e-ISSN:2602-2079

Volume 4
Issue 9
2020

JOURNAL of Surgery and Medicine

International Medical Journal

JOSAM

Volume: 4 - Issue: 9

Contents

Review

Case report

ULAKBİM Dergi Sistemleri (//dergipark.org.tr/en/)

J Surg Med. 2020;4(9):716-719.
DOI: 10.28982/josam.788906

Research article
Araştırma makalesi

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

Effectiveness and safety of using a novel endothelial damage inhibitor in arteriovenous fistula formation

Arteriovenöz fistül oluşturulmasında yeni endotelyal hasar inhibitörü kullanılmasının etki ve güvenirliği

Emced Khalil [1], Çağrı Akalın [2]

[1] Department of Cardiovascular Surgery, Ordu University Research and Education Hospital, Ordu, Turkey
[2] Department of General Surgery, Ordu University Research and Education Hospital, Ordu, Turkey

ORCID ID of the author(s)
EK: 0000-0002-9814-7056
ÇA: 0000-0003-3370-9879

Corresponding author/Sorumlu yazar:
Emced Khalil
Address/Adres: Bucak Mh. Nefsi Bucak Cad Ordu Üniversitesi Eğitim ve Araştırma Hastanesi Kalp ve Damar Cerrahisi Kliniği No: 94/1 Pk: 52200, Altınordu, Ordu, Türkiye
E-mail: emjedkhalil@gmail.com

Ethics Committee Approval: The ethic approval of the present the study was obtained from Ethical Committee of Ordu University, School of Medicine. (Approval number: 2020/165 Date: 8/20/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışmanın etik onayı Ordu Üniversitesi Tıp Fakültesi Etik Kurulundan alınmıştır. (Onay numarası: 2020/165 Tarih: 20.08.2020). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/11/2020
Yayın Tarihi: 11.09.2020

Abstract

Aim: Patients with end-stage renal disease need accurate and effective vascular access for hemodialysis. Although renal transplantation is the golden standard treatment that provides a life without hemodialysis, an arteriovenous (AV) fistula is the most frequent method for sustaining long-term hemodialysis because of insufficient renal donors. In the current study, we aimed to compare patency rates of AV fistulae created with or without the endothelial protection solution.

Methods: This single-center case-control study was conducted between August 2018 and August 2019. Patients with end-stage renal disease requiring AV fistula access for hemodialysis (n=49) were included in the study and divided into two groups. During the creation of an AV fistulae, endothelial protection solution was used in 27 patients, who constituted Group A, and not used in 22 patients, who were included in Group B (the control group). All fistulae anastomoses were performed by the same surgical team. The demographical data, maturation time, mean flow volume, complications, basal metabolism index (BMI), and patency rates at the 3rd and 6th months were compared.

Results: There was no significant difference between the two groups regarding demographical findings ($p>0.05$). The patency rates were higher in group A at both the 3rd and 6th months (96% and 93%) when compared with group B (64% and 27%) ($P<0.05$).

Conclusion: AV fistulae created with endothelial protection solution has higher patency rates compared to conventionally created AV fistulae.

Keywords: End stage renal disease, Arteriovenous fistula, Endothelial protection solution, Patency rate

Öz

Amaç: Son dönem böbrek hastalığı olan hastalar, hemodiyaliz için doğru ve etkili damar erişimine ihtiyaç duymaktadır. Böbrek nakli, hemodiyaliz gereksinimi olmadan yaşamın sürdürülmesini sağlayan kesin tedavi yöntemi olsa da, yetersiz böbrek donörü nedeniyle uzun süreli hemodiyalizin sürdürülmesinde en sık kullanılan yöntem arteriyovenöz (AV) fistüldür. Bu çalışmada, endotel koruma solüsyonu ile veya solüsyonsuz oluşturulan AV fistülün açıklık oranlarını karşılaştırmayı amaçladık.

Yöntemler: Bu tek merkezli vaka control çalışması Ağustos 2018 ile Ağustos 2019 arasında gerçekleştirilmiştir. Hemodiyaliz için son dönem böbrek hastalığı olan hastalar (toplam 49 hasta) çalışmaya dahil edilmiştir. Hastalar grup A (endotel koruma solüsyonu ile oluşturulan AV fistüller çalışma grubu olarak, n=27) ve grup B (endotel koruma solüsyonu olmadan oluşturulan AV fistüller control grubu olarak, n=22) olarak iki gruba ayrıldı. Tüm fistül anastomozları aynı cerrahi ekip tarafından yapıldı. 3. ve 6. aydaki demografik veriler, olgunlaşma süresi, ortalama akış hacmi, komplikasyonlar, bazal metabolizma indeksi (VKİ) ve açıklık oranları karşılaştırıldı.

Bulgular: Demografik bulgular açısından iki grup arasında fark yoktu ($P>0,05$). Grup A'da 3. ve 6. ayda (%96 ve %93) B grubuna (%64 ve %27) göre daha yüksek açıklık oranları saptandı ($P<0,05$).

Sonuç: Endotelyal koruma solüsyonu ile oluşturulan AV fistül, geleneksel AV fistül oluşturma ile karşılaştırıldığında daha yüksek açıklık oranlarına sahip gibi görünmektedir.

Anahtar kelimeler: Son dönem böbrek hastalığı, Arteryo-venöz fistüller, Endotelyal koruma solüsyonu, Açıklık oranı

How to cite/Atıf için: Khalil E, Akalın Ç. Effectiveness and safety of using a novel endothelial damage inhibitor in arteriovenous fistula formation. J Surg Med. 2020;4(9):716-719.

Introduction

Although renal transplantation is the best treatment method for end stage renal disease, hemodialysis is important until transplantation, and considered the last treatment method for patients who cannot find donors [1-3]. In patients requiring a hemodialysis access site, autogenous AV fistulae are the optimum method for dialysis access. National Kidney Foundation Department Outcomes Quality Initiative guidelines suggest that AV fistulae are the most sustainable and effective option for patients who require hemodialysis for a long time [3]. The artery and vein selection for AV fistula creation should start distally in the upper limbs. Hence, the common preferred site is the distal radiocephalic zone and can progress proximally if the artery and vein are not appropriate for the required procedures. Brachiocephalic site is the other popular option in patients who do not have appropriate vessels in the radiocephalic zone [3-5].

The surgical procedure, the experience of the surgeon, the quality of arteriovenous structures, and advanced strategies are the main factors that determine the patency rates of created AV fistulae. After creation of an AV fistula, arterial endothelium migrates to vein wall, which gets affected by increased blood flow and pressure. Hypoxia, hemodynamic shear stress, and inflammation are considered the main additional factors which cause the pathophysiologic changes on the vein wall. These factors lead to venous neointimal hyperplasia which can result in the failure of the AV fistula [4-6]. Endothelial protection solutions are preservation solutions used for the vein wall, containing antioxidant material to systematically protect the endothelium against these stress factors. They can be used for coronary or peripheral vascular reconstruction with autologous vascular grafts. Published studies suggest that these solutions can improve endothelial functions and increase the patency rates of vascular grafts [7,8].

In the current study, we aimed to investigate the midterm patency rates of created AV fistulas with or without endothelial protection solution.

Materials and methods

This single-center case-control study was conducted in Ordu University Training and Research Hospital. Patients with end-stage renal disease were included in the study prior to AV fistulae creation between August 2018-August 2019. Ethics Approval was obtained from the local ethics committee of Ordu University, School of Medicine (Approval number: 2020/165). All AV fistulae were created by the same surgical team and patients who did not give consent to be included in the study were excluded. During the creation of an AV fistulae, endothelial protection solution (NOESIS®, Noegenix, Ankara, Turkey) was used in 27 patients, who constituted Group A, and not used in 22 patients, who were included in Group B (the control group). All patients were followed up for 6 months. Age, gender, body mass index (BMI), accompanying diseases (diabetes mellitus [DM] and hypertension [HT]) were recorded. All patients underwent clinical evaluation and preoperative Duplex scans to assess the patency of superficial veins. A functionally mature AVF is defined per Kidney Disease Outcome Quality Initiative (KDOQI) guidelines as one that can be easily cannulated and undergoes at least six successful consecutive dialysis sessions [1,3]. AV fistulae were routinely created under a local anesthetic field block. Magnifying loupes were used for all cases. The upper extremity vein graft was identified first and clamped after injection (Figure 1) of NOESIS® [Noegenix, Ankara, Turkey] in patients in Group A. The arterial site was explored, and the artery was prepared for anastomosis. Before AV anastomosis, the vein graft was unclamped and end to site anastomosis was performed. Similar procedures were performed in group B except NOESIS® administration to the vein graft. After anastomoses, mean flow on vein graft was evaluated with duplex scans, and complications, along with patency rates at the 3rd and 6th months were recorded. The vein endothelium was visualized with color duplex scans and compared.

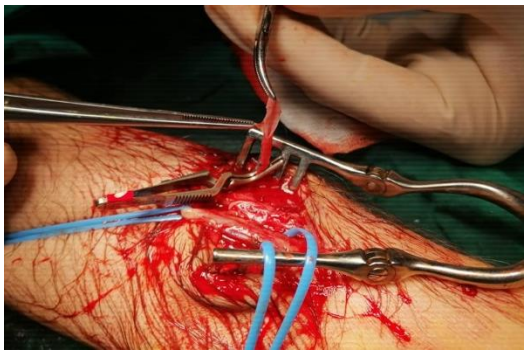


Figure 1: Preparation of a vein conduit and artery for creation of an AV fistula

Statistical analysis

Analysis of the data was conducted using SPSS (Statistical Package for Social Science) for Windows 15.0 package program. Descriptive statistics were presented as mean (standard deviation) for continuous variables, the differences between which were evaluated with Mann-Whitney U Test. Discrete variables were compared with Pearson Chi-square test. The comparison of groups was made with the Fisher exact test. $P<0.05$ was considered statistically significant.

Results

The groups were similar in terms of age, gender, and BMI values. There were 19 (70%) patients with DM in group A and 17 (77%) patients in group B. The number of patients with hypertension was 23 (85%) and 19 (86%) patients in groups A and B, respectively. The demographic findings are summarized in Table 1.

Table 1: Comparison of demographic variables between two groups

	Group A (n:27)	Group B (n:22)	*P*-value
Age mean (standard deviation)	55.88 (16.14)	60.63 (13.86)	0.334
Gender (n of males/%)	17/63	10/45	0.349
BMI mean (standard deviation)	27.74 (6.89)	26.00 (6.20)	0.537
Diabetes (n/%)	19/70	17/77	0.586
Hypertension (n/%)	23/85	19/86	0.582

BMI: Body mass index

There were 16 patients with radiocephalic (59%) and 11 patients with brachiocephalic (41%) anastomoses in group A and the distribution of fistula sites was similar with group B (Table 2). Mean (standard deviation [SD]) flows were 492.59 (135.60) mL/min and 537.05 (163.16) mL/min in groups A and B, respectively. Thrombosis was detected in 3 (11%) patients in group A and 4 (18%) patients in group B (Table 2). The 3rd month patency rates were significantly higher in group A (n=26, 96%) when compared with group B (n=14, 64% (P=0.007). Furthermore, the fistulae were patent at the 6th month in 25

(93%) (Figure 3) and 6 (27%) patients in groups A and B, respectively (P<0.001) (Table 2).

The walls of veins were more regular in Group A than those in Group B, as detected by duplex scans (Figure 2A, B). Figure 3 shows effective blood flow in the AV fistula which was created using the endothelium protection solution at the 6th month.

Table 2: Operational and follow-up findings of AV fistulae created with or without endothelial protection solution

	Group A (n:27)	Group B (n:22)	*P*-value
Fistula Type			
Radiocephalic n(%)	16 (59)	14 (64)	0.986
Brachiocephalic n(%)	11 (41)	8 (36)	0.779
Postoperative Findings			
Mean Flow on Vein After Anastomoses mean (standard deviation) (mL/min)	492.59 (135.60)	537.05 (163.16)	0.537
Complication (early thrombosis) n(%)	3 (11)	4 (18)	0.685
Patency on 3rd month n(%)	26 (96)	14 (64)	0.007
Patency on 6th month n(%)	25 (93)	6 (27)	<0.001

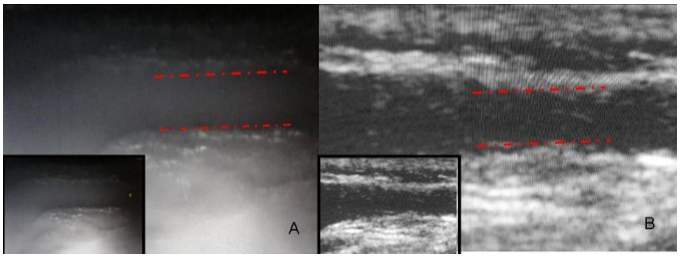


Figure 2: A: Small frame: The ultrasonographic visualization of arteriovenous (AV) fistula vein graft which was created using the endothelium protection solution, Big frame: The dashed red line shows the regularity of endothelial wall. B: Small frame: The ultrasonographic visualization of AV fistula vein graft which was transplanted without using an endothelium protection solution, Big frame: The dashed red line shows the irregularity of endothelial wall.

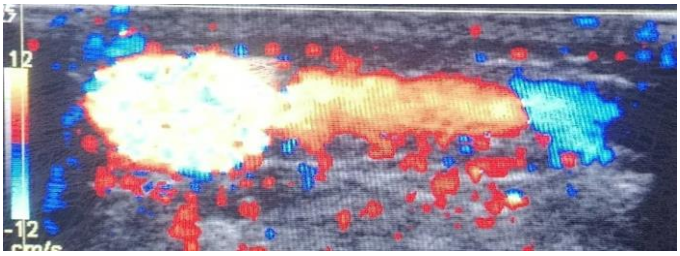


Figure 3: Effective blood flow in the AV fistula at 6th month, which was created using an endothelium protection solution

Discussion

To the best of our knowledge, this is the first study which compares the patency rates of AV fistulae that were created with or without endothelial damage inhibitor solution. Our results indicate that AV fistula creation with endothelial protection solutions yield higher patency rates. This solution seems to improve endothelial functions and provide regular venous endothelial wall, protecting the venous endothelium against neointimal hyperplasia.

AV fistula is still the best method for maintaining dialysis, which is why longer patency durations are important. The main determinants of patency are the quality of surgical anastomosis, the structures of vein and arterial endothelium, and venous endothelial hyperplasia [9-11]. Regardless of the quality of anastomosis, the vein endothelium exposed to arterialized blood flow undergoes hyperplasia and deformation along with oxidative stress factors, and occlusion begins on the venous side [10-12]. During surgery, mechanical harm may be done to the vein due to handling, harvesting and anastomotic repositioning, which leads to structural and functional damage of the grafted venous endothelium. These factors trigger three mechanisms after the creation of AV fistula: 1. Early thrombosis within hours, 2. Thrombosis due to intimal hyperplasia within months, and 3. Thrombosis in the late phase due to atherosclerosis within years [8,12]. Endothelial damage inhibitor solutions reduce these factors and prolong the patency of grafted veins. The key roles of solutions include preserving the venous conduit until implantation and protecting the endothelia against thrombosis and neointimal hyperplasia following implantation. Autologous blood, balanced saline or ringer solutions were used in the prior studies and significant results were reported [13,14]. However, determining of the best endothelium protection solution in which the conduit is stored until the time of implantation has been a major point of controversy with regards to the contents. The biocompatibility and antioxidant properties of endothelium protection solutions determine the protective capacity against ischemia-reperfusion and cellular damage, viability, and integrity during maladaptive processes due to handling, harvesting, and repositioning [8,12]. The recent studies about special endothelial protection solutions encourage their usage for harvested conduits. Haime et al. reported that utilizing endothelium protection solutions in saphenous venous grafts (before anastomosing to coronary artery) in patients undergoing coronary bypass surgery reduces the risk of long-term adverse events [15]. Moreover, some studies point the beneficial effects of hyaluronic-acid-containing products. Mochizuki et al. reported that hyaluronic acid glycosaminoglycans can regulate the endothelial functions by inducing the release of nitric oxide in canine femoral arteries. They concluded that "the hyaluronic acid (HA) glycosaminoglycans in the glycocalyx layer function as a shear-stress detection mechanism for shear-induced NO production" [16]. The disease related stress increases hyaluronidase activity, which is responsible for dissolving hyaluronic acid, and induces the generation of reactive oxygen species (ROS), causing damage to the endothelial glycocalyx. Studies claim that components of HA play a crucial role in the maintenance and enhancement of vascular integrity [17]. Bahcivan et al. studied the effect of hyaluronic acid-carboxymethyl cellulose on neointimal hyperplasia experimentally. They claimed that HA prevents the development of neointimal hyperplasia on vein grafts through a positive effect on tissue repair due to its barrier-forming nature [18]. Thus, we studied the effects of a HA-based endothelial protection solution for vein grafts for the creation of AV fistulas. The obtained results indicate that HA-based endothelial protection solution improves early and midterm patency rates of AV fistulae.

Conclusions

The HA based solutions can exert protective effects by enhancing endothelial functions and preventing neointimal hyperplasia against venous conduit occlusion in AV fistula patients. However, our study presents macroscopic findings and the cellular effects should be clarified with micro-analysis studies.

References

1. III. NKF-K/DOQI Clinical Practice Guidelines for Vascular Access: update 2000. Am J Kidney Dis. 2001; 37(Suppl 1):S137–81.
2. Allon M. Current management of vascular access. Clin J Am Soc Nephrol. 2007;2:786–800. https://doi. org/10.2215/CJN.00860207 PMID: 17699495
3. I. NKF-K/DOQI Clinical Practice Guidelines for Hemodialysis Adequacy: Update 2000. Am J Kidney Dis 2001; 37(Suppl. 1):S137eS181
4. RiellaMC, Roy-Chaudhury P. Vascular access in haemodialysis: strengthening the Achilles' heel. Nat Rev Nephrol. 2013;9(6):348-57.

5. Viecelli AK, Mori TA, Roy-Chaudhury P, Polkinghorne KR, Hawley CM, Johnson DW, et al. The pathogenesis of hemodialysis vascular access failure and systemic therapies for its prevention: Optimism unfulfilled. Semin Dial. 2018 May;31(3):244-57.
6. Simon E, Long B, Johnston K, Summers S.A Case of Brachiocephalic Fistula Steal and the Emergency Physician's Approach to Hemodialysis Arteriovenous Fistula Complications. J Emerg Med. 2017;53(1):66-72.
7. Ben Ali W, Voisine P, Olsen PS, Jeanmart H, Noiseux N, Goeken T, et al. DuraGraft vascular conduit preservation solution in patients undergoing coronary artery bypass grafting: rationale and design of a within-patient randomisedmulticentre trial. Open Heart. 2018;5(1):e000780. Published 2018 Apr 13. doi: 10.1136/openhrt-2018-000780
8. Caliskan, E., Sandner, S., Misfeld, M, Aramendi J, Salzberg SP, Choi YH, et al. A novel endothelial damage inhibitor for the treatment of vascular conduits in coronary artery bypass grafting: protocol and rationale for the European, multicentre, prospective, observational DuraGraft registry. J Cardiothorac Surg. 2019;14(1):174. https://doi.org/10.1186/s13019-019-1010-z
9. Fitts MK, Pike DB, Anderson K, Shiu YT. Hemodynamic Shear Stress and Endothelial Dysfunction in Hemodialysis Access. Open Urol Nephrol J. 2014;7(Suppl 1 M5):33-44. doi: 10.2174/1874303X01407010033
10. Brahmbhatt A, Remuzzi A, Franzoni M, Misra S. The molecular mechanisms of hemodialysis vascular access failure. Kidney Int. 2016;89(2):303-16. doi: 10.1016/j.kint.2015.12.019
11. Siddiqui MA, Ashraff S, Santos D, Carline T. An overview of AVF maturation and endothelial dysfunction in an advanced renal failure. Renal Replacement Therapy. 2017;3:42.
12. de Vries MR, Simons KH, Jukema JW, Braun J, Quax PH. Vein graft failure: from pathophysiology to clinical outcomes. Nat Rev Cardiol. 2016;13(8):451–70.
13. Cavallari N, Abebe W, Mingoli A, Sapienza P, Hunter WJ3rd, Agrawal DK, et al. Short-term preservation of autologous vein grafts: effectiveness of University of Wisconsin solution, Surgery. 1997;121:64-71.
14. Shuhaiber JH, Evans AN, Massad MG, Geha AS. Mechanisms and future directions for prevention of vein graft failure in coronary bypass surgery, European Journal of Cardio-Thoracic Surgery. 2002;22(3):387–96.
15. Haime M, McLean RR, Kurgansky KE, Emmert MY, Kosik N, Nelson C, et al. Relationship between intra-operative vein graft treatment with DuraGraft(R) or saline and clinical outcomes after coronary artery bypass grafting. Expert Rev Cardiovasc Ther. 2018;16(12):963–70.
16. Mochizuki S, Vink H, Hiramatsu O, Kajita T, Shigeto F, Spaan JA, et al. Role of hyaluronic acid glycosaminoglycans in shear-induced endothelium-derived nitric oxide release. Am J Physiol Heart Circ Physiol. 2003;285(2):H722-6.
17. Lennon FE and Singleton PA. Hyaluronan regulation of vascular integrity. Am J Cardiovasc Dis 2011;1(3):200-13.
18. Bahcivan M, Yucel S, Kefeli M, Gol MK, Can B, Keceligil HT. Inhibition of vein graft intimal hyperplasia by periadventitial application of hyaluronic acid-carboxymethyl cellulose: an experimental study. Scand Cardiovasc J. 2008;42(2):161-5.

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. 2020;4(9):720-724.
DOI: 10.28982/josam.710475

Research article
Araştırma makalesi

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

Factors affecting delay in diagnosis and treatment of lung cancer

Akciğer kanserinde tanı ve tedavi gecikme faktörleri

Fatma İrem Yeşiler [1], Filiz Çimen [2], Şükran Atikcan [2]

[1] Department of Anesthesiology and Reanimation, Intensive Care Unit, Baskent University, Ankara, Turkey
[2] Department of Pulmonary Diseases, Ataturk Chest Diseases and Chest Surgery Training and Research Hospital, Ankara, Turkey

ORCID ID of the author(s)
FİY: 0000-0002-0612-8481
FÇ: 0000-0003-0512-7473
ŞA: 0000-0001-2345-6879

Corresponding author/Sorumlu yazar:
Fatma İrem Yeşiler
Address/Adres: Anesteziyoloji ve Reanimasyon Anabilim Dalı, Yoğun Bakım Ünitesi, Başkent Üniversitesi, 06490, Ankara, Türkiye
E-mail: fatmairem84@hotmail.com

Ethics Committee Approval: Ethics committee approval was received from Ataturk Chest Diseases and Chest Surgery Training and Research Hospital Regional Ethics Committee in April 2012. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Etik kurul onayı Nisan 2012'de Atatürk Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi bölge etik kurulundan alınmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/14/2020
Yayın Tarihi: 14.09.2020

Abstract

Aim: Lung cancer (LC) is one of the most prominant causes of mortality in the world. Delays in diagnosis and treatment gravely affect the prognosis of the disease. Our aim is to investigate the factors that affect delay in diagnosis and treatment in patients with LC.

Methods: In this retrospective cohort study, LC patients who were diagnosed in the pulmonary diseases clinic between January 2010 and August 2011 were retrospectively evaluated from patient files. The sociodemographic characteristics of the patients (age, gender, occupation and educational level), symptom type, presence of other malignancies, radiological location of the lesion, diagnostic method, histological type, presence of endobronchial lesion, stage of LC, length of times between admission, diagnosis and treatment were noted.

Results: One hundred seven (87.7%) patients were male and 15 patients (12.3%) were female. Eighty-nine patients (73%) were under the age of 70 years. Ninety-eight patients were diagnosed with non-small cell (NSCLC) and 24 patients, with small cell lung cancer (SCLC). The mean duration from symptom onset to admission to the hospital (SA), from symptom onset to pathological diagnosis (SP), from symptom onset to initiating treatment (ST), from admission to the hospital until pathological diagnosis (AP), from admission to the hospital until initiating treatment (AT) were 30, 60, 75,5, 14, 33 days, respectively. There were statistically significant differences between SP, AP, AT periods (P=0.017, P=0.011 and P=0.006 respectively) with regards to education levels, and between SA, SP, ST, and from symptom onset to performing an initial radiological examination (SR) periods in terms of social security institution (P<0.05 for all). AT time of patients with SCLC was shorter than that of patients with NSCLC.

Conclusion: Early diagnosis of LC is particularly important. Therefore, determination of factors affecting the delay in diagnosis and treatment of LC, probable causes, and solutions should be investigated.

Keywords: Lung cancer, Delays, Diagnosis, Treatment

Öz

Amaç: Akciğer kanseri dünya çapında en önemli mortalite nedenlerinden biridir. Tanı ve tedavi gecikmesi hastalığın prognozunu etkileyen en önemli faktörlerdendir. Amacımız; akciğer kanseri tanısı almış hastalarda tanı ve tedavi gecikmesini etkileyen faktörleri araştırmaktır.

Yöntemler: Ocak 2010 – Ağustos 2011 tarihleri arasında göğüs hastalıkları kliniğinde tanı konulan akciğer kanserli hastaların dosyaları retrospektif olarak incelendi. Hastaların sosyodemografik özellikleri (yaş, cinsiyet, meslek ve eğitim düzeyi), semptom tipi, başka malignite varlığı, lezyonun radyolojik lokalizasyonu, tanı yöntemi, histolojik tip, endobronşiyal lezyon varlığı, akciğer kanseri evresi, başvuru, tanı ve tedavi arasındaki sürelerin uzunluğu kaydedildi. Çalışma, retrospektif kohort çalışmasıdır.

Bulgular: Olguların 107’ si (%87,7) erkek ve 15’ i (%12,3) kadındı. 89 olgu (%73) 70 yaş altındaydı. 98 olgu küçük hücre dışı akciğer kanseri (KHDAK) iken 24 olgu küçük hücreli akciğer kanseri (KHAK) idi. Semptomlarının başlangıcından hastaneye başvurusuna (SB), semptomların başlangıcından patolojik tanıya (SP), tedavi başlangıcına (ST), başvurudan patolojik tanıya (BP), başvurudan tedavi başlangıcına (BT) kadar geçen ortalama süre sırayla 30, 60, 75,5, 14, 33 gün olarak bulundu. Öğrenim düzeyi ile SP, BP, BT süreleri (sırasıyla P=0,017, P=0,011 ve P=0,006); sosyal güvence ile SB, SP, ST, SR süreleri arasında istatistiksel olarak anlamlı farklılık saptandı (P<0,05 tümü için). KHAK’ de BT süresi KHDAK’ ye göre daha kısa olduğu saptandı

Sonuç: Akciğer kanserinde erken tanı konulması oldukça önemlidir. Bu nedenle tanı ve tedaviyi geciktirecek faktörlerin saptanması, olası nedenlerinin ve çözümlerinin araştırılması gerekmektedir.

Anahtar kelimeler: Akciğer kanseri, Gecikmeler, Tanı, Tedavi

How to cite/Atıf için: Yeşiler Fİ, Çimen F, Atikcan Ş. Factors affecting delay in diagnosis and treatment of lung cancer. J Surg Med. 2020;4(9):720-724.

Introduction

Lung Cancer (LC) is a major cause of cancer-related morbidity and mortality and is responsible for an estimated 1.6 million new diagnoses and more than 1.4 million (13%) annual cancer deaths [1,2]. It is the third most common cancer, and the most frequent when considering both genders. The number of LC deaths has increased substantially due to increased prevalence of smoking and environmental pollution in industrialised countries within the last century [3].

Delay in diagnosis and treatment is a widespread problem in patients with lung and non-lung cancers. Many determinants play a role in diagnostic delay. They can be divided into delays in the patients' first seeking health care and delays within the health care system. Patient delay involves several factors, related to the patient's perception of symptoms, educational level, age, and perceived risk [4]. Diagnostic and treatment waiting times experienced by LC patients are the product of the disequilibrium between a healthcare system's supply and demand of diagnostic and treatment services, inefficient coordination between healthcare professionals, lack of defined diagnostic practice standards and an absence of system performance auditing mechanisms. Some trials show that treatment delays increase the risk of poor clinical outcomes and are associated with poorer patient experiences in subsequent cancer care [5,6]. Prolonged time between thorough radiological examination and biopsy has been reported to result in an increase in tumor size and stage [7]. Some authors showed that longer time to treatment was a significant negative prognostic factor in patients with stage III LC and in those with stage III LC undergoing surgical resection [8,9]. Early recognition of lung cancer symptoms combined with early medical help–seeking behavior can have the potential to increase survival and decrease mortality from LC [10-12]. To prevent this situation, suspected cases should be referred to centers where further examinations and treatment can be performed as soon as possible, and necessary procedures should be expeditiously performed.

The aim of the study was to investigate the factors that can affect the periods from onset of symptoms to diagnosis and the initiation of treatment.

Materials and methods

Totally, 122 (107 male and 15 female) patients who were admitted to the department of pulmonary diseases between January 2010 and August 2011 were included. Numerous factors causing a delay in diagnosis and treatment were investigated in patients who were diagnosed histologically with LC. The medical records of patients were reviewed retrospectively, and data were obtained and processed from the chest disease informed consent forms, which had been signed by each patient during admission to the hospital. This retrospective cohort study was conducted according to the Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki). The trial was approved by Research Ethics Committee and performed in accordance with accepted ethical standards (Ankara Ataturk Chest Diseases and Chest Surgery Training and Research Hospital Clinical Research Ethics Committee, date: April 9th, 2012).

The common characteristics of the patients who were included in the study were as follows:

- Histopathologically diagnosed with lung cancer
- Underwent clinical staging after necessary tests were performed [13]
- Received and completed treatment, or did not approve of the treatment

Patients who were diagnosed with LC based on clinical or radiological assessments were excluded.

The medical records of the patients were reviewed, and necessary data were obtained by filling the study forms. The sociodemographic characteristics of the patients (age, gender, occupation and educational status), place of residence, smoking habit, social security, symptom type, presence of other malignancies, family history of LC, radiological location and size of the lesion, diagnostic method, histological type of the lesion, presence of endobronchial lesion, stage of LC, performance status, time from symptom onset to admission to the hospital (SA), time from symptom onset to pathological diagnosis (SP), time from symptom onset to initiating treatment (ST), time from symptom onset to performing an initial radiological examination (SR), time from admission to the hospital to performing an initial radiological examination (AR), time from admission to the hospital to pathological diagnosis (AP) and time from admission to the hospital to initiating treatment (AT) were retrospectively obtained (Figure 1), and their relationships with each other were evaluated.

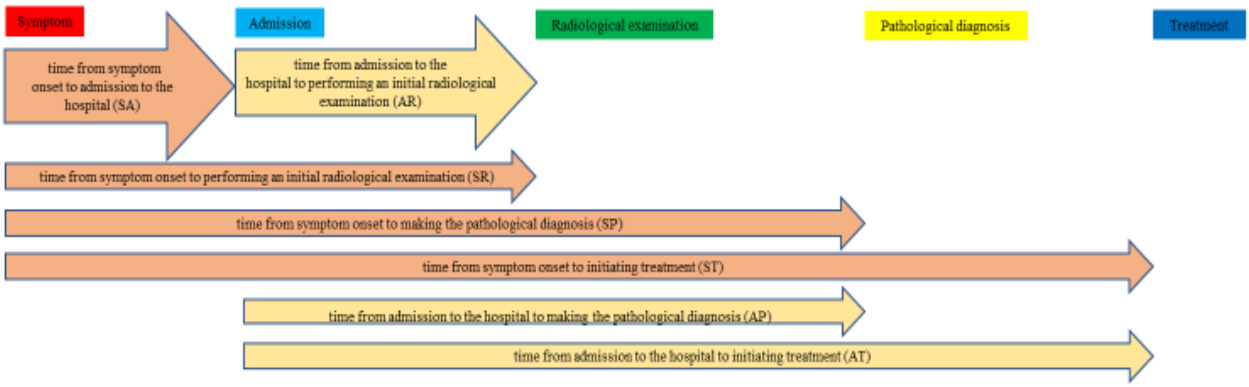


Figure 1: Timeline of symptom, admission, radiological examination, diagnosis and treatment

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences 20.00 (SPSS) software. The Mann–Whitney U test was used to compare delay times and affecting factors, and the Kruskal–Wallis multiple comparison test was performed when there was a difference in delay times between the groups. A *P*-value of <0.05 was considered statistically significant in both tests.

Results

Totally, 107 (87.7%) patients were male and 15 (12.3%) were female. Ninety-eight (80.3%) patients had non-small cell lung cancer (NSCLC): 30 (30.7%) had stage I–III and 68 (69.3%) had stage IV cancer. Twenty-four (19.7%) patients had small cell lung cancer (SCLC); 9 (37.5%) had limited stage (I-III) cancer, and 15 (62.5%) had extensive stage (IV) cancer. The performance status in 89.4% of the patients was Eastern Cooperative Oncology Group (ECOG) 1 and 2. Gender, smoking habit, histological types, cancer stage and performance status of the patients are presented in Table 1. The distribution of patients by place of residence was as follows: 72 lived in rural areas whereas 50 lived in the city center. The distribution of patients according to education level, occupational group and social security is presented in Table 2.

Chronological data of the patients was shown in Table 3. In this table, minimum, maximum, and mean values of delay times are presented.

No significant relationship was found between delay times and age, gender, occupation, and place of residence. There was no significant difference between the groups in terms of educational status and time of SA. Periods of AP and AT were longer only in the literate group.

Significant differences were detected between educational status and delay times in terms of SP, AP, AT. It was found that high school and college graduates contacted the hospital earlier than the other educational status groups, while the literate group received a diagnosis and treatment later than patients with other educational statuses (*P*=0.017, *P*=0.011 and *P*=0.006, respectively) (Table 4).

There was a significant difference between the social security groups in terms of SA, SP, ST, SR. It was found that patients with a pension fund had the shortest SA, SP, ST and SR times, whereas patients with a health card for the uninsured had the longest period of time (*P*<0.05 for all) (Table 5).

When the first complaints of patients admitted to the hospital were interpreted, those with hemoptysis were found to apply to the hospital earlier than those with chest pain (*P*=0.001).

There was no significant difference between the groups in terms of smoking history, chronic lung disease, family history of lung cancer, other malignancies, radiological tumor location, lobular location of the lesions, tumor diameter, presence of an endobronchial lesion, lung cancer stage and ECOG performance status.

The mean AT time was shorter in patients with SCLC (mean: 27 days) than in those with NSCLC (mean, 34 days) (*P*=0.027).

Table 1: Characteristics of the patients

	n	%
Age		
Under 70 years	89	73
70 years and over	33	27
Smoking habit		
Yes	105	86
No	17	14
Histological type		
NSCLC	98	80.3
Stage I–III	30	30.7
Stage IV	68	69.3
SCLC	24	19.7
Limited stage	9	37.5
Extensive stage	15	62.5
Place of Residence		
Rural	72	59
Urban	50	41

NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer

Table 2: Distribution by educational level, occupational group, and social security

	Number	%
Educational Level		
Illiterate	11	9
Literate	21	17.2
Primary school graduate	69	56.5
Secondary school graduate	6	5
High school + University graduate	15	12.3
Occupational Group		
Farmer	36	30.3
Artisan	26	21.3
Housewife	14	11.4
Worker	24	19.7
Officer	12	9.8
Driver	10	8.2
Social Security		
SSI	57	46.7
SSOASE	24	19.7
Pension fund	19	15.6
Health Card for Uninsured People in Turkey	22	18

SSI: Social Security Institution, SSOASE: Social Security Organization for Artisans and the Self-Employed

Table 3: Chronological data

Delay time (days)	Minimum	Maximum	Mean	SD
Symptom-Admission (SA)	0	365	30	69.8
Symptom-Pathological Diagnosis (SP)	1	382	60	73.0
Symptom-Treatment (ST)	18	394	75.5	65.7
Symptom-Radiological examination (SR)	0	365	30	70.3
Admission-Radiological examination (AR)	0	60	0	8.3
Admission-Pathological Diagnosis (AP)	0	228	14	24.6
Admission-Treatment (AT)	2	242	33	29.7
Pathological Diagnosis-Treatment (PT)	0	132	14	16.7

SD: Standard deviation

Table 4: Relationship between educational status and delay times

Educational Status	SP (days)	AP (days)	AT (days)
Illiterate	51.0	10.50	27.0
Literate	77.0	22.0	55.0
Primary school graduate	64.0	14.0	32.5
Secondary school graduate	44.0	11.0	30.0
High school + University graduate	36.0	10.0	34.0

Mean time SP: From symptom onset to the pathological diagnosis, AP: From admission to the hospital to the pathological diagnosis, AT: From admission to the hospital to initiating treatment

Table 5: Relationship between social security type and delay times

Social Security	SA (days)	SP (days)	ST (days)	SR (days)
SSI	37.5	67.0	82.0	45.0
SSOASE	30.0	40.0	63.0	30.0
Pension fund	20.0	35.5	50.0	20.0
Health Card for Uninsured People in Turkey	45.0	70.5	95.0	52.0

SSI: Social Security Institution, SSOASE: Social Security Organization for Artisans and the Self-Employed, mean time SA: From symptom onset to admission to the hospital, SP: From symptom onset to the pathological diagnosis, ST: From symptom onset to initiating treatment, SR: From symptom onset to performing an initial radiological examination

Discussion

Lung cancer is the leading type of cancer in the world that causes the most deaths among both men and women. Primary treatment for patients with early stage NSCLC is surgery. In cases with advanced stage of LC and where surgery cannot be performed, radiotherapy and/or chemotherapy are options of treatment [1]. It is a widely accepted principle that cancer patients should be diagnosed as early as possible. Delays in diagnosis and treatment are common in cancer patients [14]. Some studies have reported that delays in diagnosis and treatment may affect tumor stage and prognosis, whereas other

studies have reported no significant association between these delays and tumor progression and prognosis [15].

The aim of our study was to investigate whether sociodemographic characteristics, past medical and family history of patients and tumor characteristics affect time to admission, diagnosis, and treatment.

Most recommendations of recent American College of Chest Physicians LC guidelines emphasize a maximum delay of 7–14 days between visits with a general practitioner and specialist [16]. Fernandes et al. [17] reported that the mean time until the multidisciplinary committee made a final LC diagnostic decision was 20.6 (13.1) days. In our study, this time was 14 (24.6) days and shorter.

In total, in our study, 107 (87.7%) patients were male and 15 (12.3%) were female. In a similar study conducted in our hospital in 2007 [18], the number of women was low (12.1–18 %). In another study, 58.7% of patients were male [19]. The reason for this is that the smoking habit in Turkey is less common among women. Furthermore, there was also the predominance of men in another study population [4] and this is consistent with the epidemiology of lung cancer.

In the distribution of groups by occupation, farmers (30.3%) ranked first; in terms of social security type, social security institution (SSI) (46.7%) ranked first and health card for uninsured people (18%) ranked third. We found no significant relationship between delay times and occupation. In similar study in China, it was found that there was an increased risk of developing lung cancer with decreasing income [20].

In our study, we found that 105 patients (86%) had a smoking history. This rate was reported as 75.6% in the study by Fernandez et al. [17], 84.6 % in the study by Özdemir et al. [18], and 91.5% in the study by Akpınar et al [21]. Tobacco consumption is the main risk factor for LC and has been increasing in recent years.

It was determined that the patients who graduated high school and university (12.7%) admitted to a doctor earlier than the other groups and that the literate group was the only group that was diagnosed and received treatment at a longer period after admission. The knowledge and awareness of patients were associated increasing educational level. It was found that patients with a lower education level had a higher risk of developing lung cancer.

As for diagnostic methods used in our study, fibreoptic bronchoscopy (FOB) ranked first with 65 cases and transthoracic fine needle aspiration biopsy ranked second with 37 cases. Similar results were obtained in the studies of Chandra et al. [13] and Fernandez et al. [20]. We reported that 98 (80.3%) patients had NSCLC in this study. However, we found more patients with stage 4-LC in our study compared to Acharya et al. [22].

The mean time of SA was 30 days in our study. Similar results were obtained in two other studies reported from Turkey, which reported 42.5 days and 35 days for this time [21,23]. A study in the literature reported 76 days for SA [24]. In a study conducted in Cuba, similar results were obtained with 24.3 days [4]. Time of SA mostly depends on patient-related factors (symptoms, educational level, age etc) but it may be less due to environmental factors (place of residence, transfer to health centers). So, this period is very variable.

