine, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkey

ORCID ID of the author(s)
ACI: 0000-0001-9844-8599
SA: 0000-0002-2557-3812

Corresponding Author
Arzu Cennet Işık
Department of Internal Medicine, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkey
E-mail: arzukaracelik@gmail.com

Ethics Committee Approval
Ethics committee approval was obtained from the Clinical Research Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital, with the decision number 2019/514/156/9, dated 26 June 2019. 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 February 19

Abstract

Background/Aim: Living with diabetes brings psychological difficulties for many patients and puts them in a depressed state. This reduces follow-up and treatment compliance and increases anxiety in terms of complications. Incompliance of follow-up and treatment can increase macro and micro complications in patients in a vicious circle. In this respect, clinicians should be careful during the follow-up and treatment of the patients. In this study, our aim was to determine the depression rate among diabetic patients and its relationship with demographic findings and complications.

Methods: Patients who are followed up regularly at our hospital's diabetes clinic between July and August 2019 were included and a case-control study was planned. BDI questions were answered by patients under supervision after obtaining patient consent. Patients with BDI >16 were considered depressed. Demographic characteristics, habits, data about diabetes follow-up, treatments and results of BDI were analyzed. The patients were evaluated in terms of cardiovascular, neurological, and ophthalmologic complications. The control group comprised healthy volunteers without any additional diseases.

Results: A total of 281 patients participated in this study and the depression rate was 66.5%. There were 156 females (55.5%) and 125 males (44.5%). Among them, 60.3% of females and 74.4% of males had depression. The mean blood glucose and HbA1c levels were 151 mg/dl (68-475) and 8 mg/dL (4-14), respectively. Based on BDI, 68% of T2DM patients (n=83) and 50% of T1DM patients (n=11) had depression (P=0.087). Depression rates were 66.7% (n=9) between the ages of 20 and 34 years (P=0.035), 50% (n=36) between the ages of 35 and 49 years, 27.5% (n=138) between the ages of 50 and 64 years, and 32.7% (n=98) over the age of 65 years. The control group (n=50) included 32 females (64%) and the depression rate was 35% (n=17).

Conclusion: Every stage of diagnosis, treatment and follow up of diabetes causes physiological stress in patients, which reflects in their lives. We must consider that depression, a treatable disease, affects the management and treatment of diabetes.

Keywords: Diabetes mellitus, Depression, Beck depression inventory

How to cite: Işık AC, Akın S. Determination of diabetic patients' depression prevalence and comparison of demographic and complications with healthy control. J Surg Med. 2021;5(2):179-182.

Introduction

In 2017, almost half (49.7%) of individuals between the ages of 18-99 years had undiagnosed diabetes mellitus (DM). It is known that the cause of death of approximately 5 million people between the 20-99-year age range is DM. By the year of 2017, the number of patients diagnosed with DM reached 451 million, and it is expected to increase to 693 million by 2045 [1].

Depression is a serious global health problem. The World Health Organization (WHO) predicts that depression will be the second most common cause of DALY (Disability Adjusted Life Years) in 2020. According to the WHO 2017 data, the depression rate in Turkey is 4.4% [2]. Many studies conducted in recent years showed that these two diagnoses are associated [3]. It is thought that 25% of diabetic patients have depression, for which diabetes is a risk factor [4].

DM has psychiatric and psychosocial dimensions. An individual with diabetes faces physical, emotional, social and sexual problems. It is often difficult for DM patients to accept that they have a lifelong disease and lifestyle changes are essential [5-7].

We aimed to evaluate the psychiatric aspects of DM patients due to non-compliance in the treatment, follow-up, and management process. We determined the demographic characteristics of patients, their relationship with micro-macrovascular complications and depression frequency.

Materials and methods

Patients followed up regularly at our hospital's diabetes clinic between July and August 2019 were included in the study. Pregnant women, patients with terminal stage malignancies, systemic diseases with short life expectancy and advanced stage neuropsychiatric disorders were excluded from the study. In this case control study, the control group comprised healthy volunteers without known diseases. Consent of the patients were obtained for the study before routine examinations. The patients were asked to fill in the BDI form. Patients with BDI >16 were considered depressed [8].

All participants were told that their information will be kept confidential. Forms were filled in during examinations, archived in the study file and used for scientific purposes only. Demographic characteristics, habits, data about diabetes follow-up, treatments and results of BDI were analyzed. The patients were evaluated in terms of cardiovascular, nephrological, neurological and ophthalmologic complications. Previous myocardial infarction, CABG surgery or stent history, previous cerebrovascular events or presence of retinopathy were evaluated.

Statistical analysis

SPSS 20 (Statistical Package for Social Sciences) software was used in the statistical analysis of the study. Variables were stated as interquartile range. Categorical variables were presented as numbers and percentage (%) and compared with Pearson's Chi-square test. Student's t-test was used for normally distributed continuous data and Mann-Whitney U test was utilized for non-normally distributed data. *P*-value <0.05 was considered statistically significant. Ethics committee approval was obtained from the Clinical Research Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital, with the decision number 2019/514/156/9, dated 26 June 2019.

Results

A total of 281 patients participated in this study. Twenty-two patients (7.8%) had T1DM and 259 patients (92.2%) had T2DM. There were 156 females (55.5%), and the depression rate was 66.5%. According to BDI scores, 68% (n=83) of T2DM patients and 50% (*P*=0.087) of T1DM patients had depression (Table 1).

In our study 69.7% (*P*=0.480) of married patients, 46.3% of single patients and 54.3% of widowed/divorced patients had depression. The rate of patients living with their families was 94% (n=264) and 6% (n=17) lived alone. Depression rate was 34.1% (n=90) among those living with their families and 23.5% (*P*=0.438) among those living alone. The rate of smokers was %15.3 (n=43), among which 39.5% were depressed (*P*=0.358) (Table 2).

Table 1: Patients' and Control Group Distribution of Beck Depression Score
Beck Depression Score 0-16 No Depression; Beck Depression Score 17-39 Depression

Beck depression score	n	%
Patient group		
No depression	94	33.5
Depression	187	66.5
Total	281	100
Control group		
No depression	33	66
Depression	17	34
Total	50	100

Table 2: Demographic Information and Predictive Characteristics of Patients to Whom Beck Depression Index Applied

Variable	Category	Beck Depression Test Negative		Beck Depression Test Positive		*P*-value
		Total	%	Total	%	
Gender	Male	32	25.6	93	74.4	0.013
	Female	62	39.7	94	60.3	
Age	20-34	3	33.3	6	66.6	0.035*
	35-49	18	50	18	50	
	50-64	100	72.5	38	27.5	
	65 and +	66	67.3	32	32.7	
Education	Illiterate	4	26.7	11	73.3	0.972
	Elementary School	50	34.7	94	65.3	
	Secondary School	9	31.0	20	69.0	
	High School	18	34.0	35	66.0	
	University	13	32.5	27	67.5	
Living Place	Living alone	4	23.5	13	76.5	0.438
	Family	90	34.1	174	65.9	
Marital Status	Married	70	30.3	161	69.7	0.480
	Single	8	53.3	7	46.7	
	Widow/Divorced	16	45.7	19	54.3	
Job status	Not working/Retired	10	29.4	24	70.6	0.079
	Employed	19	45.2	23	54.8	
Smoking	Smoker	77	32.4	161	67.6	0.358
	Nonsmoker	17	39.5	26	60.5	
DM Type	Type 1	11	50.0	11	50.0	0.087
	Type 2	83	32.0	176	68.0	
Treatment	OAD	26	23.9	83	76.1	0.019
	Insulin	19	44.2	24	55.8	
	Insulin+OAD	49	38.0	80	62.0	
Cardiac Disease	No Cardiac Disease	72	37.1	122	62.9	0.068
	Ischemic	22	25.9	63	74.1	
Retinopathy	No	72	32.6	149	67.4	0.552
	Yes	22	36.7	38	63.3	
Hyperlipidemia	No	32	36.0	57	64.0	0.545
	Yes	62	32.3	130	67.7	
Hypothyroid	No	85	33.7	167	66.3	0.771
	Yes	9	31.0	20	69.0	
Cerebrovascular diseases	No	88	33.5	175	66.5	0.990
	Yes	6	33.3	12	66.7	
Hypertension	No	24	36.9	41	63.1	0.483
	Yes	69	32.2	145	67.8	

* Chi-square Trend test

The depression rate in our control group consisting of 50 patients (64% females) was 34% (n=17). The depression rates between the 20-34 years, 35-49 years, 50-64 years and over 65 years of age were 33.3% (n=3), 21.7% (n=23), 35.2% (n=17), and 57.1% (n=7), respectively. Fourteen individuals (14%)

smoked, and the depression rate of smokers was 42.8% (n=14). Among the control group, 46 (92%) were married, 3 (6%) were single, and 1 (2%) was widowed/divorced. The depression rates among married, single, and widowed/divorced individuals were 32.6%, 33.3% and 0%. In the control group, 94% (n=7) lived with their families, while 6% (n=3) lived alone. The depression rates were 23.4% among those who lived with their families and 66.6% among those who lived alone.

For treatment, 38.8% (n=109) were using oral anti-diabetic agent (OAD). The rate of BDI positivity in patients using OAD was 23.9% (P=0.019). The rates of patients using insulin and OAD+insulin were 15.3% (n=43) and 45.9% (n=129), respectively, among which 44.2% (n=19) and 38% (n=49), respectively, were depressed.

Among diabetic patients, 21.4% (n=60) had retinopathy, among which 36.7% (n=22) were depressed. The rate of patients with cardiovascular disease (CVD) was 30.5% (n=85) and 25.9% (n=22) of these patients had depression. Among patients with neurological diseases (n=18, 6.4%), 33.3% (n=6) had depression. Also, 32.3% (n=62) of the 192 patients with hyperlipidemia who received statin had depression while 67.7% (n=130) did not. Among eighty-nine patients without hyperlipidemia, 36% (P=0.545) were depressed.

Discussion

In our study, the depression rate was 66.5% among 187 individuals, ninety-three of which were males and ninety-four of which were females. Depression rates were significantly higher among males and increased between the ages of 20-34 years among diabetic, married, and retired male patients**.** In their systematic review article, Tapash Roy et al. [9] suggest that appropriate psychiatric suggestion support, diabetes management, and depression were related with glycemic control and diabetic complications. In the study conducted in the German community by Hermanns et al. [10], females with diabetes were at risk for depression. Rajput et al. [11] found that age, marriage, financial status and being a woman were significant risk factors for depression. In our study, contrary to the other studies we mentioned, we found a high depression rate among males.

The rate of depression was significantly high among patients receiving oral anti-diabetic therapy (OAD). The depression rates of insulin and OAD+insulin users were 44.2% and 38%, respectively. Although the mechanism is not clear, as a result of our clinical follow-up and monitoring, we concluded that the main reason is the inconsistency created by the late use of insulin due to social and cultural reasons and the increase of OAD agents. In the study of Noh JH et al. [12], insulin and OAD users were evaluated with BDI in terms of "tendency to depression" and a higher rate (48%) was observed among insulin users. The presence of diabetes complications, social factors, and the severity of hyperglycemia in the same group of patients were observed to affect the rate of depression. In the study of Işık et al. [13], BDI was increased among diabetics on insulin.

In our study, 32.3% of 62 patients under statin treatment were depressed. In the study of Alghamdi et al. [14], the depression rate was increased in patients who used statin and PCSK9 inhibitor treatment. Agustini et al. [15] followed patients using statins in terms of depression and concluded that the issue should be managed pharmaco-epidemiologically due to the increased depression rate. In a Danish study conducted with 193,977 statin users by Ole Köhler-Forsberg et al. [16], the relationship between the agent and depression was unclear and statin use was not a risk factor. In a case series examining twelve cases, Cham et al. [17] reported changes in emotion, status, personality, and behavior due to statin use and psychiatric adverse drug reactions. It would be beneficial to conduct studies in large groups to clarify the mechanism in anti-lipidemic agent users because of the high rate of depression among statin-using individuals.

Depression creates difficulties in adapting to treatment and lifestyle changes, and during the follow-up of chronic diseases. Education, sociocultural position and marital status of the patient are important in the treatment and follow-up of DM. Studies have shown that there is a strong relationship between DM and depression [18-20]. DM was found to increase the risk of depression 2-3 times [21, 22]. In various studies conducted in the USA and UK, the prevalence of depression in patients with T2DM ranges between 30%-83% [23]. Nouwen et al. [24] revealed that patients with undiagnosed DM or impaired glucose tolerance had a significantly lower depression risk than people with T2DM.

In our study, 69.7% of married, 46.3% of single and 54.3% of widowed/divorced patients had depression. In the cross-sectional study of El Mahalli et al. [25], depression prevalence of DM patients was 49.6%, and contrary to our study, there is an increased risk among unmarried patients with poorly controlled diabetes. In the study conducted by Öyeçkin et al. [26], as the education level of the patients increased, mental illness rate decreased. Similarly, in our study, 34.7% of 144 primary school graduates and 32.5% of 40 college graduates were depressed, which showed that depression rate inversely correlated with educational level.

In our study, we found that there is an increase in the risk of depression in 11 (50%) of 22 patients with T1DM, and we concluded that, although not statistically significant, it would be appropriate to evaluate the T1DM patients periodically at the end of our clinical observations. Johnson et al. [27] found that T1DM was a reason for mental health screening. In addition to this, Atasoy et al. [28] found that T1DM patients were prone to depression and anxiety, and their quality of life was worse. In these respects, closer monitoring is recommended.

When the prevalence of depression was examined according to the age groups, we observed that the rate decreased as age increased. Similarly, in the literature, Hermanns and El-Mahalli stated that depression rate decreases as age increases [10, 25]. In the study of SAHOS (South Australian Health Omnibus Survey) group, the prevalence of depression increased in the 45-50 age group [4]. We thought that because T1DM patients are young, socio-economic concerns of young people and genetic, environmental and biological factors may be effective in prevalence.

We observed an increased risk of depression among people with diabetes with concomitant cardiovascular disease. Contrary to expectations, we did not observe a significantly higher depression rate in patients with retinopathy and

neurological diseases, but it should be evaluated with a larger patient population. In the study conducted by Rajput et al. [11], all vascular and microvascular complications were significantly higher in patients with high BDI scores. In our study, we observed that depressed diabetes patients were more affected from macrovascular complications.

Limitations

The limitations of this study include its single-center design and small sample size, which decreases the generalizability of the results. Future, multi-center studies may increase the reliability of results for the general population. The demographic data on the reported disease may be required to improve the reliability of validation results.

Conclusion

Diabetes mellitus disease requires lifelong treatment and follow-up, and we found that it affects a huge portion of the patients psychologically. Early diagnosis at the beginning of the treatment will contribute positively to the process. It is our opinion that as the mental status of the patients improve with a multidisciplinary approach, the complications related to diabetes would decrease.

References

1. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018 Apr 1;138:271–81.
2. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.
3. Meurs M, Roest AM, Wolffenbuttel BHR, Stolk RP, Jonge P De, Rosmalen JGM. Association of Depressive and Anxiety Disorders With Diagnosed Versus Undiagnosed Diabetes : An Epidemiological Study of 90, 686 Participants. Psychosom Med. 2016;78(2):233–41.
4. Goldney RD, Phillips PJ, Fisher LJ, Wilson DH. Diabetes, Depression, and Quality of Life. Diabetes Care [Internet]. 2004 May 1;27(5):1066 LP – 1070.
5. Buzlu S. Diyabetin Psikososyal Boyutu. In: S. E, editor. Diyabet Hemşireliği Temel Bilgiler. 2002. p. 195–203.
6. Özkan S. Psikiyatrik Tıp: Konsultasyon Liyezon Psikiyatrisi. 1. Ed. İstanbul: Roche Publishing; 1993. 93–99 p.
7. Akbay Pırıldar Ş. Dahiliye ve Psikiyatri, Diyabette Depresyon ve Anksiyete Bozuklukları. 1. Edition. İstanbul: Okuyan Us Publishing; 2003. 7–44 p.
8. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561-71
9. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord. 2012 Oct;142 Suppl:S8-21. doi: 10.1016/S0165-0327(12)70004-6. PMID: 23062861.
10. Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. Affective and anxiety disorders in a German sample of diabetic patients: prevalence, comorbidity and risk factors. Diabet Med [Internet]. 2005 Mar 1;22(3):293–300.
11. Rajput R, Gehlawat P, Gehlan D, Gupta R, Rajput M. Prevalence and predictors of depression and anxiety in patients of diabetes mellitus in a tertiary care center. Indian J Endocrinol Metab. 2016;20(6):746–51.
12. Noh JH, Park JK, Lee HJ, Kwon SK, Lee SH, Park JH, et al. Depressive symptoms of type 2 diabetics treated with insulin compared to diabetics taking oral anti-diabetic drugs : A Korean study. 2005;69:243–8.
13. Işık NA, Buzlu S. Compared to Depressive Symptoms of Type 2 Diabetic Patients Who were Treated with Oral Anti-Diabetic Drugs and Insulin. Gazi Med J. 2016;27(4):189–92.
14. Alghamdi J, Matou-Nasri S, Alghamdi F, Alghamdi S, Alfadhel M, Padmanabhan S. Risk of Neuropsychiatric Adverse Effects of Lipid-Lowering Drugs : A Mendelian Randomization Study. Int J Neuropsychopharmacol. 2018;21(12):1067–75.
15. Agustini B, Mohebbi M, Woods RL, McNeil JJ, Nelson MR, Shah RC, et al. Association Between Statin Use and Depressive Symptoms in a Large Community-Dwelling Older Population Living in Australia and the USA: A Cross-Sectional Study. CNS Drugs [Internet]. 2019 Jul;33(7):685–94.
16. Köhler-Forsberg O, Gasse C, Petersen L, Nierenberg AA, Mors O, Østergaard SD. Statin treatment and the risk of depression. J Affect Disord [Internet]. 2019;246(December 2018):706–15.
17. Cham S, Koslik HJ, Golomb BA. Mood, Personality, and Behavior Changes During Treatment with Statins: A Case Series. Drug Saf - case reports [Internet]. 2016 Dec;3(1):1.
18. Musselman DL, Betan E, Larsen H, Phillips LS. Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. Biol Psychiatry [Internet]. 2003 Aug 1;54(3):317–29.
19. Raval A, Dhanaraj E, Bhansali A, Grover S, Tiwari P. Prevalence & determinants of depression in type 2 diabetes patients in a tertiary care centre. Indian J Med Res. 2014;132(2):195–200.
20. Reddy P, Philpot B, Ford D, Dunbar JA. Identification of depression in diabetes: the efficacy of PHQ-9 and HADS-D. Br J Gen Pract [Internet]. 2010 Jun;60(575):e239–45.
21. Nichols GA, Brown JB. Unadjusted and Adjusted Prevalence of Diagnosed Depression in Type 2 Diabetes. Diabetes Care [Internet]. 2003 Mar 1;26(3):744 LP – 749.
22. Asghar S, Hussain A, Ali SMK, Khan AKA, Magnusson A. Prevalence of depression and diabetes: a population-based study from rural Bangladesh. Diabet Med [Internet]. 2007 Aug 1;24(8):872–7.
23. Li C, Ford ES, Strine TW, Mokdad AH. Prevalence of depression among US adults with diabetes: findings from the 2006 behavioral risk factor surveillance system. Diabetes Care. 2008;31(1):105–7.
24. Nouwen A, Nefs G, Caramlau I, Connock M, Winkley K, Lloyd CE, et al. Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: a systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium. Diabetes Care [Internet]. 2011 Mar;34(3):752–62.
25. El Mahalli AA. Prevalence and Predictors of Depression among Type 2 Diabetes Mellitus Outpatients in Eastern Province, Saudi Arabia. Int J Health Sci (Qassim) [Internet]. 2015 Apr;9(2):119–26.
26. Öyekçin D. Bir devlet hastanesi psikiyatri polikliniğine bir yıl içinde başvuran olguların sosyodemografik özellikleri ve psikiyatrik tanı dağılımı. Anadolu Psikiyatr Derg. 2008;9(1):39–43.
27. Johnson B, Eiser C, Young V, Brierley S, Heller S. Prevalence of depression among young people with Type 1 diabetes: a systemaic review. Diabet Med [Internet]. 2013 Feb 1;30(2):199–208.
28. Atasoy V, Anaforoğlu İ, Algün E, Kutanis R. Depression, Anxiety and Quality of Life Among Adult Turkish Patients with Type 1 Diabetes Mellitus. Turkish J Endocrinol Metab. 2013;28–32.

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(2):183-187.
DOI: 10.28982/josam.754891

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

Tp-Te interval prolongs in hypertension independent of the left ventricular geometry

Sinan Cemgil Özbek

Department of Cardiology, Ahi Evran University Training and Research Hospital, Kirsehir, Turkey

ORCID ID of the author(s)
SCÖ: 0000-0001-9056-8350

Corresponding Author
Sinan Cemgil Özbek
Ahi Evran University, Training and Research Hospital, Department of Cardiology Kervansaray Mah. 2019. Sok. No:1, Post code: 40100, Kirsehir, Turkey
E-mail: ozbeksc@gmail.com

Ethics Committee Approval
Kırşehir Ahi Evran University Medical Faculty Clinical Research Ethics Committee approved our study design in 2019.
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 February 19

Abstract

Background/Aim: Hypertension (HT) may modulate left ventricular (LV) geometry. Electrocardiographic Tp-Te, QT and QTc interval, and Tp-Te/QTc ratio are among the parameters of ventricular repolarization (VR) that may predict ventricular arrhytmogenic potential and possess prognostic significance. It is well known that left ventricular hypertrophy is associated with increase in the parameters of VR; however, little is known about the association of these parameters with other forms of LV geometry in HT. Our aim was to assess this association.

Methods: A total of 162 newly diagnosed essential HT patients were enrolled and divided into those with concentric LV remodeling (n=79) and those with normal LV geometry (n=83). Healthy normotensive subjects (n=76) comprised the control group. Data were gathered retrospectively from electrocardiographic, echocardiographic, and demographic records.

Results: QT interval, P-wave duration, and QRS duration were similar among the 3 groups ($P>0.05$). Tp-Te, QTc and Tp-Te/QTc were greater in the HT group compared with the controls ($P<0.001$). In a pair-wise comparison between 2 HT subgroups, these parameters were similar ($P>0.05$). There was no correlation between Tp-Te interval, LV mass and LV mass index among the study population.

Conclusion: Tp-Te may be useful in prognostic stratification of HT. Regardless of the LV geometry, HT patients have prolonged Tp-Te and QTc intervals, and increased Tp-Te/QTc ratio compared to the healthy subjects. Our findings may suggest possible utilization of Tp-Te as HT-related end-organ damage in the future.

Keywords: Tp-Te interval, Hypertension, Ventricular repolarization, Left ventricle geometry

How to cite: Özbek SC. Tp-Te interval prolongs in hypertension independently of the left ventricular geometry. J Surg Med. 2021;5(2):183-187.