In our study, the time of AR varied from 0 to 60 days. In the literature, this duration was 20 days [18]. This duration in our study was shorter than that reported in other studies. It was considered that in Turkey, the patients could easily apply to tertiary healthcare institutions, so time was not wasted.

The mean time of ST and AP in our study were 75.5 days and 14 days, respectively. In similar studies, ST times were 112, 138, 154, 185, 122 and 160 days [14,15,18,20,21,24]. In a study in Spain including 415 patients, the delay between the first symptoms and the beginning of treatment was 124 days [25]. The time reported in our study is shorter that reported in other studies. AP period was also shorter than other studies [14,18,21,24]. These show the ease of access to health centers and the speed of healthcare services in our country compared to other countries.

We observed that the mean time of AT was 33 days and the mean time of PT was 14 days. AT period is shorter in our study and Turkey [14,18,21,24] and PT period is similar to another study conducted in Turkey [18] and shorter than other studies [20,24,26]. These data show that our country is better than developed countries regarding diagnosis and treatment of LC. Kim et al. [27] reported that the median treatment interval was 51 days (interval 49-53 days). Although the PT interval in our study is longer compared to other studies, we had patients were diagnosed and began treatment on the same day. Gomez et al. [28] found that the median diagnosis-to-treatment interval was 27 days and intervals <35 days were associated with improved survival for patients with localized disease and those with distant metastatic diseases surviving ⩾1 year.

In our study, the time of SP was 60 days, whereas it was 143 days in the study by Chandra et al. [20]; prolonged interval until the diagnosis was attributed to the poor performance status of the patients. In 2014, Fernandez's study found that total delay (from onset of symptoms to confirmation of diagnosis) was 67.4 days [4]. The similarity between the results of our study and results of this study, even in more technologically advanced countries, suggest that poor organization and management of health services, not just material shortages, play an important role in diagnostic delay. Chest/shoulder pain was the only first symptom associated with a shorter median SP for lung cancer and for early-stage lung cancer, the median SP for any symptom was 141 days compared with 87 days for late-stage lung cancer in the study of Walter et al [29]. However, in our study, there was no significant relationship between the mean SP time, first symptom and stages of LC.

No significant relationship was found between delay times and age, gender, occupation, and place of residence. In a similar study conducted in our hospital, there was no relationship between delay times and age, occupation, and social security status, but in terms of place of residence, people who lived in towns were found to have prolonged time in getting a diagnosis and treatment than those living in villages [21]. This result was attributed to the small number of patients included in the study groups.

There was no significant difference between the groups in terms of educational level and time of SA. Times of AP and AT were longer only in the illiterate group. Matching results were also found in the study by Özdemir et al [18]. It was

attributed to the fact that patients in the well-educated group acted more consciously after they realised the seriousness of the situation. Remarkably, in our study, delay times were shorter in the illiterate group only. This difference was attributed to the small number of patients in the group.

In our study, we found that the time of AT was shorter in patients with SCLC (mean, 27 days) than patients with NSCLC (mean, 34 days). In the study conducted by El Quazzani et al. [22], this time was shorter in patients with SCLC [24]. These results were associated with the fact that the prognosis of patients with SCLC is worse than that of patients with other types of cancer and treatment is immediately initiated, as response to chemotherapy is good. In another study, the delay in specialist visit was shorter in SCLC may be because of the acute presenting symptoms.

Comparable results were found in the study of Akpınar et al. [21]. Gender, place of residence, presence of other malignancies and presence of chronic pulmonary disease did not affect the time from the onset of first complaints to referral to a doctor as well as the time of ST. In a study, patients at elevated risk of developing cancer had greater levels of comorbidities affecting respiratory function, such as COPD. Therefore, symptoms become difficult to distinguish, and potential lung cancer symptoms can be confused with existing respiratory conditions [30].

There was no relationship between delay times and the presence of an endobronchial lesion, radiological location of tumor, tumor stage, and performance status in the study of Yaman et al. [23], akin to our study. Although Evans et al. [19] found that the PT interval was shorter for patients with early stage disease (stage I), they suggested that they were given priority for treatment over patients with stage II or III disease.

Limitations

It was a small study conducted at a single center, which limits the generalizability of the results. We did not analyze the size of the tumor and record the comorbidities of patients. Since our study was retrospective, some time periods could not be determined. There were insufficient data in the medical records of patients about the causes of shorter or longer delay times. We did not examine whether the presented data was associated with survival.

Conclusions

Delay in the diagnosis and treatment of lung cancer is an important and widespread problem. There is a need for studies that reveal the magnitude and possible causes of diagnosis and treatment delays in our country. Studies about this subject should be conducted to identify the magnitude and causes, as well as results and solutions to the problem.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebello M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar;136(5):E359–86. doi: 10.1002/ijc.29210.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. Mar-Apr 2011;61(2):69-90. doi: 10.3322/caac.20107.
3. National Cancer Institute, Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Cancer of the Lung and Bronchus. [Cited 21 Feb 2018.] http://seer.cancer.gov/statfacts/html/lungb.html.
4. Fernandez de la Vega JF, Perez H, Samper JA. Lung cancer diagnostic delay in a Havana hospital. MEDICC Review. January 2015;17(1):55-8.
5. Koo MM, Zhou Y, Lyratzopoulos G. Delays in diagnosis and treatment of lung cancer: Lessons from US healthcare settings. Cancer Epidemiol. 2015 Dec;39(6):1145–7. doi: 10.1016/j.canep.2015.08.008.
6. Vinas F, Hassen BI, Jabot L, Monnet I, Chouaid C. Delays for diagnosis and treatment of lung cancers: a systematic review. Clin Respir J. 2016 May;10(3):267–71. doi: 10.1111/crj.12217.
7. Byrne SC, Barrett B, Bhatia R. The impact of diagnostic imaging wait times on the prognosis of lung cancer. Can Assoc Radiol J. 2015 Feb;66(1):53–7. doi: 10.1016/j.carj.2014.01.003.
8. Wang L, Correa CR, Hayman JA, Zhao L, Cease K, Brenner D, et al. Time to treatment in patients with stage III non–small cell lung cancer. Int J Radiat Oncol Biol Phys. 2009 Jul 1;74(3):790–5. doi: 10.1016/j.ijrobp.2008.08.039.
9. Coughlin S, Plourde M, Guidolin K, Fortin D, Frechette E, Malthaner R, et al. Is it safe to wait? The effect of surgical wait time on survival in patients with nonsmall cell lung cancer. Can J Surg. 2015 Dec;58(6):414–8. doi: 10.1503/cjs.007015.
10. Goldberg SW, Mulshine JL, Hagstrom D, Pyenson BS. An actuarial approach to comparing early stage and late stage lung cancer mortality and survival. Popul Health Manag. 2010 Feb;13(1):33–46. doi: 10.1089/pop.2009.0010.
11. Hill LLE, Collier G, Gemine RE. A patient perspective: Identifying and understanding the barriers associated with the diagnostic delay of lung cancer. EMJ Respir. 2017;5(1):92–98.
12. Chatwin J, Povey A, Kennedy A, Frank T, Firth A, Booton R, et al. The mediation of social influences on smoking cessation and awareness of the early signs of lung cancer. BMC Public Health. 2014 Oct 7;14:1043. doi: 10.1186/1471-2458-14-1043.
13. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WEE, et al. The IASLC lung cancer staging project: Proposals for the revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. J Thorac Oncol. 2016 Jan;11(1):39-51. doi: 10.1016/j.jtho.2015.09.009.
14. Salomaa ER, Sallinen S, Hiekkanen H, Liippo K. Delays in the diagnosis and treatment of lung cancer. Chest. 2005 Oct;128(4):2282-8. doi: 10.1378/chest.128.4.2282.
15. G Myrdal, M Lambe, G Hillerdal, K Lamberg, Th Agustsson and E Stahle. Effect of delays on prognosis in patients with non-small cell lung cancer. Thorax. 2004 Jan;59(1):45-9.
16. Ost DE, Yeung SCJ, Tanoue LT, Gould MK. Clinical and organizational factors in the initial evaluation of patients with lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e121S–e141S. doi: 10.1378/chest.12-2352.
17. Fernandez VL, Roibas CM, Rodriguez EG, Rial MB, Hernandez CR, Duran MT, et al. Predicting delays in lung cancer diagnosis and staging. Thorac Cancer. 2019 Feb;10(2):296-303. doi: 10.1111/1759-7714.12950.
18. Özdemir T, Başay N, Mutluay N, Bayız H, Berktaş B, Berkoğlu M. Akciğer Kanserinde Tanı ve Tedavi Gecikmesi. Solunum Hastalıkları. 2007;18(4):100-7.
19. Evans SM, Earnest A, Bower W, Senthuren M, McLaughlin P, Stirling R. Timeliness of lung cancer care in Victoria: a retrospective cohort study. Med J Aust. 2016 Feb 1;204(2):75. doi: 10.5694/mja15.01026.
20. Chandra S, Mohan A, Guleria R, Singh V, Yadav P. Delays during the diagnostic evaluation and treatment of lung cancer. Asian Pac J Cancer Prev. Jul-Sep 2009;10(3):453-6.
21. Akpınar EE, Gülhan M. Akciğer Kanserinde Tanı ve Tedavi Gecikmesini Etkileyen Faktörler. Türkiye Solunum Araştırmaları Derneği 32. Ulusal Kongresi, 20-24 Kasım 2010; Antalya, EP-35.
22. Acharya S, Pun R, Sharma S. P1.01-048 Factors Contributing Delays during Management of Lung Cancer: A Study from Tertiary Level Hospital in Nepal. Journal of Thoracic Oncology. January 2017;12(1):S479-S480. doi.org/10.1016/j.jtho.2016.
23. Yaman N, Ozgen A, Celik P, Ozyurt BC, Nese N, Coskun AS, et al. Factors affecting the interval from diagnosis to treatment in patients with lung cancer. Tumori. Nov-Dec 2009;95(6):702-5.
24. Quazzani HE, Menchafou I, Achachi L, Ftouh ME, Fihry MTEF. Delay in the diagnosis of primary bronchial cancer. Study carried out in the pneumology unit of Ibn Sina university hospital, Rabat (Morocco). Rev Pneumol Clin. 2010 Dec;66(6):335-41. doi: 10.1016/j.pneumo.2010.02.004.
25. Barcala FJG, Prim JMG, Dobano JMA, Rodriguez MM , Sanz MTG, Reino AP, et al. Effect of delays on survival in patients with lung cancer. Clin Transl Oncol. 2010 Dec;12(12):836–42. doi: 10.1007/s12094-010-0606-5.
26. Maiga AW, Deppen SA, Pinkerman R, Lane CC, Massion PP, Dittus RS et al. Timeliness of Care and Lung Cancer Tumor-Stage Progression: How Long Can We Wait? Ann Thorac Surg. 2017 Dec;104(6):1791–7.doi: 10.1016/j.athoracsur.2017.06.051.
27. Kim JOA, Davis F, Butts C, Winget M. Waiting Time Intervals for Non-small Cell Lung Cancer Diagnosis and Treatment in Alberta: Quantification of Intervals and Identification of Risk Factors Associated with Delays. Clin Oncol (R Coll Radiol). 2016 Dec;28(12):750-9. doi: 10.1016/j.clon.2016.06.010.
28. Gomez DR, Liao KP, Swisher SG, Blumenschein GR, Erasmus Jr JJ, Buchholz TA, et al. Time to treatment as a quality metric in lung cancer: Staging studies, time to treatment, and patient survival. Radiother Oncol. 2015 May;115(2):257-63. doi: 10.1016/j.radonc.2015.04.010.
29. Walter FM, Rubin G, Bankhead C, Morris HC, Hall N, Mills K, et al. Symptoms and other factors associated with time to diagnosis and stage of lung cancer: a prospective cohort study. Br J Cancer. 2015 Mar 31;112(Suppl 1):S6-13. doi: 10.1038/bjc.2015.30.
30. Wagland R, Brindle L, Ewings S, James E, Moore M, Rivas C, et al. Promoting help-seeking in response to symptoms amongst primary care patients at high risk of lung cancer: A mixed method study. PLoS One. 2016 Nov 4;11(11):e0165677. doi: 10.1371/journal.pone.0165677.

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. 2020;4(9):725-728.
DOI: 10.28982/josam.774738

Research article
Araştırma makalesi

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

The evaluation of epicardial adipose tissue radiodensity according to age

Yaş dağılımına göre epikardiyal yağ doku radyodansitesinin değerlendirilmesi

Arslan Öcal [1], Ersin Sarıçam [2], Ali Doğan Dursun [3], Mehmet Fazıl Tolga Soyal [4], Hakkı Serkan Şahin [4], Gülçin Türkmen Sarıyıldız [5]

[1] Gulhane Education and Research Hospital, Department of Cardiology, Ankara, Turkey
[2] Medicana International Hospital, Atilim University, Cardiology Clinic, Ankara, Turkey
[3] Atilim University, Department of Physiology, Ankara, Turkey
[4] Medicana International Hospital, Atilim University, Cardiovascular Surgery Clinic, Ankara, Turkey
[5] Medicana International Hospital, General Surgery Clinic, Ankara, Turkey

ORCID ID of the author(s)
AÖ: 0000-0002-9971-1974
ES: 0000-0002-8736-1786
ADD: 0000-0001-9056-0025
MFTS: 0000-0001-6276-3140
HSŞ: 0000-0002-2460-0444

Corresponding author/Sorumlu yazar:
Ersin Sarıçam
Address/Adres: Medicana International Ankara Hastanesi, Atılım Üniversitesi, Söğütözü İlçesi 2165 Sokak No: 6, Söğütözü, Ankara, Türkiye
E-mail: saricamersin@yahoo.com

Ethics Committee Approval: The study protocol was approved by Medicana International Ankara Hospital Ethics Committee (2019-05). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolü Medicana International Ankara Hastanesi Etik Komitesi tarafından onaylandı (2019-05). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/11/2020
Yayın Tarihi: 11.09.2020

Abstract

Aim: The grading of fatty degeneration by cardiac computerized tomography (CCT) is an important bioradiological marker to discriminate biological characteristics. Epicardial adipose tissue (EAT) degeneration has been accused of causing heart disease. However, the relationship between age and EAT radiodensity is not well known. In this study we examined epicardial adipose tissue radiodensity with CCT.

Methods: A total of 147 subjects who underwent contrast-enhanced evaluation of coronary arteries with CCT between Jun 2018-July 2019 due to intermediate probability of coronary artery disease (CAD) were included in this retrospective cohort study. The radiodensities of three epicardial regions (right atrioventricular groove, posterior interventricular groove, and anterior epicardial area) and individual subxiphoid fat radiodensity ratios were obtained. Group comparisons were made according to 10-year-periods (between 10- 80 years of age).

Results: We found that epicardial adipose tissue/ subxiphoid fat radiodensity ratio decreased with increasing age. After the 3rd decade, we detected a negative correlation between EAT/subxiphoid fat radiodensity ratio (r=-0.11). The radiodensity ratios of patients between 20-30 and 30-40 years of age in the LCX, RCA and anterior epicardial regions were 1.71 (0.14) and 1.06 (0.40) (P<0.001), 1.71 (0.20) and 1.04 (0.30) (P<0.001), and 1.70 (0.07) and 1.17 (0.42), respectively (P<0.001).

Conclusion: EAT radiodensity ratio changes are associated with aging. Increased age is negatively correlated with EAT radiodensity ratio, which is considered fat degeneration. We realized that those changes occurred sharply after the third decade.

Keywords: Epicardial adipose tissue, Fatty degeneration, Radiodensity ratio

Öz

Amaç: Yağ doku dejenerasyonu değerlendirmenin sınıflanması kardiyak tomografi (KT) kullanarak biyolojik karakteristiklerin ayırmak için önemli bir biyoradyolojik göstergedir. Epikardiyal yağ doku dejenerasyonu kalp hastalıklarına neden olmakla suçlanmaktadır. Fakat yaş ile epikardiyal yağ doku dejenerasyonu arasında ilişki çok iyi bilinmemektedir. Bu çalışmada biz KT kullanarak epikardiyal yağ doku radyodansitesi inceledik.

Yöntemler: 2018 Haziran ve Temmuz 2019 yılları arasında 147 hastanın orta derece olasılık koroner arter hastalığı için orta derece olasılık nedeniyle koroner arterleri KT ile değerlendirilmesi yapıldıç Bu restrospektif kohort çalışmadır. Üç epikardiyal bölge (sağ atriyoventriküler groove, posterior interventriküler groove ve anterior epikardiyal) radyodansitesi ve bireysel subxiphoid yağ radyodansitesi elde edildi. Grup karşılaştırılmaları 10 yıllık periyodlara göre yapıldı (10 ile 80 yaş arası).

Bulgular: Epikardiyal yağ doku / subxiphoid yağ radyodansitesi oranları artan yaş ile azalmaktadır. Üçüncü 10 yıl sonrası epikardiyal yağ doku / subxiphoid yağ radyodansitesi oranları keskin bir şekilde azaldığını gözlemledik. Pearson correlation oranı negative ve r=-0,11). Yirmi ve 30 yaş arası ile 30-40 yaş arası LCX bölgesi sırasıyla 1,71 (0,14) vs. 1,06 (0,40); P<0,001). RCA bölgesinde ayni yaşlarda sırasıyla 1,71 (0,20) vs. 1,04 (0,30) P<0,001.Anterior epikardiyal bölge aynı yaşlarda sırasıyla 1,70 (0,07) vs. 1,17 (0,42) P<0,001.

Sonuç: Epikardiyal yağ doku radyodansitesi oranı değişikliği yaş ile bağlantılıdır. Artan yaş daha az epikardiyal yağ doku radyodansitesi oranı ile ilişkilidir. Bu ilişki yağ dejenerasyonu kabul edilir (negatif korelasyon). Biz bu değişikliklerin 3. 10 yıl sonrası keskin bir şekilde olduğunu gözlemledik.

Anahtar kelimeler: Epikardiyal yağ dokusu, Radyodansite oranı, Yağ dejenerasyonu

How to cite/Atıf için: Öcal A, Sarıçam E, Dursun AD, Soyal MFT, Şahin HS, Sarıyıldız GT. The evaluation of epicardial adipose tissue radiodensity according to age. J Surg Med. 2020;4(9):725-728.

Introduction

Cardiac computerized tomography (CCT) is a helpful technique for radio-density evaluation in terms of discernment of the characteristics between similar tissue types [1,2]. The grading of fatty degeneration is an important bio-radiological marker.

Epicardial adipose tissue (EAT) is positioned between the myocardial surface, the visceral layer of the pericardium and the surrounding coronary artery region. However, EAT degeneration was accused of causing heart disease. The relationship between EAT and atrial fibrillation, atherosclerosis, hypertension was shown in numerous studies [3-5]. In evaluation of EAT degeneration, radiodensity measurements are not standardized due to amorphous shape of epicardial adipose tissue. Besides, the relationship between age and EAT radiodensity is not well known. Our aim in this study was to quantify the relationship between standardized individual EAT radiodensities and age.

Materials and methods

A total of 147 subjects who underwent CCT between June 2018-July 2019 due to intermediate probability of coronary artery disease (CAD) were retrospectively evaluated. Informed consent forms were obtained from all patients. Approval for the study protocol was obtained from Medicana International Ankara Hospital Human Research Ethic Committee (2019/5), and the study was conducted in accordance with the Declaration of Helsinki principles. Patients who received antihypertensive treatment were considered to have hypertension. Those with prior coronary artery stent or coronary by-pass operations, atrial fibrillation, implanted pacemaker, cardioverter-defibrillator, and coronary narrowing above 40% were excluded.

Cardiac computed tomography (CCT) study schedule and interpretation

CCT procedures were performed with a dual source scanner (Philips Brillance 64, number 9938, Holland). Scans for CAC measurements were obtained using a standard scan protocol with 1.0-mm slice collimation. The CAC score was quantified using the Calcium Score module of Syngo software and expressed in Agatston units. Tube voltage was set to 120 or 140 kV depending on body mass. Tube current changed from 400 to 445 mA. Scan duration was 4-10 seconds. Intravenous metoprolol was used in cases where pulse>70 beats/min. The general heart rate during the scan was 60-65 beats/min. Delay time among contrast injection and scan launch was based on the time – density curve obtained after a 10-ml test bolus infusion. The average 80-100 ml of contrast dye was given at a rate of 5 ml/s, which was followed by a 40-ml saline solution flush. The scanning was made during a single inspiratory breath hold, starting at the level of bronchial carina, and finishing 10 mm beyond the heart apex.

Scans were processed and analyzed off-line on a dedicated workstation (Extended Brilliance, Workspace version 7.1.1.28 Philips medical Solutions). Analysis and measurement of the images were performed at the most motionless mid- to end-diastolic phase gated at 60–80% of the RR interval. In the presence of motion artifacts, additional reconstructions were used to evaluate the coronary arteries. The signal-to-noise ratio was calculated by dividing the difference in mean attenuation (HU) between the coronary lumen and peri-coronary tissues by the standard deviation of the mean attenuation in the aortic root.

Coronary artery lesion calculation

The recognized coronary artery lesion was evaluated for stenosis severity along multiple longitudinal, transverse, and oblique axes with the use of multi-planar reconstructions, thin-slab maximum intensity projections, and curved reconstruction techniques. The coronary lesion's severity was quantified by the maximum percentage of luminal diameter stenosis observed in any plane. In ambiguous cases, the percentage of luminal narrowing was recognized by a 2-observer consensus. CAD was identified with the presence of at least one coronary lesion with ≥40-50% luminal diameter stenosis. Coronary lesion assessment was made by interventional cardiologists experienced in acquisition and interpretation of angiography and unaware of the results of EAT measurements.

EAT Measurements

EAT is known as the adipose tissue located within the pericardial sac. EAT radiodensities were obtained using the volume module. EAT radiodensity (regions of interest (ROIs), Hounsfield unit, HU) was measured in the three different epicardial regions in 0.05 cm^2 adipose tissue area (right atrioventricular groove (RCA), posterior interventricular groove (LCX), and anterior epicardial region) (Figure 1). Due to amorphous shape of the epicardial adipose tissue, these measurements were standardized with subxiphoid fat tissue and three epicardial fat radiodensity/subxiphoid fat radiodensity ratio values were obtained as constant ratio. To identify pixels corresponding to adipose tissue within the ROIs, a threshold attenuation range from −190 to −30 HU was used, and a change from negative to positive was considered fat degeneration. Constant ratio was classified within a period of ten years. Mean EAT radiodensity was analyzed on a HU scale. All the EAT measurements were performed by one investigator (H.U); 30 randomly selected cases were re-assessed by H.U. and E.S to obtain the intra- and inter-rater variabilities.

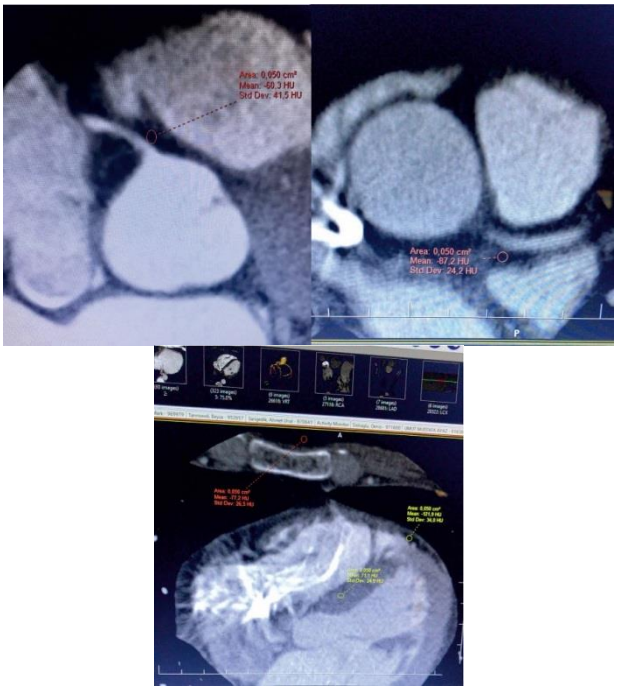


Figure 1: Three different epicardial regions in 0.05 cm^2 adipose tissue area (right atrioventricular groove, posterior interventricular groove, and anterior epicardial region)

Statistical analysis

The data was analyzed with SPSS statistical analysis software (SPSS 17.0 Inc, Chicago, IL, USA). The normality of the data was checked with Shapiro-Wilk Test. The difference between the independent groups (decades for age) was determined by one-way analysis of variance (ANOVA) and Tukey's multiple comparison in normally distributed variables, and by Kruskal Wallis test in non-normally distributed variables. The difference between the dependent groups (epicardial region) was determined by repeated ANOVA and Tukey's multiple comparison tests in case of normal distribution, and by Friedman test in non-normal distribution. Pearson correlation test was used for correlation analysis. The significance level was 0.05; when multiple comparisons were implemented for nonparametric tests, an adjusted α (α = 0.05/ number of test) was used.

Results

Three epicardial regions' (right atrioventricular groove, posterior interventricular groove, and anterior epicardial) radiodensity and individual subxiphoid fat radiodensity ratios were obtained. Each group ratio is shown in Table 1. The radiodensity ratios of patients between 10-20 and 20-30 years of age in the LCX, RCA and anterior epicardial regions were 1.73 (1.54) and 1.71 (0.14) (P=0.98), 1.99 (2.63) and 1.71 (0.20) (P=0.62), and 1.71 (1.78) and 1.70 (0.07), respectively (P=0.12).

We found that epicardial adipose tissue/ subxiphoid fat radiodensity ratio decreased with increasing age. This decrease was sharp after the 3rd decade - there was a negative correlation between EAT/subxiphoid fat radiodensity ratio (r=-0.11) (Figure 2). The radiodensity ratios of patients between 20-30 and 30-40 years of age in the LCX, RCA and anterior epicardial regions were 1.71 (0.14) and 1.06 (0.40) (P<0.001), 1.71 (0.20) and 1.04 (0.30) (P<0.001), and 1.70 (0.07) and 1.17 (0.42), respectively (P<0.001).

Table 1: The radiodensity ratio according to each decade

A decade (years)	Right atrioventricular groove mean (SD)	Posterior interventricular groove mean (SD)	Anterior epicard mean (SD)
11-20 (n=3)	1.99(2.63)	1.73(1.54)	1.71(1.78)
21-30 (n=2)	1.71(0.20)	1.71(0.14)	1.70(0.07)
31-40 (n=20)	1.04(0.30)	1.06(0.40)	1.17(0.42)
41-50 (n=61)	1.02(0.43)	1.02(0.42)	1.16(0.36)
51-60 (n=42)	0.96(0.36)	1.01(0.34)	1.11(0.28)
61-70 (n=12)	0.92(0.40)	0.98(0.45)	1.03(0.38)
71-80 (n=7)	0.89(0.36)	0.93(0.46)	0.99(0.35)
P-value	<0.001	<0.001	<0.001

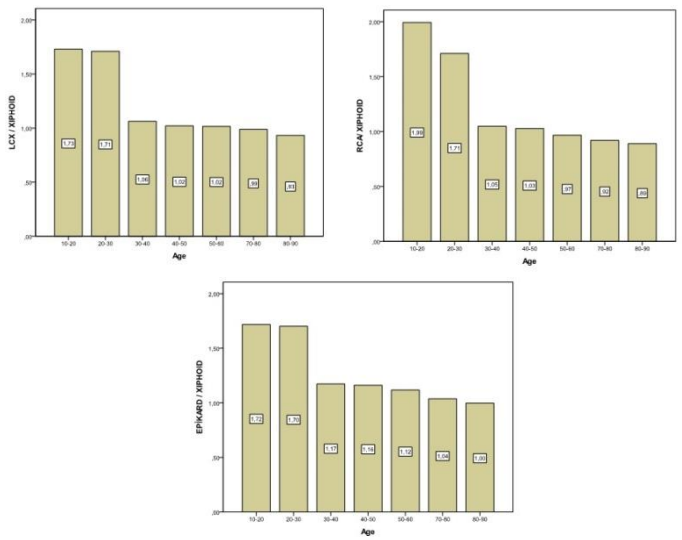


Figure 2: Epicardial adipose tissue / subxiphoid fat radiodensity ratios

Discussion

The measurement of the radiodensity of human tissues is a commonly used method that helps in discriminating among both similar and diverse tissue types and organs in routine clinical study, as evaluated by CCT [6,7]. For instance, the reduction of coronary artery atherosclerotic plaques can be examined to determine their composition and therefore, their vulnerability and the possibility of cardiovascular events [8,9]. Myocardial edema in large acute myocardial infarctions may be recognized by decreased Hounsfield units (HU) value [10]. Fat degeneration results in decreased negativity HU in radiologic terms. A greater ratio (less negativity) of EAT radiodensity suggests a transition from hypodense 'fatty' components to hyperdense 'non-fatty' components within the EAT. The 'non-fatty' appearance arises from non-adipose (inflammatory) cells, contrast-enhanced microvasculature, and interlobular septa [11].

Due to amorphous shape of epicardial adipose tissue, radiodensity measurements are not standardized. Besides, the relationship between age and EAT radiodensity is not well known. In this study, we first examined the relationship between standardized individual EAT radiodensity detected by CCT in the heart with regards to decades. Among the study population, EAT radiodensity changed to more positive with increased age. Our data demonstrate that EAT degeneration accelerates after the 3rd decade. We suggest that decreased EAT radiodensity ratio is associated with fat degeneration. Although other studies did not find any relationship between aging and epicardial fat measurements, they have only included older subjects or obese patients with high epicardial adiposity, and cases with cardiac diseases [12,13]. In our study, patients with coronary artery stents or prior coronary by-pass operations were excluded.

Aging is related to metabolic degeneration characterized by changes in fat distribution, and insulin resistance. These metabolic modifications are associated with a variety of age-related diseases that subsequently result in increased mortality [14]. Therefore, age is a degeneration marker. It has been known that the prevalence of atherosclerosis and atrial fibrillation is associated with increased age. Moreover, age has been used in decision making for thromboprophylaxis in non-valvular atrial fibrillation (CHA2DS2-VASc score) [15]. Our data support that EAT radiodensity ratio, whose decrease is considered fat degeneration, is negatively correlated with age. We have reason to suggest that EAT radiodensity ratio could be a degeneration marker.

Limitations

The current study is non-invasive, and further invasive surgical studies to confirm our results are needed.

Conclusion

EAT radiodensity ratio changes are associated with aging. Increased age is negatively correlated with EAT radiodensity ratio, which is considered fat degeneration. We realized that those changes occurred sharply after the third decade. We believe that EAT radiodensity could be used as a degeneration marker.

Acknowledgements

The authors thank Askın Yesilyurt, radiology technician, for his support.

References

1. Pracon R, Kruk M, Kepka C, Pregowski J, Opolski MP, Dzielinska Z, et al. Epicardial adipose tissue radiodensity is independently related to coronary atherosclerosis. A multidetector computed tomography study. Circ J. 2011;75(2):391-7.
2. Franssens BT, Nathoe HM, Visseren FL, van der Graaf Y, Leiner T; SMART Study Group. Relation of Epicardial Adipose Tissue Radiodensity to Coronary Artery Calcium on Cardiac Computed Tomography in Patients at High Risk for Cardiovascular Disease. Am J Cardiol. 2017;119(9):1359-65.
3. Chekakie MO, Welles CC, Metoyer R, Ibrahim A, Shapira AR, Cytron J, et al. Pericardial fat is independently associated with human atrial fibrillation. J Am Coll Cardiol. 2010;56:784-8.
4. Wang CP, Hsu HL, Hung WC, Yu TH, Chen YH, Chiu CA, et al. Increased epicardial adipose tissue (EAT) volume in type 2 diabetes mellitus and association with metabolic syndrome and severity of coronary atherosclerosis. Clin Endocrinol (Oxf). 2009;70:876-82.
5. Eroglu S, Sade LE, Yıldırır A, Demir O, Muderrisoglu H. Association of epicardial adipose tissue thickness by echocardiography and hypertension. Turk Kardiyol Dern Ars. 2013;41(2):115-22.
6. Hamrahian AH, Ioachimescu AG, Remer EM, Motta-Ramirez G, Bogabathina H, Levin HS, et al. Clinical utility of noncontrast computed tomography attenuation value (Hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic experience. J Clin Endocrinol Metab. 2005;90:871-7.
7. Korobkin M, Brodeur FJ, Yutzy GG, Francis IR, Quint LE, Dunnick NR, et al. Differentiation of adrenal adenomas from nonadenomas using CT attenuation values. Am J Roentgenol. 1996;166:531-6.
8. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol. 2009;54:49-57.
9. Pundziute G, Schuijf JD, Jukema JW, Decramer I, Sarno G, Vanhoenacker PK, et al. Head-to-head comparison of coronary plaque evaluation between multislice computed tomography and intravascular ultrasound radiofrequency data analysis. JACC Cardiovasc Interv. 2008;1:176-82.
10. Mahnken AH, Bruners P, Bornikoel CM, Kramer N, Guenther RW. Assessment of myocardial edema by computed tomography inmyocardial infarction. JACC Cardiovasc Imaging. 2009;2:1167-74.
11. Pracon R, Kruk M, Kepka C, Pregowski J, Opolski MP, Dzielinska Z, et al. Epicardial adipose tissue radiodensity is independently related to coronary atherosclerosis. A multidetector computed tomography study. Circ J. 2011;75(2):391-7.
12. Rabkin SW. Epicardial fat: properties, function and relationship to obesity. Obes Rev. 2007;8:253-61.
13. Corradi D, Maestri R, Callegari S et al. The ventricular epicardial fat is related to the myocardial mass in normal, ischemic and hypertrophic hearts. Cardiovasc Pathol. 2004;13:313-6.
14. Lip GY, Nieuwlaat R, Pisters R, Lane DA,Crijns HJ. Refining clinical risk stratificationfor predicting stroke and thromboembolismin atrial fibrillation using a novel riskfactor-based approach: the Euro HeartSurvey on Atrial Fibrillation. Chest. 2010;137:263-72.
15. Hazzard WR, Ettinger WH Jr. Aging and atherosclerosis: changing considerations in cardiovascular disease prevention as the barrier to immortality is approached in old age. Am J Geriatr Cardiol. 1995;4:16-36.

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. 2020;4(9):729-732.
DOI: 10.28982/josam.721362

Research article
Araştırma makalesi

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

Adult aplastic anemia patients can maintain remission after allogeneic hematopoietic stem cell transplantation in a mixed chimeric state

Erişkin aplastik anemi hastaları allojenik hematopoietik kök hücre nakli sonrası miks kimerik durumda remisyonda kalabilir

Semih Başcı [1], Tuğçe Nur Yiğenoğlu [1], Mehmet Bakırtaş [1], Bahar Uncu Ulu [1], Derya Şahin [1], Tahir Darçın [1], Jale Yıldız [1], Dicle İskender [1], Nuran Ahu Baysal [1], Mehmet Sinan Dal [1], Merih Kızıl Çakar [1], Fevzi Altuntaş [1]

[1] Department of Hematology and Bone Marrow Transplantation Center, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkey

ORCID ID of the author(s)

SB: 0000-0003-4304-9245
TNY: 0000-0001-9962-8882
MB: 0000-0003-3216-482X
BUU: 0000-0002-6230-9519
DŞ: 0000-0002-0945-8398
TD: 0000-0001-5073-1790
JY: 0000-0002-8235-1570
Dİ: 0000-0002-6062-6422
NAB: 0000-0002-2425-3374
MSD: 0000-0002-5994-2735
MKÇ: 0000-0003-0978-0923
FA: 0000-0001-6872-3780

Corresponding author/Sorumlu yazar:
Semih Başcı
Address/Adres: Hematoloji ve Kemik İliği Nakli Merkezi, Ankara Dr.Abdurrahman Yurtaslan Onkoloji Eğitim ve Araştırma Hastanesi, Sağlık Bilimleri Üniversitesi, 06200, Yenimahalle, Ankara, Türkiye
E-mail: dr.semihbasci@gmail.com

Ethics Committee Approval: The study protocol was approved by University of Health Sciences Dr. Abdurrahman Yurtaslan Oncology Health Practice And Research Center Clinical Research Ethics Committee (3/4/2020, 2020-03/564). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolü Sağlık Bilimleri Üniversitesi Dr. Abdurrahman Yurtaslan Onkoloji Sağlık Uygulama Ve Araştırma Merkezi Klinik Araştırmalar Etik Kurulu (04.03.2020, 2020-03/564) tarafından onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/23/2020
Yayın Tarihi: 23.09.2020

Abstract

Aim: Allogeneic stem cell transplantation (allo-SCT) is performed as a curative treatment in young, fit, severe aplastic anemia (SAA) and very severe aplastic anemia (VSAA) patients. Age is one of the most significant factors that impact survival after transplantation. With advancing age, survival rates decrease, therefore it is crucial to perform allo-SCT without any delay in appropriate SAA and VSAA patients. Mixed chimerism (MC) in the post-allo-SCT period may be a sign of relapse or graft failure. In this study, we aimed to evaluate the outcome of allo-SCT in adult SAA and VSAA patients and the significance of chimerism monitoring in follow up.

Methods: The data of 16 adult AA patients who underwent allo-SCT at our center were included in this observational study. HLA match, conditioning regimens, chimerism and remission status were recorded.

Results: Median PFS was 70.4 months and median OS was 89.7 months in all patients. During the follow-up period, 9 patients remained fully chimeric whereas 6 patients had MC. The chimerism level of one patient, who had engraftment failure, was <5%. Both fully chimeric and mixed chimeric patients remained in remission.

Conclusion: More AA patients can be treated with allo-SCT with more optimized conditioning regimens that provide sustained engraftment with minimum toxicity. Our study showed that adult AA patients can maintain remission for a long time after allo-SCT, even in a mixed chimeric state.

Keywords: Adult aplastic anemia, Allogeneic stem cell transplantation, Chimerism

Öz

Amaç: Allojenik kök hücre nakli (AKHN), uygun vericisi bulunan fit ağır aplastik anemili (SAA) ve çok ağır aplastik anemili (VSAA)hastalarda küratif tedavi yöntemi olarak uygulanmaktadır. Yaş, nakil sonrası sağkalımı belirleyen en önemli faktörlerden biridir ve ilerleyen yaş ile birlikte sağkalım oranları azalmaktadır, bu nedenle uygun hastaların geciktirilmeden nakle alınması büyük önem taşımaktadır. AKHN sonrasında miks kimerizm (MK) olması nüs ya da engraftman yetersizliğinin işareti olabilir. Biz bu çalışmada, erişkin SAA ve VSAA hastalarında AKHN sonrasındaki durumunu ve takipte kimerizmin önemini incelemeyi amaçladık.

Yöntemler: Merkezimizde AKHN olan 16 AA hastası bu gözlemsel çalışmaya dahil edildi. HLA durumu, hazırlama rejimi, kimerizm ve remisyon durumu kaydedildi.

Bulgular: Tüm hastalarda medyan PFS 70,4 ay ve medyan OS 89,7 ay olarak izlendi. Takip süresi boyunca, 9 hasta tam kimerik iken 6 hasta MK ve 1 hastada kimerizm <%5 izlendi. Kimerizmi <%5 olan hastada engraftman kaybı izlenirken, diğer tam kimerik ve miks kimerik hastalar remisyonda izlendi.

Sonuç: Minimum toksisite ile engraftmanı sağlayan optimize hazırlama rejimleri kullanılarak daha fazla hasta allo-SCT ile tedavi edilebilir. Çalışmamız, yetişkin AA hastalarının allo-SCT'den sonra, miks kimerik bir durumda bile uzun süre remisyon sağlayabildiğini göstermiştir.

Anahtar kelimeler: Erişkin aplastik anemi, Allojenik kök hücre nakli, Kimerizm

How to cite/Atıf için: Başcı S, Yiğenoğlu TN, Bakırtaş M, Ulu BU, Şahin D, Darçın T, Yıldız J, İskender D, Baysal NU, Dal MS, Çakar MK, Altuntaş F. Adult aplastic anemia patients can maintain remission after allogeneic hematopoietic stem cell transplantation in a mixed chimeric state. J Surg Med. 2020;4(9):729-732.

Introduction

Aplastic anemia (AA) is defined by hypocellular bone marrow and pancytopenia without bone marrow fibrosis and abnormal bone marrow infiltration. Its incidence in Europe is 2-3 / 1,000,000 annually. About 70-80% of cases are idiopathic. It has a biphasic age distribution and peaks between the ages of 10-25 [1].