Introduction

Exposure to hypertension (HT) gives rise to an increase in the left ventricular mass in the long run, which in turn is linked to an increase in the incidence of cardiovascular diseases (CV), and CV-related and all-cause mortality [1]. HT patients with concentric left ventricular (LV) remodeling possess a poorer prognosis compared with those with normal LV geometry, and hence concentric remodeling is an independent predictor for future CV events [2, 3].

Electrocardiographic (ECG) time interval from T-wave peak to T-wave end, also referred to as Tp-Te interval, was proposed as a novel index of transmural dispersion of ventricular repolarization (VR) in some studies [4, 5], or an index of global VR in others [6]. Tp-Te/QT and Tp-Te/QTc ratios are also novel ECG parameters indicating ventricular arrhythmogenic potential.

Previous data has reached a consensus regarding prolongation in Tp-Te interval and Tp-e/QTc ratio in the presence of left ventricular hypertrophy (LVH) in various clinical settings including HT [7-10]. However, there is confounding data about the status of the parameters of VR in HT patients with concentric remodeling compared with HT patients with normal LV geometry. To the best of our knowledge, there is no study comparing the parameters of VR between HT patients with normal LV geometry and HT patients with concentric remodeling with healthy normotensive subjects with normal LV geometry. Therefore, we aimed to assess whether deterioration in some novel parameters of VR occurs in sub-clinic settings before the emergence of gross modification in LV morphology in newly diagnosed HT patients.

Materials and methods

Patient recruitment

Our study has a retrospective and cross-sectional nature, where hospital records of a total of 162 consecutive patients with newly diagnosed and never treated essential HT were assessed between June 2018 and February 2019. The patients were subdivided based on their echocardiographic LV geometry into two subgroups as the HT patients with normal LV geometry [n=83, mean age 46.9 (9.2) years] and HT patients with concentric LV remodeling [n=79 mean age 49.2 (7.6) years]. Furthermore, 76 healthy normotensive subjects [mean age 47.4 (8.8)] admitted with nonspecific symptoms to our cardiology outpatient polyclinics in which echocardiography revealed normal LV geometry composed the control group. We did not include the HT patients with LVH in our study, since we primarily sought to reveal the possible changes in ECG parameters of VR in subjects without dramatic modifications in LV morphology. Demographic, ECG and echocardiographic data were collected on the day of outpatient clinic admission. Exclusion criteria are defined as follows: Cardiovascular atherosclerotic diseases, diabetes mellitus, smoking, severe kidney failure attributable to secondary HT, physical and clinical features, endocrine disorders, arrhythmia, inflammatory diseases, LV systolic dysfunction, cerebrovascular diseases, pulmonary disease. The body-mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. All enrolled subjects gave a written informed consent. This study follows the ethical standards defined by the Helsinki Declaration and the Kırşehir Ahi Evran University Medical Faculty Clinical Research Ethics Committee approved our study protocol in 2019.

Echocardiography

All study participants were examined with a Vivid S3 Echocardiography device (General Electric, Vingmed Ultrasound AS, Horten, Norway) by an experienced cardiologist blinded to the study. Dimensions of left ventricle, wall thicknesses, and left atrial (LA) diameters were measured from parasternal long-axis images. LA area was measured through planimetry from the apical four-chamber view. Relative wall thickness (RWT) was calculated with the formula " 2 x posterior LV wall thickness / left ventricular end diastolic diameter " [11]. The modified Simpson's rule was used to determine the left ventricular ejection fraction (LVEF). Transmitral inflow velocities (E and A velocities), and E-deceleration time (EDT) were measured as the according to the relevant guideline [12]. LVMI was calculated using the Devereux's formula [11,13]. Normal LV geometry was defined as RWT ≤0.42 accompanied by LVMI ≤95 gr/m^2 for females and ≤115 gr/m^2 for males. Concentric LV remodeling was defined as the co-existence of RWT> 0.42, and LVMI ≤95 gr/m^2 for females and ≤115 gr/m^2 for males. LVH was defined as LVMI >95 gr/m^2 for females and >115 gr/m^2 for males according to the relevant literature [11]. Accordingly, HT patients compatible with the term "LVH" were not included in the study.

Ambulatory blood pressure monitoring

The participants with office blood pressure (BP) ≥ 140/90 mmHg underwent a 24-hour ABPM (Bravo HR ABP Sun Tech Medical Inc., Morrisville, NC, USA). After selection of the appropriate size, the cuff of the device was placed on the non-dominant arm and BP readings were recorded for 24 hours. On the other hand, 24-hour AMPM was implemented in all control subjects with office BP <140/90 mmHg to unearth any probable white-coat HT. During the daytime (6:00 am -10:00 pm), the measurement of the BP was performed every 15 minutes and during nighttime (10:00 pm -06:00 am), every 30 minutes. Each participant was asked to continue his/her daily routines and stand still and quiet during each measurement. Participants were excluded from the study if the device did not successfully record ≥80% of their BP readings. For each participant, 24-hour mean systolic BP, 24-hour mean diastolic BP, daytime mean systolic BP, daytime mean diastolic BP, nighttime mean systolic BP and nighttime mean diastolic BP were calculated. The diagnosis of hypertension based on ABPM was made in any patient if 24-hour mean systolic BP >130 mmHg and/or diastolic BP >80 mmHg, daytime mean systolic BP >135 mmHg and/or diastolic BP >85 mmHg or nighttime systolic BP >120 mmHg and/or diastolic BP >70 mmHg [14].

Electrocardiography

A 12-lead ECG strip (Nihon Kohden, Tokyo, Japan) recorded at 50 mm/s paper speed in every participant, which was then scanned and analyzed under x300% magnification in a personal computer. We preferred the longest measurement of Tp-Te interval in all precordial leads, as the precordial leads were much more specific for the measurement of Tp-Te in reflecting the best the transmural dispersion of repolarization [9,15,16]. QTc intervals were calculated by Bazett's equation:

QTc=QT/√(RR). Tp-Te/QTc ratios were calculated subsequently. Tangent and tail methods [17,18] are two common methods used to measure the Tp-Te interval. The tangent method was utilized in the current study that indicates the time interval between the peak of T and the point where the tangent of the steepest down-slope of the T wave intersects the isoelectric line [17]. RR interval, QT interval and P-wave duration were measured in Lead 2. Average of three consecutive complexes was calculated to obtain the ultimate value for every relevant parameter. All ECG parameters were assessed by two experienced cardiologists blinded to design of the study. Inter- and intra-observer coefficient of variation were 3.5% and 2.7%, respectively.

Statistical analysis

Statistical analyses were performed with PASW Statistics for Windows, Version 18.0 (Chicago: SPSS Inc). Using the Kolmogorov-Smirnov test, it was evaluated whether the parameters were normally distributed. The groups were compared with chi-square test for categorical variables and One-Way Variance Analysis (ANOVA) test for continuous variables. If the p value was statistically significant in one-way ANOVA test, post-hoc Tukey's tests were used to compare the differences between the groups. Pearson rank tests were used to analyze the relationship between the Tp-e interval and other variables. Multivariate and univariate logistic regression analysis was used to determine the parameters associated with the presence of HT. *P*-value <0.05 was considered statistically significant.

Results

Demographics and clinical features of the study population are provided in Table 1. There was no difference among the 3 groups with regards to age, gender, weight, height, and BMI ($P>0.05$). Results of the blood chemistry and lipid panel were also similar between the groups. As expected, office systolic and diastolic BPs were significantly higher in overall HT group compared with the controls ($P<0.001$). Office BP and ABPM recordings were normal in the control group, thus ruling out a probable masked HT in this group. All ABPM recordings were significantly greater in the HT group; however, pair-wise comparison of these recordings between HT patients with normal LV geometry and HT patients with concentric LV remodeling did not reveal any difference.

Echocardiographic findings were also presented in Table 1. As evident in the table, LV mass, LVMI and RWT were significantly greater in the HT group with concentric LV remodeling [169 (23.2) g, 87.4 (11.7) g/m2, and 0.45 (0.03), respectively] compared with the HT group with normal LV geometry [149.2 (26.7) g, 78.8 (13.6) g/m2, and 0.40 (0.05), respectively] and the controls [145.6 (33.3) g, 76.4 (13.1) g/m2, and 0.39 (0.03), respectively] ($P<0.001$ for all). In the pair-wise comparison, however, these parameters were similar between the HT group with normal LV geometry and the controls ($P>0.05$). LVEF, transmitral E/A velocity ratio, and LA area were similar between the three groups.

ECG findings of the study population were presented in Table 2. There was no significant difference among the groups with regards to QT interval, P-wave duration, and QRS duration ($P>0.05$). On the other hand, Tp-Te interval, QTc interval and Tp-Te/QTc ratio were significantly greater in the HT group, compared with the controls ($P<0.001$). In a pair-wise comparison between 2 HT subgroups, however, these parameters were similar ($P>0.05$) (Figure 1).

Table 1: General characteristics of the study population

	Hypertensive Patients			
	Normal LV Geometry (n= 76)	Normal LV Geometry (n=83)	Concentric LV Remodeling (n=79)	ANOVA *P*-value
Clinical characteristics				
Age, y	47.4 (8.8)	46.9 (9.2)	49.2 (7.6)	0.137
Gender, female, n (%)	37 (48.6%)	38 (45.7%)	34 (43%)	0.582
Height, cm	168.4 (9,8)	166.5 (8.5)	166.6 (8.7)	0.198
Weight, kg	76.8 (14.1)	78.6 (13.8)	82.5 (13.4)	0.310
BMI, kg/m²	27.1 (4.8)	28.2 (4.5)	28.7 (4.6)	0.094
TC, mg/dL	189.1 (39.7)	189.0 (34.6)	194.8 (27.3)	0.233
HDL-C, mg/dL	49.0 (12.3)	47.3 (13.5)	48.3 (11.8)	0.687
LDL-C, mg/dL	112.9 (36.5)	109.3 (29.4)	115.1 (26.5)	0.508
TG, mg/dL	159.2 (85.69	181.3 (59.5)	176.0 (119.49	0.136
Fasting glucose, mg/dL	93.1 (14.2)	96.7 (10.4)	95.1 (9.3)	0.212
BUN, mg/dL	32.7 (10.6)	31.4 (10.4)	32.9 (11.8)	0.696
Serum creatinine, mg/dL	0.88 (0.079)	0.86 (0.08)	0.85 (0.04)	0.385
BP profile				
Clinic systolic BP, mm Hg	124.3 (12.1)[a]	148.4 (15.3) [b]	151.4 (14.2) [b]	<0.001
Clinic diastolic BP, mm Hg	81.3 (9.8)[a]	95.4 (10.1) [b]	96.3 (13.4) [b]	<0.001
Heart rate, beats per min	75.5(9.4)	74.8 (8.4)	76.6 (7.6)	0.436
24-h systolic BP, mm Hg	118 (15.7)[a]	142 (9.7) [b]	145 (10.3) [b]	<0.001
24-h diastolic BP, mm Hg	72.7 (7.7)[a]	89.7 (6.6) [b]	90.4 (4.3) [b]	<0.001
Daytime systolic BP, mm Hg	122.2 (10.4)[a]	146.4 (7.8) [b]	148.6 (9.9) [b]	<0.001
Daytime diastolic BP, mm Hg	74.5 (6.4)[a]	93.3 (5.7) [b]	93.1 (7.1) [b]	<0.001
Nighttime systolic BP, mm Hg	116.7 (13.1) [a]	140.8 (12.48) [b]	142.4 (11.2) [b]	<0.001
Nighttime diastolic BP, mm Hg	69.8 (5.8) [a]	87.6 (7.2) [b]	89,4 (7.6) [b]	<0.001
Echocardiographic Parameters				
LV mass, g	145.6 (33.3) [b]	149.2 (26.7) [b]	169 (23.2) [a]	<0.001
LV mass/BSA, g/m²	76.4 (13.1) [b]	78.8 (13.6) [b]	87.4 (11.7) [a]	<0.001
LV mass/height, g/cm	86.2 (17.6) [b]	89.6 (15.9) [b]	101.3 (12.7) [a]	<0.001
RWT	0.39 (0.03) [b]	0.40 (0.05) [b]	0.45 (0.03) [a]	<0.001
LVEF, %	63.1 (2,8)	62.6 (3.1)	63.2 (2.9)	0.234
Transmitral E/A velocity ratio	1.2 (0.28)	1.1 (0.389	1.0 (0.31)	0.065
Left atrium area, cm ²	14.9 (1.8)	15.2 (2.39	15.7 (2.29	0.245

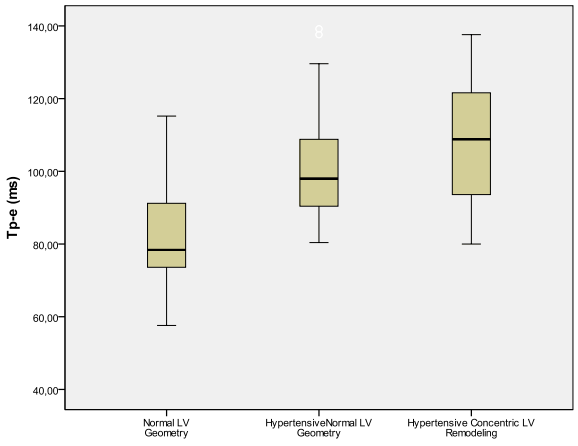
Data are given as number (percentage) for categorical variables and mean (standard deviation) for continuous variables. There is no statistically significant difference between the pairs marked with the same letter within the same line ($P>0.05$). ANOVA: analysis of variance, BMI: body mass index, BP: blood pressure, BSA: body surface area, BUN: blood urea nitrogen, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, LV: left ventricular, LVEF: left ventricular ejection fraction, RWT: Relative wall thickness, TC: total cholesterol, TG: triglycerides

Table 2: Electrocardiographic characteristics of study patients

	Hypertensive Patients			
	Normal LV Geometry (n=76)	Normal LV Geometry (n=83)	Concentric LV Remodeling (n=79)	ANOVA *P*-value
Tp-e	82.3 (12.79) [a]	102.0 (13.9) [b]	105.7 (17.0) [b]	<0.001
Tp-e/QTc ratios	0.23 (0.03) [a]	0.27 (0.049) [b]	0.28 (0.05) [b]	<0.001
Tp-e /QRS	1.03 (0.20) [a]	1.26 (0.19) [b]	1.28 (0.24) [b]	<0.001
QTc	346.1 (23.0) [a]	362.8 (26.5) [b]	361.8 (25.6) [b]	<0.001
QT	339.2 (23.7)	341.0 (25.7)	344.23 (15.6)	0.198
P wave	78.1 (13.1)	77.9 (14.0)	75.4 (16.5)	0.612
QRS	81.4 (11.7)	81.3 (12.4)	82.5 (9.5)	0.518
R wave peak	27.5 (11.0)	28.7 (7.3)	27.2 (7.1)	0.387

Data are given as mean (standard deviation) for continuous variables. There is no statistically significant difference between the pairs marked with the same letter within the same line ($P>0.05$). ANOVA: analysis of variance, LV: left ventricle

Figure 1: Comparison of Tp-Te interval among the three groups



There was no correlation between Tp-Te interval, LV mass and LVMI within the study population ($P>0.05$) (Table 3).

Table 3: Correlation of Tp-Te interval with LV mass and LVMI in study subjects

		LVMI	LVM
Hypertensive subjects	r	0.151	0.143
(n=162)	*P*-value	0.055	0.069
Normotensive subjects	r	0.110	0.115
(n=76)	*P*-value	0.338	0.312
All subjects	r	0.126	0.120
(n=238)	*P*-value	0.052	0.062

LVM: left ventricular mass, LVMI: left ventricular mass index

Discussion

The main findings of our study are that Tp-Te interval, QTc interval and Tp-Te/QTc ratio were significantly greater in overall HT patients compared with the normotensive controls. However, these ECG parameters were similar between HT patients with normal LV geometry and HT patients with concentric LV remodeling. Accordingly, our results indicate that deterioration in the ECG parameters of VR commences prior to the macroscopic changes take place in the LV geometry in patients with HT. In this respect, our findings are novel for demonstrating a worsening in the VR in HT patients with normal LV geometry compared with the healthy normotensive subjects with normal LV geometry.

A robust relationship is already known between prolonged QT and QTc intervals and ventricular arrhythmias [19-21]. Tp-Te interval has been a relatively new index of ventricular repolarization. Furthermore, prolonged Tp-Te interval is associated with ventricular arrhythmias and cardiac mortality [15, 22-24]. More recently, Tp-Te/QTc was suggested as a novel marker of VR and demonstrated to be a more accurate predictor of ventricular arrhythmias [25]. Furthermore, it is more accurate in terms of indicating the status of VR compared with Tp-Te or QT intervals [25]. Tp-Te interval is shown to be associated with increased all-cause and CV mortalities independent of HT in the general population [26]. Aside from its prognostic role, little is known about diagnostic role of Tp-Te interval in different clinical settings.

LVH is well known to associate with Tp-Te interval and Tp-e/QTc ratio in clinical setting including HT. However, the same does not hold true between these ECG parameters and concentric LV remodeling. Porthan et al. [7] reported a prolongation in Tp-Te interval, and a positive correlation between Tp-Te interval and LVMI in HT patients with LVH. In contrast, Saba et al. [8] subdivided a total of three hundred HT patients into three subgroups as those with normal LV geometry, those with concentric remodeling and those with LVH, and demonstrated a significantly prolonged Tp-Te interval in HT patients with LVH, but a significantly shorter Tp-Te interval in HT patients with concentric remodeling, compared with HT patients with normal LV geometry. In our study, however, we found no significant correlation between Tp-Te interval either with LV mass or LVMI, which propels us to consider that that it is the HT itself which incites prolongation in Tp-Te interval rather than a less dramatic LV remodeling other than LVH. In another small-sized study (n=50), Ferrucci et al. [27] detected a significant and positive correlation between Tp-Te interval and LV mass in newly diagnosed HT patients, compared with healthy subjects. Although HT patients in their study did not have LVH, they did not stratify the HT patients as those with normal geometry and the others with concentric remodeling to provide a pair-wise comparison among HT subgroups and the controls as in our study. Additionally, they demonstrated an association between Tp-Te and presence of HT. In this regard, our findings further extend their findings by stratifying the HT patients into two geometric subgroups and comparing Tp-Te between them.

Although exposure to increased BP for a sufficiently long time was reported to lead to an increase in LV mass [28], there is a weak association between the sole exposure to high BP and increase in LV mass [29]. Rather, increase in LV mass and progression of LVH are multifactorial, including a congeries of neurohormonal [30], genetic [31, 32] and renin-angiotensin system [33] contributors. Similarly, changes in the LV geometry observed in HT patients are also multifactorial and affected by chronic volume and pressure overload, race, gender, neurohormonal environment, genetics, extracellular matrix modifications [34]. Hence, to expect an absolute increase in LV mass and a change in LV geometry in all patients with HT is not reasonable due to this multifactorial nature. In a previous study, on the other hand, increase in the LV mass and wall thicknesses in normotensive subjects was proposed to associate with the development of a new HT [35]. These results, when combined, give rise to a chicken and egg situation as to which one, namely HT or change in LV geometry, comes first. For this reason, it is quite challenging to establish a robust relationship between the modification in LV geometry and BP. Lawler et al. [36] demonstrated that subclinical abnormalities at cellular level such as cardiomyocyte hypertrophy and fibrosis occurred long before the gross morphological changes in LV geometry in HT patients. Our finding that Tp-Te interval and Tp-Te/QTc ratio increased in overall HT patients regardless of the status of LV geometry compared with the controls propels us to consider that exposure to higher BP disrupts VR through subclinical modifications at cellular level.

Bombelli et al. [26] followed up both hypertensive and normotensive subjects for 16 years and demonstrated a significant association between prolonged Tp-Te interval and increased CV and all-cause mortality both in the general and hypertensive population. However, Tp-Te interval failed to predict the emergence of a future HT and LVH in normotensive patients at baseline. In this regard, prolongation of Tp-Te interval even in HT patients with normal LV geometry as compared with the healthy subjects with normal LV geometry in our study is quite likely to be associated with increased long-term mortality.

In the future, defining a probable cut-off value for such non-invasive and simple ECG parameters as Tp-Te interval and Tp-Te/QTc ratio to better predict mortality and major adverse CV events would prove especially useful in the risk stratification of newly diagnosed HT patients and even in the commence of appropriate therapy at an earlier time. More specifically, our study may prove useful in the differential diagnosis of a masked HT especially in patients without an elevated office BP, but with relevant symptomology to HT. Moreover, current guidelines offer electrocardiographic LVH as a surrogate for HT-related organ damage which necessitates prompt initiation, in addition to lifestyle modification or drug treatment even in the presence of grade-1 HT or high-normal BP [37]. Based on our findings, we conjecture that Tp-Te and Tp-Te/QTc could be used as another surrogate marker of HT-related organ damage to dictate early start of medical therapy in speculated settings such as grade 1

HT or high-normal BP when other conversional CV risks or end-organ damages are absent. However, future multicenter trials with large patient cohorts are warranted for this purpose to define likely cut-off values for these VR indices to stand conjointly for another surrogate marker of HT-related end-organ damage.

Limitations

Our study should be assessed together with a number of limitations. We conducted this study on a relatively small-scale population; and it is retrospective and cross-sectional in nature. Additionally, we did not follow patients for future adverse CV events and LV hypertrophy that may develop in both HT groups. Also, we did not include Tp-Te and P-wave dispersions in our study.

Conclusion

This study results show that regardless of the LV geometry, patients with HT are characterized with prolonged Tp-Te interval and increased Tp-Te/QTc ratio, as compared with the healthy normotensive subjects. In this regard, our findings may point out that increase in these parameters may reflect subclinical abnormalities at cellular and extracellular matrix levels long before the emergence of gross morphological changes in LV geometry, which may suggest that deterioration in VR parameters might be used as HT-related end-organ damage if can be warranted by future large-scale prospective studies.