According to the criteria of Camitta, at least two of the following values should be detected in complete blood count (CBC) for diagnosis of AA: Hemoglobin (Hb) <10g/dL, platelet $<50x10^9$/L, neutrophil $<1.5x10^9$/L [2]. Modified Camitta criteria is used to determine the severity of the disease. For the diagnosis of severe aplastic anemia (SAA), bone marrow cellularity must be less than 25% or if the cellularity is 25-50%, the ratio of residual hematopoietic cells must be less than 30%. In addition, at least two of the following values must be present in CBC: Absolute neutrophil count (ANC) $<0.5x10^9$/L, platelet count $<20x10^9$/L, reticulocyte count $<20x10^9$/L. The diagnosis is very severe aplastic anemia (VSAA) when the neutrophil count is $<0.2x10^9$/ L in peripheral blood in addition to the criteria of SAA [3].

Allogeneic stem cell transplantation (allo-SCT) is a curative treatment method in young, fit SAA and VSAA patients. Age is one of the most crucial factors which impact survival after transplantation, and with advancing age, survival rates decrease. Therefore, it is crucial to perform allo-SCT without any delay in SAA and VSAA patients [3].

Monitoring donor-patient chimerism is useful in evaluating engraftment status [4]. Especially after reduced-intensity conditioning (RIC) regimens and T-cell depletion, mixed chimerism (MC) may occur [5,6]. Increasing MC levels in the post-allo-SCT period may be a sign of disease relapse or graft failure. Conversely, decreasing MC may be a sign of graft versus host disease (GVHD) or graft-versus-tumor effect [7].

In this study, we aimed to evaluate the outcome of allo-SCT in adult age group SAA and VSAA patients and the importance of chimerism monitoring in the follow-up period.

Materials and methods

A total of 16 adult AA patients who underwent allo-SCT at our center between October 2009 and February 2020 were included. The data was analyzed retrospectively. Patients who were diagnosed with AA according to Camitta criteria and defined as SAA or VSAA according to the modified Camitta criteria were considered eligible for the study.

As conditioning regimen, 8 patients received CY-ATG [cyclophosphamide (50 mg/kg /day, 4 days) and anti-thymocyte globulin (ATG)], 2 patients received FLU-CY-ATG [Fludarabine (30 mg/m^2, 4 days), cyclophosphamide (20 mg/kg, 2 days), and ATG], 6 patients received FLU-CY-ATG-TBI [Fludarabine (30 mg/m^2, 4 days), cyclophosphamide (20 mg/kg, 2 days), ATG and total body irradiation (TBI) (2 gray on day -1)]. Bone marrow-derived stem cells were used in 11 patients and peripheral blood-derived stem cells were used in five. High-resolution typing of human leukocyte antigen (HLA) -A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQ was performed in all patients.

Post-transplant overall survival (OS) was identified as the time from transplantation until death or until the last follow-up in surviving patients. Post-transplant progression-free survival (PFS) was defined as the duration from transplantation until progression. Neutrophil engraftment was described as the first day that absolute neutrophil count (ANC) was >500/mm^3 without any granulocyte stimulating factor support for 3 consecutive days, and platelet engraftment was described as the first day that platelet count was >20000/mm^3 without any transfusion support for 3 consecutive days. Transplant-related mortality (TRM) was identified as deaths in the first 100 days after transplantation [8].

International Bone Marrow Transplant Registry (IBMTR) grading was performed to define the severity of acute graft versus host disease (GVHD) [9]. National Institute of Health (NIH) 2015 consensus criteria was used to define chronic GVHD severity [10].

Donor-patient chimerism was monitored from the peripheral blood on days 30, 60, 90, then, every 3 months in the first 2 years, every 6 months between the 2nd and 5th year and annually after 5 years. MC was defined as persistence of 5% to 95% remaining recipient hematopoietic cells. Full donor chimerism (FC) was defined as the persistence of >95% donor hematopoietic cells [11].

Statistical analysis

The data analyzed with SPSS software, V21.0 (SPSS Inc., Chicago, IL). Descriptive statistics were used to summarize the data. Categorical data were defined as ratios, and numerical data, as median (range: min-max). Kaplan-Meier test was used to estimate OS and PFS and log-rank test was applied to investigate factors affecting survival. $P<0.05$ was considered statistically significant.

Results

Characteristics of patients are presented in Table 1. Median PFS was 70.4 (95%CI: 44.89-95.91) months and median OS was 89.7 (95%CI: 67.96-111.39) months in all patients.

Table 1: Characteristics of patients

Characteristics	Patients
Gender (Male/Female)	8 male / 8 female
Age, median (range)	24 (18-53)
Source of stem cells	Bone marrow derived: 11
	Peripheral blood derived: 5
Donor type	Related: 12
	Unrelated: 4
HLA Match	Full Match: 12
	Mismatch: 3
	Haploidentical: 1

HLA: Human leukocyte antigen

In patients ≤24 years of age, between 25-39 years of age and ≥40 years of age, OS were 67.2 (95%CI: 46-88.3) months, 92.5 (95%CI: 59.4-125.6) months and 19.5 (95%CI:0-45.1) months, respectively. PFS were 51.4 (95%CI:26.6-76.1) months, 77.7 (95%CI: 40.2-115.2) months and 19.5 (95%CI:0-45.1) months, respectively. There was no statistically significant difference between age groups in terms of OS and PFS (P= 0.479 and P=0.729). The median duration between the date of diagnosis and allo-SCT was 7 months. Twelve patients had acquired AA, while 4 patients had Fanconi Anemia (FA). In acquired AA patients, median OS and PFS were 91.3(95%CI: 66.4-116.1) months and 75.3 (95%CI: 46.8-103.9) months, respectively. The same values were 30.3(95%CI: 13.7-46.8) months and 30.3 (95%CI: 6.8-53.7) months, respectively, in FA

patients. The median EBMT score was 2 (range: 0-5) and the median Sorror comorbidity score was 0 (range: 0-3). The median number of CD34+ stem cells was 3.17×10^6/kg (range: 1.62-7.26×10^6/kg) in patients who received bone marrow-derived stem cells and 5.26×10^6/kg (range: 4.23-6.40×10^6/kg) in patients who received peripheral blood-derived stem cells. The median platelet engraftment was 34 (range: 31-39) days in FA patients and 17 (range: 14-34) days in those with acquired AA. The median neutrophil engraftment was 14 (range: 12-15) days in FA patients and 17 (range: 14-28) days in patients with acquired AA.

During the follow-up period, 9 patients remained fully chimeric while 6 patients had mixed chimerism and 1 patient had a chimerism level of <5%. The chimerism level of one patient, who had engraftment failure, was <5%. Both fully chimeric and mixed chimeric patients remained in remission.

TRM was 12.5%. Median platelet engraftment was 34 (range: 31-39) days in FA patients and 17 (range: 14-34) days in acquired AA. Median neutrophil engraftment was 14 (range: 12-15) days in FA patients and 17 (range: 14-28) days in acquired AA.

Severe acute hepatic GVHD was observed in 1 patient who received peripheral blood-derived stem cells. Severe chronic GVHD was not observed in anyone.

Discussion

Allo-SCT is the curative treatment option for fit SAA and VSAA patients. Performing allo-SCT in adult age group AA patients is particularly important as survival rates decrease with advancing age [3]. Although allo-SCT is the standard approach in fit SAA and VSAA patients, there is no standard conditioning regimen. The optimal conditioning regimen was investigated by many researchers to provide continuous engraftment with minimal complications. In a previous study, in allo-SCTs performed in matched siblings using CY conditioning regimen, graft failure was observed at a high rate, especially in severely transfused patients [12]. Lower incidence of graft failure was found when CY-TBI was used as a conditioning regimen in allo-SCT from fully matched sibling donors, but in the long-term follow-up, higher morbidity and mortality incidences were observed [13-16]. Many researchers performed allo-SCT from sibling donors using CY- ATG conditioning regimen [13,17-19]. In a phase II prospective study by the Seattle group, in AA patients who received CY- ATG conditioning regimen, 3-year OS was 92%. This OS was significantly higher than the historical control group that received CY conditioning regimen alone (92% vs 72% in 3 years, P=0.043) [17]. In a large study based on the data of the Center for International Blood and Marrow Transplant Research (CIBMTR) comparing the results of patients using peripheral blood-derived stem cells and bone marrow-derived stem cells, a higher rate of chronic GVHD (27% vs 12%, P=0.002) and lower OS duration (5 year OS 73% vs 85%, P=0.024) was determined in patients who received peripheral blood-derived stem cell [20]. In our study, grade 3-4 chronic GVHD was observed in 2 patients. One of these patients received bone marrow-derived stem cells while the other received peripheral blood-derived stem cells. Severe acute GVHD was observed in none.

In the analysis by CIBMTR, the incidence of neutrophil engraftment was similar among all age groups, whereas the incidence of platelet engraftment was significantly lower in patients older than 40 years of age (P=0.010) when compared to patients ≤20 years of age, but no statistically significant difference was found compared to those aged 20 to 40 years (P=0.098) [21]. In our study, median platelet engraftment was 34 (range: 31-39) days in FA patients and 17 (range: 14-34) days in acquired AA. Median neutrophil engraftment was 14 (range: 12-15) days in FA patients and 17 (range: 14-28) days in acquired AA.

In the analysis by CIBMTR, the incidence of mortality was significantly higher in patients older than 40 years of age compared to those aged under 20 years (P<0.001) and those aged between 20 to 40 years (P=0.008) [21]. In our study, TRM was 12.5%. In the phase II prospective study of The European Society for Blood and Marrow Transplantation (EBMT) analyzing the results of patients who underwent allo-SCT from sibling donors using FLU-CY-ATG conditioning regimen, no significant difference was detected in terms of OS between patients aged ≥40 years and 30-40 years of age [22]. In the study evaluating the results of 82 SAA patients who underwent allo-SCT from sibling donors using the FLU-CY-ATG conditioning regimen, no significant difference was found in terms of OS in patients aged <20 years, 20-39 years, 40-49 years, and 50-59 years of age (88%, 97%, 92% and 86%) [23]. In our report, we found no differences regarding OS and PFS when patients were classified according to their ages as ≤24 years, 25-39 years and ≥40 years.

In a phase II prospective study by EBMT, the incidence of graft failure was 18%, and 2-year OS was 73% in patients who underwent allo-SCT from unrelated donors using FLU-CY-ATG conditioning regimen. In this study, in patients older than 14 years, the incidence of graft failure was higher (32% and 5%, P=0.030), and OS was lower (61% and 84% in 2 years, P=0.2) [24]. In addition, examination of the results of patients who underwent allo-SCT from unrelated donors using FLU-CY-ATG- ± low dose TBI from the EBMT data yielded no significant difference in OS durations between patients older and younger than 27 years of age (5 year OS; 78 vs 79%, p> 0.050) [24].

There have been conflicting results regarding the correlation between disease relapse and chimerism levels after allo-SCT [25-28]. RIC allo-SCT often results in varying degrees of MC, compared to myeloablative transplants [25,26]. In addition, MC can maintain steadiness and might be associated with sustained remission, especially in nonmalignant diseases, where MC may imply a tolerant condition associated with low frequency of GVHD [29,30]. In our study, through the follow-up period, 9 patients remained fully chimeric whereas 6 patients had mixed chimerism. The chimerism level of one patient, who had engraftment failure, was <5%. Both fully chimeric and mixed chimeric patients remained in remission.

Limitations

The limitations of the study were small and heterogenous cohort with varying donor types and dissimilar sources of stem cells received from allo-SCT.

Conclusion

Allo-SCT is a curative treatment method in patients with suitable donors and no serious comorbid conditions in SAA and VSAA patients, but there is no standard conditioning regimen. More AA patients can be treated with allo-SCT using more optimized conditioning regimens that provide sustained engraftment with minimum toxicity. In our study, mix chimeric adult AA patients remained in remission after allo-SCT during the follow-up period. Mechanisms of AA remission with mixed chimerism warrants further investigation.

References

1. Killick S, Bown N, Cavenagh J, Dokal I, Foukaneli T, Hill A, et al. Guidelines for the diagnosis and management of adult aplastic anemia. Br J Haematol. 2016;172:187–207.
2. Camitta BM, Rappeport JM, Parkman R, Nathan DG. Selection of patients for bone marrow transplantation in severe aplastic anemia. Blood. 1975;45:355–63.
3. Bacigalupo A, Hows J, Gluckman E, Nissen C, Marsh J, Van Lint MT, et al. Bone marrow transplantation (BMT) versus immunosuppression (IS) for the treatment of severe aplastic anemia (SAA): a report of the EBMT SAA working party. Br J Haematol. 1988;70(2):177-82
4. Antin JH, Childs R, Filipovich AH, Giralt S, Mackinnon S, Spitzer T, et al. Establishment of complete and mixed donor chimerism after allogeneic lymphohematopoietic transplantation: recommendations from a workshop at the 2001 Tandem Meetings of the International Bone Marrow Transplant Registry and the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2001;7:473–85.
5. Van Leeuwen JEM, Van Tol MJD , Joosten AM, Wijnen JT, Verweij PJ, Khan PM, et al. Persistence of host-type hematopoiesis after allogeneic bone marrow transplantation for leukemia is significantly related to the recipient's age and/or the conditioning regimen, but it is not associated with an increased risk of relapse, Blood. 1994;83:10;3059–67.
6. Bretagne S, Vidaud M, Kuentz M, Cordonnier C, Henni T, Vinci G, et al. Mixed blood chimerism in T cell-depleted bone marrow transplant recipients: evaluation using DNA polymorphisms, Blood. 1987;70:5;1692–95.
7. Levrat E, Roosnek E, Masouridi S, Mohty B, Ansari M, Villard J, et al. Very Long Term Stability of Mixed Chimerism after Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Hematologic Malignancies. Bone Marrow Res. 2015;2015:176526
8. Rihn C, Cilley J, Naik P, Pedicano AV, Mehta J. Definition Of Myeloid Engraftment After Allogeneic Hematopoietic Stem Cell Transplantation. Haematologica. 2004;89(6):763-4
9. Rowlings PA, Przepiorka D, Klein JP, Gale RP, Passweg JR, Henslee-Downey PJ, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. Br J Haematol. 1997;97:855.
10. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11(12):945–56.
11. Bader P, Niethammer D, Willich A, Kreyenberg H, Klingebiel T. How and when should we monitor chimerism after allogeneic stem cell transplantation? Bone Marrow Transplant.2005;35:107-19.
12. McCann SR, Bacigalupo A, Gluckman E, Hinterberger W, Hows J, Ljungman P, et al. Graft rejection and second bone marrow transplants for acquired aplastic anemia: a report from the Aplastic Anaemia Working Party of the European Bone Marrow Transplant Group. Bone Marrow Transplant. 1994;13:233-7.
13. Champlin RE, Horowitz MM, van Bekkum DW, Camitta BM, Elfenbein GE, Gale RP, et al. Graft failure following bone marrow transplantation for severe aplastic anemia: risk factors and treatment results. Blood. 1989;73:606-13.
14. Gluckman E, Horowitz MM, Champlin RE, Hows JM, Bacigalupo A, Biggs JC, et al. Bone marrow transplantation for severe aplastic anemia: influence of conditioning and graft-versus-host disease prophylaxis regimens on outcome. Blood. 1992;79:269-75.
15. Deeg HJ, Socie G, Schoch G, Henry-Amar M, Witherspoon RP, Devergie A, et al. Malignancies after marrow transplantation for aplastic anemia and fanconi anemia: a joint Seattle and Paris analysis of results in 700 patients. Blood. 1996;87:386-92.
16. Gale RP, Ho W, Feig S, Champlin R, Tesler A, Arenson E, et al. Prevention of graft rejection following bone marrow transplantation. Blood. 1981;57:9-12.
17. Storb R, Etzioni R, Anasetti C, Appelbaum FR, Buckner CD, Bensinger W, et al. Cyclophosphamide combined with anti-thymocyte globulin in preparation for allogeneic marrow transplants in patients with aplastic anemia. Blood. 1994;84:941-9.
18. Ades L, Mary JY, Robin M, Ferry C, Porcher R, Esperou H, et al. Long-term outcome after bone marrow transplantation for severe aplastic anemia. Blood. 2004;103:2490-7.
19. Kahl C, Leisenring W, Deeg HJ, Chauncey TR, Flowers ME, Martin PJ, et al. Cyclophosphamide and anti-thymocyte globulin as a conditioning regimen for allogeneic marrow transplantation in patients with aplastic anemia: a long-term follow-up. Br J Haematol. 2005;130:747-51.
20. Schrezenmeier H, Passweg JR, Marsh JC, Bacigalupo A, Bredeson CN, Bullorsky E, et al. Worse outcome and more chronic GVHD with peripheral blood progenitor cells than bone marrow in HLA matched sibling donor transplants for young patients with severe acquired aplastic anemia. Blood. 2007;110:1397-400.
21. Gupta V, Eapen M, Brazauskas R, Carreras J, Aljurf M, Gale RP, et al. Impact of age on outcomes after bone marrow transplantation for acquired aplastic anemia using HLA-matched sibling donors. Haematologica. 2010;95:2119-25.
22. Maury S, Bacigalupo A, Anderlini P, Aljurf M, Marsh J, Socié G, et al. Improved outcome of patients older than 30 years receiving HLA-identical sibling hematopoietic stem cell transplantation for severe acquired aplastic anemia using fludarabine-based conditioning: a comparison with conventional conditioning regimen. Haematologica. 2009;94:1312-5.
23. Shin SH, Yoon JH, Yahng SA, Lee SE, Cho BS, Eom KS, et al. Influence of recipient's age on the outcome of HLA-matched sibling transplants in adult patients with severe aplastic anemia who conditioned with fludarabine-based regimen. Paper presented at: 54th ASH Annual Meeting and Exposition; 2012;1921-2.
24. Bacigalupo A, Locatelli F, Lanino E, Marsh J, Socié G, Maury S, et al. Fludarabine, cyclophosphamide, and anti-thymocyte globulin for alternative donor transplants in acquired severe aplastic anemia: a report from the EBMT-SAA Working Party. Bone Marrow Transplant. 2005;36:947-50.
25. Valcarcel D, Martino R, Caballero D,Mateos MV, Pérez-Simón JA, Canals C, et al. Chimerism analysis following allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning. Bone Marrow Transplant. 2003;31:387–92.
26. Baron F, Baker JE, Storb R, Gooley TA, Sandmaier BM, Maris MB, et al. Kinetics of engraftment in patients with hematologic malignancies given allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. Blood. 2004;104:2254–62.
27. Childs R, Clave E, Contentin N, Jayasekera D, Hensel N, Leitman S, et al. Engraftment kinetics after nonmyeloablative allogeneic peripheral blood stem cell transplantation: full donor T-cell chimerism precedes alloimmune responses. Blood. 1999;94:3234–41.
28. Saito B, Fukuda T, Yokoyama H, Kurosawa S, Takahashi T, Fuji S, et al. Impact of T cell chimerism on clinical outcome in 117 patients who underwent allogeneic stem cell transplantation with a busulfan-containing reduced-intensity conditioning regimen. Biol Blood Marrow Transplant. 2008;14:1148–55.
29. Park M, Koh KN, Seo JJ, Im HJ. Clinical implications of chimerism after allogeneic hematopoietic stem cell transplantation in children with non-malignant diseases. Korean J Hematol. 2011;46(4):258-64.
30. Svenberg P, Mattsson J, Ringdén O, Uzunel M. Allogeneic hematopoietic SCT in patients with non-malignant diseases, and importance of chimerism, Bone Marrow Transplant. 2009;44(11):757-63.

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

J Surg Med. 2020;4(9):733-737.
DOI: 10.28982/josam.759207

Research article
Araştırma makalesi

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

Prediction of the number of oocytes based on AMH and FSH levels in IVF candidates

IVF adaylarında AMH ve FSH seviyelerine göre oosit sayısının tahmini

Nur Dokuzeylül Güngör [1], Tuğba Gürbüz [2]

[1] Department of Gynecology and IVF Clinic, Bahcesehir University Göztepe Medical Park Hospital, Istanbul, Turkey
[2] Department of Gynecology and Obstetrics, Medistate Hospital, Istanbul, Turkey

ORCID ID of the author(s)
NDG: 0000-0002-7234-3876
TG: 0000-0003-3555-3767

Abstract

Aim: The purpose of this study was to predict the number of oocytes using anti-Mullerian hormone (AMH) and Follicle Stimulating Hormone (FSH) levels in In Vitro Fertilization (IVF) candidates.

Methods: This retrospective cohort study included 121 (23 cases with poor response, 92 cases with normal response, and 6 cases with excessive response) infertile patients. We examined the relationship between AMH and FSH levels and the number of oocytes. The method used in this study was to consider the number of oocytes as the response variable and identify the effective factors. All analyses were performed with free R software.

Results: The results show that although the ovarian response is associated with serum AMH levels and the women's age (P=0.04 and P<0.001, respectively), the negative linear and binomial regression yield a significant collinearity and the natural logarithm of AMH alone can be a good estimate of the ovarian response (P<0.001). ROC curves in logistic regression were used to determine cutoff points. The results of this regression showed that the natural logarithm of AMH with a cutoff value of 1.36 ng/ml can determine the line between the poor and normal ovarian response (P<0.01). The natural logarithm of AMH cannot determine the cutoff value of normal and excessive ovarian response (P>0.05).

Conclusion: The use of serum AMH levels is important for the prediction of poor ovarian response.

Keywords: Anti-Mullerian hormone, Ovarian response, Oocytes

Öz

Amaç: Bu çalışmanın amacı IVF tedavisi planlanan olgularda serum AMH ve FSH düzeylerini kullanarak oosit sayısını tahmin etmektir.

Yöntemler: Bu retrospektif kohort çalışma 121 infertil hastayı (düşük over rezervi (n=23), normal over rezervi (n=92) ve yüksek over rezervi (n=6)) kapsamaktadır. Çalışmada AMH, FSH ve oosit sayıları arasındaki ilişki değerlendirilmiştir. Oosit sayısı değişken yanıt olarak kabul edilip etkileyen faktörler tanımlanmıştır. Tüm analizler ücretsiz R software ile yapılmıştır.

Bulgular: Sonuçlar, over cevabının serum AMH seviyeleri ve ayrıca kadınların yaşı (sırasıyla P=0,04 ve P<0,001) ile ilişkili olmasına rağmen, negatif doğrusal ve binom regresyonunun, anlamlı bir eşdoğrusallık ve tek başına AMH'nin doğal logaritmasının olduğunu gösterdiğini göstermektedir ve over cevabı için iyi bir tahmini olabilir (P<0,001). Kesim noktalarını belirlemek için lojistik regresyondaki ROC eğrileri kullanılmıştır. Bu regresyonun sonuçları, 1,36 ng/ml'lik bir kesme değerine sahip doğal AMH logaritmasının, zayıf ve normal yumurtalık tepkisi arasındaki sınırı belirleyebileceğini gösterdi (P<0,01). AMH'nin doğal logaritması, normal ve aşırı over cevabının kesim değerini belirleyemez (P>0,05).

Sonuç: AMH özellikle düşük over rezervinin tahmininde predikte edici önemli bir faktördür.

Anahtar kelimeler: Anti-Mülleryan hormon, Over cevabı, Oosit

Corresponding author/Sorumlu yazar:
Tuğba Gürbüz
Address/Adres: Rüzgarlıbahçe Mahallesi. Cumhuriyet Caddesi. No: 24, Medistate Hastanesi, Beykoz, İstanbul, Türkiye
E-mail: drtgurbuz@hotmail.com

Ethics Committee Approval: The study protocol was approved by Ethical Committee of Beykoz University (CAAE number: 2020/8.1, Decision no: 1). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolü Beykoz Üniversitesi Etik Komitesi (CAAE numarası: 2020/8.1, Karar no: 1) tarafından onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/24/2020
Yayın Tarihi: 24.09.2020

How to cite/Atıf için: Güngör ND, Gürbüz T. Prediction of the number of oocytes based on AMH and FSH levels in IVF candidates. J Surg Med. 2020;4(9):733-737.

Introduction

Infertility, a problem related to the reproductive abilities of humans and a global public health challenge [1], can cause enormous treatment costs, personal distress, and sometimes ostracism and discrimination [2]. The prevalence of infertility has significantly increased recently [3]. Epidemiological investigations have demonstrated the prevalence of infertility experienced by couples was 8 to 12% worldwide [4]. However, infertility involved 13% of the female population [5]. Some procedures, particularly In Vitro Fertilization (IVF), have significantly contributed to the success of fertility aids. IVF, an assisted reproductive technology (ART), is used to cure infertility in females [6]. One of the crucial factors affecting IVF success is the number of oocytes produced by the ovary in response to hormonal stimulation [7]. In other words, IVF success is limited by poor ovarian response, which is observed in 10 to 15% of women undergoing IVF [8].

Achieving competent quality oocytes is one of the essential parameters of IVF [19]. Pregnancy rates in IVF are related to the number of oocytes [10]. The fertilization method also affects the number and the quality of embryos obtained from in vitro maturation of human oocytes [11]. Lack of fertility or low fertility in the IVF cycle is due to the hormone levels achieved through ovulation induction protocols [12]. In ART, success depends on obtaining large numbers of high-quality eggs [13]. Gonadotropin hormones such as Follicle-Stimulating Hormone (FSH) primarily regulate menstrual cycles in women. Infertile women with high FSH levels have a poor response to ovulation [14]. FSH stimulates the conversion of androgen to estrogen in granulosa cells by enzymes of the aromatase system [15].

Some studies have identified ovarian volume and antral follicles as a way of determining the number of oocytes. FSH, serum inhibin B levels, and Antral Follicle Count (AFC) levels show the number of oocytes [16]. Anti-Müllerian Hormone (AMH), which is produced by the ovarian granulosa cells and disappears during menopause, has been recently used to predict ovarian response [17]. These functions include inhibition of primary follicle utilization, FSH-dependent growth inhibition, and selection of perinatal follicles and small antral follicles [18].

AMH is used to evaluate fertility potential and ovarian response in IVF due to the relationship between serum levels of AMH and the number of primary antral follicles [17]. According to Chang HJ et al., ideally determining ovarian reserve involves measuring AMH levels, due to better sensitivity and specificity. In the early stages of ovarian reserve depletion, Inhibin-B, FSH and estradiol levels are low. Then the serum levels of these three hormones undergo changes late in the reproductive process when the ovarian reserve reaching a critical level reduces the chance of pregnancy [20]. However, serum levels of AMH are independent of the menstrual cycle and are not affected by GnRH agonists or oral contraceptives [21].

The follicular response to gonadotropin stimulation also decreases due to reduced ovarian reserve [22]. Results of the IVF are strongly dependent on ovarian stimulation with gonadotropins and ovarian response [23]. The purpose of this study is to predict the number of oocytes using AMH levels and FSH levels in IVF candidates.

Materials and methods

This retrospective study was conducted between November 2014 and September 2019 at the Gynecology and IVF Department. The procedures were conducted in accordance with the regulations established by the Clinical Research and Ethics Committee and the Helsinki Declaration of World Medical Association. The study was carried out with the permission of Research Ethics Committee of Beykoz University (Permission granted/CAAE number. 2020/8.1, Decision no: 1). Signed informed consents were obtained from all patients. The study included 121 infertile patients (23 cases with poor response, 92 cases with a normal response, and 6 cases with excessive response).

We considered the number of oocytes as the response variable to find the effective factors i.e. AMH and FSH; and our covariates included maternal age and body mass index (BMI). The number of oocytes was thoroughly and precisely analyzed once quantitatively, and then qualitatively.

We ran three different models, logistic regression, linear regression, and negative binomial regression, to see which one fits better with our dataset. In the logistic regression model, response variables were defined as poor response, normal response, and excessive ovarian response. Regarding multiple regression, these responses were considered continuous variables. The response variable included the number of oocytes released in the period to be studied based on the negative binomial model. In the case of logistic regression, we recorded our response at three distinct levels. Patients were divided into three groups in which normal ovarian response contained 6-15 oocytes, the poor ovarian response contained 5 or less oocytes, and excessive ovarian response contained >15 oocytes.

Statistical analysis

Statistical analysis was performed with free R software. $P<0.05$ was considered statistically significant. To calculate the relationship between the ovarian number and AMH and FSH, we applied the Pearson correlation test because our response variable was not normal. To compare the different results of the oocyte in terms of the distribution of variables, we applied ANOVA with the following multiple comparisons. We used the Pearson correlation test to find the relationship between the number of ovarian responses, AMH and FSH.

Results

Analysis of variance (ANOVA)

Results of the ANOVA model on the variables in the study show that there is a significant difference among three groups in terms of AMH and women's age at a probability level of 5% ($P=0.04$, and $P<0.001$, respectively). Based on these results, FSH values in the poor response group were not significantly higher than those in the normal and excessive response groups ($P=0.48$). However, the AMH value also showed a significant difference between two poor and excessive response groups but none of them showed a significant difference from the normal group. In this research, the ages of the women were equal between the poor and normal response

groups and the age of the excessive response group was significantly lower than that of the two other groups (P=0.04) (Table 1).

Negative binomial and linear regression

To evaluate the relationship between the studied variables and Ovarian Response, two negative binomial and linear multivariate regression models were used. In both models, the independent variables were included in the model based on the AIC value and finally, the significant variables remained in the model. On this basis, variables of the mother's age, AMH, and the natural logarithm of AMH remained in the linear regression model. The highest coefficient rate of the R-square relates to the natural logarithm of AMH, which could elaborate 24% of the changes in the ovarian reserve in the model. AMH and age of the women have been considered responsible for 4% and 2.5% of the changes. Variance Inflation Factor (VIF) below 5 for the variables indicates the weak collinearity. In the negative binomial model, both variables of AMH and normal logarithm of AMH remained in the model, with the difference being that the *P*-value of AMH in the negative binomial model is significantly lower than that of the linear regression model (Table 2). The Penalized B-spline regression model in Figure 1 also shows predictability of the ovarian response to the natural logarithm of AMH which first shows an increasing and then a decreasing slope.

ROC and Cut-off for both models indicate that AUC in the poor ovarian response is 0.796 and the Cutoff is 1.36 ng/ml based on the crossover of sensitivity and specificity against probability. At this point, the sensitivity and specificity of the model are 78% and 76%, respectively (Figure 2).

Table 1: Comparing the mean of the research variables in poor, normal, and excessive response groups (different letters indicate significant difference at a probability level of 0.05)

Variable	Ovarian Response		
	Poor Response (n=23)	Normal Response (n=92)	Excessive Response (n=6)
FSH (mIU/ml)	9.62(2.67^{a})	7.04(2.47^{b})	5.64(0.75^{b})
AMH (ng/ml)	1.42(1.35^{b})	2.77(2.24^{ab})	3.33(0.82^{a})
Age (y)	32.52(3.9^{a})	30.88(4.04^{a})	26.3(3.67^{b})
BMI (kg/m^2)	23.83(1.85^{a})	25.32(5.27^{a})	25.5(4.46^{a})

FSH: Follicle Stimulating Hormone, AMH: Anti-Mullerian Hormone, BMI: Body Mass Index

Table 2: Results of the stepwise method in the linear regression modeling and negative binomial regression model

Model	Variables	Coefficients					
		Estimate	Std. Error	Partial R-square	VIF	*P*-value	Model R-square
Multiple Regression	Age	-0.132	0.064	0.025	1.08	0.04	0.31
	AMH	-0.62	0.25	0.04	4.49	0.015	
	Ln AMH	3.47	0.71	0.244	4.63	<0.001	
	FSH	0.166	0.233	-	5.9	0.48	-
Negative Binomial Regression	AMH	-0.131	0.038	-	4.49	<0.001	-
	Log AMH	0.69	0.118		4.63	<0.001	
	FSH	0.031	0.033	-	5.9	0.35	-

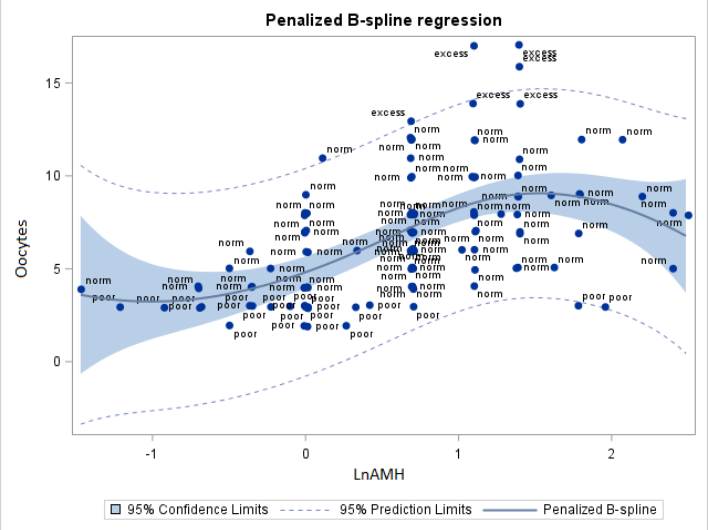


Figure 1: Penalized B-spline regression model in prediction of the ovarian response based on the natural logarithm of AMH

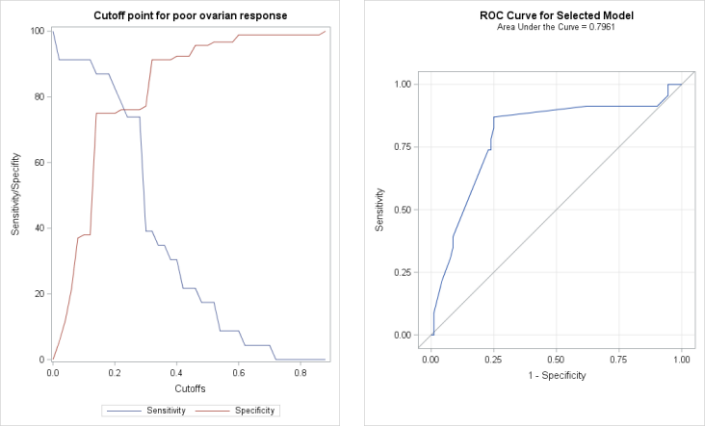


Figure 2: ROC for prediction of poor ovarian response using the AMH natural logarithm indicating a sensitivity and specificity of 78% and 76%, respectively with an optimal cut-off of 0.31 and AUC of 0.796

Discussion

The results of the current study demonstrated that every unit decrease in the log scale of AMH increased the value by 6.7% for the poor response group compared to the normal group. The optimal cut-off point of AMH for predicting poor response was 1.36 ng/ml, and the area under the ROC curve was 0.796. This finding revealed that AMH could be a useful marker to distinguish between poor ovarian response and the normal response levels with the cut-off point of 1.36 ng/ml of AMH blood levels with an area under the curve of 80%. The result of the negative binomial regression model demonstrated that one unit increase in the log of AMH blood levels increased the odds of releasing an oocyte by 50%.

Besides, based on the negative binomial regression model, FSH has a significant effect on the response so that every unit of increase in FSH increases the odds of a single response unit by 3%. Therefore, FSH levels had a significant effect on the number and quality of fertile oocytes. In most assisted reproductive procedures, basal FSH levels are often used as prognostic factors for ovarian function.

Different studies have investigated the correlation between AMH and FSH levels and the quality and number of oocytes in fertile and infertile women. Some of these studies will be reviewed to study the correlation between these two hormones and the quality of ovulation in women.

In women of reproductive age, the granulosa cells of the prenatal and small antral follicles are responsible for AMH secretion. As mentioned previously, AMH regulates ovarian response and follicular steroidogenesis. Hence, AMH can be used as a valuable predictor of ovarian response [24]. In a study conducted by Xiao-dong et al. [24] evaluating the levels of AMH in women of reproductive age, all participants were divided into three groups based on their age: Group A (24-30 years), group B (31-35 years) and group C (36-41 years). The study showed a negative correlation between age and AMH (r=-0.416, $P<0.05$), so that the AMH serum levels in women of older childbearing age are lower (2.10 (1.61)) than the women of middle childbearing age (3.52 (2.17)) and women of lower childbearing age (5.81 (3.98)). Another valuable result of this included that the number of infertile women with lower AMH serum levels (<1.1 ng/mL) was significantly higher than that of the fertile women *(*$P<0.05$) [24].

There were some methods for ovarian stimulation before IVF in infertile women [25]. GnRH agonist long protocol is one of these approaches used for evaluating the ovarian response and decreasing the potential bias in a study on the Iranian infertile women. In this study, Heidar et al. [26] evaluated ovarian stimulation using AMH serum levels. A positive pregnancy test was found in 30 % of patients. One unit increase in the AMH log scale has led to a 64% decrease in the odds ratio of having a poor response in comparison with the normal response (OR 0.36, 95% CI 0.19–0.68). Besides, every unit increase in the AMH log scale increased the odds of releasing an oocyte by 24% (OR 1.24, 95 % CI 1.14–1.35) [26].

A study by Aydın et al. [27] in patients undergoing ICSI showed that all women received the long protocol. The results yielded that 32 women had a good response (72.7%) and 12 women had poor responses (27.3%) and the serum level of AMH in poor and good responses group was significantly different ($P<0.01$). To evaluate the cut-off point of AMH, ROC analysis was used, demonstrating that the cut-off point of AMH was 1.90 ng/ml and women with good response had higher AMH serum levels (>1.90 ng/ml). Also, the age of patients with >1.90 ng/ml AMH serum levels was lower (31.47 (3.77)) than that of patients with <1.90 ng/ml AMH serum levels (33.67 (3.93)); but this difference was not significant ($P=0.09$) [27]. Our results show that AMH can be an applicable predictor of the number of oocytes.

The predictive role of FSH and LH serum levels on the third day of the menstrual cycle was demonstrated in Iranian women undergoing ART. According to the results, there is a significant correlation between FSH serum levels and the number of oocytes ($P=0.041$), the number of metaphase II oocytes ($P=0.049$), and pregnancy ($P=0.017$) but the optimum effect was found in patients with FSH: 10-15 miu/Ml. Besides, there was no significant correlation between LH serum levels and the mentioned variables, but optimum effects were observed in patients with LH ≥ 8 [28].

Applicability of FSH and AMH were independently demonstrated in different studies for the evaluation of IVF success, while some others evaluated the discordant and concordant combinations of AMH and FSH measurements to predict ovarian responses in women undergoing ART. Buyuk et al. [29] evaluated the correlation between AMH and ovarian responses in women with elevated early follicular FSH levels. Results of the study found a significant correlation between AMH serum levels and the number of retrieved oocytes (r=0.55). Patients with ≥0.6 ng/mL AMH serum levels had 11 (1.3) retrieved oocytes, while patients with ≤0.6 ng/mL AMH serum levels had 5.6 (0.6) retrieved oocytes. There is no significant correlation between AMH serum levels and the age of participants. Besides, clinical pregnancy in patients with ≥0.6 ng/mL AMH serum levels was insignificantly higher than that among women with ≥0.6 ng/mL serum levels (28% vs. 14%), ($P=0.1$) [29].

Ligon et al. [30] evaluated discordant and concordant values of AMH and FSH on live birth rate and IVF cycle cancellation rate. The live birth rate of patients with normal AMH and elevated FSH was higher than those of patients with low AMH and normal FSH (39% vs. 26%). The live birth rate in patients with normal AMH and normal FSH (concordant) was higher than in any other group (44%). Besides, the IVF cycle cancellation rate in patients with normal AMH and FSH was lower than that of other groups (4%) and this rate was higher in patients with elevated FSH and low AMH compared to other groups (30%) [30].

Limitations

The main limitation of our study is the low number of patients. Retrospective design analyses are among other limitations of this study. Further studies with larger patient cohort are needed to derive conclusions supported by statistical analysis.

Conclusion

Our study results and other reviewed studies show that there is a significant correlation between AMH serum levels and the quality of ovarian responses (particularly the number and quality of oocytes). The rate of FSH varies in distinct groups of ovarian response and there is a significant relationship between FSH and ovarian response rate but predicting ovarian response rate using FSH was not successful. Besides, AMH levels vary in different groups of ovarian responses, and there is a significant relationship between AMH and ovarian response. AMH can be used to predict poor ovarian response. The age of women, despite having significant differences in different groups of ovarian responses, has not been successful in predicting poor ovarian responses.

FSH level is not a good predictor of poor ovarian response. Also, it is not possible to correctly predict ovarian reserve. Therefore, further studies should be conducted on both FSH and AMH variables and age classification to evaluate the ovarian responses in infertile patients.