References

1. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322(22):1561-6. Epub 1990/05/31. doi: 10.1056/nejm199005313222203. PubMed PMID: 2139921.
2. Pierdomenico SD, Lapenna D, Bucci A, Manente BM, Cuccurullo F, Mezzetti A. Prognostic value of left ventricular concentric remodeling in uncomplicated mild hypertension. Am J Hypertens. 2004;17(11 Pt 1):1035-9. Epub 2004/11/10. doi: 10.1016/j.amjhyper.2004.06.016. PubMed PMID: 15533730.
3. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Bartoccini C, et al. Adverse prognostic significance of concentric remodeling of the left ventricle in hypertensive patients with normal left ventricular mass. J Am Coll Cardiol. 1995;25(4):871-8. Epub 1995/03/15. doi: 10.1016/0735-1097(94)00424-o. PubMed PMID: 7884090.
4. Antzelevitch C. T peak-Tend interval as an index of transmural dispersion of repolarization. Eur J Clin Invest. 2001;31(7):555-7. Epub 2001/07/17. PubMed PMID: 11454006.
5. Antzelevitch C, Sicouri S, Di Diego JM, Burashnikov A, Viskin S, Shimizu W, et al. Does Tpeak-Tend provide an index of transmural dispersion of repolarization? Heart rhythm. 2007;4(8):1114-6; author reply 6-9. Epub 2007/08/07. doi: 10.1016/j.hrthm.2007.05.028. PubMed PMID: 17675094; PMCID: PMC1994816.
6. Xia Y, Liang Y, Kongstad O, Holm M, Olsson B, Yuan S. Tpeak-Tend interval as an index of global dispersion of ventricular repolarization: evaluations using monophasic action potential mapping of the epi- and endocardium in swine. Journal of interventional cardiac electrophysiology: an international journal of arrhythmias and pacing. 2005;14(2):79-87. Epub 2005/12/24. doi:10.1007/s10840-005-4592-4. PubMed PMID: 16374554.
7. Porthan K, Virolainen J, Hiltunen TP, Viitasalo M, Vaananen H, Dabek J, et al. Relationship of electrocardiographic repolarization measures to echocardiographic left ventricular mass in men with hypertension. J Hypertens. 2007;25(9):1951-7. Epub 2007/09/01. doi: 10.1097/HJH.0b013e328263088b. PubMed PMID: 17762661.
8. Saba MM, Arain SA, Lavie CJ, Abi-Samra FM, Ibrahim SS, Ventura HO, Milani RV. Relation between left ventricular geometry and transmural dispersion of repolarization. Am J Cardiol. 2005;96(7):952-5. Epub 2005/09/29. doi: 10.1016/j.amjcard.2005.05.053. PubMed PMID: 16188523.
9. Castro-Torres Y, Carmona-Puerta R, Katholi RE. Ventricular repolarization markers for predicting malignant arrhythmias in clinical practice. World J Clin Cases. 2015;3(8):705-20. doi: 10.12998/wjcc.v3.i8.705. PubMed PMID: 26301231; PMCID: PMC4539410.
10. Akboga MK, Gulcihan Balci K, Yilmaz S, Aydin S, Yayla C, Ertem AG, et al. Tp-e interval and Tp-e/QTc ratio as novel surrogate markers for prediction of ventricular arrhythmic events in hypertrophic cardiomyopathy. Anatol J Cardiol. 2017;18(1):48-53. Epub 2017/03/21. doi: 10.14744/AnatolJCardiol.2017.7581. PubMed PMID: 28315570; PMCID: PMC5512198.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70. doi: 10.1093/ehjci/jev014. PubMed PMID: 25712077.
12. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA, Doppler Quantification Task Force of the N, Standards Committee of the American Society of E. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr. 2002;15(2):167-84. PubMed PMID: 11836492.
13. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol. 1986;57(6):450-8. PubMed PMID: 2936235.
14. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219. doi: 10.1093/eurheartj/eht151. PubMed PMID: 23771844.
15. Castro Hevia J, Antzelevitch C, Tornes Barzaga F, Dorantes Sanchez M, Dorticos Balea F, Zayas Molina R, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol. 2006;47(9):1828-34. doi: 10.1016/j.jacc.2005.12.049. PubMed PMID: 16682308; PMCID: PMC1474075.
16. Antzelevitch C, Oliva A. Amplification of spatial dispersion of repolarization underlies sudden cardiac death associated with catecholaminergic polymorphic VT, long QT, short QT and Brugada syndromes. Journal of internal medicine. 2006;259(1):48-58. Epub 2005/12/13. doi: 10.1111/j.1365-2796.2005.01587.x. PubMed PMID: 16336513; PMCID: PMC1474026.
17. Charbit B, Samain E, Merckx P, Funck-Brentano C. QT interval measurement: evaluation of automatic QTc measurement and new simple method to calculate and interpret corrected QT interval. Anesthesiology. 2006;104(2):255-60. PubMed PMID: 16436843.
18. Salles GF, Cardoso CR, Leocadio SM, Muxfeldt ES. Recent ventricular repolarization markers in resistant hypertension: are they different from the traditional QT interval? Am J Hypertens. 2008;21(1):47-53. doi: 10.1038/ajh.2007.4. PubMed PMID: 18091743.
19. Peters RW, Byington RP, Barker A, Yusuf S. Prognostic value of prolonged ventricular repolarization following myocardial infarction: the BHAT experience. The BHAT Study Group. J Clin Epidemiol. 1990;43(2):167-72. PubMed PMID: 2406377.
20. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. Circulation. 1991;83(6):1888-94. PubMed PMID: 2040041.
21. Wheelan K, Mukharji J, Rude RE, Poole WK, Gustafson N, Thomas LJ, et al. Sudden death and its relation to QT-interval prolongation after acute myocardial infarction: two-year follow-up. Am J Cardiol. 1986;57(10):745-50. PubMed PMID: 2870632.
22. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, et al. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. Circ Arrhythm Electrophysiol. 2011;4(4):441-7. doi:10.1161/CIRCEP.110.960658. PubMed PMID: 21593198; PMCID: PMC3157547.
23. Kors JA, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. J Electrocardiol. 2008;41(6):575-80. doi: 10.1016/j.jelectrocard.2008.07.030. PubMed PMID: 18954608.
24. Özbek SC, Sökmen. Usefulness of Tp-Te interval and Tp-Te/QT ratio in the prediction of ventricular arrhythmias and mortality in acute STEMI patients undergoing fibrinolytic therapy. J Electrocardiol. 2019, 56: 100-105. doi:10.1016/j.jelectrocard.2019.07.004. PubMed PMID:31351370.
25. Tse G. Novel conduction-repolarization indices for the stratification of arrhythmic risk. Journal of geriatric cardiology: JGC. 2016;13(9):811-2. Epub 2016/12/03. doi: 10.11909/j.issn.1671-5411.2016.09.008. PubMed PMID: 27899947; PMCID: PMC5122508.
26. Bombelli M, Maloberti A, Raina L, Facchetti R, Boggioni I, Pizzala DP, et al. Prognostic relevance of electrocardiographic Tpeak-Tend interval in the general and in the hypertensive population: data from the Pressioni Arteriose Monitorate E Loro Associazioni study. J Hypertens. 2016;34(9):1823-30. Epub 2016/06/28. doi: 10.1097/hjh.0000000000001005. PubMed PMID: 27348518.
27. Ferrucci A, Canichella F, Battistoni A, Palano F, Francia P, Ciavarella GM, et al. A Novel Electrocardiographic T-Wave Measurement (Tp-Te Interval) as a Predictor of Heart Abnormalities in Hypertension: A New Opportunity for First-Line Electrocardiographic Evaluation. J Clin Hypertens (Greenwich). 2015;17(6):441-9. Epub 2015/03/17. doi: 10.1111/jch.12522. PubMed PMID: 25772633.
28. Rowlands DB, Glover DR, Ireland MA, McLeay RA, Stallard TJ, Watson RD, Littler WA. Assessment of left-ventricular mass and its response to antihypertensive treatment. Lancet. 1982;1(8270):467-70. Epub 1982/02/27. PubMed PMID: 6121138.
29. Abi-Samra F, Fouad FM, Tarazi RC. Determinants of left ventricular hypertrophy and function in hypertensive patients. An echocardiographic study. Am J Med. 1983;75(3a):26-33. Epub 1983/09/26. PubMed PMID: 6226191.
30. Hill JA, Olson EN. Cardiac plasticity. N Engl J Med. 2008;358(13):1370-80. Epub 2008/03/28. doi: 10.1056/NEJMra072139. PubMed PMID: 18367740.
31. Radice M, Alli C, Avanzini F, Di Tullio M, Mariotti G, Taioli E, et al. Left ventricular structure and function in normotensive adolescents with a genetic predisposition to hypertension. Am Heart J. 1986;111(1):115-20. Epub 1986/01/01. PubMed PMID: 3946138.
32. Adams TD, Yanowitz FG, Fisher AG, Ridges JD, Nelson AG, Hagan AD, et al. Heritability of cardiac size: an echocardiographic and electrocardiographic study of monozygotic and dizygotic twins. Circulation. 1985;71(1):39-44. Epub 1985/01/01. PubMed PMID: 4038369.
33. Ganau A, Devereux RB, Pickering TG, Roman MJ, Schnall PL, Santucci S, et al. Relation of left ventricular hemodynamic load and contractile performance to left ventricular mass in hypertension. Circulation. 1990;81(1):25-36. Epub 1990/01/01. PubMed PMID: 2297829.
34. Aronow WS. Hypertension and left ventricular hypertrophy. Annals of translational medicine. 2017;5(15):310. Epub 2017/09/01. doi: 10.21037/atm.2017.06.14. PubMed PMID: 28856150; PMCID: PMC5555990.
35. Post WS, Larson MG, Levy D. Impact of left ventricular structure on the incidence of hypertension. The Framingham Heart Study. Circulation. 1994;90(1):179-85. Epub 1994/07/01. PubMed PMID: 8025994.
36. Lawler PR, Hiremath P, Cheng S. Cardiac target organ damage in hypertension: insights from epidemiology. Current hypertension reports. 2014;16(7):446. Epub 2014/05/08. doi:10.1007/s11906-014-0446-8. PubMed PMID: 24801135; PMCID: PMC4051880.
37. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021-104. Epub 2018/08/31. doi: 10.1093/eurheartj/ehy339. PubMed PMID: 30165516.

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(2):188-192.
DOI: 10.28982/josam.841679

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

Experience of chronic thromboembolic pulmonary hypertension (CTEPH) in two cases with scleroderma and immunopathogenesis overview: Case report

Burak Okyar [1], Fatih Albayrak [1], Bekir Torun [1], Nurhan Atilla [2], Betül Kızıldağ [3], Fatih Yıldız [1], Gözde Yıldırım Çetin [1]

[1] Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Kahramanmaraş, Turkey
[2] Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Department of Chest Diseases, Kahramanmaraş, Turkey
[3] Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Department of Radiology, Kahramanmaraş, Turkey

ORCID ID of the author(s)

BO: 0000-0001-9680-7535
FA: 0000-0002-6052-3896
BT: 0000-0002-9117-9514
NA: 0000-0003-4127-4924
BK: 0000-0002-2567-4330
FY: 0000-0003-3628-8870
GYÇ: 0000-0001-9680-7535

Corresponding Author
Gözde Yıldırım Çetin
Kahramanmaraş Sütçü İmam University, School of Medicine, Rheumatology Department, Onikişubat, Kahramanmaraş, Turkey
E-mail: gozdeyildirimcetin@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 January 29

Abstract

Systemic Sclerosis (SSc) is a multi-systemic connective tissue disease of unknown etiology. Although many pathological processes play a role in the basis of pulmonary hypertension (PHT) that develops secondary to SSc, vasculopathy has an important place. Chronic thromboembolic hypertension (CTEPH) is in the group 4 PHT class. CTEPH distinguishes it from other causes of PHT by having both surgical and medical treatment options. CTEPH is a pathology that develops chronically and can be overlooked due to its nonspecific symptoms. Early diagnosis and treatment can reduce morbidity and mortality. The physiopathology of vasculopathy secondary to CTEPH and vasculopathy of SSc made us suspect that similar processes operate in both diseases. The processes that cause and follow endothelial damage are similar in both diseases. If this pathophysiological mechanism can be clarified, possible new treatment options can be discovered. We diagnosed CTEPH with the examinations we performed in two of our patients with SSc and interstitial lung disease, both of which developed PHT. We aimed to discuss the immunopathogenesis with two case reports.

Keywords: Scleroderma, Pulmonary Hypertension, CTEPH

Introduction

Systemic sclerosis (SSc) is a chronic and multisystemic disease of unknown etiology and is characterized by fibrosis that develops because of connective tissue accumulation in the circulatory system, musculoskeletal system, gastrointestinal system, heart, lungs, and kidneys, especially the skin [1]. Multiple hypotheses might explain the complex pathogenesis of SSc. In individuals with suitable genetic background, vasculopathy starts with the contribution of various triggering factors, and at the end of the process of immune activation and oxidative stress, SSc occurs with increased fibroblastic activation. Vasculopathy has an essential role in the development of pulmonary hypertension. The immunological process in the formation of vasculopathy is not fully understood and is thought to develop due to multiple mechanisms.

Chronic thromboembolic pulmonary hypertension (CTEPH) causes significant morbidity and mortality. The differential diagnosis of thromboembolic involvement in the pulmonary arteries is of great importance because of the definitive treatment potential with pulmonary endarterectomy (PEA) [2, 3]. Condliffe et al.'s [4] study showed that one and 3-year survival rates of patients with inoperable CTEPH were 82% and 70%, respectively. Although the pathophysiological process underlying CTEPH has not been fully elucidated, it is possible that immunological mechanisms play a significant role in the development of scleroderma vasculopathy, and trigger the development of CTEPH. In these two case reports, we aimed to discuss our experience after diagnosing CTEPH in the follow-up of two patients with interstitial lung disease, who were diagnosed with SSc in our center, and discuss whether a pathophysiological relationship between the two diseases exists. In addition, we discussed the importance of the CTEPH diagnosis, which can be reversed with treatment among PHTs, for SSc patients.

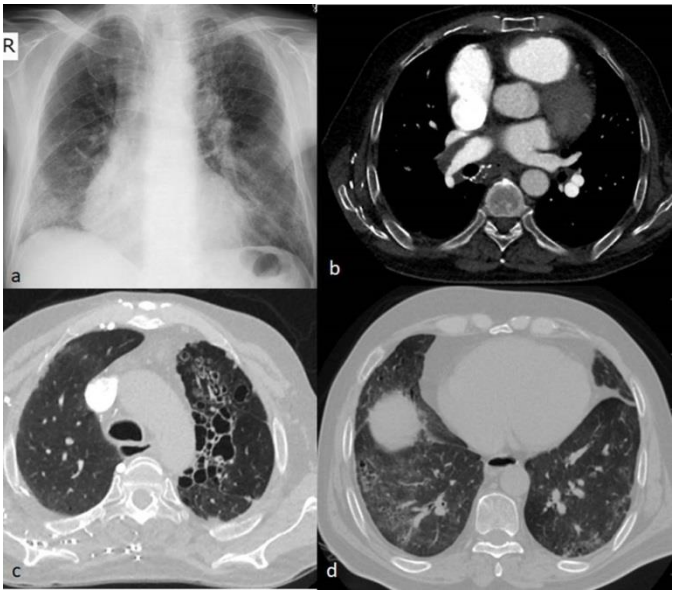
How to cite: Okyar B, Albayrak F, Torun B, Atilla N, Kızıldağ B, Yıldız F, Çetin GY. Experience of chronic thromboembolic pulmonary hypertension (CTEPH) in two cases with scleroderma and immunopathogenesis overview: Case report. J Surg Med. 2021;5(2):188-192.

Case presentation

Case 1

A 55-year-old male patient with a diagnosis of SSc for two years presented with complaints of wheezing, shortness of breath, and cough. Previously, this patient was followed up with findings of skin involvement, sclerodactylitis, Raynaud's phenomenon, interstitial lung disease (non-specific interstitial pneumonia (NSIP)) (Figure 1), the positivity of antinuclear antibody (granular pattern), and anticentromere autoantibody. He had no diseases other than scleroderma. Previous immunosuppressive treatments were cyclophosphamide 1000 mg/month intravenously (IV) for one year, azathioprine 150 mg/day for eight months, and mycophenolate mofetil 1500 mg/day for one year. He was using mycophenolate mofetil and methylprednisolone at the time of admission. On physical examination, there were Velcro crackles in the bilateral lower zones. Oxygen saturation measured from the fingertip was 88%. In the blood analysis performed after the patient was hospitalized, C-reactive protein (CRP) was 15 mg/L and erythrocyte sedimentation rate (ESR) was 15 mm/h. The carbon monoxide diffusion capacity (DLCO) value was 64%, the forced expiratory volume per second (FEV1) value was 86%, and the forced vital capacity (FVC) value was 87%. The FEV1/FVC ratio was %81. Pulmonary artery pressure (PAP) was 110 mmHg in echocardiography, and the mean PAP value was 43 mmHg in right heart catheterization. Computed tomography (CT) showed ground-glass density areas increasing towards the basal in both lungs, traction bronchiectasis, interlobular and interseptal thickening, and reticular density areas that tend to merge were consistent with the interstitial lung disease (NSIP) pattern. Pulmonary angiographic CT revealed thromboembolism that started before the lobar arterial branching of both pulmonary arteries and continued to the lower lobe branches on the left and right, all of which were consistent with CTEPH (Figure 1). The homocysteine, protein C, protein S, and antithrombin III levels in the patient's thrombophilia panel were normal. The patient had been on enoxaparin therapy for more than three months before being diagnosed with CTEPH, after which his treatment was re-planned.

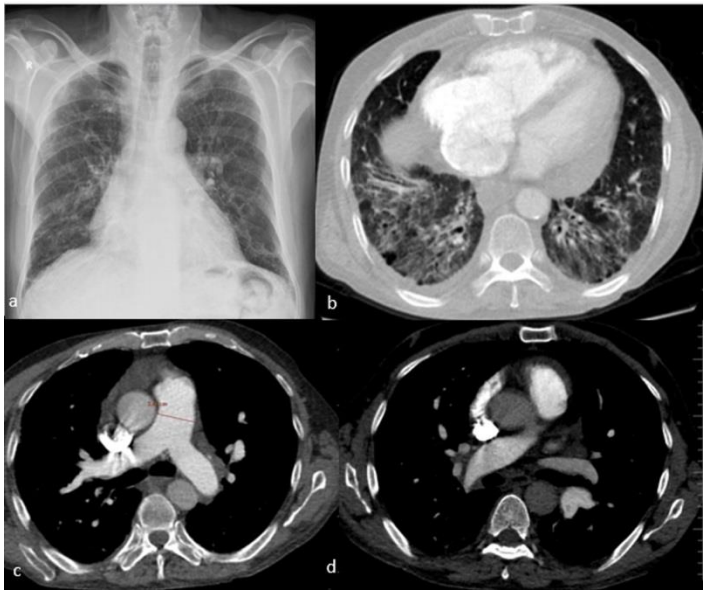
Figure 1: Plain radiography of a 55-year-old male patient (a) shows interstitial reticular opacities in the lower zones of both lungs, parenchymal cystic changes in the left upper zone, an increase in the cardiothoracic index and a prominence in the pulmonary conus. In the mediastinal window section of pulmonary CT angiography (b), filling defect causing wall thickening in the right descending pulmonary artery, collateral arterial structures in the mediastinum and enlargement in the right heart cavities are observed. In the section passing through the upper lobe of the lung window (c), cystic bronchiectasis in the left upper lobe (a) and the section passing through the lower lobe basal (d) thin reticular densities joining each other, traction bronchiectasis, NSIP pattern of interstitial involvement are observed. It is seen that the esophageal lumen is accompanied by air-containing enlargement.



Case 2

A 60-year-old male patient was followed for ten years with sclerodactylitis, Raynaud's phenomenon, skin findings, NSIP and ANA (granular pattern), and anti-centromere autoantibody positivity. Previous immunosuppressive treatments were IV cyclophosphamide 1000 mg /month for one year, azathioprine 100 mg/day (stopped immediately due to side effects), and 1000 mg rituximab on days 0 and 15 and 6 months for one year. He was using cyclophosphamide and rituximab combination therapy at admission. In routine blood tests, CRP was 8 mg/L and ESR: 12 mm/h. DLCO value was 86%, FEV1 value was 84%, FVC value was 72%, and FEV1/FVC ratio was 72%. The PAP value measured on echocardiography was 85 mmHg. Right heart catheterization of the patient could not be performed. In CT, the pulmonary trunk increased by 39 mm, and its ratio to ascendant aorta diameter was less than 1. Also, the pulmonary artery diameter was enlarged at the segmental level, and the findings were compatible with pulmonary hypertension. Right heart chambers were enlarged. An appearance compatible with cystic bronchiectasis was detected, being more common in the upper lobe apical posterior segment and lower lobe superior segment of the left lung. Besides, increasing reticular density towards the lower lobe and traction bronchiectasis were observed in both lungs, the subpleural areas were relatively unaffected, which was considered the NSIP pattern. In the patient's CT pulmonary angiogram, the diameter of the pulmonary trunk was measured as 39 mm, where it is widest, and it had increased. An increase was observed in pulmonary artery diameters at both main pulmonary artery and segmentary levels, which was considered a sign of pulmonary hypertension. An appearance compatible with thin vein-like thromboembolism was detected in the upper lobe anterior segment on the right, at the level of the lower lobe branching level and the lower lobe posterobasal segment branch, and in the lower lobe posterobasal segment branch on the left, all of which were compatible with CTEPH (Figure 2). Homocysteine, protein C, protein S, and antithrombin III levels were normal in the patient's thrombophilia panel evaluation. The patient had been on enoxaparin therapy for more than three months before being diagnosed with CTEPH. The patient was diagnosed with CTEPH, and his treatment was re-planned.

Figure 2: On plain radiography (a) of a 60-year-old male patient, interstitial reticular opacities in the lower zones of both lungs and an increase in cardiothoracic index are seen. Interstitial involvement of systemic sclerosis in the form of NSIP pattern in the form of continuing thin reticulations, traction bronchiectasis and bronchiectasis, ground glass densities are observed in the lung window section (b) passing through the lower lobe basales of CT angiography. An enlargement is noticed in the right heart chambers. In sections of the mediastinal window (c), enlarged pulmonary truncus pericardial effusion and air-containing enlargement in the esophageal lumen are seen. In the lower section (d), a thin web-like linear filling defect in the lumen of the left descending pulmonary artery is noticeable.



Discussion

Vasculopathy has an important role in the development of interstitial lung disease and pulmonary hypertension in SSc. It develops with the contribution of both the humoral and the cellular immune system. Antibodies developed by B lymphocytes, one of the most critical parts of the humoral immune system, against Type IV collagen and laminin, an important element of the subendothelial basement membrane in the vascular wall, are related to the severity of interstitial lung disease [5]. In cellular mediated immunity, T lymphocytes exposed to Type I collagen are activated to produce interleukin-2 (IL-2), and studies have shown that the level of IL-2 and IL-2 receptors in the blood correlate with the severity of the disease [6]. The increased level of IL-2 is thought to directly induce endothelial damage by converting natural killer (NK) cells into lymphokine-activated killer (LAK) cells [7]. As a result, humoral and/or cellular immunity triggered by various reasons causes endothelial damage. In SSc, vasculopathy has the potential to affect arterioles with a diameter of 150-500µm, and intimal proliferation is observed with mononuclear cell infiltration due to the cytokines and adhesion molecules released in this region. The cause of the pathologies that develop in these regions is the development of vascular restructuring at the end of the process leading to endothelial activation, mononuclear cell infiltration, the intimal proliferation of arterioles, capillary necrosis, and occlusion of blood vessels [8]. This pathological process occurs in organs such as muscle, lung, heart, kidney, and this process is called vasculopathy. Endothelial cell apoptosis plays a central role in the vasculopathy in SSc. It results from multiple pathophysiological processes involving environmental factors, infectious agents, reperfusion injury, autoantibodies, and cytotoxic T lymphocytes. Endothelial apoptosis can be induced for reasons such as the induction of EAM by infectious agents such as human cytomegalovirus (hCMV) with TGF-β

stimulation through TNF-α, IL-1, and IL-6, which causes EAM upregulation by autoantibodies, T lymphocytes exposed to collagen in the region stimulating IL-2 [9-12]. Another pathophysiological process is reperfusion injury. In the formation of mononuclear cell infiltration, events such as capillary necrosis, triggering of endothelial cell damage by oxygen radicals due to reperfusion after occlusion, upregulation of TNF-α, IL-1, IL-6, and IL-8, and increase in EAMs occur. IL-8 can also trigger in situ thrombotic events by platelet activation.