References

1. Sonaliya KN. Infertility: Ongoing Global challenge of new millennium. Indian Journal of Community Health. 2016;28(2):113-5.
2. Bell AV. Beyond (financial) accessibility: inequalities within the medicalisation of infertility. Sociology of health & illness. 2010;32(4):631-46.
3. Petraglia F, Serour GI, Chapron C. The changing prevalence of infertility. International Journal of Gynecology & Obstetrics. 2013;123:4-8.
4. Vander Borght M, Wyns C. Fertility and infertility: Definition and epidemiology. Clinical biochemistry. 2018;62:2-10.
5. Barbieri RL. Female infertility. Yen and Jaffe's Reproductive Endocrinology: Elsevier; 2019;7:556-81.
6. Elder K, Dale B. In-vitro fertilization: Cambridge University Press; 2000;1-30.
7. Ubaldi F, Vaiarelli A, D'Anna R, Rienzi L. Management of poor responders in IVF: is there anything new? BioMed research international. 2014;20:146.

8. Jirge PR, Chougule SM, Gavali VG, Bhomkar DA. Impact of dehydroepiandrosterone on clinical outcome in poor responders: a pilot study in women undergoing in vitro fertilization, using bologna criteria. Journal of human reproductive sciences. 2014;7(3):175.
9. Balaban B, Urman B. Effect of oocyte morphology on embryo development and implantation. Reproductive biomedicine online. 2006;12(5):608-15.
10. Templeton A, Morris JK. Reducing the risk of multiple births by transfer of two embryos after in vitro fertilization. New England Journal of Medicine. 1998;339(9):573-7.
11. Russell JB, Knezevich KM, Fabian KF, Dickson JA. Unstimulated immature oocyte retrieval: early versus midfollicular endometrial priming. Fertility and sterility. 1997;67(4):616-20.
12. Matter H, Talansky B, Gordon J, Cohen J. Monospermy and polyspermy after partial zona dissection of reinseminated human oocytes. Gamete research. 1989;23(4):377-86.
13. Nakahara K, Saito H, Saito T, Ito M, Ohta N, Sakai N, et al. Incidence of apoptotic bodies in membrana granulosa of the patients participating in an in vitro fertilization program. Fertility and sterility. 1997;67(2):302-8.
14. Chen Q, Wang Y, Sun L, Zhang S, Chai W, Hong Q, et al. Controlled ovulation of the dominant follicle using progestin in minimal stimulation in poor responders. Reproductive Biology and Endocrinology. 2017;15(1):71.
15. Ben-Ze'ev A, Amsterdam A. Regulation of cytoskeletal proteins involved in cell contact formation during differentiation of granulosa cells on extracellular matrix. Proceedings of the National Academy of Sciences. 1986;83(9):2894-8.
16. Chang M-Y, Chiang C-H, T'sang-T'ang Hsieh M, Soong Y-K, Hsu K-H. Use of the antral follicle count to predict the outcome of assisted reproductive technologies. Fertility and Sterility. 1998;69(3):505-10.
17. Yassin MM, Sharif FA, Laqqan MM. Anti-mullerian hormone as a predictor of ovarian reserve and ovarian response in IVF women from Gaza strip. Iranian Journal of reproductive medicine. 2013;11(4):261.
18. Lin P-Y, Huang F-J, Kung F-T, Chiang H-J, Lin Y-J, Lin Y-C, et al. Evaluation of serum anti-Mullerian hormone as a biomarker of early ovarian aging in young women undergoing IVF/ICSI cycle. International journal of clinical and experimental pathology. 2014;7(9):6245.
19. Chang HJ, Han SH, Lee JR, Jee BC, Lee BI, Suh CS, et al. Impact of laparoscopic cystectomy on ovarian reserve: serial changes of serum anti-Müllerian hormone levels. Fertility and sterility. 2010;94(1):343-9.
20. Singh N, Malik E, Banerjee A, Chosdol K, Sreenivas V, Mittal S. "Anti-Mullerian Hormone: Marker for Ovarian Response in Controlled Ovarian Stimulation for IVF Patients": A First Pilot Study in the Indian Population. The Journal of Obstetrics and Gynecology of India. 2013;63(4):268-72.
21. Li HWR, Wong CYG, Yeung WSB, Ho PC, Ng EHY. Serum anti-müllerian hormone level is not altered in women using hormonal contraceptives. Contraception. 2011;83(6):582-5.
22. Scott RT, Toner JP, Muasher SJ, Oehninger S, Robinson S, Rosenwaks Z. Follicle-stimulating hormone levels on cycle day 3 are predictive of in vitro fertilization outcome. Fertility and sterility. 1989;51(4):651-4.
23. Muasher SJ. Treatment of low responders. Journal of assisted reproduction and genetics. 1993;10(2):112-4.
24. Xiao-dong M, Yi Z, Ya-jun C, Kang-sheng L. Detection of Serum Anti-Müllerian Hormone Level for Women of Reproductive Age: A Cross-Sectional Study. Journal of International Translational Medicine. 2017;5(2):67-70.
25. Kucuk T, Kozinoglu H, Kaba A. Growth hormone co-treatment within a GnRH agonist long protocol in patients with poor ovarian response: a prospective, randomized, clinical trial. Journal of assisted reproduction and genetics. 2008;25(4):123-7.
26. Heidar Z, Bakhtiyari M, Mirzamoradi M, Zadehmodarres S, Sarfjoo F, Mansournia M. Prediction of different ovarian responses using anti-Müllerian hormone following a long agonist treatment protocol for IVF. Journal of endocrinological investigation. 2015;38(9):1007-15.
27. Aydın GA, Yavuz A, Terzi H, Kutlu T. Assessment of the relationship of basal serum anti-mullerian hormone levels with oocyte quality and pregnancy outcomes in patients undergoing ICSI. Iranian Journal of reproductive medicine. 2015;13(4):231.
28. Erfanian Ahmadpoor M, Saraf Razavi M, Afsharnejad S, Mansouri Torshizi M. Studying the FSH and LH Hormones in The Cycle Third Day and Its Effect On the Number and Quality of Oocytes Among the Infertile Women as Candidate for Assisted Reproductive Technology Cycle. Mashhad Journal of Medical Sciences. 2009;5;1-17.
29. Buyuk E, Seifer DB, Younger J, Grazi RV, Lieman H. Random anti-Müllerian hormone (AMH) is a predictor of ovarian response in women with elevated baseline early follicular follicle-stimulating hormone levels. Fertility and sterility. 2011;95(7):2369-72.
30. Ligon S, Lustik M, Levy G, Pier B. Low antimüllerian hormone (AMH) is associated with decreased live birth after in vitro fertilization when follicle-stimulating hormone and AMH are discordant. Fertility and sterility. 2019;112(1):73-81.

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. 2020;4(9):738-742.
DOI: 10.28982/josam.788917

Research article
Araştırma makalesi

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

Effects of hypercaloric enteral intervention on malnutrition patients with a history of febrile seizure before the age of six

Hiperkalorik enteral müdahalenin altı yaşından önce ateşli nöbet geçmişi olan malnütrisyon hastalarına etkileri

Eda Sünnetçi Silistre [1], Özlem Özpenpe [1], Halil Uğur Hatipoğlu [1], Ali Evrim Doğan [2], Fatih Özdener [3]

[1] University of Health Sciences, Istanbul Research and Training Hospital, Department of Pediatric Health and Diseases, Istanbul, Turkey
[2] Nutricia, Advanced Medical Nutrition, Medical Department, Istanbul, Turkey
[3] Bahcesehir University, School of Medicine, Department of Pharmacology, Istanbul, Turkey

ORCID ID of the author(s)

ESS: 0000-0003-0450-0152
ÖÖ: 0000-0002-6137-5936
HUH: 0000-0002-7393-677X
AED: 0000-0002-9040-2737
FÖ: 0000-0002-0163-318X

Corresponding author/Sorumlu yazar:
Eda Sünnetçi Silistre
Address/Adres: Sağlık Bilimleri Üniversitesi, İstanbul Eğitim ve Araştırma Hastanesi Çocuk Sağlığı ve Hastalıkları Kliniği Kasap İlyas mah. Abdurrahman Nafiz Gürman cad. Etyemez-Samatya, İstanbul, Türkiye
E-mail: edasunnetci@gmail.com

Ethics Committee Approval: This study was approved by the ethics committee of University of Health Sciences, Istanbul Research and Training Hospital, Istanbul on 2/7/2020 at session number 2180. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma 07.02.2020 tarihinde 2180 numaralı oturumda İstanbul Sağlık Bilimleri Üniversitesi İstanbul Eğitim ve Araştırma Hastanesi etik kurulu tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/24/2020
Yayın Tarihi: 24.09.2020

Abstract

Aim: Febrile seizure is the most prevalent (~5%) convulsion in children between 3 to 60 months of age and has been related to iron deficiency. Thus, when it is combined with malnutrition, it may increase negative outcomes. In this study, we present the effects of hypercaloric (1.5 kcal/mL) nutritional intervention on undernourished children with a history of febrile convulsions prior to the age of 6.
Methods: A cohort of 44 patients between ages 1-6 years with a history of a febrile seizure was included in the study. Hypercaloric nutritional intervention was applied to all patients. Baseline patient records containing anthropometrical and micronutrient measurements were compared with the 3rd month and the 6th month visits. All patient records were retrospectively obtained from Istanbul Research and Training Hospital, İstanbul, Turkey.
Results: There were significant improvements in the z-scores of weight (P=0.002) and body mass index (P<0.001). Approximately 50% of iron and 25-hydroxyvitamin D3 (25D3) deficient patients were cured and their serum concentrations increased significantly (P<0.001 for both). Treatment did not affect iron concentrations in patients without iron deficiency (P=0.074). Normal concentrations of 25D3, folate, and vitamin B12 improved inside the optimal micronutrient ranges without toxicity.
Conclusion: Overall, hypercaloric nutritional intervention abated iron and 25D3 deficiency and significantly improved the z-scores of BMI and weight in malnourished pediatric patients under the age of 6 with a history of febrile seizures without toxicity.
Keywords: Febrile seizure, Malnutrition, Micronutrients, Body mass index, Enteral nutrition

Öz

Amaç: Ateşli nöbet en yaygın olarak 3 ila 60 aylık çocuklarda görülen (~% 5) ve demir eksikliği ile ilişkilendirilen bir konvülsiyondur. Bu nedenle, yetersiz beslenme ateşli nöbetin olumsuz sonuçlarını artırabilir. Bu çalışmada, 6 yaşından önce ateşli konvülsiyon öyküsü olan yetersiz beslenen çocuklarda hiperkalorik (1,5 kcal/mL) beslenme müdahalesinin etkilerini sunulmaktadır.
Yöntemler: Çalışma kohortu ateşli nöbet öyküsü olan 1-6 yaş arası 44 hastadan oluşmakta olup, tüm hastalara hiperkalorik beslenme müdahalesi uygulanmıştır. Hastaların ilk başvuruları sırasında kaydedilen antropometrik değerler ve mikronütrient ölçümleri, 3. ay ve 6. ay vizitleri ile karşılaştırılmıştır. Tüm hasta kayıtları, İstanbul, Türkiye İstanbul Eğitim ve Araştırma Hastanesi'nden geriye dönük olarak alınmıştır.
Bulgular: Müdahale sonrasında ağırlık (P=0,002) ve vücut kitle indeksi (P<0,001) z-skorlarında anlamlı iyileşmeler görülmüştür. Demir ve 25-hidroksivitamin D3 (25D3) eksikliği olan hastaların yaklaşık% 50'si düzelme gösterirken serum konsantrasyonlarında da önemli ölçüde artış gözlemlenmiştir (her ikisi için de P<0,001). Tedavi, demir eksikliği olmayan hastalarda demir konsantrasyonlarını etkilememiştir (P=0,074). 25D3, folat ve vitamin B12 konsantrasyonları normal olan hastalarda, bu mikronütrientler herhangi bir toksisiteye neden olmaksızın optimal aralıklar içinde kalmıştır.
Sonuçlar: Hiperkalorik beslenme müdahalesi herhangi bir toksisiteye neden olmaksızın ateşli nöbet öyküsü olan 6 yaşın altındaki malnütrisyon teşhisi konulan pediatrik hastalarda demir ve 25D3 eksikliğini azaltmıştır ve vücut kitle indeksi ile ağırlık z-skorlarını anlamlı ölçüde düzeltmiştir.
Anahtar kelimeler: Ateşli nöbet, Yetersiz beslenme, Mikronütrientler, Vücut kitle indeksi, Enteral beslenme

How to cite/Atıf için: Silistre ES, Özpenpe Ö, Hatipoğlu HU, Doğan AE, Özdener F. Effects of hypercaloric enteral intervention on malnutrition patients with a history of febrile seizure before the age of six. J Surg Med. 2020;4(9):738-742.

Introduction

Febrile seizures are often seen in children with a fever higher than 38°C, who are older than 3-6 months but younger than 6 years of age. They most frequently occur between the 12th and 18th months. It is the most prevalent neurologic disorder, affecting 2% to 5% of all children between 3 to 60 months of age. Additionally, due to its high (30% to 40%) risk of reoccurrence before the age of five, febrile seizures are one of the most familiar conditions in pediatrics [1].

The brain loses its excitability over time. Thus, the threshold of the developing brain for generating a seizure in children is relatively low when compared to the adult brain. However, the resistance of the developing brain to excitation stress is higher, which makes early age febrile seizures mostly benign [2]. Secretion of pyrogenic cytokines inside the CNS and temperature-dependent ion channels are related to increased neural excitation during high fever [3,4]. Although the exact mechanism is unknown, iron deficiency may play an indirect role in brain excitation during fever by lowering the seizure threshold in the developing brain. Moreover, fever may exacerbate the effects of an iron deficiency [5].

Iron deficiency is significantly related to febrile seizures in numerous studies as children with iron and ferritin deficiencies (<22 ng/dl and <30 ng/ml respectively) have an approximately three-fold increased tendency to develop a febrile seizure compared to children without iron deficiency. Additionally, iron and ferritin deficiencies have been correlated with increased probability of developing a febrile seizure [6]. It has been found that 42.9 of 737 children who were hospitalized by having seizure had iron deficiency [7]. Iron is a valuable element for achieving homeostasis in multiple organs by regulating various cellular physiological events, such as DNA synthesis, respiration, differentiation, energy balance, and growth [8]. In the brain, iron has important roles in neurotransmitter functionality, metabolism, and myelin formation [5].

Nutritional interventions are the primary treatment widely applied in malnutrition of children as well adults. In children, an early intervention against malnutrition is crucial due to the exaggerated effects of malnutrition on metabolism and development directly proportional to time [9]. In this retrospective study, we performed a comparative analysis between baseline and follow-up measurements of anthropometric scores and micronutrient (Iron, vitamin B12, folate, and 25D3) concentrations in the presence of hypercaloric nutritional intervention on malnourished patients having a history of febrile seizure.

Materials and methods

Sample

This study included 44 pediatric outpatients between the ages of 1-6 years with a history of a febrile seizure with at least 1 incidence. Additionally, same patients were classified as malnourished by a physician due to their weight scores being under 10 weight percentiles at the first presentation to the hospital. Our exclusion criteria consisted of having a chronic disease, an infectious disease, and having been prescribed vitamin or mineral supplements. This is a retrospective single-centered study and all patient records were obtained from Istanbul Research and Training Hospital, İstanbul, Turkey. The authors state that the study protocol was approved by the ethics committee of University of Health Sciences, Istanbul Research and Training Hospital, Istanbul on 2/7/2020 at session number 2180.

Observation

The biochemical and anthropometrical effects of hypercaloric (1.5 kcal/mL) enteral nutrition were investigated on a cohort of 44 malnutrition patients who had a febrile seizure history. Our hypercaloric supplement includes 1.5 kcal mL^{-1} of energy, 9% protein, 40% fat, 37.6% carbohydrates, 2% dietary fiber, 64 mg of sodium, 153 mg of potassium, and 84 mg of calcium. The three-layered comparative analysis was conducted by retrospectively obtaining the patient records of measurements taken at the first presentation to the hospital and at the 3^{rd} and 6^{th} months. To assess the effects of the hypercaloric intervention, weight z-scores, height z-scores, and body mass index (BMI) z-scores as well as laboratory findings covering iron, vitamin B12, folate, and 25D3 were compared. Additionally, a more detailed analysis was made by separately assessing the effects of the hypercaloric intervention on patients with and without micronutrient deficiency. Tolerability, indications, contraindications, and compatibility to the treatment of the hypercaloric enteral intervention will later be discussed in the study.

Standardization of weight, height, body mass index scores, and micronutrient reference ranges

Weight, height, and BMI reference values of the population in Turkey were taken from the referred study completed in 2008 [10]. Z-score calculations were obtained via growth references and blood pressure calculation tools indicated in the referred study [11]. Micronutrient reference ranges were as follows: 60-120 ug/dL for iron, 20-100 ng/mL for 25D3, 5-21 ng/mL for folate, and 145-914 pg/mL for vitamin B12.

Ethical Statement

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the ethics committee of University of Health Sciences, Istanbul Research and Training Hospital, Istanbul on 07/02/2020 at session number 2180. The authors state that they have obtained the required informed patient consents regarding the study.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v20.0 (IBM Corp., Armonk, NY, US). The normality of the data was tested via the Shapiro-Wilk test. Repeated measures of ANOVA followed by Wilks' lambda were utilized as a multivariate test for parametric data. Bonferroni correction with the significance of $P<0.05$ was utilized as a post hoc test during repeated ANOVA tests. Friedman's test was utilized to analyze non-parametric dependent datasets. The level of statistical significance was set at $P<0.05$.

Results

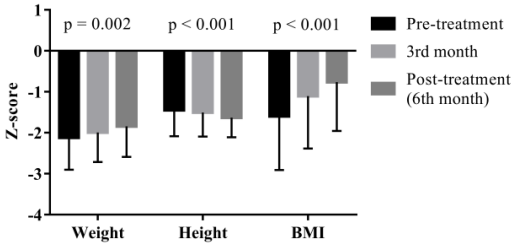
Demographic information of our cohort included in the study is presented in Table 1. Our cohort includes 44 participants between the ages of 1-6 years with the mean age of 3.64 years. It

included 14 (31.8%) male and 30 (68.2%) female participants. All patients were intervened with hypercaloric (1.5 kcal/mL) enteral supplement after their first presentation to the hospital.

Detailed information of pre-treatment and post-treatment anthropometrical statuses are given in Table 1. The nutritional intervention yielded significant improvements in weight z-scores and BMI z-scores (P=0.002 and P<0.001 respectively) (Figure 1). Mean weight z-scores improved from -2.1 (0.79) to -1.91 (0.68) and -1.7 (0.64) at the 3rd and the 6th months of treatment, respectively. Similarly, BMI z-scores improved from -1.53 (1.32) to -1 (1.23) and -0.67 (1.18) at the 3rd and the 6th month of treatment, respectively. On the contrary, height z-scores significantly deteriorated (P<0.001) from -1.45 (0.57) to -1.51 (0.53) and -1.6 (0.46) at the 3rd and the 6th month of treatment, respectively (Figure 1).

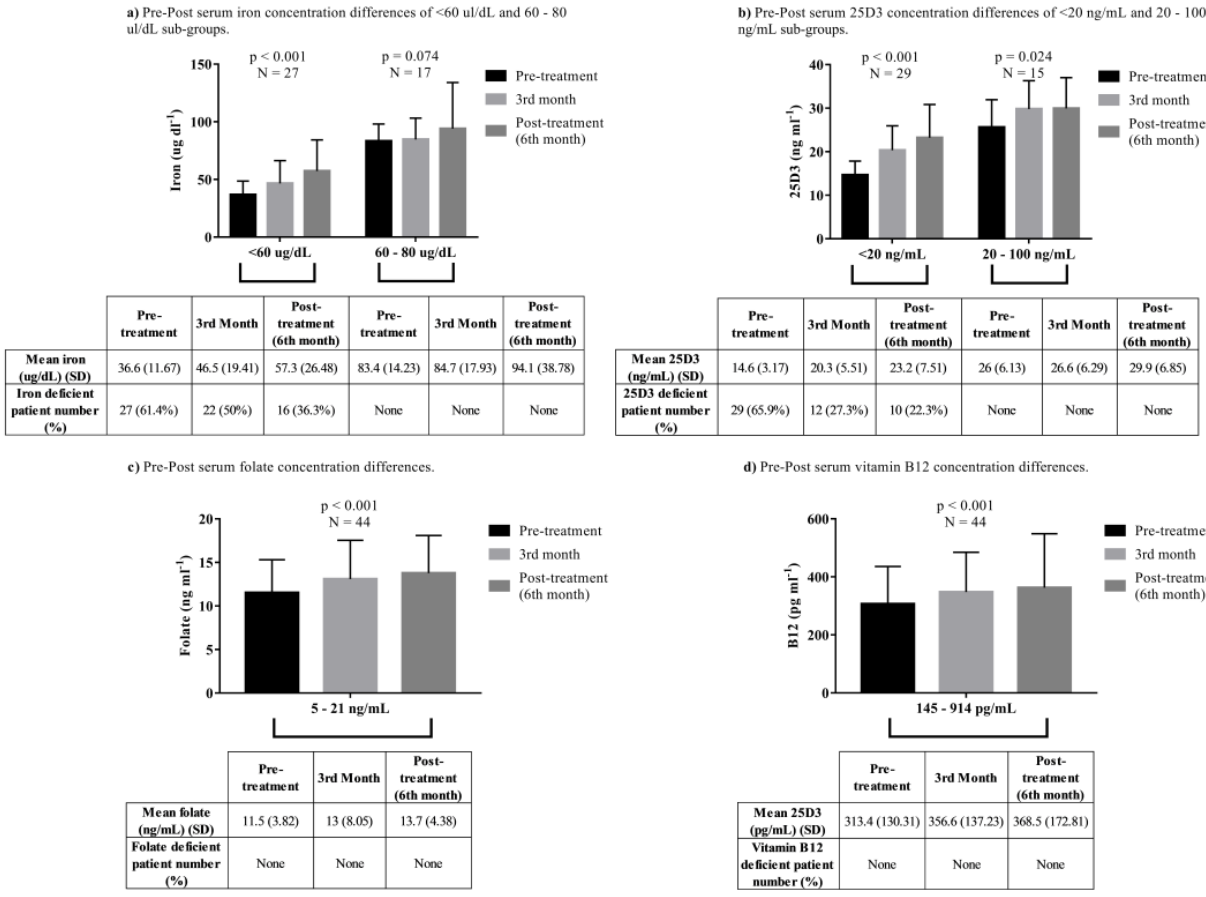
Detailed information of pre-treatment and post-treatment micronutrient status are presented in Tables 2 and 3. In iron deficient (< 60 ug/dL) patients, there was a significant (P<0.001) overall increase (Figure 2a). Mean iron concentrations of iron deficient patients increased from 36.6 (11.67) ug/dL to 46.5 (19.41) ug/dL and 57.3 (26.48) ug/dL at the 3rd and the 6th month of treatment, respectively, thus reducing the number of iron deficient patients from 27 (61.4%) to 22 (50%) and 16 (36.3%). On the contrary, there was no significant difference (P=0.074) in iron concentrations of patients without an iron deficiency (60-120 ug/dL). Mean iron concentrations of patients without an iron deficiency were as follows: 83.4 (14.23) ug/dL for baseline, 84.7 (17.93) ug/dL in the 3rd month and 94.1 (38.78) in the 6th month. None of the patients exceeded the 120 ug/dL upper limit for serum iron concentration.

Both 25D3 deficient (<20 ng/mL) and non-25D3 deficient (20-100 ng/mL) patients showed a significant increment (P<0.001 and P=0.024 respectively) over a duration of 6 months (Figure 2b). Mean 25D3 concentrations of 25D3 deficient patients increased from 14.6 (3.17) ng/mL to 20.3 (5.51) ng/mL and 23.2 (7.51) ng/mL at the 3rd and the 6th months of treatment, respectively. The number of 25D3 deficient patients reduced from 29 (65.9%) to 12 (27.3%) and 10 (22.3%) at the 3rd and the 6th month of treatment, respectively. Mean 25D3 concentrations of patients without 25D3 deficiency were as follows: 26 (6.13) ng/mL at baseline, 26.6 (6.29) ng/mL at the 3rd month and 29.9 (6.85) at the 6th month, and none of the patients exceeded 100 ng/mL upper limit for serum 25D3 concentration.



	Pre-treatment	3rd Month	Post-treatment (6th month)	Post - Pre z-score difference (Improvement / Deterioration
Mean weight z-score (SD)	-2.1 (0.79)	-1.91 (0.68)	-1.7 (0.64)	0.4 (Improvement)
Mean height z-score (SD)	-1.45 (0.57)	-1.51 (0.53)	-1.6 (0.46)	-0.15 (Deterioration)
Mean BMI z-score (SD)	-1.53 (1.32)	-1 (1.23)	-0.67 (1.18)	0.86 (Improvement)

Figure 1: Anthropometrical status of patients at pre-treatment compared with post-treatment. Respective P-values were indicated on the graph and mean z-scores of all visits were indicated in the merged table along with the mean difference between pre- and post-treatment.



	Pre-treatment	3rd Month	Post-treatment (6th month)	Pre-treatment	3rd Month	Post-treatment (6th month)
Mean iron (ug/dL) (SD)	36.6 (11.67)	46.5 (19.41)	57.3 (26.48)	83.4 (14.23)	84.7 (17.93)	94.1 (38.78)
Iron deficient patient number (%)	27 (61.4%)	22 (50%)	16 (36.3%)	None	None	None

	Pre-treatment	3rd Month	Post-treatment (6th month)	Pre-treatment	3rd Month	Post-treatment (6th month)
Mean 25D3 (ng/mL) (SD)	14.6 (3.17)	20.3 (5.51)	23.2 (7.51)	26 (6.13)	26.6 (6.29)	29.9 (6.85)
25D3 deficient patient number (%)	29 (65.9%)	12 (27.3%)	10 (22.3%)	None	None	None

	Pre-treatment	3rd Month	Post-treatment (6th month)
Mean folate (ng/mL) (SD)	11.5 (3.82)	13 (8.05)	13.7 (4.38)
Folate deficient patient number (%)	None	None	None

	Pre-treatment	3rd Month	Post-treatment (6th month)
Mean 25D3 (pg/mL) (SD)	313.4 (130.31)	356.6 (137.23)	368.5 (172.81)
Vitamin B12 deficient patient number (%)	None	None	None

Figure 2: Micronutrient status of patients with insufficient and normal concentrations at pre-treatment compared with post-treatment. Respective P-values were indicated on the graph and mean z-scores of all visits were indicated in the merged table along with the number of patients with deficiencies at the related visit.

There were not any folate nor vitamin B12 deficient patients at baseline as well as at the post-treatment measurement. However, there was a significant increment (P<0.001 for folate and P<0.001 for vitamin b12) in both micronutrient concentrations without exceeding their upper limits (>21 ng/mL for folate and >914 pg/mL for vitamin B12) (Figure 2c and 2d respectively). Mean folate concentrations increased from 11.5 (3.82) ng/mL to 13 (8.05) ng/mL and 13.7 (4.38) ng/mL at the 3rd and the 6th months of treatment, respectively, while Vitamin B12 concentrations increased from 313.4 (130.31) pg/mL to 356.6 (137.23) pg/mL and 368.5 (172.81) pg/mL.

In addition, the hypercaloric enteral supplementation was well-tolerated among the majority of our patients (72.9%, n=35). Six patients (12.5%) had distension, 3 patients vomited (6.3%), and 4 patients (8.3%) had not tolerated the nutritional intervention at the 6th month after the initial intervention.

Table 1: Pre-treatment and post-treatment mean anthropometrical z-scores of the patients, mean differences and significances

		Total	Males	Females
Pre-treatment	Mean weight z-score (SD)	-2.1 (0.79)	-2.01 (1.08)	-2.08 (0.60)
	Mean height z-score (SD)	-1.45 (0.57)	-1.43 (0.54)	-1.45 (0.48)
	Mean BMI z-score (SD)	-1.53 (1.32)	-1.19 (0.98)	-1.69 (1.42)
Post-treatment (6th month)	Mean weight z-score (SD)	-1.7 (0.64)	-1.7 (0.71)	-1.8 (0.61)
	Mean height z-score (SD)	-1.6 (0.46)	-1.56 (0.51)	-1.61 (0.44)
	Mean BMI z-score (SD)	-0.67 (1.18)	-0.3 (0.74)	-0.85 (1.30)
Mean difference (post - pre)	Weight z-score	0.4	0.31	0.28
	Height z-score	-0.15	-0.13	-0.16
	BMI z-score	0.86	0.89	0.84
P-values	Weight z-score	0.002 Improvement		
	Height z-score	<0.001 Deterioration		
	BMI z-score	<0.001 Improvement		

BMI: Body mass index, SD: Standard deviation

Table 2: Pre-treatment mean serum micronutrient status of the patients and respective demographic distributions

		Mean age (SD)	Number of patients (%)	Mean serum concentration (SD)
Serum micronutrient concentrations	Concentration range sub-groups	Males Females Total	Males Females Total	Males Females Total
Iron	< 60 ug/dL	3.3 (1.47) 3.4 (1.35) 3.4 (1.39)	8 (57.1%) 19 (63.3%) 27 (61.4%)	59.64 (14.57) 37.2 (10.14) 36.6 (11.67)
	60-120 ug/dL	3.6 (1.49) 3.5 (1.01) 3.5 (1.21)	6 (42.9%) 11 (36.6%) 17 (38.6%)	92.3 (7.06) 78.5 (14.76) 83.4 (14.23)
	> 120 ug/dL	None	None	None
25D3	< 20 ng/mL	3.7 (1.56) 4.2 (1.42) 4 (1.48)	9 (64.3%) 20 (45.5%) 29 (65.9%)	14.5 (3.08) 14.7 (3.20) 14.6 (3.17)
	20-100 ng/mL	3.5 (1.73) 3.2 (1.18) 3.3 (1.4)	5 (35.7%) 10 (22.3%) 15 (34.1%)	22.8 (2.78) 27 (6.83) 26 (6.13)
	> 100 ng/mL	None	None	None
Folate	< 5 ng/mL	None	None	None
	5-21 ng/mL	3.6 (1.62) 3.9 (1.44) 3.8 (1.51)	14 (100%) 30 (100%) 44 (100%)	12.3 (3.92) 11 (3.71) 11.5 (3.82)
	> 21 ng/mL	None	None	None
Vitamin B12	< 145 pg/mL	None	None	None
	145-914 pg/mL	3.6 (1.62) 3.9 (1.44) 3.8 (1.51)	14 (100%) 30 (100%) 44 (100%)	268.9 (84.46) 334.2 (142.19) 313.4 (130.31)
	> 914 pg/mL	None	None	None

25D3: 25-Hyrdoxyvitamin D3, SD: Standard deviation

Table 3: Post-treatment mean micronutrient status of the patients and respective demographic distributions

		Mean age (SD)	Number of patients (%)	Mean serum concentration* (SD)
Serum micronutrient concentrations	Concentration range sub-groups	Males Females Total	Males Females Total	Males Females Total
Iron	< 60 ug/dL	3.6 (1.88) 4.2 (1.54) 4 (1.70)	6 (42.9%) 10 (33.3%) 16 (36.3%)	52.8 (31.8) 59.3 (23.62) 57.3 (26.48)
	60-120 ug/dL	3.6 (1.41) 3.7 (1.35) 3.7 (1.37)	8 (57.1%) 20 (66.7%) 28 (63.6%)	108.8 (51.64) 86 (26.18) 90.9 (31.26)
	> 120 ug/dL	None	None	None
25D3	< 20 ng/mL	5 (0.82) 4.9 (1.36) 4.9 (1.22)	3 (21.4%) 7 (23.3%) 10 (22.3%)	26.2 (9.34) 21.9 (6.04) 23.2 (7.51)
	20-100 ng/mL	3.2 (1.59) 3.6 (1.32) 3.5 (1.42)	11 (78.6%) 23 (76.7%) 34 (77.3%)	31 (8.60) 29.4 (5.70) 28.3 (6.87)
	> 100 ng/mL	None	None	None
Folate	< 5 ng/mL	None	None	None
	5-21 ng/mL	3.6 (1.62) 3.9 (1.44) 3.8 (1.51)	14 (100%) 30 (100%) 44 (100%)	14.9 (4.02) 13.1 (4.43) 13.7 (4.38)
	> 21 ng/mL	None	None	None
Vitamin B12	< 145 pg/mL	None	None	None
	145-914 pg/mL	3.6 (1.62) 3.9 (1.44) 3.8 (1.51)	14 (100%) 30 (100%) 44 (100%)	370.6 (203.38) 367.5 (156.50) 368.5 (172.81)
	> 914 pg/mL	None	None	None

* Mean micronutrient concentrations were based on patients who belong to the related concentration range sub-groups during pre-treatment to demonstrate the mean difference. 25D3: 25-Hyrdoxyvitamin D3, SD: Standard deviation

Discussion

Febrile seizures are one of the most prevalent neurological disorder complications mostly encountered in children under the age of 6 caused by a fever above 38°C. In addition to its high reoccurrence rate (30% to 40%), it has a high prevalence rate, affecting 2% to 5% of children under the age of 5 years [1].

Various micronutrient deficiencies (MNDs) can be observed in patients with malnutrition and protein-energy malnutrition (PEM). The peak prevalence of MNDs has been observed in children under the age of five and iron is one of the most common MNDs encountered during early childhood worldwide [12]. Iron deficiency anemia is encountered in 78% of 1120 children between 6 months of age to 18 years [13], and is related with febrile seizures [5,7]. Iron deficiency caused by malnutrition may render the patient susceptible to developing a febrile seizure [13]. Additionally, vitamin D deficiency has also been found in 15% of 265 children, which requires supplementation [14]. Importance of vitamin B12 on BMI values of newborns and future risk of malnutrition has been also underlined [15]. In this study, we tried to cover both micronutrients that have been underlined as the most prevalent MNDs.

BMI is a widely accepted measurement of malnutrition according to the World Health Organization (WHO) [16]. Thus, it was considered the most important anthropometrical variable in this study to evaluate malnutrition. Weight z-scores and BMI z-scores of our patients had significantly improved over 6 months. However, although height z-scores deteriorated, none of the patients' decreased below a -2-height z-score, which is considered the threshold for being stunted by the WHO. Monitoring the same cohort for a longer duration in the presence of a nutritional intervention may or may not replace deterioration with an improvement in the case of height z-scores because of its slowness to catch-up due to the impaired bone development that

may even cause irreversible damage on the longitudinal bone growth [17].

Improving iron concentrations in malnourished children via proper nutritional intervention has been considered important in terms of preventing further febrile seizures from recurring or occurring in the first place, by increasing the upper limit of the seizure threshold [6,18]. Present findings showed significant improvements in all four micronutrients (iron, vitamin B12, folate, and 25D3), except iron concentrations of patients without iron deficiency, due to hypercaloric enteral nutritional intervention over 6 months. More specifically, there was no significant difference between pre- and post-treatment measurements of iron concentrations in patients without its deficiency. Based on this finding, we can say that hypercaloric enteral supplementation prevents unnecessary increment of iron concentration. On the contrary, mean iron concentrations of iron deficient patients significantly increased from pre-treatment to post-treatment of hypercaloric supplementation, reducing the number of iron deficient patients significantly. In the case of patients without 25D3 deficiency there was a slight difference between pre- and post-treatment values and all were within non-toxic range. Similar to iron concentration improvement, 25D3 concentrations were also significantly increased in patients with 25D3 deficiency when comparing pre-treatment with post-treatment, significantly reducing the number of 25D3 deficient patients. These results indicate the two-tailed improvement of hypercaloric intervention on iron and 25D3 deficiencies in undernourished children with a history of a febrile seizure. Hypercaloric intervention was well tolerated in our patients, as most our cohort did not show any signs of intolerability.

There were no folate and vitamin B12 deficient patients at the pre-treatment or at the post-treatment measurements. Significant increase of these micronutrients did not show any toxic results as the optimal range was preserved. In fact, both folate and vitamin B12 mean values were approximated to middle values inside their optimal range, which may be considered an improvement. Middle values inside the optimum range of these micronutrients are as follows: 13 ng/mL for folate and 529.5 pg/mL for vitamin B12.

None of the patients in our cohort encountered another febrile seizure for 6 months. It is expected that the reoccurrence rate of febrile seizure may diminish via hypercaloric treatment due to normalized iron concentrations. However, much longer monitoring with a larger cohort is required to state it for certain.

Limitations

Longer monitoring and a larger cohort is required for more certain results in the case of height z-scores due to its slowness to change and the status of the rate of febrile seizure reoccurrence after normalized serum iron concentrations.

Conclusion

Hypercaloric enteral nutritional intervention significantly improved weight z-scores and BMI z-scores of our cohort, and reduced the number of iron and 25D3 deficient patients by increasing serum concentrations while preserving, or even improving, the non-deficient values of micronutrients. Lastly, our nutritional intervention was well tolerated among many of our patients without any signs of side effects. According to our results, hypercaloric intervention is a feasible nutritional intervention that can be used to treat malnutrition in children with a history of febrile seizure due to its highly beneficial outcome and high tolerability.

References

1. Leung AK, Hon KL, Leung TN. Febrile seizures: an overview. Drugs in Context. 2018;7:212536-. doi: 10.7573/dic.212536. PubMed PMID: 30038660.
2. Holmes GL, Ben-Ari Y. The Neurobiology and Consequences of Epilepsy in the Developing Brain. Pediatr Res. 2001;49(3):320-5. doi: 10.1203/00006450-200103000-00004.
3. Dubé CM, Brewster AL, Baram TZ. Febrile seizures: mechanisms and relationship to epilepsy. Brain Dev. 2009;31(5):366-71. Epub 02/15. doi: 10.1016/j.braindev.2008.11.010. PubMed PMID: 19232478.
4. Shibasaki K, Suzuki M, Mizuno A, Tominaga M. Effects of body temperature on neural activity in the hippocampus: regulation of resting membrane potentials by transient receptor potential vanilloid 4. J Neurosci. 2007;27(7):1566-75. Epub 2007/02/16. doi: 10.1523/jneurosci.4284-06.2007. PubMed PMID: 17301165; PubMed Central PMCID: PMCPmc6673744.
5. Idro R, Gwer S, Williams TN, Otieno T, Uyoga S, Fegan G, et al. Iron deficiency and acute seizures: results from children living in rural Kenya and a meta-analysis. PLoS One. 2010;5(11):e14001-e. doi: 10.1371/journal.pone.0014001. PubMed PMID: 21103365.
6. Jang HN, Yoon HS, Lee EH. Prospective case control study of iron deficiency and the risk of febrile seizures in children in South Korea. BMC Pediatr. 2019;19(1):309. doi: 10.1186/s12887-019-1675-4.
7. Kocak O, Icagasioglu FD. Demographic and clinical characteristics of children who were hospitalized and followed due to seizures. J Surg Med. 2020;4(7):545-9. doi: 10.28982/josam.773784.
8. Ferreira A, Neves P, Gozzelino R. Multilevel Impacts of Iron in the Brain: The Cross Talk between Neurophysiological Mechanisms, Cognition, and Social Behavior. Pharmaceuticals (Basel). 2019;12(3). Epub 2019/09/01. doi: 10.3390/ph12030126. PubMed PMID: 31470556; PubMed Central PMCID: PMCPmc6789770.
9. Schoeman J, Dannhauser A, Kruger M. Malnutrition in paediatric oncology patients2010.
10. Neyzi O, Günöz H, Furman A, Bundak R, Gokcay G. Türk çocuklarinda vücut ağirliği, boy uzunluğu, baş çevresi ve vücut kitle indeksi referans değerleri. Çocuk Sağlığı ve Hastalıkları Dergisi. 2008;51.
11. Demir K, Konakci E, Ozkaya G, Kasap Demir B, Ozen S, Aydin M, et al. New Features for Child Metrics: Further Growth References and Blood Pressure Calculations. J Clin Res Pediatr Endocrinol. 2019. Epub 2019/09/03. doi: 10.4274/jcrpe.galenos.2019.2019.0127. PubMed PMID: 31475511.
12. Bailey RL, West KP, Jr., Black RE. The epidemiology of global micronutrient deficiencies. Ann Nutr Metab. 2015;66 Suppl 2:22-33. Epub 2015/06/06. doi: 10.1159/000371618. PubMed PMID: 26045325.
13. Duyuran Ö, Acıpayam C, Seringec N, Ipek S, Duyuran R. Etiology of anemia in children aged between 6 months and 18 years. J Surg Med. 2019;3(5):402-5. doi: 10.28982/josam.568900.
14. Celep G, Durmaz Z, Demir H, Erdoğan Y. Vitamin D status in infancy: What is the solution? J Surg Med. 2019;3(8):579-82. doi: 10.28982/josam.555486.
15. Unsur E, Kinas B. The relationship between maternal and neonatal vitamin B12 and folate levels, anthropometric measurements, and metabolic indicators. J Surg Med. 2020;4(1):43-7. doi: 10.28982/josam.669066.
16. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser. 1995;854:1-452. Epub 1995/01/01. PubMed PMID: 8594834.
17. Gat-Yablonski G, Phillip M. Nutritionally-induced catch-up growth. Nutrients. 2015;7(1):517-51. doi: 10.3390/nu7010517. PubMed PMID: 25594438.
18. Yousefichaijan P, Eghbali A, Rafeie M, Sharafkhah M, Zolfi M, Firouzifar M. The relationship between iron deficiency anemia and simple febrile convulsion in children. J Pediatr Neurosci. 2014;9(2):110-4. doi: 10.4103/1817-1745.139276. PubMed PMID: 25250062.