Endothelin-1 (ET-1), which is a potent vasoconstrictor, is also released after endothelial damage. It causes proliferation, especially in pulmonary arterial smooth muscle cells, and by decreasing the level of nitric oxide (NO) released from the endothelium, it prevents vasodilation and becomes vulnerable to radical oxygen damage, contributing to endothelial dysfunction. In the chronic process, ET-1 triggers vascular restructuring [13-15]. As a result, dysfunction develops in endothelial cells exposed to cytokines, mononuclear cells, and autoantibodies, remodeling occurs in the vascular endothelium, and the process leading to pulmonary hypertension is triggered. Similarly, this pathophysiological process is also experienced in CTEPH patients. The diagnosis of CTEPH is based on the presence of at least one segmental perfusion defect on scintigraphy with or without a prior episode of pulmonary thromboembolism, or a mean pulmonary arterial pressure (PAP) ≥25 mmHg with intraluminal filling defects on computed tomography (CT) and pulmonary capillary wedge pressure <15 mmHg [16]. To be diagnosed with CTEPH, patients must use anticoagulant therapy for at least three months, and their findings must be continuous [17]. It has been shown that a significant portion of patients diagnosed with CTEPH have not been diagnosed with PTE before [18, 19].

The pathophysiology of CTEPH is a combination of incomplete thrombus resolution, abnormal coagulation, inflammation, oxidative stress, defective fibrinolysis, and endothelial dysfunction. According to the Jaimeson classification, CTEPH patients have organized incomplete thromboembolism in Type-1 and Type-2. Vascular intimal thickening is present in Type-3 and Type-4, and chronic inflammation has been shown in most patients [20-22]. Histological studies of resected PEA material showed that lymphocytes, macrophages, and neutrophils were present with chronic thrombus [23]. Studies have shown that fibrinogen and cytokines are very important in the pathophysiology of CTEPH. In retrospective studies, fibrinogen plasma levels were significantly higher in CTEPH patients than in the control group [24]. TNF-α, IL-1β, IL-6, and IL-8 levels are high in patients with CTEPH [25-27]. In particular, IL-6 and IL-8 levels are useful in predicting the disease's prognosis in the long term after PEA [27]. It was also observed that TNF-α levels significantly decreased in the first 24 hours after PEA [28]. In another study, IL-6 level correlates with hemodynamic parameters and exercise capacity in patients with CTEPH [29].

C-reactive protein (CRP) is a well-known biomarker for inflammation, and it is one of the first inflammation markers identified in CTEPH. CRP triggers vascular remodeling and in situ thrombosis. Larger et al. [30] showed that CRP decreases gradually in CTEPH patients in the first 12 months after PEA, which correlates with the reduction of mononuclear phagocytic cell migration to that area. As we previously described in the pathogenesis of SSc vasculopathy, ET-1 acts with a similar mechanism in the development of CTEPH. The resulting endothelial damage releases ET-1 and contributes to the proliferation and restructuring of vascular smooth muscles. Studies have shown that pre-PEA ET-1 level correlates with disease severity.

All these inflammatory markers suggest that the pathophysiology of CTEPH has some similarities with the development of SSc vasculopathy. In both cases, the main process appears to be chronic inflammation and consequent endothelial dysfunction, increased adhesion molecules, mononuclear phagocytic cell migration, and the restructuring of the vascular structure. No deep vein thrombosis was detected in the lower extremity Doppler USG performed in both of our patients. There were no findings suggestive of acute pulmonary embolism in the patients. This suggested a chronic process. In addition, when the blood values measured during the follow-up of both patients were analyzed retrospectively, CRP values were consistently high. In the light of these data, we think that chronic inflammation triggered pulmonary endothelial damage and remodeling in these two cases with SSc. This complex inflammatory process may have caused in situ thromboembolism in the damaged endothelium by activating the platelets and triggering the development of CTEPH. Moreover, thickening and vasoconstriction of the vascular wall may have contributed to the development of CTEPH, a type of PAH. Detection of thromboembolism and absence of DVT by pulmonary angiographic CT performed due to the slowly and insidiously developing symptoms in these two cases, and the high inflammatory markers support our thought. New studies are needed to prove these thoughts.

Conclusion

The possibility of CTEPH should be considered in cases such as increased effort dyspnea, decreased exercise capacity, and increased oxygen demand in SSc patients with pulmonary arterial hypertension (PAH) and/or interstitial lung disease. Early diagnosis of CTEPH contributes to reducing morbidity and mortality, as shown by Condliffe et al. Development of PTH should be carefully investigated in SSc patients with interstitial lung disease. CTEPH is in the group 4 class of PHTs and differs in terms of surgical and medical treatment, and morbidity and mortality can be reduced with treatment.

References

1. Allanore Y, Simms R, Distler O, Trojanowska M, Pope J, Denton CP, Varga J. Systemic sclerosis. Nature Reviews Disease Primers. 2015;15002. doi:10.1038/nrdp.2015.2
2. Jamieson SW, Kapelanski DP, Sakakibara N, Manecke GR, Thistlethwaite PA, Kerr KM, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. Ann Thorac Surg. 2003;76:1457-62.
3. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37:67–119.
4. Condliffe R, Kiely DG, Gibbs JS, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med. 2008;177:1122–7.
5. Mackel AM, DeLustro F, Harper FE, LeRoy EC. Antibodies to collagen in scleroderma. Arthritis Rheum. 1982;25:522-31.
6. Khaleh MB, LeRoy EC. Interleukin-2 in scleroderma:correlation of serum level with extent of skin involvement and dissease duration Ann Intern Med. 1989;110:446-50.
7. Silver RM. Lymphokine activated killer (LAK) cell activity in the peripheral blood of lymphosites of systemic sclerosis patients. Clin Exp Rhematology. 1990;8:481-6.
8. Rodnan GP, Myrewitz RL, Justh GO. Morphologicchanges in the digital arteries of patients with progresive systemic sclerosis and Raynaud phenomenon. Medicine. 1980;59:393-408.
9. Madge LA, Li JH, Choi J, Pober JS. Inhibition of phosphatidylinositol 3-kinase sensitizes vascular endothelial cells to cytokine-initiated cathepsin-dependent apoptosis. J Biol Chem. 2003;278(23):21295-306.

10. Hussein MR, Hassan HI, Hofny ER, et al. Alterations of mononuclear inflamatory cells, CD4/CD8+ T cells, interleukin 1beta, and tumour necrosis factor alpha in the bronchoalveolar lavage fluid, peripheral blood, and skin of patients with systemic sclerosis. J Clin Pathol. 2005;58(2):178-84.
11. Wusirika R, Ferri C, Marin M, et al. The assessment of anti-endothelial cell antibodies in scleroderma-associated pulmonary fibrosis. A study of indirect immunofluorescent and western blot analysis in 49 patients with scleroderma. Am J Clin Pathol. 2003;120(4):596-606.
12. Krogsgaard M, Davis MM. How T cell'see'antigen. Nat Immunol. 2005;6(3):239-45.
13. Zamora MR, O'Brien RF, Rutherford RB, Weil JV. Serum endothelin-1 concentrations and cold provocation in primary Raynaud's phenomenon. Lancet. 1990;336:1144.
14. Vancheeswaran R, Magoulas T, Efrat G, et al. Circulating endothelin-1 levels in systemic sclerosis subsets--a marker of fibrosis or vascular dysfunction? J Rheumatol. 1994;21:1838.
15. Debendra Pattanaik, Monica Brown, Bradley C. Postlethwaite, and Arnold E. Pathogenesis of Systemic Sclerosis. Postlethwaite. Front Immunol. 2015;6:272. doi: 10.3389/fimmu.2015.00272
16. Zhang M, Zhang Y, Pang W, Zhai Z, Wang C. Circulating biomarkers in chronic thromboembolic pulmonary hypertension. Pulm Circ. 2019 Apr-Jun;9(2):2045894019844480. doi: 10.1177/2045894019844480
17. Moser KM, Auger WR, Fedullo PF. Chronic major-vessel thromboembolic pulmonary hypertension. Circulation. 1990;81:1735-43.
18. Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, et al. Prognostic and aetiological factors in chronic thromboembolic pulmonary hypertension. Eur Respir J. 2009;33:332-8.
19. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011;124:1973-81.
20. Skoro-Sajer N, Marta G, Gerges C, Hlavin G, Nierlich P, Taghavi S, Sadushi-Kolici R, Klepetko W, Lang IM. Surgical specimens, haemodynamics and long-term outcomes after pulmonary endarterectomy. Thorax. 2014;69(2):116–22.
21. Bernard J, Yi ES. Pulmonary thromboendarterectomy: a clinicopatho- logic study of 200 consecutive pulmonary thromboendarterectomy cases in one institution. Hum Pathol. 2007;38(6):871–7.
22. Matthews DT, Hemnes AR. Current concepts in the pathogenesis of chronic thromboembolic pulmonary hypertension. Pulm Circ. 2016 Jun;6(2):145-54.doi: 10.1086/686011.
23. Quarck R, Wynants M, Verbeken E, Meyns B, Delcroix M. Contribution of inflammation and impaired angiogenesis to the pathobiology of chronic thromboembolic pulmonary hypertension. Eur Respir J. 2015;46(2):431–43.
24. Kato F, Tanabe N, Ishida K, et al. Coagulation-fibrinolysis system and postoperative outcomes of patients with chronic thromboembolic pulmonary hypertension. Circ J. 2016;80:970–9.
25. Yang M, Deng C, Wu D, et al. The role of mononuclear cell tissue factor and inflammatory cytokines in patients with chronic thromboembolic pulmonary hypertension. J Thromb. 2016;42:38–45.
26. Rozenn Quarck, Marijke Wynants, Erik Verbeken, et al. Contribution of inflammation and impaired angiogenesis to the pathobiology of chronic thromboembolic pulmonary hypertension. Eur Respir J. 2015;46:431–43.
27. Soon E, Holmes AM, Barker L, et al. Inflammatory cytokines are elevated In patients with operable chronic thromboembolic pulmonary hypertension and predict outcome post-endarterectomy. Thorax. 2010;65(Suppl 4):A45.
28. Langer F, Schramm R, Bauer M, et al. Cytokine response to pulmonary thromboendarterectomy. Chest. 2004;126:135–41.
29. Zabini D, Heinemann A, Foris V, et al. Comprehensive analysis of inflammatory markers in chronic thromboembolic pulmonary hypertension patients. Eur Respir J. 2014;44:951–62.
30. Langer F, Bauer M, Tscholl D, et al. Circulating big endothelin-1: an active role in pulmonary thromboendarterectomy? J Thoracic Cardiovasc Surg. 2005;130:1342–7.