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. 2020;4(9):743-745.
DOI: 10.28982/josam.775192

Research article
Araştırma makalesi

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

Impact of oral immunonutrition on functional outcomes in patients who underwent radical prostatectomy for prostate cancer

Oral immünonütrisyonun prostat kanseri için radikal prostatektomili hastalarda fonksiyonel sonuçlar üzerindeki etkisi

Sinan Çelen [1], Yusuf Özlülerden [1]

[1] Department of Urology, Pamukkale University, Denizli, Turkey

ORCID ID of the author(s)
SÇ: 0000-0003-4309-2323
YÖ: 0000-0002-6467-0930

Corresponding author/Sorumlu yazar:
Sinan Çelen
Address/Adres: Pamukkale Üniversitesi Üroloji Anabilim Dalı, Denizli, Türkiye
E-mail: sinancelen@hotmail.com

Ethics Committee Approval: This study was approved by Pamukkale University's Clinical Research Ethics Committee (06/08/2019, 2019/14). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Pamukkale Üniversitesi Klinik Araştırmalar Etik Kurulu (06/08/2019, 2019/14) tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/27/2020
Yayın Tarihi: 27.09.2020

Abstract

Aim: The effect of oral nutritional support on prostate cancer (PCa), especially the functional outcomes, has been severely questioned. We present the results of a controlled trial to determine the effects of oral nutritional support on functional outcomes after radical prostatectomy.

Methods: This is a prospectively designed, randomized controlled trial to evaluate oncological outcomes in the initial period and functional outcomes in the third and sixth months, but the data were obtained retrospectively. Thirty-six patients who underwent laparoscopic radical prostatectomy performed by a single surgeon between October 2017 and August 2018 were included in the study. Eighteen were started on oral immunonutrition (Oral-Impact, Nestle, 3 × 237 ml per day for seven days at home) in the postoperative period for 6 months and 18 control patients received elemental nutrition support without immune-nutrition components.

Results: There were no significant differences in demographic and baseline characteristics between the groups. There was no wound infection, urinary tract infection, urinary extravasation, hem-o-lock clip migration to bladder, urinoma, or infected lymphocele after surgery in either group. Continence rates at the third and sixth months and potency rates (P=0.630, P=0.37, respectively) six months after radical prostatectomy were similar. Despite the similarity in both continence rates, they were numerically in favor of the study group.

Conclusion: Immunonutrition is associated with early recovery of stress urinary incontinence (SUI) following radical prostatectomy but there was no association between immunonutrition, postoperative morbidity or infectious complications. However, further clinical trials are needed to confirm these promising results.

Keywords: Nutrition, Prostate cancer, Urinary incontinence

Öz

Amaç: Oral beslenme desteğinin prostat kanseri (PK) üzerindeki etkisi, özellikle fonksiyonel sonuçları ciddi şekilde sorgulanmıştır. Oral beslenme desteğinin radikal prostatektomi sonrası fonksiyonel sonuçlar üzerindeki etkisini belirlemek için kontrollü bir çalışmanın sonuçlarını sunuyoruz.

Yöntemler: Bu çalışma erken dönem onkolojik sonuçlarını değerlendirmek ve ayrıca üçüncü ve altıncı aylardaki fonksiyonel sonuçları değerlendirmek için prospektif olarak tasarlanmış olup, veriler geriye dönük olarak elde edilmiş, randomize kontrollü bir çalışmadır. Çalışma için Ekim 2017 ile Ağustos 2018 tarihleri arasında tek bir cerrah tarafından laparoskopik radikal prostatektomi yapılan 36 hasta değerlendirildi. Onsekiz hastaya postoperatif dönemde 6 ay boyunca oral immünonütrisyon (Oral-Impact, Nestle, 7 gün evde 3 × 237 ml) başladı ve 18 kontrol hastasına immün beslenme bileşenleri olmayan elemental beslenme desteği verildi.

Bulgular: Gruplar arasında demografik ve başlangıç özellikleri açısından önemli bir farklılık yoktu. Her iki grupta da ameliyat sonrası yara enfeksiyonu, idrar yolu enfeksiyonu, üriner ekstravazasyon, hem-o-kilit klipsinin mesaneye göçü, ürinom veya enfekte lenfosel görülmedi. Radikal prostatektomiden altı ay sonra kontinans oranları ve potens oranları (sırasıyla P=0,630, P=0,37) benzerdi. Radikal prostatektomiden üç ay sonra kontinans oranları benzer olmasına rağmen, her ikisi de sayısal olarak çalışma grubu lehine idi.

Sonuç: İmmünonütrisyon, radikal prostatektomi sonrası stres üriner inkontinansın (SUI) erken iyileşmesi ile ilişkilidir, ancak immünonütrisyon ve postoperatif morbidite arasında ne enfeksiyöz komplikasyonlar üzerinde bir ilişki yoktur. Bununla birlikte, bu umut verici sonuçları doğrulamak için daha fazla klinik araştırmaya ihtiyaç vardır.

Anahtar kelimeler: Beslenme, Prostat kanseri, İdrar kaçırma

How to cite/Atıf için: Çelen S, Özlülerden Y. Impact of oral immunonutrition on functional outcomes in patients who underwent radical prostatectomy for prostate cancer. J Surg Med. 2020;4(9):743-745.

Introduction

Despite recent advancements in minimally invasive surgical technique, post-radical prostatectomy stress urinary incontinence (SUI), which is one of the most common and significant complications of radical prostatectomies (RP) as it strongly reduces quality of life in RP patients, is much more common. Prostate cancer databases suggest that following RP, 1% to 40% of patients complain of persistent urinary incontinence (UI) [1-5]. Recently, there have been reports that nutritional support affects postoperative infectious complications by the intake of oral nutrient preparations which enhance immune functions, such as ω-3 fatty acids, arginine, and nucleic acid [6-9]. Inflammatory mediators that have anti-inflammatory effects such as prostaglandin (PG) E3, thromboxane (TX) A2, and leukotriene (LT) 5 are derived from ω-3 fatty acids. Taking oral nutritional preparations containing prominent levels of ω-3 fatty acids could control postoperative inflammation, immunosuppression, and infections [10]. Patients receiving oral nutrient preparations had lower complication rates and shorter hospital stay lengths compared to patients receiving standard enteral diets. However, none of these studies considered the functional outcomes in prostate cancer patients. Immunonutrition after radical prostatectomy is not as prevalent as before surgeries of the esophagus, colon, and other parts of the digestive tract. However, functional outcomes after radical prostatectomy, including complications such as SUI and erectile dysfunction, may be worse. It is hypothesized that oral immunonutrition has a significant role in tissue recovery and may contribute to faster recovery of urethral sphincter structure, hence, it could be started after radical prostatectomy.

We aimed to establish whether supplying peri-operative and post-operative oral immunonutrition for prostate cancer patients undergoing radical prostatectomy was associated with reduced rates of postoperative complications and superior functional outcomes.

Materials and methods

This pilot study was designed prospectively, but the data of thirty-six patients who underwent radical prostatectomy performed by a single surgeon at the Department of Urology, Pamukkale University, between 2017 and August 2018 were collected retrospectively. All patients signed an informed consent form after the approval of the study by the Research Ethics Committee of Pamukkale University Hospital (File number: 60116787-020/53607). Thirty-six consecutive patients who underwent radical prostatectomy within six months were enrolled into the immunonutrition and control groups (n=18 in each group). The patients in the study group received Impact ® (Nestle Health Science) on the first day of surgery, up until the sixth postoperative month. Control group received elemental nutrition support without immune-nutrition components. Before the surgery, both the surgeon and the nutrition team including dietitians evaluated all patients. Demographic characteristics, clinical outcomes and functional outcomes including potency and continence rates in the third and sixth postoperative months were recorded.

Inclusion and exclusion criteria

We included patients who underwent laparoscopic radical prostatectomy for prostate cancer by a single surgeon. Patients were excluded if they had renal dysfunction (Ccr <30 ml/min), required insulin injection, were unable to take oral nutrition, had an American Society of Anesthesiologists (ASA) score >2, or severe malnutrition (loss >5% in 1 month, NRS score ≥3). We also excluded patients with a follow-up of less than 6 months and those who did not complete the immunonutrition protocol during the follow-up period.

Nutrition therapy

The patients in the study group received Impact ® (Nestle Health Science) formulation as it contains omega-3 fatty acids, arginine, nucleotides, minerals, and medium chain triglycerides up until six months after the first day of surgery per day, as recommended by various studies and the national (DGEM) and international (ESPEN) guidelines [11-13].

Statistical analysis

Kruskall–Wallis and independent samples T tests were used to compare the groups to evaluate the patient characteristics. The medians and the proportions of variables were compared. The $\chi 2$ test was used to analyze categorical variables. $P<0.05$ was considered statistically significant. The data was tested for normality of distribution. All statistical analyses were performed using SPSS version 22.0 (IBM Inc., Armonk, NY, USA).

Results

Table 1 shows the demographic and clinical characteristics of the two groups. No significant differences were found between the groups in terms of age, BMI, ASA score, nerve sparing rate, or pathological stage ($P=0.086$, $P=0.659$, $P=0.215$, $P=0.106$ and $P=0.310$, respectively). There was no wound infection, urinary tract infection, urinary extravasation, hem-o-lock clip migration to bladder, urinoma, or infected lymphocele after surgery in either group.

Table 1: Population characteristics of the two groups of patients

	Study group (Oral Impact®)	Control group	*P*-value
Age (years)	63.28 (7.43)	67.44 (6.70)	0.086
BMI	28.45 (4.07)	29.28 (6.83)	0.659
ASA	1.94 (0.540)	2.17 (0.514)	0.215
PSA ng/mL	9.94 (7.74)	10.98 (7.78)	0.692
Gleason grade			
≤6	1 (67%)	8 (44%)	0.403
7	4 (22%)	7 (39%)	
>7	2 (11%)	3 (17%)	
Pathologic stage			
pT2	6 (33%)	9 (50%)	0.310
pT3	12 (67%)	9 (50%)	
Nerve Sparing			
None	9 (50%)	14 (78%)	0.106
Unilateral	3 (17%)	0	
Bilateral	6 (33%)	4 (22%)	
Positive Surgical Margins	5 (28%)	5 (28%)	0.644
Lymph node			
Nx	9 (50%)	9 (50%)	
N0	9 (50%)	9 (50%)	
Transfusion rate	6 (33%)	1 (6%)	
Blood loss (ml)	209.44 (135.88)	170.56 (42.39)	0.254
Hospital stay (days)	4.84 (0.9)	5.33 (1.65)	0.322
Operative time (minutes)	176.83 (46.55)	179 (44.81)	0.888
Blood loss (ml)	1.66 (0.88)	1.05 (1.29)	0.105
Drainage time (days)	2.22 (0.43)	2.33 (0.49)	0.471
Duration of catheterization (days)	9.56 (1.86)	9.17 (1.1)	0.449

ASA: American Society of Anesthesiologists. BMI: Body Mass Index. PSA: Prostate-specific antigen

Table 2 shows functional and oncological outcomes. Continence rates at three and six months, along with potency rates (22% versus 11%, $P=0.371$) six months after radical

prostatectomy were similar; however, both continence rates were numerically in favor of the study group.

Table 2: Functional outcomes

	Study group (Oral Impact®)	Control Group	*P*-value
Continence rates at six months	9 (50%)	9 (50%)	0.630
Continence rates at three months	9 (50%)	5 (72%)	0.171
Potency rates at six months	4 (22%)	2 (11%)	0.371
Follow up time	12.33 (3.48)	14.17 (1.76)	0.054
PSA recurrence	0	1 (0.6)	0.5

PSA: Prostate-specific antigen

Discussion

To the best of our knowledge, this is a rare study evaluating the efficacy of immunonutrition in preventing postoperative complications and reducing incontinence after radical prostatectomy.

It is known that malnutrition is a clinical condition of multifactorial etiologies that affects surgical site infections and mortality in the postoperative period. Immunonutrition was first described to stimulate gut immune system, protecting against enteropathogen infections [14].

Senkal et al. [15] showed that immunonutrition reduced the rate of postoperative infections and wound complications. They also reported that the immunonutrition group was more cost-effective than the control group.

Evoy et al. [16] reported that arginine reduced severe sepsis, postoperative stress, and rate of postoperative infections. Bertrand et al. [17] reported that global morbidity was significantly less in patients who received immunonutrition (P=0.008); and preoperative immunonutrition before cystectomy reduced postoperative infections (P=0.008) along with paralytic ileus (0.02). Gregg et al. reported that malnourishment before cystectomy leads to higher mortality [18].

Cerantola et al. [19] showed that higher nutritional risk score in patients after major urological surgery leads to more complications. Jill et al. [20] showed that patients who received preoperative immunonutrition had lower complication rates after radical cystectomy (RC). Major abdominal surgeries induce general inflammation in all tissues.

Immunonutrition leads to better wound healing. We aimed to evaluate the effect of immunonutrition on the urethral sphincter after radical prostatectomy and whether incontinence can be reversed earlier, based on this hypothesis. The study group had reduced rates of incontinence numerically but not statically due to the small number of patients in each group. If the number of study patients was greater, grander effects regarding incontinence rate could be expected.

Limitations

This study had several limitations, first one being its retrospective nature, and the second being the small number of patients. Also, no propensity score matching was done.

Conclusion

The present findings show that immunonutrition taken postoperatively may reduce incontinence but prospective and randomized trials with more patients are needed.

References

1. Hu JC, Elkin EP, Pasta DJ, Lubeck DP, Kattan MW, Carroll PR Predicting quality of life after radical prostatectomy: results from CaPSURE. The Journal of urology. 2004;171(2):703-8.
2. Rodriguez Jr E, Skarecky DW, Ahlering TE, Post-robotic prostatectomy urinary continence: Characterization of perfect continence versus occasional dribbling in pad-free men. Urology. 2006;67:785-8.
3. Krupski TL, Saigal CS, Litwin MS. Variation in continence and potency by definition. J Urol. 2003;170:1291-94.
4. Olsson LE, Salomon L, Nadu A, Hoznek A, Cicco A, Saint F, et al. Prospective patient-reported continence after laparoscopic radical prostatectomy. Urology. 2001;58:570-2.
5. Penson DF, McLerran D, Feng Z, Li L, Albertsen PC, Gilliland FD, et al. 5-year urinary and sexual outcomes after radical prostatectomy: Results from the prostate cancer outcomes study. J Urol. 2005;173:1701-05.
6. Muzii VF, Bistazzoni S, Zalaffi A, Carangelo B, Mariottini A. Chronic subdural hematoma: comparison of two surgical techniques. J Neurosurg. 2005;49:41-7.
7. Zakaraia AM, Adnan JS, Haspani MSM, Naing NN, Abdullah JM. Outcome of 2 different types of operative techniques practiced for chronic subdural hematoma in Malaysia: an analysis. Surg Neurol. 2008;69:608-16.
8. Ernestus RI, Beldzinski P, Lanfermann H, Klug N. Chronic subdural hematoma: Surgical treatment and outcome in 104 patients. Surg Neurol. 1997;48:220-5.
9. Tsutsumi K, Maeda K, Iijima A, Usui M, Okada Y, Kirino T, et al. The relationship of preoperative magnetic resonance imaging findings and closed system drainage in the recurrence of chronic subdural hematoma. J Neurosurg. 1997;87:870- 5.
10. Teasdale GM, Pettigrew LE, Wilson JT, Murray G, Jannett B. Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. J Neurotrauma. 1988;15:587-97.
11. Marik PE, Zaloga GP. Immunonutrition in high-risk surgical patients: a systematic review and analysis of the literature. JPEN J Parenter Enter Nutr. 2010;34(4):378–86.
12. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P. et_al. ESPEN guidelines on enteral nutrition: surgery including organ transplantation. Clin Nutr. 2006;25(2):224–44.
13. Weimann A, Ebener C, Hausser L, Holland−Cunz S, Jauch KW, et al. Leitlinie parenterale ernährung der DGEM: Chirurgie und transplantation. Aktuel Ernaehr Med. 2007;32:114–23.
14. McClave SA, Lowen CC, Snider HL. Immunonutrition and enteral hyperalimentation of critically ill patients. Dig Dis Sci. 1992;37(8):1153-61.
15. Senkal M, Mumme A, Eickhoff U, Geier B, Spa¨th G, Wulfert D, et al. Early postoperative enteral immunonutrition: clinical outcome and cost-comparison analysis in surgical patients. Crit Care Med. 1997;25(9):1489-96.
16. Evoy D, Lieberman MD, Fahey TJ III, Daly JM. Immunonutrition: the role of arginine. Nutrition. 1998;14(7–8):611–7.
17. Bertrand J, Siegler N, Murez T, Poinas G, Segui B, Ayuso D, et al. Impact of preoperative immunonutrition on morbidity following cystectomy for bladder cancer: a case–control pilot study. World J Urol. 2014;32:233-7.
18. Gregg JR, Cookson MS, Phillips S, Salem S, Chang SS, Clark PE, et al. Effect of preoperative nutritional deficiency on mortality after radical cystectomy for bladder cancer. J Urol. 2011;185(1):90-6.
19. Cerantola Y, Valerio M, Hubner M, Iglesias K, Vaucher L, Jichlinski P. Are patients at nutritional risk more prone to complications after major urological surgery? J Urol. 2012;190(6):2126-32.
20. Hamilton-Reeves JM, Stanley A, Bechtel MD, Yankee TM, Chalise P, Hand LK, et al. Perioperative Immunonutrition Modulates Inflammatory Response after Radical Cystectomy: Results of a Pilot Randomized Controlled Clinical Trial, The Journal of Urology. 2018;200(2):292-301.

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. 2020;4(9):746-749.
DOI: 10.28982/josam.714340

Research article
Araştırma makalesi

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

The association between red cell distribution width to total calcium ratio and syntax score in patients with acute coronary syndrome

Akut koroner sendromlu hastalarda kırmızı hücre dağılım genişliğinin total kalsiyuma oranının syntax skoru ile ilişkisi

Uğur Küçük [1]

[1] **Department of Cardiology, Numune State Hospital, Sivas, Turkey**

ORCID ID of the author(s)
UK: 0000-0003-4669-7387

Abstract

Aim: The relationship of both red blood cell distribution width (RDW) and Syntax risk score with prognosis and mortality in patients with acute coronary syndrome (ACS) has been shown. Besides, there is insufficient information about the use of red cell distribution width to total serum calcium (RDW-to-TSC) ratio in patients with ACS. We aimed to research the relationship between RDW-to-TSC and Syntax risk scores in our study.

Methods: For our retrospective cohort study, 270 patients hospitalized in the cardiology intensive care unit with the diagnosis of myocardial infarction between January 2019 and December 2019 were screened. A total of 115 patients who were eligible were included in the study. The patients were classified into two groups: 58 had NSTE-ACS and 57 had STEMI. The included age range was 18-80 years. RDW-to-TSC was calculated as the ratio of red cell distribution width to total serum calcium count. By using Pearson's correlation analysis, the relationship between RDW-TAF ratio and Syntax score was obtained.

Results: Among 115 patients, there were 50 males (43.5%), and 65 females (56.5%). The mean age was 58.09 (9.55) years. There were more hypertensive patients in the NSTE-ACS group (P=0.003). There was no statistically significant difference in RDW-to-TSC ratio between the two groups (P=0.809). The correlation of RDW and RDW / TSC ratio with syntax score were statistically significant (P<0.001).

Conclusions: RDW-to-TSC ratio is a simple, cost-effective, and readily available test in all health centers. This may be used as a risk calculation tool like the Syntax score for patients with ACS.

Keywords: Acute coronary syndrome, Serum calcium, Red cell distribution width

Öz

Amaç: Eritrosit dağılım genişliğinin (RDW) ve Syntax risk skorunun akut koroner sendrom (AKS) tanılı hastalarda prognoz ve mortalite ile ilişkileri gösterilmiştir. Bununla birlikte eritrosit dağılım genişliğinin serum kalsiyuma oranı (RDW/TSK) ile ilgili yeterli bilgiler yoktur. Bu çalışmanın amacı RDW-TSK oranının Syntax risk skoru ile ilişkisini araştırmayı hedefledik.

Yöntemler: Çalışmamız retrospektif kohort çalışması olup, Ocak 2019-Aralık 2019 tarihleri arasında kardiyoloji yoğun bakım ünitesinde miyokard enfarktüsü tanısı ile yatışı olan 270 hasta tarandı. Dışlama kriterlerinden sonra uygun olan 115 hasta çalışmaya alındı. Bu alınan hastaların 58 tanesi NSTE-AKS'li ve 57 tanesi STEMI olarak iki gruba sınıflandırıldı. Çalışmaya 18-80 yaş arası hastalar dahil edildi. RDW-TSK, eritrosit dağılım genişliğinin toplam serum kalsiyum sayısına oranı olarak hesaplandı. Pearson korelasyon analizi kullanılarak RDW-TSK oranı ile Syntax skoru arasındaki ilişki elde edildi.

Bulgular: 115 hastanın 50 tanesi erkek (%43,5), 65 tanesi kadın (%56,5) ve ortalama yaşları 58,09 (9,55) yıldı. NSTE-AKS grubunda daha fazla hipertansiyon hastası vardı (P=0,003). Gruplar arasında RDW / TSK oranında istatistiksel olarak anlamlı fark yoktu (P=0,809). RDW ve RDW / TSK oranı korelasyonu syntax skoru ile istatistiksel olarak anlamlı idi (P<0,001).

Sonuç: RDW / TSK oranı, tüm sağlık merkezlerinde basit, uygun maliyetli ve kolay ulaşılabilir bir testtir. Bununla birlikte AKS hastalarında Syntax skoru gibi risk hesaplama aracı olabilir.

Anahtar kelimeler: Akut koroner sendrom, Serum kalsiyum, Eritrosit dağılım dağıtım genişliği

Corresponding author/Sorumlu yazar:
Uğur Küçük
Address/Adres: Numune Devlet Hastanesi Kardiyoloji Kliniği, Sivas, Türkiye
E-mail: drugurkucuk@hotmail.com

Ethics Committee Approval: All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/27/2020
Yayın Tarihi: 27.09.2020

How to cite/Atıf için: Küçük U. The association between red cell distribution width to total calcium ratio and syntax score in patients with acute coronary syndrome. J Surg Med. 2020;4(9):746-749.

Introduction

Despite advances in technology and medicine, coronary artery diseases (CAD) have significant mortality and morbidity rates. Acute coronary syndromes (ACS) are responsible for the largest proportion of deaths worldwide. ACS is examined under two groups, ST elevated acute coronary syndrome (STEMI) and Non-ST elevated acute coronary syndrome (NSTE-ACS) [1].

In cardiology practice, risk and lesion classification of the coronary artery disease and life expectancy are the most significant problems in patients diagnosed with ACS. There are many related invasive and noninvasive tests. Many cardiac risk classification tests such as Grace, Syntax, Gensini provide information on mortality and morbidity [2-4]. Unfortunately, many parameters are needed to calculate such risk scoring tests in patients diagnosed with ACS, and for some scores, images obtained from coronary angiography (CAG) are used. There are recent studies showing the relationship between the cost effective and easy-to-calculate tests such as the red cell distribution width (RDW) blood test, C-reactive protein (CRP), Neutrophil/lymphocyte ratio (NLR), Monocyte/lymphocyte ratio (MLR) with cardiac risk scores [5]. Although there are enough studies on both cardiac and noncardiac diseases associated with RDW, studies on the ratio of the red cell distribution width (RDW) to total serum calcium (RDW-to-TSC) are insufficient.

The studies conducted with RDW in the literature showed an association of RDW-to-TSC with mortality, morbidity and cardiac risk scores in cardiovascular diseases, however, data related to whether RDW-to-TSC rate could be used as a risk score in patients with ACS are limited [6]. Syntax score is associated with increased mortality and morbidity in patients with ACS, and in our study, we aimed to investigate the relationship between the RDW-TSC ratio and Syntax risk scores.

Materials and methods

Our retrospective cohort study consists of 115 patients who were hospitalized in the coronary intensive care unit between January 2019 and December 2019. It includes patients older than 18 years and younger than 80 years of age. In the STEMI and NSTE-ACS groups, there were 57 and 58 patients, respectively. Out of 270 patients who were admitted to the emergency department of our hospital with chest pain and diagnosed with ACS, 115 underwent coronary angiography (CAG) after meeting the appropriate criteria. Stenoses of 50% and above were considered significant in at least one coronary artery. Consent form was obtained from all patients before the procedure.

The study excluded patients who underwent coronary artery bypass graft (CABG) surgery but did not want to receive further CAG, patients with renal insufficiency (serum creatinine level >1.5 mg/dL), moderate to severe valvular disease, liver failure (liver function values greater than twice the upper limit of the 'normal' value), hypertrophy, chronic obstructive pulmonary disease (COPD), septic manifestations, and diagnosis of malignancy.

The patients were diagnosed with STEMI and NSTE-ACS in accordance with current guidelines and treatment was initiated accordingly [7].

STEMI was defined as ST-segment elevation of 0,1 mV in all leads in both genders at the J- point in two continuous leads except for in V2–V3, where 0.2 mV was required for males older than 40 years old, 0.25 mV was required for males younger than 40 years old and 0.15 mV was required for females, new-onset left bundle-branch block, new-onset wall motion abnormalities and troponin elevation. NSTE-ACS was defined as troponin levels above the 99th percentile of the upper normal reference limit, ischemic symptoms such as chest pain lasting longer than 20 minutes and the absence of ST- segment elevation on ECG.

Hypertension was defined as antihypertensive medication use or systolic blood pressure above 140 mmHg and diastolic blood pressure above 90 mmHg. Diabetes mellitus was defined as fasting blood glucose ≥126 mg / dL or drug use for glucose regulation.

Calculation of coronary angiography and Syntax Score

Coronary angiography (CAG) was performed via the femoral or radial arteries using standardized Judkins technique. Each coronary artery was evaluated with at least two different images. Percutaneous coronary intervention was performed using the standardized technique. The Syntax score was calculated using the most up-to-date system for vessels with a stenosis over p value and a diameter of ≥1.5 mm (www.syntaxscore.com) [8]. Based on the calculated Syntax score, patients were divided into two groups - those having a score of 22 and below (considered low), and those having a score of 23 and above (considered moderate- high).

Laboratory measurements

A hematology analyzer was used to calculate hemogram parameters and other biochemical measurements (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, Illinois, US And Abbott Architect C16000 auto-analyzer (Architect C16000 auto-analyzer; Abbott Laboratory, Abbott Park, Illinois, USA), which were located in the laboratory of our institution. RDW-to-TSC ratio was calculated as RDW count divided by TSC.

Statistical analysis

SPSS 21.0 (IBM 1989, 2012) package program was used for all statistical analyses. Kolmogorov-Smirnov test was used for normal distribution assumptions of continuous variables. Continuous variables were presented as mean (standard deviation) and comparison was made with the Student's t-test. Correlation analysis was performed using Pearson test. *P*-value <0.05 was considered statistically significant.

Results

The study included 115 patients with acute coronary syndrome. Mean age of the patients was 58.09 (9.55) years. Sixty-one (53%) patients were male and 54 (47%) were female. Fifty-seven patients were assigned to the STEMI group and 58 patients, to the NSTE-ACS group.

Demographic, clinical and laboratory information of the patients are summarized in Tables 1 and 2. Except for hypertension and age, there was a numerical difference between the demographic, clinical and laboratory values between the groups, which was not statistically significant (*P*>0.05 for each). RDW-to-TSC ratios were 1.49 (0.18) in the STEMI group, and 1.48 (0.16) the NSTE-ACS group.

Syntax scores were 14.63 **(**2.03) and 14.75 (1.77) in the STEMI and NSTE-ACS groups, respectively (Table 2). There was a positive correlation between SYNTAX score and RDW and RDW-to-TSC ratio (r=0.670, *P*<0.001 and r=0.939, *P*<0.001, respectively) (Table 3).

Table 1: Baseline clinical, demographic features and laboratory findings

	STEMI (n=57)	NSTE-ACS (n=58)	*P*-value
Age, mean (SD)	59.94 (9.66)	45.94 (14.96)	0.039
Glucose (mg/dL) mean (SD)	119.62 (31.12)	123.19 (13.17)	0.374
Creatinine, mg/dL	0.82 (0.15)	0.78 (0.16)	0.192
Hypertension, (n)	28	44	0.003
Diabetes mellitus, (n)	14	20	0.244
Hemoglobin, g/L	13.24 (1.23)	13.50 (1.42)	0.298
Platelet count, $x10^3/\mu L$	235.24 (44.73)	237.98 (49.14)	0.755
WBC count, $x10^3/\mu L$	11.73 (2.24)	12.00 (2.42)	0.527
Total serum calcium (mg/dl)	8.99 (0.72)	9.05 (0.75)	0.676

NSTE-ACS: Non-ST elevated acute coronary syndrome, STEMI: ST elevated acute coronary syndrome, WBC: white blood cell

Table 2: Biochemical and Syntax score measurements of the two groups

	STEMI	NSTE-ACS	*P*-value
RDW (%)	13.30 (1.12)	13.34 (1.13)	0.877
RDW-to-TSC ratio	1.49 (0.18)	1.48 (0.16)	0.809
SYNTAX score	14.63 (2.03)	14.75 (1.77)	0.956

RDW: red cell distribution width, RDW-to-TSC ratio: red cell distribution width to total serum calcium ratio

Table 3: Correlation of RDW and RDW-to-TSC ratio with Syntax score

	Syntax score	
	r	*P*-value
RDW	0.670	<0.001
RDW-to-TSC ratio	0.939	<0.001

RDW: red cell distribution width, RDW-to-TSC ratio: red cell distribution width to total serum calcium ratio

Correlation analysis revealed a significant relationship between the Syntax score and the RDW-to-TSC ratio, which is presented in Figure 1 (r=0.836, *P*<0.001).

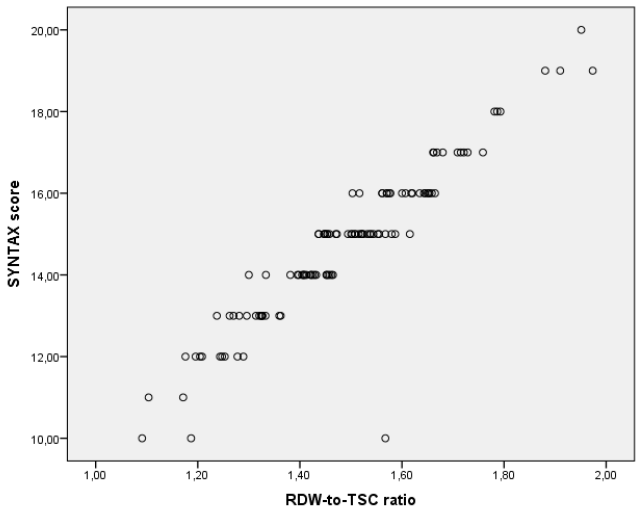


Figure 1: The relationship between RDW-to-TSC ratio and SYNTAX score in patients with acute coronary syndrome

Discussion

Atherosclerosis occurs at an early age and is seen as "fat lines" in the coronary arteries. ACS is one of the leading causes of death due to its onset at young ages. Identifying patients at risk will reduce costs, as well as mortality and morbidity [9]. The risk scores for patients with ACS allow us to identify patients at risk in clinical practice and to take important precautions such as lifestyle changes. There are many risk scores on this subject, including GRACE, SYNTAX, TIMI, and GENSINI.

Syntax risk score not only provides valuable information regarding the number, importance, and location of angiographic lesions, but it is also a predictor of elevated mortality and morbidity in patients with CAD [10]. Since the Syntax score is complex and time consuming, simpler tests are needed. Recently, RDW has been shown to be associated with risk scores in many domains and has established its place in clinical practice. RDW is a strong risk factor for mortality in patients with systemic inflammation, stroke, chronic kidney disease and coronary artery [11]. In their study, Nagula et al. [12] demonstrated that RDW is a marker that can be used in predicting coronary artery disease and severity of coronary artery stenosis. In another study, Magri et al. [13] demonstrated that RDW is an independent marker in predicting myocardial scar tissue and left ventricular functions. There are adequate number of studies regarding RDW in patients diagnosed with CAD; however, the studies on the RDW-to-TSC ratio are limited.

The study by Gravito-Soares et al. [14] demonstrated that RDW-to-TSC ratio is a good marker in predicting mortality in patients with acute pancreatitis.

As the syntax score increases in patients diagnosed with ACS, mortality and morbidity increase simultaneously. It is known that treatment alternatives that can be applied according to the severity of coronary artery disease determined by the score will contribute to the prognosis of the patient. Since calculating the syntax score is difficult and time-consuming, clinicians need a score that can be calculated quickly and easily. As a result of our study, we showed that RDW and Syntax scores were correlated in patients diagnosed with acute coronary syndrome, as in previous studies. In addition, we showed that there was a relationship between the RDW-to-TSC ratio and the Syntax risk score, on which there are few studies [15].

Limitations

The major limitations of our study include its retrospective nature and the small number of cases, since most of the patients' past information could not be reached. Multi-center studies will provide realistic and meaningful statistical results.

Conclusion

Syntax score has been proven to correlate with mortality and morbidity in CAD patients, and the RDW-to-TSC ratio is feasible for use in patients with ACS. As a result of our work, we showed that there is a positive relationship between RDW-to-TSC ratio and Syntax risk score. RDW-to-TSC ratio is a simple, cost-effective, and readily available test in all health centers, which we can use in clinical practice to learn about the patients' cardiac risk score and take necessary precautions to minimize risks.

References

1. Wang TKM, Grey C, Jiang Y, Jackson RT2, Kerr AJ. Nationwide trends in acute coronary syndrome by subtype in New Zealand 2006-2016. Heart. 2020;106:221-7.
2. Lang Y, Ran X, Wang L. [Risk Factors of Death in Patients with Acute ST-segment Elevation Myocardial Infarction after PCI and the Combined Application of CTRP-1 with GRACE Score in Prognosis Evaluation of PCI Treated Patients]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2019;50:941-5.
3. Kang J, Han JK, Kang DY, Zheng C, Jang HG, Park KW, et al. SYNTAX Score and SYNTAX Score II Can Predict the Clinical Outcomes of Patients with Left Main and/or 3-Vessel Disease Undergoing Percutaneous Coronary Intervention in the Contemporary Cobalt-Chromium Everolimus-Eluting Stent Era. Korean Circ J. 2020;50:22-34.
4. Huang J, Zhang Q, Wang R, Ji H, Chen J, Quan X, et al. Systemic Immune-Inflammatory Index Predicts Clinical Outcomes for Elderly Patients with Acute Myocardial Infarction Receiving Percutaneous Coronary Intervention. Med Sci Monit. 2019;25:9690-701.
5. Uthamalingam S, Patvardhan EA, Subramanian S, Ahmed W, Martin W, Daley M, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. Am J Cardiol. 2011;107:433-8.
6. Qian H, Luo Z, Xiao C, Chen J, Li D, Xu H, et al. Red cell distribution width in coronary heart disease: prediction of restenosis and its relationship with inflammatory markers and lipids. Postgrad Med J. 2018;94:489-94.
7. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et all. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40:87-165.
8. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein A-P, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention. 2009;5(1) 50-6.
9. Barquera S, Pedroza-Tobias A, Medina C, Hernández-Barrera L, Bibbins-Domingo K, Lozano R, et al. Global Overview of the Epidemiology of Atherosclerotic Cardiovascular Disease. Arch Med Res. 2015;46:328-38.

10. Sullivan PG, Wallach JD, Ioannidis JP. Meta-Analysis Comparing Established Risk Prediction Models (EuroSCORE II, STS Score, and ACEF Score) for Perioperative Mortality During Cardiac Surgery. Am J Cardiol. 2016;118:1574-82
11. Agarwal S. Red cell distribution width, inflammatory markers and cardiorespiratory fitness: results from the National Health and Nutrition Examination Survey. Indian Heart J. 2012;64:380-7.
12. Nagula P, Karumuri S, Otikunta AN, Yerrabandi SRV. "Correlation of red blood cell distribution width with the severity of coronary artery disease-A single center study". Indian Heart J. 2017;69:757-61.
13. Magri CJ, Tian TX, Camilleri L, Xuereb R, Galea J, Fava S. Red blood cell distribution width and myocardial scar burden in coronary artery disease. Postgrad Med J. 2017;93:607-12.
14. Gravito-Soares M, Gravito-Soares E, Gomes D. Red cell distribution width and red cell distribution width to total serum calcium ratio as major predictors of severity and mortality in acute pancreatitis. BMC Gastroenterol. 2018;18:108.
15. Vogiatzis I, Samaras A, Grigoriadis S, Sdogkos E, Koutsampasopoulos K, Bostanitis I. The Mean Platelet Volume in the Prognosis of Coronary Artery Disease Severity and Risk Stratification of Acute Coronary Syndromes. Med Arch. 2019;73:76-80.

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. 2020;4(9):750-753.
DOI: 10.28982/josam.784237

Research article
Araştırma makalesi

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

The effects of age, parity and body mass index on 50 g oral glucose tolerance test results and its predictive value in gestational diabetes mellitus

Yaş, parite ve vücut kitle indeksinin 50 gr glukoz tarama testi üzerine etkileri ve gestasyonel diabetes mellitus ile ilişkisi

Alparslan Deniz [1]

[1] **Alanya Alaaddin Keykubat University, Faculty of Medicine, Department of Obstetrics and Gynecology, Antalya, Turkey**

ORCID ID of the author(s)
AD: 0000-0003-1421-9962

Corresponding author/Sorumlu yazar:
Alparslan Deniz
Address/Adres: Alanya Alaaddin Keykubat Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı Kestel Kampüsü, Alanya, Antalya, Türkiye
E-mail: dralparslandeniz@gmail.com

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Alanya Alaaddin Keykubat University, Faculty of Medicine (Date:05/06/2020 No:19-21). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolü Alanya Alaaddin Keykubat Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından onaylandı (Tarih: 05/06/2020 No: 19-21). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/27/2020
Yayın Tarihi: 27.09.2020

Abstract

Aim: The aim of this study was to investigate the effects of age, parity, body mass index (BMI) and maternal risk factors on 50 g oral glucose tolerance test (OGTT) positivity and to evaluate the predictive value of 50 g OGTT in the diagnosis of gestational diabetes mellitus (GDM).

Methods: Medical data of pregnant women who were followed in a private obstetrics and gynecology clinic between June 2012 and April 2020 were analyzed in this retrospective cohort study. All patients underwent 50 g OGTT between 24 and 28 weeks of gestation. A 1-h postprandial venous plasma glucose cut-off of ≥140 mg/dL was considered positive for OGTT and the diagnosis was confirmed by 2-h 75 g OGTT. The relationship between the GDM and OGTT results, BMI, parity, age, and other maternal risk factors was analyzed in the regression analysis.

Results: A total of 323 pregnant women were included in the study. The mean age was 29.35 (5.29) years and the mean BMI was 27.23 (6.07) kg/m^2. Among them, 35.9% had ≥1 risk factors. The sensitivity, specificity, positive predictive value, and negative predictive value of 50 g OGTT for GDM were 100%, 80.7%, 27.5%, and 100%, respectively. Regression analysis revealed that family history of diabetes, history of GDM, and macrosomic birth increased the GDM risk by 5.73, 4.95, and 1.43 folds, respectively.

Conclusion: Evaluation of advanced maternal age, pre-pregnancy BMI, and maternal risk factors is useful to predict GDM. In addition, 50 g OGTT is helpful in diagnosing GDM for both maternal and fetal health.

Keywords: Oral glucose tolerance test, Diabetes, Obesity, Advanced maternal age

Öz

Amaç: Bu çalışmada yaş, parite, vücut kitle indeksi (VKİ)ile gebenin öyküsünde saptanan risk faktörlerinin 50 g glikoz tarama testi (OGTT) pozitifliği üzerine etkileri ve 50g OGTT'nin gestasyonel diabetes mellitus (GDM) tanısında etkinliği araştırıldı.

Yöntemler: Haziran 2012-Nisan 2020 tarihleri arasında özel bir kadın doğum kliniğinde takip edilen gebelerin tıbbi verileri bu retrospektif kohort çalışmasında incelendi. Gebeliğin24 ila 28. haftaları arasında tüm gebelere 50 g OGTT uygulandı. 1 saatlik venöz kan şekeri düzeyi 140 mg/dL üzerinde ise test pozitif kabul edildi ve tanı için 75 g 2 saatlik glikoz tolerans testi yapıldı. Gebelerin OGTT sonuçları, VKİ, parite, yaş ve diğer risk faktörlerinin GDM ile ilişkisi regresyon analizi ile incelendi.

Bulgular: Çalışmaya toplam 323 gebe dahil edildi. Ortalama yaş 29,35 (5,29) yıl ve ortalama vücut kitle indeksi 27,23 (6,07) kg/m^2 idi. Grubun %35,9'unda en az bir risk faktörü mevcuttu. 50g OGTT'nin GDM tanısında duyarlılığı, özgüllüğü, pozitif prediktif değeri ve negatif prediktif değeri sırayla %100, %80,7, %27,5 ve %100 olarak bulundu. Regresyon analizinde ailede diyabet öyküsü GDM riskini 5,73 kat, GDM öyküsü 4,95 kat ve iri bebek öyküsü 1,43 kat artırdı.

Sonuç: İleri gebelik yaşı, gebelik öncesi VKİ ve öykudeki risk faktörlerinin değerlendirilmesi GDM'nin öngörülmesi açısından faydalıdır. Ayrıca 50 g OGTT, anne ve bebeğin sağlığı için GDM tanısında yararlıdır.

Anahtar kelimeler: Oral glikoz tolerans testi, Diyabet, Obezite, İleri yaş gebelik

How to cite/Atıf için: Deniz A. The effects of age, parity and body mass index on 50 g oral glucose tolerance test results and its predictive value in gestational diabetes mellitus. J Surg Med. 2020;4(9):750-753.

Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy, and it usually resolves after delivery [1]. With varying degrees, it accounts for 1 to 14% (average 4 to 5%) of all pregnancies [2]. In Turkey, its prevalence ranges from 1.9 to 27.9% with a mean prevalence of 7.7% [3]. The variation in the prevalence of GDM depends on maternal anthropometric measurements such as the height and body mass index (BMI), as well as diagnostic instruments and criteria used. In previous studies, advanced maternal age and increased body weight were associated with a higher prevalence of GDM [4].

It has been well established that GDM is associated with adverse maternal outcomes including gestational hypertension, preeclampsia, polyhydramnios, vasculopathy and even type 2 diabetes mellitus (DM) in the long-term and adverse fetal outcomes including macrosomia, congenital malformation, and intrauterine fetal demise [5]. In addition, GDM increases the risk of neonatal birth trauma, hypoglycemia, respiratory distress syndrome, hyperbilirubinemia, hypocalcemia, polycythemia, and even mortality [6].

The oral glucose tolerance test (OGTT) is the gold standard for the diagnosis of GDM [7]. It is recommended for all pregnant women between 24 and 28 weeks of gestation. The test can be done as a one-step or two-step method [8]. The treatment of GDM decreases the maternal, fetal, and neonatal risks [9]. In the literature, the risk of GDM as assessed by the 50 g OGTT was higher in women aged >30 years, having a BMI of ≥25 kg/m2, and those who had given multiple births (≥4) [10].

The aim of the present study was to investigate the effects of age, parity, BMI, and maternal risk factors on 50 g OGTT results and to evaluate the predictive value of 50 g OGTT in the diagnosis of GDM.

Materials and methods

This single-center, retrospective study was conducted at a private obstetrics and gynecology clinic between June 2012 and April 2020. A written informed consent was obtained from each participant. The study protocol was approved by the Clinical Research Ethics Committee of Alanya Alaaddin Keykubat University, Faculty of Medicine (Date:05/06/2020-No:19-21). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Of all pregnant women, those having a healthy singleton pregnancy, who were non-diabetic, visited the clinic within the first six weeks of gestation and are still under regular follow-up were included. Data regarding the first examination within six weeks of gestation were collected and maternal age, gestational week at the time of screening, parity, and BMI were recorded. Considering no weight gain at the time of first examination within six weeks of gestation, pre-pregnancy BMI was defined as the value calculated at the time of first examination. Maternal and fetal risk factors including history of intrauterine fetal demise of unknown origin, macrosomic birth (birth weight >4,000 g), recurrent pregnancy loss, polyhydramnios, and family history of DM were evaluated.

All patients who were at low risk for GDM underwent fasting blood glucose (FBG) measurement between six and eight weeks of gestation. If the FBG level was >100 mg/dL, 2-h (postprandial) 75 g OGTT was performed to diagnose latent pre-gestational DM (PGDM). Irrespective of the GDM risk, all the remaining patients underwent 50 g OGTT between 24th and 28th weeks of gestation. A 1-h (postprandial) venous plasma glucose cut-off of ≥140 mg/dL was considered positive for OGTT and the diagnosis was confirmed by 2-h (postprandial) 75 g OGTT. Women who were at high risk for GDM and having unknown diabetic status (i.e., those having a history of macrosomic birth, recurrent pregnancy loss, unexplained intrauterine fetal demise, congenital fetal malformations, previous GDM and a family history of DM) underwent 2-h (postprandial) 75 g OGTT following the first examination. If the test result indicated a cut-off value or higher (FBG: 92 mg/dL; 1-h: 180 mg/dL; 2-h 153 mg/dL), the diagnosis of PGDM was established and excluded from the study. Women with DM were treated with dietary modifications alone or combined with insulin.

Statistical analysis

Statistical analysis was performed using the SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean (Standart Deviation, SD), median (min-max) or number and frequency. Visual histogram and likelihood graphics and analytic methods such as Kolmogorov-Smirnov or Shapiro-Wilk tests were used to check the normal distribution of the variables. The chi-square and Fisher exact tests were performed for inter-group comparison. The Bonferroni-corrected Z multiple comparisons were used to compare multiple groups. A logistic regression analysis was performed using the backward elimination method to predict GDM based on clinical data. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 323 pregnant women were included in the study. The mean age was 29.35 (5.29) years and the mean BMI was 27.23 (6.07) kg/m^2. Of the patients, 35.9% had ≥1 risk factors. Baseline sociodemographic and clinical characteristics of the patients are shown in Table 1.

Among all, 24.8% (n=80) had positive 50 g OGTT results and 6.8% (n=22) were diagnosed with GDM. The sensitivity, specificity, positive predictive value, and negative predictive value of 50 g OGTT for GDM were 100%, 80.7%, 27.5%, and 100%, respectively (Table 2).

According to the age groups, 50 g OGTT yielded the highest positive results in the 30-35 age group, while most women aged >35 years were diagnosed with GDM. The rates of OGTT positivity and GDM diagnosis according to the age groups are summarized in Table 3.

According to the BMI values, women with >35 kg/m^2 had the highest rate of 50 g OGTT positivity, indicating a statistically significant difference (*P*=0.001). However, there was no statistically significant difference in the rate of GDM diagnosis among the BMI groups (Table 4).

According to the number of parities, there was no statistically significant difference in the rate of GDM diagnosis, based on 50 g OGTT (Table 5).

Table 1: Baseline sociodemographic and clinical characteristics of patients

n=323	Mean (SD)	Median (min-max)
Age, years	29.35 (5.29)	29.00 (18-41)
BMI, kg/m^2	27.23(6.07)	27.00 (18-39)
Parity	1.02(0.82)	1.00 (0-4)
Having risk factors	35.9%	n=116
Family history of DM	27.2%	n=88
History of GDM	4.6%	n=15
History of macrosomic birth	4.6%	n=15
History of recurrent pregnancy loss	4.6%	n=15
History of unexplained intrauterine fetal demise	0.3%	n=1

BMI: body mass index; DM: diabetes mellitus; GDM: gestational diabetes mellitus.

Table 2: Correlation between GDM and 50 g OGTT

	GDM+	GDM-
50g OGTT+	22 (22.5%)	58 (72.5%)
50g OGTT-	0 (0.0%)	243 (100.0%)

Sensitivity: 100.0%; specificity: 80.7%; PPV:27.5%; NPV:100.0%. GDM: gestational diabetes mellitus; OGTT: oral glucose tolerance test; PPV: positive predictive value; NPV: negative predictive value.

Table 3: Rates of OGTT positivity and GDM diagnosis according to the age groups

Age group	n (%)	50g OGTT+ n (%)	χ^2	*P*-value	GDM n (%)	χ^2	*P*-value
<25 years	72 (22.3)	11 (15.3)	11.302	0.010	1 (1.4)	8.391	0.039
25-30 years	123 (38.1)	25 (20.3)			7 (5.7)		
30-35 years	61 (18.9)	22 (36.1)			5 (8.2)		
>35 years	67 (20.7)	22 (32.8)			9 (13.4)		

GDM: gestational diabetes mellitus; OGTT: oral glucose tolerance test; χ^2: chi-square.

Table 4: Rates of OGTT positivity according to the BMI values

BMI group	n (%)	50g OGTT+ n (%)	χ^2	*P*-value	GDM n (%)	χ^2	*P*-value
<20 kg/m^2	58 (18.0)	9 (15.5)	25.417	0.001	2 (3.4)	8.588	0.072
20-25 kg/m^2	77 (23.8)	8 (10.4)			2 (2.6)		
25-30 kg/m^2	84 (26.0)	26 (31.0)			5 (6.0)		
30-35 kg/m^2	40 (12.4)	9 (22.5)			5 (12.5)		
>35 kg/m^2	64 (19.8)	28 (42.8)			8 (12.5)		

BMI: body mass index; GDM: gestational diabetes mellitus; OGTT: oral glucose tolerance test; χ^2: Chi-square.

Table 5: Rates of OGTT positivity according to the number of parity

Parity	n (%)	50g OGTT+ n (%)	χ^2	*P*-value	GDM n (%)	χ^2	*P*-value
0	90 (27.9)	16 (17.8)	5.196	0.268	3 (3.3)	8.721	0.068
1	150 (46.4)	38 (25.3)			13 (8.7)		
2	71(22.0)	21 (29.6)			4 (5.6)		
3	10 (3.1)	4 (40.0)			1 (10.0)		
≥4	2 (0.6)	1 (50.0)			1 (50.0)		

GDM: gestational diabetes mellitus; OGTT: oral glucose tolerance test; χ^2: chi-square.

Risk factor analysis showed no significant difference in the OGTT results between the groups. However, family history of DM (*P*=0.001) and a history of GDM (*P*=0.013) were significant risk factors for GDM (Table 6).

Table 6: Risk factor analysis results

Risk factor	n (%)	50g OGTT+ n (%)	χ^2	*P*-value	GDM n (%)	χ^2	*P*-value
Family history of DM	88 (27.2)	58 (24.7)	0.023	0.538	14 (15.9)	15.721	0.001
History of GDM	15 (4.6)	6 (40.0)	1.959	0.138	4 (26.7)	9.771	0.013
History of macrosomic birth	15 (4.6)	5 (33.3)	0.619	0.303	2(13.3)	1.053	0.272
History of recurrent pregnancy loss	15 (4.6)	3 (20.0)	0.192	0.467	1 (6.7)	0.012	0.728
History of unexplained intrauterine fetal demise	1 (0.3)	1 (100.0)	0.248	3.047	1 (100.0)	13.724	0.068

DM: diabetes mellitus; GDM: gestational diabetes mellitus; OGTT: oral glucose tolerance test; χ^2: chi-square.

A logistic regression analysis was performed using the backward elimination method to predict GDM based on the family history of DM, history of GDM, macrosomic birth, recurrent pregnancy loss, and unexplained intrauterine fetal demise. The analysis yielded statistically significant results (χ2: 48.402, *P*=0.001). The model explained 15.9% of variance in heart disease (NagelkerkeR^2) and classified 93.2% of the patients accurately. Family history of DM, history of GDM, history of macrosomic birth increased the GDM risk by 5.73, 4.95, and 1.43 folds, respectively (Table 7).

Table 7: Logistic regression analysis results

	χ^2	R^2	*P*-value	OR	95%CI
Model	48.402	0.159	0.001		
Family history of DM			0.001	5.73	1.72-94.37
History of GDM			0.002	4.95	1.30-56.45
History of macrosomic birth			0.048	1.43	0.94-2.21

DM: diabetes mellitus; GDM: gestational diabetes mellitus; OR: odds ratio; CI: confidence interval; χ^2: chi-square.

Discussion

In the present study, the primary objective was to examine the effects of age, parity, BMI, and maternal risk factors on 50 g OGTT results and to evaluate the predictive value of 50 g OGTT in the diagnosis of GDM. The study results showed that a total of 323 pregnant women were included, the mean age was 29.35 (5.29) years and the mean BMI was 27.23 (6.07) kg/m^2. Among all patients, 35.9% had ≥1 risk factor and 6.8% were diagnosed with GDM based on 2-h 75 g OGTT. These results are consistent with the literature [3].

The 50 g OGTT is a simple and cost-effective test, as it requires blood collection at a single session without a prerequisite of fasting state [11]. In the current study, a1-h postprandial venous plasma glucose cut-off of ≥140 mg/dL was considered positive for OGTT and sensitivity, specificity, positive predictive value, and negative predictive value of 50 g OGTT for GDM were 100%, 80.7%, 27.5%, and 100%, respectively. In a previous study, De Sereday et al. [12] examined an alternative cut-off point to increase the predictive value in pregnancies at elevated risk for GDM. A total of 473 healthy pregnant women underwent a screening test with 1-h 50 g OGTT and the sensitivity was 66.7%, when the cut-off value was established at 137 mg/dL. In another study conducted in Turkey, the sensitivity, specificity, positive predictive value, and negative predictive value were 96.30%, 80.34%, 24.07%, and 99.70%, respectively, using a cut-off value of 145 mg/dL [13]. Although some authors have advocated that a cut-off value of 140 mg/dL is more accurate, the results of the present study are consistent with previous findings. In the current study, the American Diabetes Association (ADA) classification was used for the diagnosis of GDM. According to this classification, the positive predictive value of 50 g OGTT was 17.6% in previous studies [14], consistent with the findings of the current study.

According to the age groups, 50 g OGTT yielded the highest positive results in the 30-35 years age group, while most women aged >35 years were diagnosed with GDM. In previous studies, there was a significant correlation between the maternal age and GDM diagnosis based on the 50 g OGTT. In a recent study including 307 healthy pregnant women, the incidences of a positive OGTT and GDM increased significantly with advanced maternal age from 20% and 2.2%, respectively in women aged ≤25 years to 37.8% and 14.7%, respectively in women aged >35 years [15]. These results indicate that women aged >35 years are at a higher risk for GDM, consistent with the findings of the current study. In another study conducted in Turkey, the GDM risk increased by 7.84-fold in women aged >40 years [16].

Similarly, the rate of GDM was higher among women aged 31-35 years compared to the other age groups in another study [13].

According to the BMI values, the majority of women with >35 kg/m^2 had the highest rate of 50 g OGTT positivity, indicating a statistically significant difference. However, there was no statistically significant difference in the rate of GDM diagnosis among the BMI groups. In a study, there was a significant correlation between a BMI value of >25 kg/m^2 and GDM diagnosis based on the 50 g OGTT [15]. In another study, a BMI value of ≥25 kg/m^2 increased the risk of GDM by 1.74-fold [16]. According to the current guidelines, a BMI value of ≥30 kg/m^2 before pregnancy indicates an elevated risk for GDM and routine screening test between 24 and 28 weeks of gestation should be performed, even if the first-trimester screening test results are normal [8].

According to the number of parities, there was no statistically significant difference in the rate of GDM diagnosis based on 50 g OGTT. Although there are studies showing a correlation between the number of parities and GDM in the literature [17], a growing number of studies showed no statistically significant correlation, despite a constant increase in the GDM incidence based on the 50 g OGTT results [10,15].

In the current study, 35.9% of the women had ≥1 risk factors. According to the risk factor analysis, there was no significant difference in the OGTT results between the groups. However, family history of DM and history of GDM were significant risk factors for GDM. In addition, family history of DM, history of GDM, history of macrosomic birth increased the GDM risk by 5.73, 4.95, and 1.43 folds, respectively. In previous studies, family history of DM in the first-degree relatives (3.2-fold), history of GDM in previous pregnancies (23-fold), history of recurrent pregnancy loss, intrauterine fetal demise, and macrosomic birth (3.3-fold) were shown to be primary risk factors of GDM [8,18]. Furthermore, a correlation was found between the history of GDM in previous pregnancies based on 50 g OGTT and increased GDM risk [19]. Review of the literature revealed that history of GDM is the most significant predictor of GDM in the current pregnancy [20]. Similarly, some authors demonstrated that both history of GDM and family history of DM were the major predictors of GDM and 50 g OGTT positivity [15]. In a study investigating the relationship between the GDM risk factors and 50 g OGTT efficacy, a total of 426 pregnant women were divided into two groups according to the presence of risk factors and all underwent 50 g OGTT [21]. The positive predictive value of 50 g OGTT was 40.9% in the women having risk factors, while it was 22.2% in those having no risk factors, indicating a statistically significant difference between the groups. The authors concluded that 50 g OGTT should be applied to only pregnant women having risk factors in the screening of GDM.

Conclusion

The results of the present study suggest that evaluation of advanced maternal age, pre-pregnancy BMI, and maternal risk factors is useful to predict GDM. In addition, 50 g OGTT is helpful to diagnose GDM for both maternal and fetal health.

References

1. Kampmann U, Madsen LR, Skajaa GO, Iversen DS, Moeller N, Ovesen P. Gestational diabetes: a clinical update. World J Diabetes. 2015;6(8):1065. doi: 10.4239/wjd.v6.i8.1065
2. Menato G, Bo S, Signorile A, Gallo ML, Cotrino I, Poala CB, et al. Current management of gestational diabetes mellitus. Expert Review of Obstetrics & Gynecology. 2008;3(1):73-91. doi: 10.1586/17474108.3.1.73
3. Lee KW, Ching SM, Ramachandran V, Yee A, Hoo FK, Chia YC, Sulaiman WAW, et al. Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2018;18(1):494. doi: 10.1186/s12884-018-2131-4.
4. Bardenheier BH, Elixhauser A, Imperatore G, Devlin HM, Kuklina EV, Geiss LS et al. Variation in prevalence of gestational diabetes mellitus among hospital discharges for obstetric delivery across 23 states in the United States. Diabetes Care. 2013;36(5):1209-14. doi: 10.2337/dc12-0901.
5. Lindqvist M, Persson M, Lindkvist M, Mogren I. No consensus on gestational diabetes mellitus screening regimes in Sweden: pregnancy outcomes in relation to different screening regimes 2011 to 2012, a cross-sectional study. BMC Pregnancy Childbirth. 2014;14(1):185. doi: 10.1186/1471-2393-14-185
6. Öztürk FY, Altuntas Y. Gestational diabetes mellitus. Şişli Etfal Hastanesi Tip Bülteni. 2015;49(1):1-10. doi: 10.5350/SEMB.20150317014238.
7. Shrestha A, Chawla C. The glucose challenge test for screening of gestational diabetes. Kathmandu Univ Med J. 2011;9(2):22-5.
8. Bayram M, Biri A, Büyükbayrak EE, Dağlar K, Ercan F, Erzincan SG, et al. Perinatoloji Uzmanlari Derneği Gebelik Ve Diyabet Kilavuzu. 2019. http://puder.org.tr/wp-content/uploads/2019/12/PUDER-Gebelik-ve-Diyabet-K%C4%B1lavuzu-6.10.2019.pdf
9. HAPO Study Cooperative Research Group; Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. N England J Med. 2008;358(19):1991-2002. doi: 10.1056/NEJMoa0707943.
10. Nielsen KK, Kapur A, Damm P, Courten M, Bygbjerg IC. From screening to postpartum follow-up–the determinants and barriers for gestational diabetes mellitus (GDM) services, a systematic review. BMC Pregnancy Childbirth. 2014;14(1):41. doi: 10.1186/1471-2393-14-41.
11. Neelakandan R, Sethu PS. Early universal screening for gestational diabetes mellitus. J Clin Diagn Res. 2014;8(4):OC12-4. doi; 10.7860/JCDR/2014/8199.4264.
12. de Sereday MS, Damiano MM, Gonzalez CD, Bennett PH. Diagnostic criteria for gestational diabetes in relation to pregnancy outcome. J Diabetes Complications. 2003;17(3):115-9. doi: 10.1016/s1056-8727(02)00173-3.
13. İnan C, Ağır MÇ, Sağır FG. Efficacy of 50-G Glucose Challenge Test in The Diagnosis of Gestational Diabetes Mellitus. Medical Bulletin of Haseki. 2014;52(3).
14. Gülbahar Ö, Çaycı AB, Budakoğlu İ, Erçin U, Bukan N, Paşaoğlu H, et al. Gestasyonel Diabetes Mellitus Tanısı İçin OGTT Değerlendirmesinde ADA Kriterlerinin Yeri. Türk Klinik Biyokimya Derg. 2010;8(2):63-7.
15. Abu-Heija AT, Al-Bash MR, Al-Kalbani MA. Effects of maternal age, parity and pre-pregnancy body mass index on the glucose challenge test and gestational diabetes mellitus. J Taibah Univ Med Sci. 2017;12(4):338-42. doi: 10.1016/j.jtumed.2017.01.005
16. Kutay NG, Gönenç G, İşçi H, Yiğiter AB, Dünder İ. Gestasyonel diabetes mellitus riskinin maternal yaş ve gebeliğin başlangıcındaki vücut kitle indeksi ile ilişkisi. Dicle Tıp Dergisi. 2013;40(3):406-9. doi: 10.5798/diclemedj.0921.2013.03.0298
17. Far MA, Ziaei S, Kazemnejad A. The impact of maternal age, pre-pregnancy body mass index, weight gain and parity on glucose challenge test (GCT). Int J Fertil Steril. 2012;5(4):207-10.
18. Pridjian G, Benjamin TD. Update on gestational diabetes. Obstet Gynecol Clin North Am. 2010;37(2):255-67.
19. Al-Khaduri MM, Abudraz RM, Rizvi SG, Al-Fasri Y. Risk factors profile of shoulder dystocia in Oman: a case control study. Oman Med J. 2014;29(5):325. doi: 10.5001/omj.2014.88.
20. Catalano P. Trying to understand gestational diabetes. Diabet Med. 2014;31(3):273-81. doi: 10.1111/dme.12381.
21. Sagün M, Tosun M, Malatyalı E, Çetinkaya MB, Alper T, Kökçü A. Gestasyonel diabet taramasında 50 gr oral glukoz testinin etkinliği. J Turk Soc Obstet Gynecol. 2008;5(4):258-62.

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

J Surg Med. 2020;4(9):754-756.
DOI: 10.28982/josam.774124

Research article
Araştırma makalesi

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

The relationship between sarcopenia and cognitive dysfunction in bladder tumor patients

Mesane kanseri hastalarında sarkopeni ve postoperatif kognitif fonksiyon bozukluğu ilişkisi

Semih Kalyon [1], Perihan Özkan Gümüşkaya [1], Neslihan Özsoy [1], Mustafa Özcan [1], Şengül Aydın Yoldemir [1], İlkim Deniz Toprak [2], Özgür Altun [1], Murat Akarsu [1], Eylem Özgün Çil [1], Yücel Arman [1], Tufan Tükek [3]

[1] Prof. Dr. Cemil Taşcıoğlu City Hospital, Department of Internal Medicine, Istanbul, Turkey
[2] Health Sciences University, Gaziosmanpaşa Education and Research Hospital, Department of Internal Medicine, Istanbul, Turkey
[3] Istanbul University Istanbul Faculty of Medicine, Department of Internal Medicine, Istanbul, Turkey

ORCID ID of the author(s)

SK: 0000-0003-4207-0800
PÖG: 0000-0002-0838-9220
NÖ: 0000-0001-8660-1648
MÖ: 0000-0002-5613-0336
ŞA: 0000-0003-4236-1181
İDT: 0000-0002-9320-1252
ÖA: 0000-0003-1810-7490
MA:0000-0002-2675-4252
EÖÇ: 0000-0003-3193-9056
YA: 0000-0002-9584-6644
TT: 0000-0002-4237-1163

Corresponding author/Sorumlu yazar:
Semih Kalyon
Address/Adres: Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi, İç Hastalıkları Kliniği, İstanbul, Türkiye
E-mail: semihkalyon@hotmail.com

Ethics Committee Approval: The study protocol was approved by Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (Date: 2/14/2017, No: 600). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolü Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi Etik Kurulu (Tarih: 14.02.2017, No: 600) tarafından onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/27/2020
Yayın Tarihi: 27.09.2020

Abstract

Aim: There is no study in the literature to show whether there is a negative effect of sarcopenia on cognitive functions in patients over 65 years of age in the early postoperative period, who were operated under general anesthesia. The aim of this study was to determine the relationship between sarcopenia and cognitive dysfunction in the early postoperative period of transurethral resection of bladder tumor operation in the elderly population with bladder cancer.

Methods: The cognitive functions of patients over the age of 65 years who underwent transurethral resection of bladder tumor were evaluated before and 24 hours after the surgery with mini-mental tests in this single center, cross sectional study. All patients underwent a preoperative gait test and muscle mass was measured. The muscle strength of the patients with walking speed >0.8 m / sec in the walking test was measured by hand grip dynamometer. Low walking speed and muscle mass, and normal walking speed, but with low handgrip power and muscle mass were the accepted criteria of Sarcopenia.

Results: In the early postoperative period, a decrease in cognitive functions was observed in the population of 54 geriatric patients, 43 of whom were male. The mean age was 74 years in both sarcopenic and non-sarcopenic groups. Cognitive dysfunction was more common in the sarcopenic patient group of 15 patients in the early postoperative period compared to the non-sarcopenic group of 39 patients (P=0.001, P=0.026 respectively). However, this decrease in cognitive function in sarcopenic patients was not statistically significant compared to non-sarcopenic patients (P=0.644).

Conclusion: We demonstrated that cognitive functions decreased in early postoperative period in the geriatric patient population. The decrease in postoperative cognitive functions in sarcopenic patients was higher than that in non-sarcopenic patients, although the difference was not statistically significant. Therefore, larger studies with more patients are needed to achieve a statistically significant difference.

Keywords: Sarcopenia, Geriatrics, Gerontology, Cognition

Öz

Amaç: Sarkopeninin 65 yaş üzeri genel anestezi almış hastalarda ameliyat sonrası erken dönemde kognitif fonksiyonlar üzerine olumsuz etkisinin olup olmadığını gösterir çalışma literatürde yoktur. Postoperatif erken dönemde trans ürektal mesane kanseri rezeksiyonu olmuş yaşlı hasta popülasyonunda sarkopeni ve kognitif fonksiyon bozukluğu ilişkisini saptamak bu çalışmanın amacıdır.

Yöntemler: Trans uretral mesane rezeksiyonu operasyonu geçirecek olan 65 yaş üzeri hasta popülasyonunda; operasyon öncesi ve operasyondan 24 saat sonra erken dönemde minimental test yapılarak kognitif fonksiyonlar tek merkezli kesitsel bu çalışmada değerlendirildi. Tüm hastalara operasyon öncesi yürüme testi yapıldı ve kas kitlesi, kg/m² cinsinden biyoimpedans terazi ile ölçüldü. Yürüme testinde hızı >0,8 m/sn olan hastaların kas gücü ise, el sıkma dinamometresi ile ölçüldü. Düşük yürüme hızı ve kas kütlesi, normal yürüme hızı ancak düşük kavrama gücü ve kas kütlesi sarkopeni kriterleri olarak kabul edildi.

Bulgular: Postoperatif erken dönemde, çalışmaya alınan 43'ü erkek 54 kişilik tüm geriatrik hasta popülasyonunda kognitif fonksiyonlarda azalma saptandı. Hem sarkopenik hem de sarkopenik olmayan grupta ortalama yaş 74 idi. 15 kişilik Sarkopenik hasta grubunda postoperatif erken dönemde kognitif fonksiyon bozukluğu 39 kişilik sarkopenik olmayan gruba göre daha fazlaydı (sırasıyla P=0,001, P=0,026). Ancak Sarkopenik hastalardaki kognitif fonksiyondaki bu azalma Sarkopenik olmayan hastalara göre istatistiksel olarak anlamlı değildi (P=0,644).

Sonuç: Biz bu çalışmada anestezi sonrası erken ameliyat sonrası dönemde kognitif fonksiyonların tüm geriatrik hasta popülasyonunda azaldığını gösterdik. Sarkopenik hasta grubunda postoperatif kognitif fonksiyonlardaki azalma istatistiksel olarak anlamlı olmasa da Sarkopenik olmayanlara göre daha fazladır. Dolayısıyla, istatistiksel olarak anlamlı farkı yakalayacak daha çok hasta sayılı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Sarkopeni, Geriatri, Gerontoloji, Kognisyon

How to cite/Atıf için: Kalyon S, Gümüşkaya PÖ, Özsoy N, Özcan M, Yoldemir ŞA, Toprak İD, Altun Ö, Akarsu M, Çil EÖ, Arman Y, Tükek T. The relationship between sarcopenia and cognitive dysfunction in bladder tumor patients. J Surg Med. 2020;4(9):754-756.

Introduction

Sarcopenia is muscle loss characterized by a decrease in physical performance because of one or more numerous factors such as nutrition, decreased hormone levels and chronic inflammation. Inflammation, especially the proinflammatory cytokines IL-6, IL-1, TNF-alpha, play a prominent role in sarcopenia. It was first described in 1989 by Irwin Rosenberg. Its prevalence is highly different in diverse studies, ranging between 0.9-85.4 percent. Sarcopenia is associated with diabetes mellitus, depression and cardiovascular comorbid diseases, prolonged hospital stays, and increased mortality and morbidity, especially in the geriatric population [1-7].

Although several studies have shown that sarcopenia-related cognitive functions deteriorate more in the long term than non-sarcopenic ones, there are few studies investigating whether sarcopenic patients lose their cognitive functions more than non-sarcopenic patients in short-term stresses (such as anesthesia and operation).

We planned this study to determine whether there is a relationship between sarcopenia and cognitive dysfunction in the early postoperative period in the geriatric patient population.

Materials and methods

After the approval of the Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (Date: 2/14/2017, No:600), patients who visited the internal medicine outpatient clinic for preoperative evaluation were included in the study on a voluntary basis. The acceptance time of volunteers for study was nine months. To standardize the operation and the anesthesia time as much as possible, male and female patients over 65 years of age who were to undergo transurethral resection of bladder tumor (TUR-BT) were selected instead of patients requiring different kinds of surgeries. Patients who were under 65 years of age, who required any surgeries other than TUR-BT, who are under antidepressant and antipsychotic treatments affecting cognitive functions, people with previous dementia, neurological and / or psychiatric diagnoses, and patients whose bioimpedance scales and handgrip manometers could not be measured for any reason were excluded from the study. Mini mental test was performed to evaluate cognitive functions for two times, before and 24 hours after the operation. Appropriate mini-mental test was preferred according to the educational status of the patients. To diagnose sarcopenia, bioimpedance measurements were performed with Tanita BC 532 InnerScan weighing scale and free fat mass index was measured, along with a walking test. Baseline digital handgrip manometer was used to determine the handgrip strength in patients with a walking test speed > 0.8 m / s. Handgrip force was performed 3 times when the patient was standing, with the preference of the strongest arm, while the elbow was at the 90 degree angle close to the body and the average handgrip power was recorded. Free fat mass index (FFMI) was calculated with FFMI calculator using body fat (%), height (cm) and length (kg) and evaluated according to the gender. Handgrip power according to age and Body Mass Index (BMI) was evaluated regarding the Cardiovascular Hearth Survey (CHS) table. Patients with low walking speed and muscle mass, and normal walking speed, but with low handgrip power and muscle mass, were diagnosed with sarcopenia.

Statistical analysis

Power analysis was performed with the G*power (version 3.1.9.7) program. The minimum calculated sample size was 16 (effect size 1.2, alpha error 0.05, power 0.95).

Percentage changes in the preoperative and postoperative cognitive function scores of the patients with and without sarcopenia were examined. The following formula was used to calculate this change:

Percent change (Δ) = (new value - old value) / (old value) X100.

The results were statistically analyzed with SPSS 25.0 version. Non-normally distributed data were evaluated using Mann-Whitney U and Wilcoxon tests. Pearson and spearman correlation tests were used for correlation analyses. Results were presented as mean (standard deviation (SD)). In the statistical evaluation of the data, *P*-value <0.05 was considered significant.

Results

In our study, 54 TUR-BT patients over the age of 65 years, 11 women and 43 men, were included.

Among study participants, 15 were sarcopenic and 39 patients did not have sarcopenia. The mean age was 74 (6) years in both sarcopenic and non-sarcopenic groups. While the mean result of the hand-grip test was 38.4 kg in the non-sarcopenic group, it was 23.5 in the sarcopenic group (*P*=0.004). The free fat mass index was 19.1 in the non-sarcopenic group and 16.6 in the sarcopenic group. A statistically significant difference was found between the non-sarcopenic and the sarcopenic groups regarding BMI, handgrip power, fat, free fat mass index and muscle ratios (*P*=0.01, *P*=0.004, *P*=0.02, *P*=0.001 and *P*=0.01, respectively) However, age, pre- and postoperative water, bone, and internal organ adiposity of the two groups were similar (*P*=0.65, *P*=0.05, *P*=0.09 and *P*=0.15, respectively) (Table 1).

The percentage change in the preoperative and postoperative cognitive function scores was 2.6% in the non-sarcopenic group and 3.1% in the sarcopenic group. There was a statistically significant decrease in postoperative cognitive functions compared with the preoperative results in both non-sarcopenic and sarcopenic groups (*P*=0.01 and *P*=0.026, respectively), however, the percentage changes of sarcopenic and non-sarcopenic groups were similar (*P*=0.644) (Table 2, 3).

Table 1: Comparison of data between sarcopenic and non-sarcopenic groups

	Non-Sarcopenic Patients (n=39) Mean (SD)	Sarcopenic Patients (n=15) Mean (SD)	*P*-value
Age (years)	74.5 (6)	74 (6.6)	0.656
Gender (M/F)	30/9	13/2	0.420
The mean handgrip strength (kg)	38.4 (19)	23 (5.4)	0.004
BMI (kg/m²)	27.8 (5.3)	22.4 (3.2)	0.001
Total Body Fat Percentage	27 (8.8)	21.2 (6.6)	0.028
Total Body Water Percentage	50.1 (6)	53.7 (4.4)	0.058
Free Fat Mass Index (kg/m2)	19.1 (2.7)	16.6 (1.3)	0.001
Total Body Internal Organ Fat Mass (kg)	14.2 (3.1)	12.8 (2.9)	0.150
Total Body Muscle Mass (kg)	53 (10.9)	46.8 (3.8)	0.012
Total Body Bone Mass (kg)	2.7 (0.5)	2.6 (0.4)	0.099

Table 2: Comparison of preoperative and postoperative cognitive function scores of all patients, and non-sarcopenic and sarcopenic group

	Preoperative Cognitive Function Score Mean (SD)	Postoperative Cognitive Function Score Mean (SD)	*P*-value
Al patients (n=54)	26.3 (3.4)	25.6 (3.5)	<0.001
Non-Sarcopenic Patients (n=39)	26.4 (3.1)	25.7 (3)	0.001
Sarcopenic Patients (n=15)	26 (4.3)	25 (4.6)	0.026

Table 3: Comparison of percentage changes between preoperative and postoperative cognitive function scores of non-sarcopenic and sarcopenic patients

	Non-Sarcopenic Patients (n=39)	Sarcopenic Patients (n=15)	*P*-value
Cognitive Function Score Percentage Change (Δ) Mean (SD)	-2.6 (4.7)	-3.1 (4.9)	0.644

Discussion

Although there have been studies in the literature stating that sarcopenia impairs cognitive functions, especially in geriatric patients over a long period of time, there are few studies showing the extent to which acute stress, such as an operation, affects cognition in the geriatric patient population. In fact, there is no study in the literature that evaluates the early postoperative cognitive functions in the sarcopenic patient group. Therefore, this study is a first. In this study, we examined patients over 65 years of age who underwent only TUR-BT operation to standardize patient population, operation, anesthetic agents and duration, and we found that cognitive functions decreased in all patients regardless of sarcopenia in the first 24 hours following surgery.

In the meta-analysis of Chang et al. [1] including 5994 patients, in the study of Cabett Cipolli et al. [8] on 7045 patients and in the studies of Tolea et al. [9] and Landi et al. [10], a strong relationship between sarcopenia and cognitive functions was reported. All previous studies clearly demonstrated the long-term relationship between sarcopenia and cognitive functions [11,12]. However, in our study investigating the early cognitive functions in the case of acute stress in sarcopenic patients, we found that a similar relationship was also present.

Although there is more than one factor in the etiology of sarcopenia, proinflammatory cytokines IL-6 and TNF-alpha play a significant role, especially with increasing age. Surgical trauma also stimulates the inflammatory response and inflammatory cytokines have a negative effect on cognition.

In their study on geriatric patients, Chen et al. [13] showed the relationship between cognitive functions and IL-6 levels on the 3rd postoperative day, reporting that decreased IL-6 levels with peroperative lidocaine administration revealed better postoperative cognitive functions. Similarly, Shan et al. [14] also reported that in the geriatric patient group, cognitive functions were better preserved with the use of Ulinastatin, which has anti-inflammatory effects, and suppresses neutrophil accumulation and activity, regardless of sarcopenia. These studies show that proinflammatory cytokines play an active role in the deterioration of cognitive functions. The greater loss of cognitive function in sarcopenic patients is likely due to proinflammatory cytokines, which also play a role in the etiology.

However, it is difficult to say the exact answer to the question of whether the decrease in muscle mass contributes to the deterioration of cognitive functions after anesthesia in the elderly patient group. Each patient's operation time, pre-existing disease states, different drugs used, the success of the operation, and the operator's experience can affect this process. Therefore, to standardize patients, we tried to recruit similar patients to the same operation team and patients to undergo the same operation. Although this slightly limited the number of patients, we can say that the operation still causes a decrease in cognitive functions in this study. Likewise, the greater decrease in sarcopenic patients showed that in these patients, we should be more careful in terms of postoperative mental changes.

As a result of our study, we found that, although statistically insignificant, there was a higher loss in cognitive functions in sarcopenic patients compared to non-sarcopenic patients, which may be due to the increased postoperative cytokine activity in sarcopenic patients. With larger studies including more patients, statistically significant results may be achieved in revealing the difference.

Limitation

This study has two potential limitations, one being the small number of sarcopenic patients. The second one is selecting patients who have malignancy, because cognitive functions may be affected in cancer patients due to depression or anxiety. Studies with more sarcopenic patients without malignancy could yield more valid results.

Conclusion

In conclusion, it was seen that operation in the geriatric patient population caused a decrease in cognitive functions in both the non-sarcopenic and sarcopenic patients in the early postoperative period. The decrease in cognitive functions in the sarcopenic geriatric group was more pronounced. In the geriatric sarcopenic patient group, more studies with different types of operations, durations of anesthesia, varying anesthetic drugs and measurement of cytokine levels should be conducted in order to explain the mechanism that disrupts the cognitive functions in acute stress conditions such as operation and anesthesia.