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(2):193-195.
DOI: 10.28982/josam.740047

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

A case of chronic granulomatous disease diagnosed in adulthood

Mehmet Selim Şahin [1], Hakan Sezgin Sayiner [2], Hüseyin Vural [3]

[1] Adıyaman University, Faculty of Medicine, Training and Research Hospital Department of Clinical Infectious Diseases and Medical Microbiology, Adıyaman, Turkey
[2] Adıyaman University, Faculty of Medicine, Training and Research Hospital Department of Clinical Infectious, Adıyaman, Turkey
[3] Adıyaman University, Kahta Vocational School, Computer Technologies, Adıyaman, Turkey

ORCID ID of the author(s)
MSŞ: 0000-0001-8742-6386
HSS: 0000-0002-4693-3784
HV: 0000-0001-9290-6317

Abstract

Chronic granulomatous disease (CGD) is a heterogeneous, inherited primary immunodeficiency disease. It is characterized by granulomatous formations due to increased inflammatory response and recurrent and life-threatening infections occurring because of the defects in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system. Diagnosis is made by medical history, clinical findings, and neutrophil function tests, and is confirmed by genotyping. A 26-year-old male patient presented to our emergency polyclinic with complaints of fever, abdominal pain, diarrhea, fatigue, left ear discharge and was hospitalized in our ward for examination and treatment. Since childhood, he suffered from failure to thrive, frequent pneumonia, and skin pruritus. Since the age of 15 years, he underwent surgery for liver abscess and ear surgery due to ear discharge and chronic otitis. Ultrasonography revealed an abscess on the right psoas muscle, compressing the right kidney. Abscess culture was positive for the methicillin-sensitive strain of Staphylococcus aureus and negative for acid-resistant staining (ARB). Aspergillus spp. reproduced in the ear discharge culture. CGD, which is one of the primary immunodeficiency diseases, should be considered in patients presenting with recurrent intraabdominal abscess and respiratory system infections in adulthood.

Keywords: Primary immunodeficiency, Dihydrorhodamine 123 test, Chronic granulomatous disease

Corresponding Author
Hüseyin Vural
Adıyaman University, Kahta Vocational School, Computer Technologies, Adıyaman, Turkey
E-mail: hvural@adiyaman.edu.tr

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 February 20

Introduction

Chronic granulomatous disease (CGD) is an inherited primary immunodeficiency disease with a defect in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme [1]. In this disease, phagocytic cells do not produce reactive oxygen species (ROS), which are crucial to kill ingested microorganisms. It is characterized by inflammatory findings such as granuloma formation due to increased inflammatory response to some recurrent, life threatening bacterial and fungal infections [2,3]. It may be X-linked (Mutations in the CYBB gene encoding gp91phox protein) or autosomal recessive (mutations in NCF1, NCF2, CYBA or NCF4 genes coding for p47phox, p67phox, p22phox or p40phox, respectively) [1]. Most patients are diagnosed before the age of five. The use of antibiotics and prophylaxis greatly improved overall survival [4]. The most common clinical findings include infections, granulomatous diseases, inflammation, and failure to thrive [1]. Typical infections include purulent bacterial pneumonia, sinusitis, liver abscess or necrotizing fungal infections in deep tissue and the bones [5]. There are various tests based on measurement of neutrophil oxidative burst response, in which superoxide production is measured, including ferric cytochrome c reduction test, anti-HIV (by chemiluminescence assay), nitroblue tetrazolium reduction test (NBT) and dihydrorhodamine - 123 (DHR) oxidation [1].

We aimed to present a case of an adult patient who was diagnosed with chronic granulomatous disease with recurrent episodes of abdominal abscesses and respiratory infections.

How to cite: Şahin MS, Sayiner HS, Vural H. A case of chronic granulomatous disease diagnosed in adulthood. J Surg Med. 2021;5(2):193-195.

Case presentation

A 26-year-old male patient presented to our emergency clinic with complaints of fever, abdominal pain, diarrhea, fatigue, and left ear discharge, and was hospitalized for treatment. His complaints continued for about one month. From the early ages, he had complaints of frequent pneumonia attacks and failure to thrive. He underwent liver abscess operations and ear drainage in various hospitals since the age of 15 years, and ear operation due to chronic otitis. Earlier test results were negative for methicillin-sensitive Staphylococcus aureus (MSSA), ARB, and autoimmunity markers. No pathology was detected in tuberculosis culture. In our clinic, we obtained the following test results: WBC: 21.61 K / uL, NEU: 18.09, PLT: 339000 10^{-3}/uL, EOS: 0.00283 10^{-3}/uL, CRP: 17.2 mg/dL, sedimentation: 20 mm/h, hydatid indirect hemagglutination: Negative, IgA: 658 mg/dL (60-200), IgM: 118 mg/dL (40-110), IgG: 1090 mg/dL (550-1900), Total IgE: (2500 ng/ -240), Antigliadin IgG: Negative, Antigliadin IgA: Negative, Brucella agglutination test: Negative, Grubel-Vidal agglutination test: Negative. There were no pathogenic bacteria in the stool culture, and dense leukocyte and erythrocytes were observed in stool microscopy. Metronidazole 4 x 500 mg and ciprofloxacin 2 x 400 mg were administered parenterally to the patient. Ultrasonography revealed an abscess on the right psoas muscle, compressing the right kidney. Abscess drainage was performed by the General Surgery Department. MSSA reproduced in the abscess culture, which was ARB negative. Aspergillus spp. reproduced in the ear discharge culture. Cefazolin 3 x 1 gr and Metronidazole 4 x 500 mg were administered parenterally. Considering the history of the patient and with a pre-diagnosis of primary immunodeficiency, dihydrorhodamine 123 test was requested. Trimethoprim-sulfamethoxazole (TMP-SMX) 80/160 mg tablets (2x1), itraconazole 100 mg capsules (1x2), and IV methylprednisolone (1x80 mg) were administered for the treatment of the patient whose test result were consistent with CGD. Steroid therapy was discontinued after two weeks. He was discharged with TMP-SMX and itraconazole treatment. There was no recurrence of infections during one-year follow-up. Written consent was obtained from the patient presented in the study.

Discussion

Although CGD is a heterogeneous disease, clinical findings and prognosis vary widely due to different genotype and phenotypic interactions. Patients with CGD are characterized by recurrent severe bacterial and fungal infections from infancy or childhood. In some cases, the diagnosis can be made with recurrent abnormal infections during late childhood or early adulthood [6]. The diagnosis was made at the age of 26 years, although there was recurrent hepatic abscess since the age of 15 years.

Recurrent infections, granulomatous diseases, inflammation, and weight loss are the most common clinical manifestations of CGD [1]. In our case, recurrent infections and failure to thrive were apparent.

Liver involvement is obvious and important. Liver abscess is seen in approximately 35% of patients. Until recently, almost all cases required surgical treatment [7]. Studies have shown that liver abscess can be controlled with antibiotics and corticosteroids without the need for surgical treatment [8, 9]. In our case, the patient, who was operated due to liver and psoas abscesses in various hospitals, was diagnosed with CGD. Corticosteroids and antibiotic therapy were used to control the abscess and no recurrence was observed within the one-year follow-up period.

Typically, fungal infections, more specifically, *Aspergillus spp.* are the main cause of mortality in CGD [10, 11]. The effects of fungal infections in CGD can be altered by administering a therapy of highly active antifungals using itraconazole, voriconazole and posaconazole [12]. In our case, aspergillus was found in ear drainage culture and complaints of the patient regressed with itraconazole. Infections with catalase-producing microorganisms such as *S. aureus* and Aspergillus species are seen in the preliminary plan [13]. *S. aureus*, *Burkholderia cepacia complex*, *Serratia marcescens*, *Nocardia species* and *Aspergillus species* are responsible for the majority of infections in CGD in North America [14]. In our case, MSSA was found in abscess culture and *Aspergillus spp* reproduced in ear drainage culture.

Flow cytometry is used to measure the oxidation of dihydrorhodamine 123 versus rhodamine 123 in phorbol myristate acetate (PMA) -induced neutrophils as a marker for cellular NADPH oxidase activity [15].

Antimicrobial prophylaxis (TMP-SMX, itraconazole) consists of the IFN-γ triad, an immunostimulatory treatment [1]. We started treatment with TMP-SMX, itraconazole, and corticosteroids, after which steroid treatment was gradually stopped. The patient was discharged with TMP-SMX and itraconazole therapy.

CGD, one of the causes of primary immunodeficiency, presents with recurrent infections. Therefore, the diagnosis of the disease is usually made in childhood and rarely during adulthood.

Conclusion

Our patient's complaints began at childhood and he remained undiagnosed with CGD until adulthood. In patients with recurrent staphylococcal and aspergillus infections, CGD is one of the diseases to be considered.

References

1. Holland SM. Chronic granulomatous disease. Clin Rev Allergy Immunol. 2010;38:3–10.
2. Segal BH, Leto TL, Gallin JI, Malech HL, Holland SM. Genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine. 2000;79:170–200.
3. Stasia MJ, Cathebras P, Lutz MF, Durieu I. La granulomatose septique chronique [Chronic-granulomatous disease]. Rev Med Interne. 2009;30:221–32.
4. Leiding JW, Holland SM. Chronic granulomatous disease. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, LJH B, Mefford HC, et al. GeneReviews. 2016. University of Washington, Seattle, WA, USA.
5. Stasia MJ, Li XJ. Genetics and immunopathology of chronic granulomatous disease. Semin Immunopathol. 2008;30:209-35.
6. Song E, Jaishankar GB, Saleh H, Jithpratuck W, Sahni R, Krishnaswamy G. Chronic granulomatous disease: a review of the infectious and inflammatory complications. Clin Mol Allergy. 2011;9:10.
7. Lublin M, Bartlett DL, Danforth DN, Kauffman H, Gallin JI, Malech HL, et al. Hepatic abscess in patients with chronic granulomatous disease. Ann Surg. 2002;235:83–91.
8. Leiding JW, Freeman AF, Marciano BE, Anderson VL, Uzel G, Malech HL, et al. Corticosteroid therapy for liver abscess in chronic granulomatous disease. Clin Infect Dis. 2011;54:694–700.
9. van den Berg JM, van Koppen E, Ahlin A, Belohradsky BH, Bernatowska E, Corbeel L. Chronic granulomatous disease: the European experience. PLoS One. 2009;4:5234.
10. Blumental S, Mouy R, Mahlaoui N, Bougnoux ME, Debre M, Beaute J, et al. Invasive mold infections in chronic granulomatous disease: a 25-year retrospective survey. Clin Infect Dis. 2011;53:159–69.
11. Segal BH, Leto TL, Gallin JI, Malech HL, Holland SM. Genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine (Baltimore). 2000;79:170-200.
12. Marciano BE, Spalding C, Fitzgerald A. Common severe infections in chronic granulomatous disease. Clin Infect Dis. 2015;60:1176–83.
13. Vowells SJ, Fleisher TA, Sekhsaria S. Genotype-dependent variability in flow cytometric evaluation of reduced nicotinamide adenine dinucleotide phosphate oxidase function in patients with chronic granulomatous disease. J Pediatr. 1996;128:104–7.
14. Kuhns DB, Alvord WG, Heller T. Residual NADPH oxidase and survival in chronic granulomatous disease. N Engl J Med. 2010;363:2600–10.

15.Filiz S, Kocacık Uygun DF, Yeğin O. Chronic Granulomatous Disease. Turk J Immunol. 2013;1:22-31.

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.