References

1. Chang KV, Hsu TH, Wu WT, Huang KC, Han DS. Association Between Sarcopenia and Cognitive Impairment: A Systematic Review and Meta-Analysis. J Am Med Dir Assoc. 2016 Dec 1;17(12):1164.e7-1164.e15. doi: 10.1016/j.jamda.2016.09.013. Epub 2016 Nov 2.
2. Buch A, Carmeli E, Boker LK, Marcus Y, Shefer G, Kıs O, et al. Muscle function and fat content in relation to sarcopenia, obesity and frailty of old age. An overview. Exp Gerontol. 2016;76:25e32.
3. Han DS, Chang KV, Li CM, Lin YH, Kao TW, Tsai KS, et al. Skeletal muscle mass adjusted by height correlated better with muscular functions than that adjusted by body weight in defining sarcopenia. Sci Rep. 2016;6:19457.
4. Pagotto V, Silveira EA. Methods, diagnostic criteria, cutoff points, and prevalence of sarcopenia among older people. Sci World J. 2014;2014:231312.
5. Budui SL, Rossi AP, Zamboni M. The pathogenetic bases of sarcopenia. Clin Cases Miner Bone Metab. 2015;12:22e26.
6. Yanai H. Nutrition for sarcopenia. J Clin Med Res. 2015;7:926e931.
7. Peterson SJ, Braunschweig CA. Prevalence of sarcopenia and associated outcomes in the clinical setting. Nutr Clin Pract. 2016;31:40e48.8
8. Cabett Cipolli G, Sanches Yassuda M, Aprahamian I. Sarcopenia Is Associated with Cognitive Impairment in Older Adults: A Systematic Review and Meta-Analysis. J Nutr Health Aging. 2019;23(6):525-31. doi: 10.1007/s12603-019-1188-8.
9. Tolea MI, Galvin JE. Sarcopenia and impairment in cognitive and physical performance. Clin Interv Aging. 2015 Mar 30;10:663-71. doi: 10.2147/CIA.S76275. eCollection 2015.
10. Landi F, Cruz-Jentoft AJ, Liperoti R, Russo A, Giovannini S, Tosato M, et al. Sarcopenia and mortality risk in frail older persons aged 80 years and older: Results from ilSIRENTE study. Age Ageing. 2013;42:203e209.
11. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults. J Gerontol Ser A Biol Sci Med Sci. 2001;56:146e157.
12. Landi F, Cesari M, Calvani R, Cherubini A, Di Bari M, Bejuit R, et al. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial. Aging Clin Exp Res. 2017 Feb;29(1):89-100. doi: 10.1007/s40520-016-0715-2. Epub 2017 Jan 31.
13. Chen K, Wei P, Zheng Q, Zhou J, Li J. Neuroprotective effects of intravenous lidocaine on early postoperative cognitive dysfunction in elderly patients following spine surgery. Med Sci Monit. 2015 May 15;21:1402-7. doi: 10.12659/MSM.894384.
14. Shan X, Zhang X, Li X, Xu G, Li Z. Effect of ulinastatin on postoperative cognitive function in the elderly with fracture. Zhonghua Yi Xue Za Zhi. 2015 May 26;95(20):1586-9.

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. 2020;4(9):757-760.
DOI: 10.28982/josam.723413

Research article
Araştırma makalesi

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

Relationship between Syntax I - Syntax II and Spielberger State-Trait Anxiety Inventory in stable angina pectoris patients

Kararlı anjina pectoris hastalarında Syntax I - Syntax II ve Spielberger Durumluk-Sürekli Kaygı Ölçeği arasındaki ilişki

Mustafa Çelik [1]

[1] **Department of Cardiology, Ahi Evran University Training and Research Hospital, Kirsehir, Turkey**

ORCID ID of the author(s)
MÇ: 0000-0003-4102-1564

Corresponding author/Sorumlu yazar:
Mustafa Çelik
Address/Adres: AhiEvran Üniversitesi, Eğitim ve Araştırma Hastanesi, Kardiyoloji Anabilim Dalı, Kervansaray Mah. 2019. Sok. No: 1, Posta kodu: 40100, Kırşehir, Türkiye
E-mail: muscelik50@gmail.com

Ethics Committee Approval: The study protocol was approved by the institutional Ethics Committee of Kırşehir Ahi Evran University Medical Faculty. Ethical Committee Decision No: 2018-22/180, Approval Date: 27-11-2018. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolü Kırşehir Ahi Evran Üniversitesi Tıp Fakültesi kurumsal Etik Kurulu tarafından onaylandı. Etik Kurul Karar No: 2018-22/180, Onay Tarihi. 27-11-2018. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/27/2020
Yayın Tarihi: 27.09.2020

Abstract

Aim: State-trait anxiety inventory (STAI) is a parameter used to measure anxiety levels. SYNTAX score is an anatomically based scoring system used to determine the complexity of coronary artery disease (CAD). We investigated the relationship between SYNTAX-I, SYNTAX-II scores, and STAI.

Methods: A questionnaire-based cross-sectional study was conducted on 150 consecutive patients (54 female and 96 male) who presented to our hospital with the diagnosis of stable angina pectoris and underwent elective coronary angiography (CAG). Patients answered the STAI questionnaire at least 1 hour prior to elective CAG. Assessment of the cineangiographic images was performed by two experienced cardiologists blinded to the study data.

Results: The evaluation of Spearman's Rho correlation coefficients revealed a significant, strong, and positive relationship between STAI score and SYNTAX I (r=0.757, P<0.001), as well as SYNTAX II (r=0.811, P<0.001). SYNTAX I and SYNTAX II scores were also significantly positively correlated (r=0.681, P<0.001).

Conclusion: We found a strong and significant correlation between SYNTAX I, SYNTAX II and STAI score variables. STAI score level is an independent and strong predictor of SYNTAX score and can be used a pretest indicator to identify patients with CAD.

Keywords: Syntax-I, Syntax-II, Spielberger State-Trait Anxiety Inventory, Stable angina pectoris

Öz

Amaç: Durumluk sürekli kaygı ölçeği (STAI), kaygı düzeylerini ölçmek için kullanılan bir parametredir. SYNTAX skoru, koroner arter hastalığının (KAH) ciddiyetini belirlemek için kullanılan anatomik tabanlı bir skorlama sistemidir. Çalışmamızda SYNTAX-I ve SYNTAX-II skorları ile STAI arasındaki ilişkiyi araştırdık.

Yöntemler: Anket tabanlı kesitsel bir çalışma planlandı. Hastanemize stabil anjina pektoris tanısı ile başvuran ve elektif koroner anjiyografi (KAG) uygulanan 150 ardışık hasta dahil ettik.(54 kadın ve 96 erkek). Hastalar STAI anketini KAG'den en az 1 saat önce cevaplandırdı. Çalışma verisine körlenmiş iki deneyimli kardiyolog tarafından sineangiyografik görüntüler değerlendirildi.

Bulgular: Spearman'ın Rho korelasyon katsayılarının değerlendirilmesi STAI skoru ile SYNTAX I arasında güçlü ve pozitif bir istatistiksel korelasyon olduğunu ortaya koydu (r=0,757, P<0,001). STAI skoru ile SYNTAX II de pozitif ve kuvvetli bir ilişkiye sahipti (r=0,811, P<0,001). SYNTAX I ve SYNTAX II arasındaki pozitif ilişkinin istatistiksel olarak anlamlı olduğu bulunmuştur (r=0,681, P<0,001).

Sonuç: Çalışmamızda SYNTAX I, SYNTAX II ve STAI skor değişkenleri arasında güçlü ve istatistiksel olarak anlamlı bir ilişki bulunmuştur. STAI skor seviyesi, SYNTAX skorunun bağımsız ve güçlü bir ön gördürücü olabilir ve koroner arter hastalığını tanımlamak için ön test olarak kullanılabilir.

Anahtar kelimeler: Syntax-I, Syntax-II, Spielberger Durumluk-Sürekli Kaygı Ölçeği, Stabil anjina pektoris

How to cite/Atıf için: Çelik M. Relationship between Syntax I - Syntax II and Spielberger State-Trait Anxiety Inventory (STAI) in stable angina pectoris patients. J Surg Med. 2020;4(9):757-760.

Introduction

Coronary artery disease (CAD) is common in the general population and affects majority of the adults older than 60 years of age. CAD is estimated to result in 17.3 million deaths per year worldwide [1,2]. Although CAD death rates have decreased in the last 40 years, it remains to be responsible for one third or more of the deaths in individuals older than 35 years of age [3-5]. Despite the presence of many methods for CAD diagnosis, including effort stress test, dynamic echocardiogram, cardiac ultrasound and myocardial perfusion scintigraphy, coronary angiography (CAG) is still the standard criterion for its spatial and temporal resolution superiority.

Patients to undergo CAG are hospitalized and monitored. They may feel fear, anxiety and stress while waiting for the angiography procedure. Studies reported anxiety in 82% of these patients [6,7], the incidence of which was higher than the other patients and the general population [8].

Elevated levels of anxiety cause restricted perspective on the compliance to intervention at the time of diagnosis and treatment and after hospitalization [9,10]. The state-trait anxiety inventory (STAI) is a parameter used to measure anxiety levels [11].

State anxiety can be defined as fear, nervousness, discomfort, and arousal of the autonomic nervous system induced temporarily by situations perceived as dangerous (i.e. how a person is feeling at the time of a perceived threat), while trait anxiety can be defined as a relatively enduring disposition to feel stress, worry, and discomfort. The study titled "The Relationship between Cardiac Symptoms and Anxiety" has shown the association between coronary artery disease and anxiety severity [12].

The 'Synergy Between Percutaneous Coronary Intervention (PCI) with TAXUS and Cardiac Surgery (SYNTAX) score (www.syntaxscore.com) is an anatomically based scoring system used to determine the complexity of CAD, and a guide for decision-making between coronary artery bypass grafting (CABG) surgery and PCI. The SYNTAX score is related to mortality and morbidity in stable CAD [13,14].

In this study, we investigated the relationship between SYNTAX-I and SYNTAX-II scores, which have been used in the recent years to demonstrate the severity of coronary artery disease, and STAI.

Materials and methods

Study population

The questionnaire-based cross-sectional study was conducted between January - June 2019 at a single center. The sample size of the study was calculated by power analysis, with the effect size d=0.5, Power (1-**β** err prob) = 0.85 using G*power 3.1.9.7.

Our study included a total of 150 consecutive patients (54 female and 96 male) who presented to our hospital with the diagnosis of stable angina pectoris and underwent elective CAG. CAG was performed to investigate ischemic heart disease in patients with a positive treadmill test, myocardial perfusion scintigraphy, or typical chest pain.

Exclusion criteria included known CAD, acute coronary syndromes, patients with any psychiatric disorder history who receive related medical treatment, malignancy, liver and/or kidney disease, systemic inflammatory disease.

Either a written or an oral-witnessed informed consent was obtained from all participating patients. This study was performed in accordance with the principals of the Declaration of Helsinki. The study protocol was approved by the institutional Ethics Committee of Kırşehir Ahi Evran University Medical Faculty (Ethical Committee Decision No: 2018-22/180, Approval Date. 27-11-2018).

Coronary angiography

Once the written informed consent for cardiac catheterization was obtained, coronary angiography was performed in all patients using the standard techniques.

Calculation of the SYNTAX I and SYNTAX II Scores

Cineangiographic images were assessed with Axiom (Siemens Medical Solution, Erlangen, Germany) workstation by two experienced cardiologists blinded to the study data. Each lesion with a diameter stenosis ≥50% in coronary vessels ≥1.5 mm in diameter was scored using the online SYNTAX score calculator (http://www.syntaxscore.com). If the cardiologists' opinions about the lesions differed, the ultimate score was decided by averaging the scores calculated by each cardiologist. SS1 and SS2 scores were obtained for each patient.

STAI score

Stable angina pectoris patients answered the STAI questionnaire at least 1 hour prior to elective CAG procedure. The STAI questionnaire was made by the nurse of the cardiology department who was blind to the patients. STAI is a well-standardized, 40 item questionnaire, designed as a self-report instrument for the evaluation of both state and trait anxiety.

Statements in the STAI are also rated on a four-point scale (almost never, sometimes, often, and almost always). The overall (total) score for STAI ranges from a minimum of 20 to a maximum of 80; STAI scores are commonly classified as 'no or low anxiety' (20–37), 'moderate anxiety' (38–44), and 'high anxiety' (45–80) [11].

Statistical analysis

Statistical analyses of the study were performed on Statistical Package for Social Sciences version 21.0 software for Windows (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp., USA). Normality was tested by using Kolmogorov-Smirnov and Shapiro-Wilk tests. Group comparisons were evaluated with Mann-Whitney U test. Spearman's Rho rank correlation coefficient was used to determine the relationship between variables. *P*-value <0.05 was considered significant for all statistical analyses.

Results

Descriptive statistics of the study participants are presented in Table 1 in terms of n (%). There were 96 males and 54 females (total of 150 patients) and their mean age was 56.81 (9.66) years.

Spearman's Rho correlation coefficients between the variables of SYNTAX I, SYNTAX II and STAI scores are presented in Table 2. The evaluation of these coefficients

revealed a strong and positive significant correlation between STAI score and SYNTAX I (r=0.757, $P<0.001$), as well as SYNTAX II (r=0.811, $P<0.001$). SYNTAX I and SYNTAX II scores were also significantly, positively correlated (r=0.681, $P<0.001$).

The evaluation of the effect of gender on STAI, SYNTAX I and SYNTAX II values showed that men had insignificantly higher STAI scores [35.0 (29.0−44.0)] than women [30.0 (28.75−37.25)], ($P=0.077$). The effect of gender on SYNTAX I and SYNTAX II was also insignificant ($P=0.118$, $P=0.103$). There was no statistically significant difference in terms of STAI score, SYNTAX I and SYNTAX II values between smoking and non-smoking patients, patients with and without COPD, and those with and without HT ($P>0.05$ for all). STAI score and SYNTAX II values of DM and non-DM patients were similar ($P=0.208$, $P=0.406$), however, they significantly differed in terms of SYNTAX I values ($P=0.022$). SYNTAX I value of DM patients [14.0 (9.50−16.75)] was higher than non-DM patients [7.5 (5.0−12.0)] (Table 3).

Table 1: Descriptive statistics of the variables

Variables		n (%)
Sex	Male	96 (64)
	Female	54 (36)
Smoking	No	110 (73.3)
	Yes	40 (26.7)
DM	No	122 (81.3)
	Yes	28 (18.7)
HT	No	94 (62.7)
	Yes	56 (37.3)
COPD	No	118 (78.7)
	Yes	32 (21.3)

DM: Diabetes Mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease

Table 2: Spearman's Rho correlation coefficients

	SYNTAX I	SYNTAX II	STAI Score
SYNTAX I	1	0.681**	0.757**
SYNTAX II		1	0.811**
STAI score			1

** Significant at 0.01 level

Table 3: Descriptive statistics of SYNTAX I, SYNTAX II and STAI score

		STAI score	SNYTAX I	SYNTAX II
Sex	Female (n=54)	30.0(28.753−7.25)	7.50(5.0−12.00)	16.5(14.75−19.00)
	Male (n=96)	35.0(29.0−44.0)	9.00(6.00−19.00)	19.00(15.0−22.00)
		$P=0.077$	$P=0.118$	$P=0.103$
Smoking	No	33.0(28.5−38.5)	9.00(5.50−14.5)	17.0(15.0−22.0)
	Yes	37.0(30.0−44.0)	9.0(5.25−14.62)	18.5(16.25−21.95)
		$P=0.668$	$P=0.295$	$P=0.127$
COPD	No	33.0(28.75−38.25)	9.0(5.0−14.25)	17.0(15.0−22.0)
	Yes	37.0(30.0−44.00)	9.0(6.0−15.00)	18.3(15.0−22.0)
		$P=0.176$	$P=0.837$	$P=0.652$
HT	No	33.0(27.75−38.0)	7.50(5.0−12.25)	17.0(15.0−22.0)
	Yes	37.0(29.0−44.0)	9.0(6.0−15.5)	17.0(15.0−22.0)
		$P=0.060$	$P=0.191$	$P=0.735$
DM	No	33.0(28.25−39.0)	7.5(5.0−12.0)	17.0(15.0−21.77)
	Yes	35.0(30.5−45.5)	14.0(9.50−16.75)	20.3(15.0−26.75)
		$P=0.208$	$P=0.022$	$P=0.406$

COPD: Chronic obstructive pulmonary disease, HT: Hypertension, DM: Diabetes Mellitus, Values were given as median (25-75 IQR)

Discussion

In this study, the correlations between STAI score, SYNTAX I and SYNTAX II were worth noting. In daily clinical practice, using a specific questionnaire before CAG procedure provides new data on the relationship between anxiety levels and the severity of coronary artery disease. CAD is a compelling cause of death and disability in developed and developing countries. It is estimated to develop in almost half of the middle-aged men and one third of the middle-aged women in USA [15]. CAG is essential for the diagnosis of CAD. Anxiety is commonly observed in patients prior to the CAG procedure. Patients may experience fear, anxiety, and stress due to environmental factors, personal factors, and lack of information about the procedure to be performed while they wait for it.

Anxiety causes the secretion of norepinephrine and epinephrine by activating the sympathetic nervous system through a series of physiological and biochemical pathways. As result, heart rate, blood pressure, respiratory rate and myocardial oxygen need increase.

Depression state and anxiety are strongly correlated with CAD. Anxiety is quite common among these patients. In a study investigating the clinical value of anxiety in these patients, a relationship was shown between anxiety and cardiac symptom indicators (nocturnal angina, nitroglycerin use, shortness of breath and angina frequency) [12].

We evaluated the extent and severity of CAD with the SYNTAX score, the most popular scoring tool. The SYNTAX score is vital in determining the treatment strategy by detecting the anatomical extent of CAD. It is also an independent predictor of overall vascular mortality, cardiac death, myocardial infarction, and target vessel revascularization ratio in patients with acute coronary syndrome [16,17].

In a study by Rutledge et al. [12] evaluating anxiety and the severity of coronary artery disease, Gensini score was used instead of SYNTAX and only female patients were included. Authors concluded that anxiety should be addressed more carefully in female patients with suspected CAD. The most recent studies and meta-analyses support associations between anxiety, CAD incidence and cardiac events in both genders [18-20].

The relationship between anxiety and CAD is debatable. Cardiac symptoms can cause anxiety, symptom sensitivity may be increased among patients with anxiety and direct physiological changes due to anxiety may be observed [21].

There are different anxiety scorings available in the evaluation of the anxiety levels. Mei et al. [22] assessed the anxiety level by using Hamilton Anxiety Rating Scale (HAM-A) in patients to undergo CAG. The HAM-A is a clinician-based questionnaire; however, being available in the public domain, it has been employed as a self-scored survey. It consists of 14 symptom-defined elements and caters for both psychological and somatic symptoms [23]. For the scoring of HAM-A based on symptoms, STAI, designed as a self-report instrument for the evaluation of both state and trait anxiety, was used.

The presence and extent of CAD closely affects human health and the cost of treatment [24].

In our study, there was a correlation between anxiety levels and CAD in patients with stable coronary artery disease. For CAD diagnosis, anxiety level can be used as a new parameter in addition to others including effort stress test, dynamic echocardiogram, cardiac ultrasonography, and myocardial perfusion scintigraphy.

Limitation

There were some obvious limitations in the current study. First, our study population is relatively small and future studies conducted on larger populations may yield a correlation between STAI and SYNTAX I and SYNTAX II scores in stable angina pectoris patients. Secondly, this is a single-center study and demographic, genetic, and racial features of our patient cohort display distinctions from that of other centers.

Future perspective

Dynamic echocardiogram, effort stress test, cardiac ultrasound and myocardial perfusion scintigraphy are the currently used noninvasive pretests for the diagnosis of CAD. The addition of STAI anxiety score to non-invasive tests can increase the pre-test probability of non-invasive tests.

Conclusion

In our study, a strong and statistically significant correlation was found between SYNTAX I, SYNTAX II and STAI score variables. STAI score is associated with a higher SYNTAX score in patients with stable CAD. STAI score level is an independent and strong predictor of the SYNTAX score and may be used as a pre-test indicator to identify patients with CAD at an elevated risk for atherosclerotic burden.

References

1. Laslett LJ, Alagona P Jr, Clark BA 3rd, Drozda JP Jr, Saldivar F, Wilson SR, et al. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. J Am Coll Cardiol. 2012 Dec 25;60(25 Suppl):S1-49. doi: 10.1016/j.jacc.2012.11.002.
2. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation. 2015 Oct 27;132(17):1667-78. doi: 10.1161
3. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008 Jan 29;117(4):e25-146. doi: 10.1161/CIRCULATIONAHA.107.187998
4. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J. 2014 Nov 7;35(42):2950-9. doi: 10.1093/eurheartj/ehu299.
5. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018 Mar 20;137(12):e67-e492. doi: 10.1161/CIR.0000000000000558.
6. Caldwell PH, Arthur HM, Natarajan M, Anand SS. Fears and beliefs of patients regarding cardiac catheterization. Soc Sci Med. 2007 Sep;65(5):1038-48. doi: 10.1016/j.socscimed.2007.04.010.
7. De Jong-Watt WJ, Arthur HM. Anxiety and health-related quality of life in patients awaiting elective coronary angiography. Heart Lung. 2004 Jul-Aug;33(4):237-48. doi: 10.1016/j.hrtlng.2004.03.006.
8. Heikkilä J, Paunonen M, Laippala P, Virtanen V. Nurses' ability to perceive patients' fears related to coronary arteriography. J Adv Nurs. 1998 Dec;28(6):1225-35. doi: 10.1046/j.1365-2648.1998.00852.x.
9. Guzzetta CE. Relationship between stress and learning. ANS Adv Nurs Sci. 1979 Jul;1(4):35-49. doi: 10.1097/00012272-197907000-00004.
10. Nyamathi A, Kashiwabara A. Preoperative anxiety. Its affect on cognitive thinking. AORN J. 1988 Jan;47(1):164-70. doi: 10.1016/s0001-2092(07)70065-0.
11. Pedrabissi L, Rolland JP, Santinello M. Stress and burnout among teachers in Italy and France. J Psychol. 1993 Sep;127(5):529-35. doi: 10.1080/00223980.1993.9914889.
12. Rutledge T, Kenkre TS, Bittner V, Krantz DS, Thompson DV, Linke SE, et al. Anxiety associations with cardiac symptoms, angiographic disease severity, and healthcare utilization: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation. Int J Cardiol. 2013 Oct 3;168(3):2335-40. doi: 10.1016/j.ijcard.2013.01.036.
13. Kurtul A, Murat SN, Yarlioglues M, Duran M, Ocek AH, Koseoglu C, et al. Usefulness of Serum Albumin Concentration to Predict High Coronary SYNTAX Score and In-Hospital Mortality in Patients With Acute Coronary Syndrome. Angiology. 2016 Jan;67(1):34-40. doi: 10.1177/0003319715575220.
14. van Gaal WJ, Ponnuthurai FA, Selvanayagam J, Testa L, Porto I, Neubauer S, et al. The Syntax score predicts peri-procedural myocardial necrosis during percutaneous coronary intervention. Int J Cardiol. 2009 Jun 12;135(1):60-5. doi: 10.1016/j.ijcard.2008.03.
15. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. Lancet. 1999 Jan 9;353(9147):89-92. doi: 10.1016/S0140-6736(98)10279-9.
16. Acet H, Ertaş F, Bilik MZ, Aydın M, Yüksel M, Polat N, et al. The relationship of TIMI risk index with SYNTAX and Gensini risk scores in predicting the extent and severity of coronary artery disease in patients with STEMI undergoing primary percutaneous coronary intervention. Ther Adv Cardiovasc Dis. 2015 Oct;9(5):257-66. doi: 10.1177/1753944715574814.
17. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005 Aug;1(2):219-27.
18. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol. 2010 Jun 29;56(1):38-46. doi: 10.1016/j.jacc.2010.03.034.
19. Watkins LL, Blumenthal JA, Babyak MA, Davidson JR, McCants CB Jr, O'Connor C, et al. Phobic anxiety and increased risk of mortality in coronary heart disease. Psychosom Med. 2010 Sep;72(7):664-71. doi: 10.1097/PSY.0b013e3181e9f357.
20. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: a meta-analysis. Psychosom Med. 2010 Jul;72(6):563-9. doi: 10.1097/PSY.0b013e3181dbff97.
21. Valeriani M, Sestito A, Le Pera D, De Armas L, Infusino F, Maiese T, et al. Abnormal cortical pain processing in patients with cardiac syndrome X. Eur Heart J. 2005 May;26(10):975-82. doi: 10.1093/eurheartj/ehi229.
22. Mei L, Miao X, Chen H, Huang X, Zheng G. Effectiveness of Chinese Hand Massage on Anxiety Among Patients Awaiting Coronary Angiography: A Randomized Controlled Trial. J Cardiovasc Nurs. 2017 Mar/Apr;32(2):196-203. doi: 10.1097/JCN.0000000000000309.
23. Thompson E. Hamilton Rating Scale for Anxiety (HAM-A). Occup Med (Lond). 2015 Oct;65(7):601. doi: 10.1093/occmed/kqv054.
24. Hayıroğlu Mİ, Çınar T, Bıçakçı B, Dağaşan İ, Demir K, Keskin M, et al. Predictors of femoral hematoma in patients undergoing elective coronary procedure: a trigonometric evaluation. Int J Cardiovasc Imaging. 2018 Aug;34(8):1177-84. doi: 10.1007/s10554-018-1339-8.

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. 2020;4(9):761-765.
DOI: 10.28982/josam.784382

Research article
Araştırma makalesi

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

Image-guided biopsy-proven lung and skeletal tuberculosis cases mimicking malignancy

Görüntüleme eşliğinde biyopsi ile kanıtlanmış olan, maligniteyi taklit eden akciğer ve iskelet tüberkülozu vakaları

Cennet Şahin [1], Eyüp Çamurcuoğlu [1], Burçin Ağrıdağ Üçpınar [1], Selahattin Durmaz [1]

[1] University of Health Sciences, Istanbul Sisli Hamidiye Etfal Training and Research Hospital, Radiology Clinic, Istanbul, Turkey

ORCID ID of the author(s)
CŞ: 0000-0002-8695-327X
EÇ: 0000-0002-2382-2555
BAÜ: 0000-0001-5406-9116
SD: 0000-0002-2456-9483

Corresponding author/Sorumlu yazar:
Cennet Şahin
Address/Adres: Sağlık Bilimleri Üniversitesi, İstanbul Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi, Radyoloji Kliniği, İstanbul, Türkiye
E-mail: cennetsahin2@hotmail.com

Ethics Committee Approval: This study was approved by Sisli Hamidiye Etfal Education and Research Hospital Ethical Committee (Number: 2506; Date: 9/3/2019). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından onaylandı (Sayı: 2506; Tarih: 03.09.2019). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Previous presentation: This study is accepted as an electronical poster presentation in CIRSE (European Society of Cardiovascular and Interventional Radiology) 2020 (September 2020, Munich).

Published: 9/28/2020
Yayın Tarihi: 28.09.2020

Abstract

Aim: Tuberculosis diagnosis may be challenging and percutaneous biopsy may be required for definitive diagnosis. In this study, we aimed to investigate the utility of percutaneous biopsy in diagnosis of tuberculosis and radiological features of the tuberculosis cases diagnosed by image-guided biopsy.

Methods: The patients who were diagnosed with tuberculosis by image-guided biopsy between 2016 and 2020 in our institution were reviewed retrospectively in these case series. Histories of malignancy or immune deficiency, age and genders of the patients, localizations and radiological imaging findings of the lesions, needle types, imaging methods used for the biopsies and presumptive diagnoses before the biopsies were noted.

Results: A total of 16 patients (5 Females, 11 Males) with a mean age of 41 years (range: 17-74 years) had image-guided biopsy with presumptive diagnosis of infection or malignancy. Four patients had transthoracic core-needle-biopsy for lung masses, 12 had curettage-bone-biopsy for lytic lesions of vertebral and pelvic bones under CT-guidance. Four of the patients had immune deficiency and one had a history of malignancy. All patients were diagnosed with tuberculosis by both histopathological and culture analysis.

Conclusion: Image-guided-biopsy is safe and useful in the diagnosis of tuberculosis cases who could not be diagnosed by laboratory and sputum tests or those with presumptive diagnoses of malignancy. Tuberculosis should be kept in mind during percutaneous biopsy of radiologically suspicious cases as a differential diagnosis, even though they are clinically negative.

Keywords: Tuberculosis, Polymerase chain reaction, Biopsy, Diagnosis

Öz

Amaç: Tüberküloz tanısı bazı hastalarda zor olabilir ve kesin tanı için perkütan biyopsi gerekebilir. Bu çalışmada, görüntüleme eşliğinde biyopsi ile tanı alan tüberküloz olgularının radyolojik özelliklerini ve tüberküloz tanısında perkütan biyopsinin tanı koymadaki faydasını paylaşmayı amaçladık.

Yöntemler: Kurumumuzda 2016-2020 yılları arasında görüntüleme eşliğinde biyopsi ile tüberküloz tanısı alan hastalar, bu vaka serisi çalışmasında retrospektif olarak incelendi. Hastaların yaş ve cinsiyet bilgileri, biyopsi öncesi malignite veya immün yetersizlik öykülerinin olup olmadığı, lezyonların lokalizasyonları ve radyolojik görüntüleme bulguları, biyopsi için kullanılan iğne tipleri ve görüntüleme yöntemleri ile biyopsi öncesi ön tanıları not edildi.

Bulgular: Toplam 16 hastaya (5 Kadın, 11 Erkek; ortalama yaş 41; yaş aralığı 17-74), enfeksiyon veya malignite varsayımıyla birlikte görüntü rehberliğinde biyopsi yapıldı. Dört hastaya BT kılavuzluğunda akciğer kitleleri için transtorasik kalın iğne biyopsisi, 12 hastaya vertebral ve pelvik kemiklerdeki litik lezyonlar için kemik-küretaj biyopsisi uygulandı. Hastaların dördünde immün yetmezlik ve birinde malignite hikayesi vardı. Tüm hastalara hem histopatolojik hem de kültür analizi ile tüberküloz tanısı kondu.

Sonuç: Görüntüleme rehberliğinde biyopsi, laboratuvar ve balgam testleri ile teşhis edilemeyen veya malignite ön tanısı olan tüberküloz vakalarının tanısında güvenli ve yararlıdır. Radyolojik olarak şüpheli vakaların perkütan biyopsi işlemi sırasında, klinik olarak negatif de olsa, ayırıcı tanı olarak tüberküloz akılda tutulmalıdır.

Anahtar kelimeler: Tüberküloz, Polimeraz zincirleme reaksiyonu, Biyopsi, Teşhis

How to cite/Atıf için: Şahin C, Çamurcuoğlu E, Üçpınar BA, Durmaz S. Image-guided biopsy-proven lung and skeletal tuberculosis cases mimicking malignancy. J Surg Med. 2020;4(9):761-765.

Introduction

Tuberculosis (TB) is an important public health issue all over the world [1]. It has a higher incidence among people with immunodeficiency. A well-known and frequent form of the infection is lung TB. In some cases, TB bacillus can also affect many other systems and organs such as the lymphatics, central nervous system, urogenital tract, and the musculoskeletal system [1,2].

Diagnosis involves positive blood and sputum tests for active tuberculosis, that are supported by clinical history. Sometimes, the diagnosis of tuberculosis may be challenging, and it may mimic malignancy [3]. Due to the steadily decreased incidence in many countries, differential diagnosis of TB may be overlooked. That can cause overuse of diagnostic tests, delay in diagnosis and even death [4]. Thus, being familiar with common radiological features of TB is important for differential diagnosis and treatment.

Tuberculosis infection (TBI) in the bones and lungs may mimic primary or secondary involvement of malignancy [5-10]. The bone (especially spinal bones) and the lungs are the most frequent sites of metastasis in patients with a primary cancer. Both typical TBI and cancer may show similar radiological findings in the lungs and bones: Solitary or multiple nodular lesions in the lung parenchyma with or without cavitation, consolidations with irregular margins and thick-walled cavities may be present in both. In some cases, differentiating one from another by imaging is challenging. In spinal vertebral bodies, paraspinal soft tissue and intervertebral disc involvement may accompany destructive-lytic lesions with or without compression fractures [11,12]. Continuous vertebral body involvement with skip lesions may be present in both TBI and malignancy due to hematogenous spreads. Thus, especially when the patient has ambiguous laboratory findings and clinical symptoms, Computed Tomography (CT)-guided percutaneous biopsy is a valuable diagnostic tool to confirm the diagnosis by pathological and microbiological tests [13,14].

Diagnostic yield of image-guided biopsy for tuberculosis has been investigated in a few studies [13,14]. However, these studies investigated lung or bone tuberculosis cases separately. We have not encountered any studies evaluating lung and bone cases together. To the best of our knowledge, this is one of the very few studies investigating both in one study. We aimed to share the utility of percutaneous biopsy in the diagnosis of lung and bone tuberculosis and review the radiological features of the tuberculosis cases diagnosed by image-guided biopsy in our institution.

Materials and methods

This retrospective study was approved by our institution's ethical committee (Sisli Hamidiye Etfal Education and Research Hospital; Number: 2506; Date: 9/3/2019). The patients who had a diagnosis of tuberculosis by image-guided biopsies between 2016 and 2020 in our institution were reviewed retrospectively. Regardless of underlying immunodeficiency or a history of cancer, male and female patients of all age groups were included in the study. Informed patient consent was obtained from all patients before image-guided biopsy interventions. Coagulation profile, antiplatelet-anticoagulant medication usage and capability for the procedure of the patients were evaluated before the biopsies. Preprocedural radiological examinations were reviewed before planning the biopsies. A semi-automatic core needle (18 Gauge, 15 cm) was used for trans-thoracic lung mass biopsies, a bone biopsy needle (11 Gauge, 10 cm) was used for curettage bone biopsies and a 20 Gauge Chiba was used for Fine Needle Aspiration Biopsies (FNAB). Same sized needles were used for every patient to prevent a potential source of bias. The biopsies were performed under CT (Toshiba, Alexion, Japan and Siemens, Somatom Emotion, Germany) guidance in the CT room or under ultrasound (US) (Mindray, China) guidance in outpatient clinic room in our institution. All the biopsies were performed under local analgesia and aseptic conditions. The biopsy samples were obtained from the most suspicious and solid parts of the masses. The samples were fixed in formalin for core needle and curettage biopsies. Those obtained by FNAB were prepared as cell blocks fixed in 96% alcohol. As a routine procedure in our clinic, in case of any suspicion of infection, samples were obtained for culture analyses. All patients had histopathological and microbiological analysis (including polymerase chain reaction (PCR) for tuberculosis) for either malignancy or infection. After the biopsy, patients were observed in the hospital for about 2 hours for complications. Radiological images, histopathological results and laboratory tests were reviewed from picture archiving communication system (PACS) and hospital information system (HIS) retrospectively. Localizations, sizes and multiplicity of all the lesions were evaluated. For lung masses, presence of cavitation, involvement of surrounding lung parenchyma, presence of lymphadenopathy in the mediastinum and pleural effusion was noted. For bone lesions, involvement of adjacent joint, intervertebral disc or surrounding soft tissue was noted. History of malignancy or immune deficiency, age and gender of the patients, localizations and radiological imaging findings of the lesions, needle types, imaging methods used for the biopsies and presumptive diagnosis before the biopsies were recorded. The demographical characteristics of the patients, localizations of the lesions and histories of malignancy or immune deficiency is presented in Table 1.

Statistical analysis

For statistical analysis, Statistical Package for the Social Sciences (SPSS) for Windows (Version 21.0, Chicago, SPSS Inc.) program was used. Descriptive statistics were presented as number and percentage for categorical variables and as mean, standard deviation, minimum, maximum, and median for numerical variables. Ratios in independent groups were tested by Chi-Square Analysis.

Results

A total of 16 patients (5 Females, 11 Males) with a mean age of 41 years (range: 17-74 years) had image guided biopsies with presumptive diagnoses of infection or malignancy. Four patients had transthoracic core needle biopsy for lung masses, and 12 had curettage-bone-biopsy for lytic lesions of vertebral and pelvic bones under CT-guidance. Four of the patients had immune deficiency and one had a history of malignancy (Table 1). All patients were diagnosed with

tuberculosis by both histopathological and culture analysis with positive PCR tests**.**

Among 4 lung lesions, 75% presented as solitary cavitary nodular lesions while 25% were non-cavitary multiple nodular lesions (in the patient with a history of nasal squamous cell cancer and differential diagnosis of metastasis) (Figure 1 and 2). Mediastinal lymphadenopathy accompanied 75% of the lung lesions while pleural effusion was present in 25%. All bone lesions, which presented as osteolytic lesions, were localized in the axial skeleton (67% in spinal vertebra columns, 33% in pelvic bones) (Figure 3, 4 and 5). All the bone lesions were multifocal except the four that were localized in pelvic bones. Intervertebral disc or adjacent joint involvement was present in all bone lesions. Four patients had immune deficiency (1 had tuberculous spondylodiscitis previously, 2 were Human Immunodeficiency Virus (HIV) positive, 1 had Systemic lupus erythematosus (SLE) disease) and 1 had a history of nasal squamous cell cancer. A total of 19% of the patients were immigrants. None of the patients with spine lesions had a history of disc operation.

A total of 80% of the patients had pain that was unresponsive to medical treatment. Seventy-six percent had weight loss. Three patients with lung lesions had cough while the fourth one, whose lung lesions were incidentally detected during cancer follow-up imaging, did not. White blood cell (WBC) and C-reactive protein (CRP) counts were in normal ranges in 81% and 43% of the patients, respectively. In our hospital, since the patients were not referred for anti-TB therapy without a definite diagnosis proven microbiologically, the patients with presumed to have infection. Those who did not improve with routine antibiotherapy and anti-inflammatory drugs were referred for percutaneous biopsy to find out the causative pathogen and rule out a malignancy. No significant complication was observed during treatment or the recovery period according to Society of Interventional Radiology (SIR)-complication criteria [15].

Table 1: List of patients with lesion localizations

Patients	Gender	Age	Lesion localization	Malignancy or immune deficiency history in background
1	M	62	Right lung, lower lobe	No
2	M	71	Left lung, lingular segment	Yes, nasal squamous-cell carcinoma
3	M	74	Right lung, lower segment	No
4	M	41	Right lung, apex	No
5	F	19	Bone, L3 spine vertebra	No
6	F	33	Bone, right sacroiliac	No
7	F	34	Bone, L4 spine vertebra	No
8	M	37	Bone, L3 spine vertebra	No
9	M	30	Bone, D10 spine vertebra	No
10	M	33	Bone, L4 spine vertebra	No
11	M	37	Bone, iliac bone	Yes, HIV (+)
12	F	40	Bone, ischium	Yes, Systemic lupus erythematosus
13	M	45	Bone, L4 spine vertebra	Yes, HIV (+)
14	F	42	Bone, acetabulum	No
15	M	39	Bone, L5 spine vertebra	Yes, tuberculosis spondylodiscitis
16	M	17	Bone, L5 spine vertebra	No

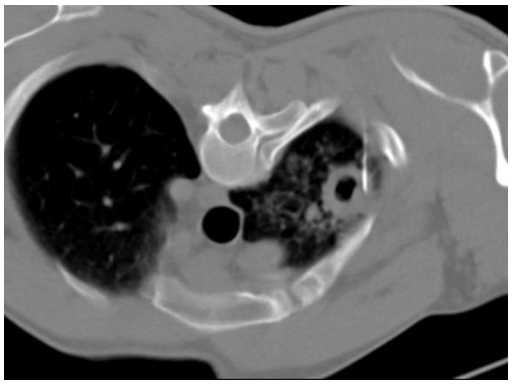
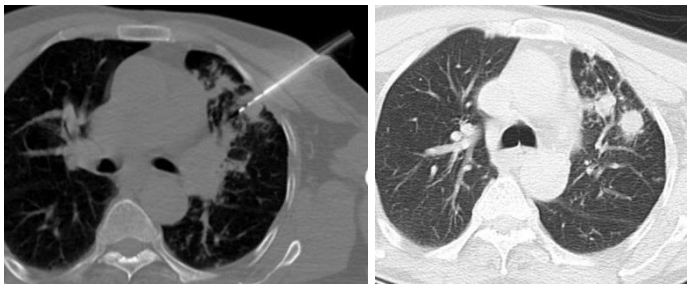


Figure 1: A 41-year-old heavy smoker male without any malignancy history. The patient was referred with the presumptive diagnosis of malignancy. Axial CT scan shows the thick walled cavitated lesion with irregular margins and ground glass opacity in surrounding lung parenchyma. He was diagnosed with tuberculosis with a positive PCR test both microbiologically and histopathologically after CT-guided transthoracic biopsy.



Figures 2: A 71-year-old patient with nasal squamous cell cancer history. The patient was referred with the presumptive diagnosis of metastasis. Axial CT scan shows the multi-nodular lesions with irregular margins and ground glass opacity in surrounding lung parenchyma. The patient had CT-guided percutaneous core needle biopsy. Histopathological and microbiological test results revealed tuberculosis infection with a positive PCR test after CT-guided transthoracic biopsy.

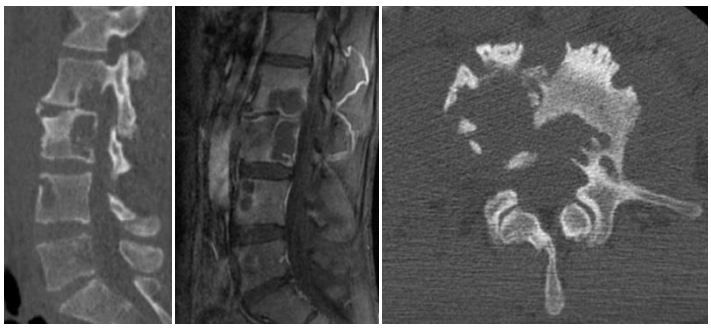
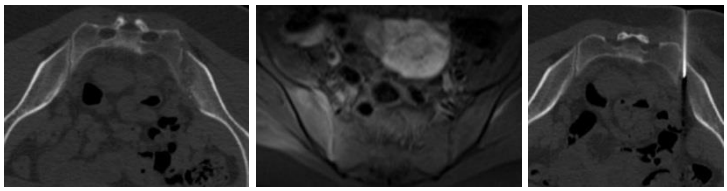


Figure 3: A 33-year-old male with spondylitis. CT (a) and contrast enhanced T1-weighted MR (b) images demonstrating the skip vertebral body lesions of lumbar spine. In axial CT image (c) destruction of the vertebral body is clearly seen. Pay attention to the destruction of the right pedicle in the vertebral body, which may be assumed as a sign of malignancy. Histopathological and microbiological test results revealed tuberculosis infection with a positive PCR test after CT-guided transpedicular biopsy.



Figures 4: A 31-year-old female with sacroiliitis that did not heal with medication. Axial CT (a) and non-contrast enhanced T2-weighted MR (b) images demonstrating the destruction in cortical bone adjacent to the joint and bone marrow edema. CT guided biopsy and the laboratory results revealed tuberculosis infection (c).

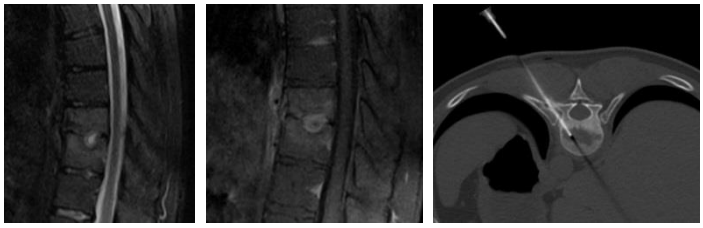


Figure 5: A 30-year-old male with spondylitis in dorsal vertebral bodies. Non-contrast enhanced T2-weighted (a) and contrast enhanced T1-weighted MR (b) images demonstrate the destruction of vertebral body endplates and involvement of the adjacent intervertebral disc. Since the patient had negative clinical history and laboratory tests for TBI, he was referred with presumptive diagnosis of malignancy. The patient had CT-guided percutaneous-transpedicular bone biopsy (c). Histopathological and microbiological test results revealed tuberculosis infection.

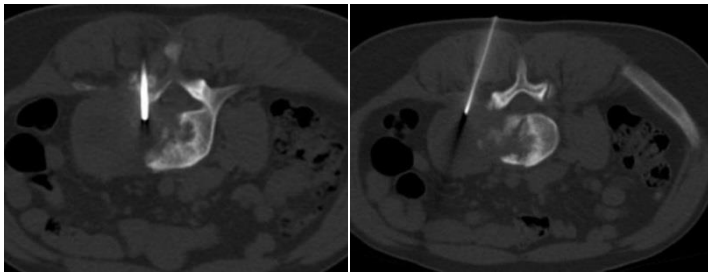


Figure 6: A 37-year-old male patient with spondylitis. Axial CT image shows vertebral body and left pedicle destruction. Since the enlargement of the left psoas muscle was highly suspicious for a Pott abscess, CT guided bone biopsy from vertebral body (a) and needle aspiration from adjacent soft tissue (b) were performed. Histopathological and microbiological test results revealed tuberculosis infection.

Discussion

There has been an increase in the prevalence of tuberculosis, especially among the patients with immunodeficiency and immigrant populations. Early diagnosis promotes effective treatment of the disease [1-3]. A positive sputum or tuberculin skin test support the diagnosis of TBI. Nevertheless, a negative result does not rule it out [16]. Thus, being familiar with the common radiologic features of tuberculosis may prevent wasting time until diagnosis and accordingly, reducing the morbidity.

Tuberculosis usually involves the respiratory system and lungs. However, any organ system may be affected, particularly in the patients with immunodeficiency [1-3]. In lungs, TBI and malignancy may show typical imaging features. In some cases, cavitated nodular masses with thick, irregular walls, mediastinal lymphadenopathy and pleural effusion may mimic lung cancer. Also, clinical symptoms present in TB, such as fever, hemoptysis, and weight loss, may be seen in malignancy as well. Consequently, definitive diagnosis of these two diseases remain a diagnostic dilemma in the clinic. In our study, among 4 lung lesions, 75% presented as solitary cavitary nodular lesions while 25% were non-cavitary multiple nodular lesions (in the patient with a history of nasal squamous cell cancer (SCC), in which differential diagnosis of metastasis was needed) (Figure 1 and 2). Of the 3 cavitary masses, only one was localized in apical segment of the right lung, while the 2 others were localized in lower lobes. Mediastinal lymphadenopathy accompanied 75% of the lung lesions, which was not consistent with usual radiological presentation of post-primary TBI. Pleural effusion was present in 25% of the patients. On the other hand, in one patient, who had a history of nasal SCC, multiple nodular lesions in the lingular lobe was assumed as metastasis. Therefore, malignancy was presumed; and biopsy was required to prove the diagnosis. All lung lesions were diagnosed with tuberculosis with both histopathological and culture analysis by CT guided biopsy, and malignancy was excluded in all.

In musculoskeletal involvement, bone and joint destruction may result in severe morbidity [9,10]. Especially in patients with spinal involvement, severe neurological deficit may be seen. Almost 50% of musculoskeletal tuberculosis affects the spine. Usually, the lower thoracic and upper lumbar vertebral bodies are involved due to hematogenous spread via the Batson's paravertebral venous plexus. Infection usually spreads to the intervertebral disc from the involved part of the vertebral body close to the end plate. Also, it may disseminate into adjacent spinal segments, resulting in skip lesions as well as into the paraspinal tissues that results as paravertebral Pott abscess (Figure 6). TBI tends to involve the anterior part of the vertebral body, while metastasis tends to involve the posterior part and pedicles. Nevertheless, radiological findings are nonspecific in the early stages. In our study, all bone lesions were osteolytic lesions that were localized in axial skeleton (67% in spinal vertebra columns, 33% in pelvic bones) (Figure 3, 4 and 5). They were all multifocal, except the four that were localized in pelvic bones. Intervertebral disc and adjacent joint involvement were present in all bone lesions. Involvement of the posterior part of the vertebral body was present in 5 of 8 vertebral body lesions (Figure 3) and cortical lysis was present in all. Pott abscess accompanied prominent spondylodiscitis in two patients (Figure 6). In suspected patients, if TBI cannot be diagnosed with noninvasive techniques, percutaneous biopsy should be performed for histologic analysis and culture [13,14]. The interventional radiologist may not be informed of the possible diagnosis prior to intervention many times and the malignancy or metastasis may be the only presumptive diagnosis for reason of referring the patient for biopsy. We should be aware of the possibility of TBI according to common radiological features and obtain an additional sterile sample for culture analysis during the biopsy to get prevent an additional biopsy procedure and delaying the diagnosis. Specimens should be placed in a sterile container and referred to the laboratory for culture analysis, as well as in a formalin cup for histopathological analysis.

Limitations

The are some limitations in this study. Due to its retrospective nature, we could not reach the files of all patients. Some of the patients were referred for biopsy only from different centers. Thus, the physical assessments were performed in different centers by different physicians for every patient. We did not know if sputum tests were repeated for the patients who had clinically high suspicion of TBC disease. Also, the number of the patients was small. Nevertheless, we think this study will contribute to the literature by presenting the utility of percutaneous biopsy to shorten time until diagnosis with a positive PCR test. Further research with a considerable number of patients is needed to emphasize the diagnostic yield of image-guided biopsy for tuberculosis.

Conclusion

The diagnosis of tuberculosis may be challenging, and it may mimic malignancy. Image-guided-biopsy is safe and useful in diagnosis of tuberculosis cases who could not be diagnosed by laboratory and sputum tests or those with presumptive diagnoses of malignancy. Tuberculosis should be kept in mind during percutaneous biopsy procedures of radiologically suspicious cases as a differential diagnosis, despite being clinically negative.

References

1. World Health Organization. Global tuberculosis control: WHO report 2011. World Health Organization. https://apps.who.int/iris/handle/10665/44728. Accessed: 8 March 2020.
2. Global tuberculosis report 2017. Geneva: World Health Organization, 2017. http://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf. Accessed 8 March 2020.
3. Hammen I. Tuberculosis mimicking lung cancer. Respir Med Case Rep. 2015;16:45–7. doi: 10.1016/j.rmcr.2015.06.007.
4. Virenfeldt J, Rudolf F, Camara C, Furtado A, Gomes V, Aaby P, Petersen E, Wejse C. Treatment delay affects clinical severity of tuberculosis: a longitudinal cohort study. BMJ Open. 2014;4(6). doi: 004818 10.1136/bmjopen-2014-004818.
5. Pesut DP, Marinkovic DM. Lung cancer and pulmonary tuberculosis-A comparative population-genetic study British. J Med Genetics. 2009;12:45–52.

6. Bhatt M, Kant S, Bhaskar R. Pulmonary tuberculosis as differential diagnosis of lung cancer. South Asian J Cancer. 2012;1(1):36–42. doi: 10.4103/2278-330X.96507.
7. Morikawa K, Misumi S, Fukuda T. A case of pulmonary tuberculosis with multiple nodules mimicking lung metastases. BJR Case Rep. 2019;5:20180124. doi: 10.1259/bjrcr.20180124.
8. Falagas ME, Kouranos VD, Athanassa Z, Kopterides P. Tuberculosis and malignancy. Q J Med. 2010;103:461–87. doi: 10.1093/qjmed/hcq068.
9. Ye M, Huang J, Wang J, Ren J, Tu J, You W, et al. Multifocal musculoskeletal tuberculosis mimicking multiple bone metastases: a case report. BMC Infect Dis. 2016;16:34. doi: 10.1186/s12879-016-1376-7.
10. Lee Chul-Min, Lee S, Bae J. Contiguous Spinal Metastasis Mimicking Infectious Spondylodiscitis. Journal of the Korean Society of Radiology. 2015;73(6):408-12. doi: 10.3348/jksr.2015.73.6.408.
11. Alavi SM, Sharifi M. Tuberculous spondylitis: risk factors and clinical/paraclinical aspects in the south west of Iran. J Infect Public Health. 2010;3(4):196-200. doi: 10.1016/j.jiph.2010.09.005
12. Altuwairgi O, Baharoon S, Alkabab Y, Alsafi E, Almoweqel M, L-Jahdali HA. Ultrasound-guided core biopsy in the diagnostic work-up of tuberculous lymphadenitis in Saudi Arabia, refining the diagnostic approach. Case series and review of literature. J Infect Public Health. 2014;7(5):371-6.
13. Choo JY, Lee KY, Kim MY, Kang EY, Oh YW, Lee SH, et al. Pulmonary tuberculosis confirmed by percutaneous transthoracic needle biopsy: analysis of CT findings and review of correlations with underlying lung disease. Balkan Med J. 2014;31:208–13. doi: 10.5152/balkanmedj.2014.13187.
14. Joo EJ, Yeom JS, Ha YE, Park SY, Lee CS, Kim ES, et al. Diagnostic yield of computed tomography-guided bone biopsy and clinical outcomes of tuberculous and pyogenic spondylitis. Korean J Intern Med. 2016;31(4):762–71. doi: 10.3904/kjim.2013.019.
15. Cardella JF, Kundu S, Miller DL, Millward SF, Sacks D. Society of Interventional Radiology. Society of Interventional Radiology clinical practice guidelines. J Vasc Interv Radiol. 2009;20(7):189-91. doi: 10.1016/j.jvir.2009.04.035.
16. Burrill J, Williams CJ, Bain G, Conder G, Hine AL, Misra RR. Tuberculosis: a radiologic review. Radiographics. 2007;27(5):1255-73. doi: 10.1148/rg.275065176.

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. 2020;4(9):766-770.
DOI: 10.28982/josam.727963

Research article
Araştırma makalesi

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

Relationship between suicidal patients and vitamin D: A prospective case-control study

İntihar girişim olan hastalar ile D vitamini arasındaki ilişki: Prospektif vaka-kontrol çalışma

Dilek Atik [1], Başar Cander [2], Serkan Doğan [2], Bensu Bulut [2], Ramiz Yazıcı [2], Bahadır Taşlıdere [3]

[1] Department of Emergency Medicine, Yozgat Bozok University, Yozgat, Turkey
[2] Department of Emergency Medicine, University of Health Sciences, Kanuni Sultan Suleyman Research and Training Hospital, İstanbul, Turkey
[3] Department of Emergency Medicine, Bezmialem Vakıf University, İstanbul, Turkey

ORCID ID of the author(s)
DA: 0000-0002-3270-8711
BC: 0000-0002-3308-5843
SD: 0000-0001-8923-2489
BB: 0000-0002-5629-3143
RY: 0000-0001-9210-914X
BT: 0000-0002-5920-8127

Corresponding author / Sorumlu yazar:
Dilek Atik
Address / Adres: Yozgat Bozok Üniversitesi, Acil Tıp Bölümü, Menderes mh. Adnan Menderes Blv. Merkez, Yozgat, 66200, Türkiye
E-mail: dr.dilekgok82@hotmail.com

Ethics Committee Approval: The approval of Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee was obtained by the protocol numbered 2018/11/47. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından, 2018/11/47 sayılı protokol ile onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: When a person ends their life consciously and intentionally, it is called suicide. One of the most investigated issues related to suicide is mental disorders. It has been reported that vitamin D has a prominent role in the treatment of many chronic diseases in recent years. Growing evidence implicates sunlight, or vitamin D, is a key environmental factor in the etiology of neuropsychiatric diseases. The aim of this study was to investigate the vitamin D levels in patients admitted to our emergency department due to suicide intervention and contribute to the treatment of clinical applications according to the results.

Methods: This study included 59 individuals with suicidal attempt and 42 control group subjects. The gender, age, educational level, marital status, and economic status of the patients, whether they had previously received psychiatric treatment, or attempted suicide were recorded in a separate Sociodemographic Information Form (SBF) for each patient. Mann Whitney U test was used for statistical evaluations based on categorical (nominal or ordinal) and binary variables.

Results: The minimum and maximum Vitamin D laboratory parameters of the study group were 4.4 ng/ml and 33 ng/ml, respectively. The mean vitamin D levels in the suicide and control groups were 9.6 ng/ml and 13.8 ng/ml, respectively. There were statistically significant relationships between vitamin D levels, the presence of psychiatric disease (P<0.001) and previous suicide attempts (P=0.02).

Conclusion: Suicidal tendency increases in depression, which is a psychiatric illness. We believe that suicide attempts may be reduced by adding vitamin D to treatment protocols, especially in depression, and that it may direct future studies in this direction.

Keywords: Vitamin D, Suicide, Depression

Öz

Amaç: Kişinin bilinçli olarak ve isteyerek yaşamına son vermesine intihar denir. İntihar ile ilgili en çok araştırılan konulardan biri de zihinsel bozukluklardır. Son yıllarda birçok kronik hastalığın tedavisinde D vitamininin önemli bir rol oynadığı bildirilmiştir. Artan kanıtlarda güneş ışığının veya D vitaminin, nöropsikiyatrik hastalıkların etiyolojisinde önemli bir çevresel faktör olduğu bildirilmektedir. Bu çalışmanın amacı acil servisimize intihar girişimi nedeniyle başvuran D vitamini düzeylerini araştırmak ve sonuçlara göre klinik uygulamaların tedavisine katkıda bulunmaktı.

Yöntemler: Çalışmaya intihar girişimi olan 59 kişi ve kontrol grubu olan 42 kişi dahil edildi. Sosyodemografik Bilgi Formu (SBF) Hastaların cinsiyeti, yaşı, eğitim düzeyi, medeni durumu ve ekonomik durumu, daha önce psikiyatrik tedavi almış veya intihar girişiminde bulunmuş olması her hasta için ayrı bir forma kaydedildi. Kategorik (nominal veya sıralı) ve ikili değişkenlere dayalı istatistiksel değerlendirmeler için Mann Whitney U testleri kullanıldı.

Bulgular: Çalışma grubunun laboratuvar D vitamini düzeyleri minimum 4,4 ng/ml maksimum 33 ng/ml değerleri bulundu. İntihar girişiminde bulunanların D vitamin ortalaması 9,6 ng/ml, kontrol grubunun D vitamin ortalaması 13,8 ng/ml idi. D vitamini düzeyleri ile psikiyatrik hastalık varlığı arasındaki ilişki istatistiksel olarak anlamlı bulundu (P<0,001).D vitamini düzeyleri ile önceki intihar girişimleri arasındaki ilişki anlamlı bulundu (P=0,02).

Sonuç: Psikiyatrik bir hastalık olan depresyonda intihar eğilimi artmaktadır. Özellikle depresyon hastalığında tedavi protokollerine D vitamini eklenerek intihar girişimlerinin azaltılabileceğini ve bu doğrultuda gelecekteki çalışmalara yön verebileceği kanaatindeyiz.

Anahtar kelimeler: Vitamin D, İntihar, Depresyon

How to cite/Atıf için: Atik D, Cander B, Doğan S, Bulut B, Yazıcı R, Taşlıdere B. Relationship between suicidal patients and vitamin D: A prospective case-control study. J Surg Med. 2020;4(9):766-770.

Introduction

When a person and their life consciously and intentionally, it is called suicide. Although suicide is a way out of an overwhelming crisis or problem, it is not a random and purposeless act. The person who committed suicide carries out this action with the thoughts of despair and the lack of people around to help. Suicide attempt is related to the decrease in solutions with the continuation of stress factors [1,2]. The most common method used for suicide is the use of multiple drugs. It has been reported that the possibility of suicide is high in family members of people who have attempted to commit suicide repeatedly [3,4]. In the studies in the literature, it was reported that mental disorders are high in individuals who have attempted suicide or died due to suicide [5-9]. According to past reviews, most persons who die by suicide have an identifiable psychiatric condition at the time of death [10]. In a study involving 100 people in the literature, 70% had depression, 15% had alcoholism, 3% had schizophrenia and 5% had other disorders [11]. The psychiatric diseases which have resulted in suicide are related to many organic pathologies [12], one of them being vitamin D deficiency. The vitamin D molecule plays a key role in the treatment of vitamin D deficiency [13].

Vitamin D and its metabolism

Vitamin D was originally classified as a nutrient when cod liver oil (a source of vitamin D) was found to have antirachitic effect in infants. However, after the discovery of the vitamin D receptor in 1969, it was considered a more complex molecule of the endocrine system [14]. There are two types of vitamin D: Cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). The most important of the sterols belonging to the vitamin D family is cholecalciferol (vitamin D3), which is produced from 7- dehydrocholesterol (7-DHC, provitamin D3) in the skin with ultraviolet rays [15]. Cholecalciferol is also obtained from dietary sources (oily fish, such as salmon and mackerel, animal liver, fish liver oils, eggs). During exposure to light, 7-DHC absorbs solar radiation (ultraviolet B rays or UVB, wavelengths 290-315 nm), which causes its transformation to previtamin D3. It undergoes a temperature dependent isomerization within a few hours and is then transported from the skin to the circulation, where it is bound by the vitamin D-binding protein [16]. Ergocalciferol is created from viosterol, which in turn is created when ultraviolet light activates ergosterol. Ergosterol, is a component that functions like cholesterol in animal cells. Ergocalciferol is therefore a synthetic molecule, which can be found in fortified foods (milk, cereals, bread products) in some countries or administered as a supplement, orally or parenterally. Recently, Armas et al. [17] demonstrated that ergocalciferol is much less effective than cholecalciferol in humans. Evidence that vitamin D regulates nerve growth factor and glial cell line-derived neurotrophic factor suggests that it may be neuroprotective [18]. Vitamin D can protect the brain against reactive oxygen species via upregulation of antioxidant molecules, such as glutathione, in non-neuronal cells [19]. It has been reported that vitamin D3 receptors and 1α-hydroxylase, the enzyme responsible for active vitamin D in the human brain, were found in both neurons and glial cells in the human brain. The strongest immunohistochemical staining for both the receptor and enzyme was in the hypothalamus and in the large (presumably dopaminergic) neurons within the substantia nigra. This report suggests that vitamin D may have autocrine/paracrine properties in the human brain [20]. Today, vitamin D deficiency is known affect primarily the bones, such as in the case of osteoporosis, and poses a risk for autoimmune diseases, cardiovascular system diseases, type 2 diabetes, some cancer diseases, and infectious diseases [21-24].

Vitamin D has previously been studied in many chronic diseases, but the study of vitamin D levels in suicidal patients has not been adequately studied yet. The aim of this study was to investigate the vitamin D levels in patients admitted to our emergency department due to suicide intervention and contribute to the treatment, according to the results.

Materials and methods

Patient Group

This study was conducted prospectively in patients presenting with suicide in Istanbul Health Sciences University Kanuni Sultan Suleyman Training and Research Hospital Emergency Medicine Clinic between 01.12.2018-01.02.2019 with the approval of Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee by the protocol numbered 2018/11/47. The patients were informed about the study and a separate interview was performed with the volunteers to obtain the necessary information and for clinical evaluations. Our study involved two groups. Power analysis was performed to determine the appropriate sample size. Accordingly, the minimum sample size of this study was calculated as at least 41 individuals for each group, with 0.50 effect, 85% power and 0.05 α error. The study included 59 individuals with suicidal attempt and 42 subjects in the control group. All patients in the study group were evaluated by a psychiatrist when they were able to meet after the completion of their emergency medical treatment. Patients with psychiatric diseases were divided into two groups based on their diagnosis.

Gender, age, educational level, marital status, and economic status of the patients, whether they had previously received psychiatric treatment, or attempted suicide were recorded in a separate Sociodemographic Information Form (SIF) for each patient. The families of the patients were also interviewed to complete the possible deficiencies in sociodemographic information.

For vitamin D measurement, blood samples were collected in disposable, 10 ml, vacuumed, anticoagulant-containing, biochemical tubes. About 5-7 ml of blood was drawn from the patients and the control group, which were centrifuged at 2500 rpm for 10 minutes to separate the serum. Separated serums were stored at -80°C until examined. Each serum was only dissolved once on the day of the study. Values under 20 ng/ml, between 20-29 ng/ml, >30 ng/ml and > 150 ng/ml were considered as deficiency, insufficiency, normal (normal value 40-60 ng/ml), and intoxication, respectively [25].

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 20.0 was used for the analysis. All variables were tested for conformity to normal distribution, and compliance with

parametric test criteria with the Kolmogorov Smirnov test. In addition, the normality of distribution of the data was evaluated by histogram, one of the graphical methods. Descriptive statistics were used in the demographic evaluation of the patients. Within the scope of clinical research, Chi-Square (χ^2) was used to evaluate independent, categorical variables. In the study data, numerical values are expressed as mean (SD). The data obtained from the study conducted within the scope of clinical research were used in student t test for variables that were statistically parametric. For the non-statistical data obtained by the study, Mann Whitney U test was used for statistical evaluations based on categorical (nominal or ordered) and binary variables. The results were evaluated for a significance level of $P<0.05$.

Results

A total of 59 patients and 42 individuals were included in our study. Among all, 65% (n=38) of the patients were female and 35% (n=21) were male. Of those in the control group, 63.4% (n=27) were female and 36.6% (n=15) were male. There was no statistically significant difference in terms of gender between the two groups (x^2:4.768; $P=0.078$). The mean age of the patients was 30.9 (10.7) years, and the mean age of the healthy control group was 30.5 (7.84) years, which were also similar ($P=0.082$).

Among the patients, 50.8% (n=30) were discharged healthily, 29.5% (n=17) were hospitalized and 20.4% (n=12) were admitted to the intensive care unit. When the time zone of the patients was evaluated by suicide intervention, 16.4% (n=10) of the patients had attempted suicide between 08:00-16: 00, 41% (n=24), between 16:00-24: 00 and 42.6%, between 24:00-08:00 (n=25) (Table 1). All patients with suicide attempts were evaluated by the consultant psychiatrist. Of the patients, 57.6% (n=34) had psychiatric diseases and 42.3% (n=25) were not diagnosed with one. 69% (n=23) of the patients who had attempted suicide with psychiatric diseases before were diagnosed with depression, 31% (n=11) with anxiety, panic attack, and post-traumatic stress disorder. 22% (n=13) of the patients had previously attempted suicide, while 78% (n=46) had not. Laboratory values of vitamin D ranged between 4.4 ng/ml and 33 ng/ml. The mean vitamin D levels in the suicide and control groups were 9.6 ng/ml and 13.8 ng/ml, respectively (Figure 1) (Table 1). A significantly negative relationship was found between vitamin D and suicidal attempt (z:-3.630, $P<0.001$) (Table 2). The mean vitamin D values of those with and without prior suicide attempts were 7.6 (5.08) and 10.04 (4.05), respectively. There was a significant relationship between vitamin D levels and previous suicide attempts (z: -2.260, $P=0.02$) (Table 2). Mean vitamin D levels of the patients with and without previous psychiatric diseases was 8.15 (3.23) ng/ml and 11.3 (3.45) ng/ml, respectively (Figure 2), the difference between which was statistically significant (z: -2.494, $P=0.013$) (Table 2). The mean vitamin D levels of patients who attempted suicide and who were diagnosed with depression and other psychiatric diseases were 7.1 (2.1), and 13.2 (3.2), respectively. This difference in vitamin D levels between suicidal patients with other psychiatric diseases and those with depression was statistically significant (z: -3.589, $P<0.001$).

Table 1: Demographic characteristics of participants

Independent variables		Number	Percent (%)	Mean (SD)	*P*-value
Patients groups' gender	Female	38	65		0.078[b]
	Male	21	35		
Control groups' gender	Female	27	63.4		
	Male	15	36.6		
Patients groups' age				30.9(10.7)	0.082[b]
Control groups' age				30.5(7.84)	
Presence of psychiatric disease		34	57.6		
No psychiatric diseases present		25	42.3		
Previously attempted suicide		13	22		
Did not previously attempt suicide		46	78		
Attempt hours of the patients	08:00-16:00	10	16.4		
	16:00-24:00	24	41		
	24:00-08:00	25	42.6		
Vitamin D level average (ng/ml)	Suicide group			9.59(4.37)	0.001[a]
	Control group			13.80(6.59)	
Clinical outcomes of the patients	Discharged With health	30	50.8		
	Hospitalized	17	28.8		
	Intensive care unit	12	20.4		

a: Significant at the 0.05 level ($P<0.05$), b: Not significant

Table 2: Statistical results of vitamin D levels of patients with suicide attempt

Groups	Vitamin D Mean (SD)	Z	*P*-value
Previously attempted suicide	7.6 (5.08)	-2.260	0.02
Did not previously attempt suicide	10.04 (4.05)		
Previous psychiatric diseases	8.15 (3.23)	-2.494	0.013*
No previous psychiatric disease	11.3 (3.45)		
Patients diagnosed with depression	7.1 (2.1)	-3.589	0.001*
Patients with other psychiatric diseases	13.2 (3.2)		

*: Significant at the 0.05 level ($P<0.05$)

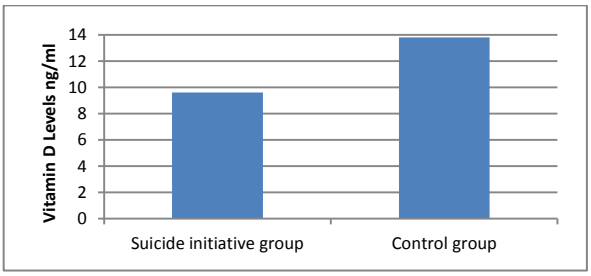


Figure 1: Vitamin D averages of suicide initiative group and control group

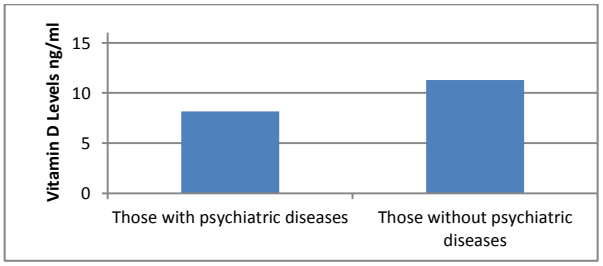


Figure 2: Vitamin D averages of those with and without psychiatric diseases

Discussion

The phenomenon of ending life is an increasing trend in societies. To decrease its incidence, studies regarding the risk factors of individuals are conducted among patients who attempted suicide. The results of our study indicate low vitamin D levels in both the control and suicide attempt groups, which shows that people in Turkey cannot adequately benefit from the sunlight and supplements. We concluded that vitamin D levels were lower in patients who attempted suicide compared to the healthy control group, especially in patients with suicidal ideation and history of depression.

Until recently, little was known about the role of vitamin D in brain function. Growing evidence implicates sunlight, or vitamin D, is a key environmental factor in the etiology of neuropsychiatric diseases [26]. The risk of suicide is different in every psychiatric disorder. Various psychiatric

disorders are more commonly associated with increased risk of suicide, such as major depression [27-29]. Like these studies, suicidal attempt was present in our study, and previous diagnoses of depression was found in the majority of patients with a prior psychiatric diagnosis. In some studies related to depression, depressive symptoms were reported to increase with low vitamin D [30-32], while in others, no relationship was found between low vitamin D and depressive symptoms [33,34]. Unlike our study, Park et al. [35] reported that low vitamin D was not a risk factor in their study on depression and suicidal ideation. The difference may be due to the fact that it was performed in the general population and on individuals who had not finalized suicide. The study of Umhau et al. [36] was conducted on patients who had attempted suicide, and its results regarding vitamin D levels resemble ours. The identification of vitamin D receptors in brain regions affecting depression has strengthened the relationship between vitamin D and depression. In human and animal studies, vitamin D receptors and 1-α-hydroxylase enzyme are found in the brain and the role of vitamin D in central nervous system functions have been shown [37,38]. In another laboratory study, brain development was assessed in neonatal rats whose mothers were rendered vitamin D deficient by eliminating vitamin D from the diet and UVB radiation from the lighting in the animal holding room [39]. The effects on the brain of the offspring were dramatic. Vitamin D deficiency changed the size and shape of the neonatal brain, altered growth factor expression, and cell proliferation. These data confirm that vitamin D deficiency can have effects on the structure of brain, like enlarged ventricles and cortical thinning [40,41]. There is increasing evidence that there is a relationship between depressive symptoms and low serum/plasma 25 (OH) D levels. Cross-sectional studies and prospective data also support that low vitamin D levels are associated with an increased risk of depression [42,43]. In a study showing that vitamin D deficiency and mood disorders were very common among the elderly, the quality of life of the elderly women with low vitamin D (<400 IU/day) was lower than those with higher vitamin D levels. To improve the quality of life in the elderly, it was emphasized that the recommended daily intake of vitamin D (≥400 IU/day) is important [43]. According to the results of our study, the level of vitamin D of the patients with psychiatric diseases was lower in the patient group than those without psychiatric disease. In addition, the vitamin D levels of the group diagnosed with depression in our study were lower than that of the other group. Studies in the literature emphasize low vitamin D in depressive symptoms, especially in psychiatric disorders. Motsingera's previous study on mood disorders and quality of life also yielded similar results [44]. This suggests that vitamin D level is low in suicidal patients and it may be important to measure vitamin D level in patients with suicide ideation. Nutrition plays an important role in the treatment of mental disorders [45]. Recent epidemiologic investigations have reported interesting and consistent associations between dietary patterns and symptoms of anxiety and depression [46,47]. In our study, low levels of vitamin D were found in suicidal patients who were associated with depressive mood.

Limitations

The participants in our study could not be further grouped due to the low number of patients.

Conclusion

Suicide attempts are reduced when the underlying risk factors are eliminated. In especially depression, suicide attempts increase. In addition to the current treatments in depression, we believe that suicide attempt can be indirectly reduced with vitamin D supplements.

Acknowledgements

We would like to thank the Consultant psychiatrist doctors.

References

1. Alec R. Psychiatric Emergencies Suicide. 2031-2040. In: BJ Sadock, VA Sadock (Eds). Comprehensive Textbook of Psychiatry 2. Volume 8. Printing, Philadelphia, Williams & Wilkins 2000.
2. Garnfinkel BD. Suicide attempts in children and adolescents. Am J Psychiatry. 1982;139:1257-62.
3. Robbins D, Alessi NE. Depressive symptoms and suicidal behaviour in adolescents. Am J Psychiatry. 1985;142:588-92.
4. Goldstein RB, Black DW, Nasrallah A, et al. The prediction of suicide. Arch Gen Psychiatry. 1991;48:418-22.
5. Henrikson MM, Aro HM, Marttunen MJ, Heikkinen ME, Isometsä ET, Kuoppasalmi KI. Mental disorders and comorbidity in suicide. Am J Psychiatry. 1993;150:935-40.
6. Isometsa ET, Henriksson MM, Hillevi MA. Suicide in major depression. Am J Psychiatry. 1994;151:530-6.
7. Conner KR, Duberstein PR, Conwell Y, Seidlitz L, Caine ED. Psychological vulnerability to completed suicides: A review of empirical studies. Suicide and Life Threatening Behavior. 2001;31:367–86.
8. Bertolote JM, Fleischmann A, De Leo D, Wasserman D. Psychiatric diagnosis and suicide: Revisiting the evidence. Crisis. 2004;25:147–55.
9. Cavanagh JT, Carson AJ, Sharpe M, Lawrie SM. Psychological autopsy studies of suicide: A systematic review. Psychological Medicine. 2003;33:395–405.
10. Milner A, Jerneja SJ, Leo DD. Suicide in the absence of mental disorder? A review of psychological autopsy studies across countries. International Journal of Social Psychiatry. 2012;59(6):545–54.
11. Pfeiffer CP, Klerman GL, Hurt SW. Suicidal children grow up: Demographic and clinical risk factors for adolescent suicide attempts. J Am Acad, Child Adolesc Psychiatry. 1991;30:609-16.
12. Rund BR. Is schizophrenia a neurodegenerative disorder? Nord J Psychiatry. 2009;63:196–201.
13. Enkhjargal B, McBride DW, Manaenko A, Reis C, Sakai Y, Tang J, Zhang JH. Intranasal administration of vitamin D attenuates blood–brain barrier disruption through endogenous upregulation of osteopontin and activation of CD44/P-gp glycosylation signaling after subarachnoid hemorrhage in rats. Journal of Cerebral Blood Flow & Metabolism. 2017;37(7):2555–66.
14. Reinhart TA, Ramberg CF, Horst RL. Comparison of receptor binding, biological activity, and in vivo tracer kinetics for 1,25-dihydroxyvitamin D3 and, 1,25-dihydroxyvitamin D2, and its 24 epimer. Arch Biochem Biophys. 1989;273:64-71.
15. Guyton AC, Hall JE. Medical Physiology. 9. Printing, (Trans. H Çavuşoğlu), Istanbul, Nobel Medical Bookstores. 1996, pp: 985-998.
16. Holick MF. Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. In: Favus, MJ (eds). Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. Washington, DC: American Society for Bone and Mineral Research, 2003, pp: 129-137.
17. Armas LAG, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab. 2004;89:5387-91.
18. Garcion E, Sindji L, Montero-Menei C, Andre C, Brachet P, Darcy F. Expression of inducible nitric oxide synthase during rat brain inflammation: regulation by 1,25-dihydroxyvitamin D3. Glia. 1998;22:282–94.
19. Garcion E, Sindji L, Leblondel G, Brachet P, Darcy F. 1,25-dihydroxyvitamin D3 regulates the synthesis of gamma-glutamyl transpeptidase and glutathione levels in rat primary astrocytes. J Neurochem. 1999;73:859–66.
20. Kalueff A, Tuohimaa P. Neurosteroid hormone vitamin D and its utility in clinical nutrition. Curr Opin Clin Nutr Metab Care. 2007;10:12–9.
21. Hahn S, Haselhorst U, Tan S, Quadbeck B, Schmidt M, Roesler S, et al. Low 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes. 2006;114:577-83.
22. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. 2004;80:1678-88.
23. Orces CH, Gavilánez EL. Determinants of vitamin D supplementation among older adults and its effect on 25(OH)D levels according to bone mineral density status. Nutr Hosp. 2020;37(1):28-36.
24. Yenilmez E, Çetinkaya R. Evaluation of initial results of naïve HIV-infected patients regarding bone health. J Surg Med. 2019;3(5):384-9.
25. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality- a review of recent evidence. Autoimmun Rev. 2013;12:976-89.
26. Yüksel RN, Altunsoy N, Tikir B, Külük MC, Unal K, Goka S, et al. Correlation between total vitamin D levels and psychotic psychopathology in patients with schizophrenia: therapeutic implications for add-on vitamin D augmentation. Therapeutic Advances in Psychopharmacology. 2014;4(6):268-75.
27. Serafini G, Pompili M, Elena SM, Stefani H, Palermo M, Coryell W et al. The role of inflammatory cytokines in suicidal behavior: a systematic review. Eur Neuropsychopharmacol. 2013;23(12):1672-86.
28. Chesney E, Goodwin GM, Fazel S. Risks of all cause and intihare mortality in mental disorders: a meta-review. World Psychiatry. 2014;13(2):153-60.
29. Sagınc H, Kugu N, Akyuz G, Dogan O. Investigation of suicide history in inpatients. Anadolu Psikiyatri Derg. 2000;1:83-88.
30. Jaddou HY, Batieha AM, Khader YS, et al. Depression is associated with low levels of 25-hydroxyvitamin D among Jordanian adults: results from a national population survey. Eur Arch Psychiatry Clin Neurosci. 2012;262:321–7.
31. Kjaergaard M, Joakimsen R, Jorde R. Low serum 25-hydroxyvitamin D levels are associated with depression in an adult Norwegian population. Psychiatry Res. 2011;190:221–5.

32. Yavuz YC, Biyik, Z, Ozkul D, Abusoglu S, Eryavuz D, Dag M, et al. Association of depressive symptoms with 25(OH) vitamin D in hemodialysis patients and effect of gender. Clin Exp Nephrol. 2020;24:63–72.
33. Zhao G, Ford ES, Li C, Balluz LS. No associations between serum concentrations of 25-hydroxyvitamin D and parathyroid hormone and depression among US adults. Br J Nutr. 2010;104:1696–702.
34. Pan A, Lu L, Franco OH, Yu Z, Li H, Lin X. Association between depressive symptoms and 25-hydroxyvitamin D in middle-aged and elderly Chinese. J Affect Disord. 2009;118:240–3.
35. Park J, Yang JC, Park TW, Chung SK. Is serum 25-hydroxyvitamin D associated with depressive symptoms and suicidal ideation in Korean adults? The International Journal of Psychiatry in Medicine. 2016;51(1):31–46.
36. Umhau JC, George DT, Heaney RP, Lewis MD, Ursano RJ, Heilig M et al. Low vitamin D status and suicide: a casecontrol study of active duty military service members. PLoS One. 2013;8(1):e51543.
37. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. Journal of Chemical Neuroanatomy. 2005;29(1):21-30.
38. Prufer K, Veenstra TD, Jirikowski GF, Kumar R. Distribution of 1,25-dihydroxyvitamin D3 receptor immuno reactivity in the rat brain and spinal cord. Journal of Chemical Neuroanatomy. 1999;16(2):135-45.
39. Eyles D, Brown J, Mackay-Sim A, McGrath J, Feron F. Vitamin D3 and brain development.Neuroscience. 2003;118:641–53.
40. Lawrie S, Abukmeil S. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry. 1998;172:110–20.
41. Selemon L, Rajkowska G, Goldman-Rakic P. Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. Arch Gen Psychiatry. 1995;52:805–20.
42. Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. Psychopharmacology (Berl). 1998;135:319-23.
43. Sanders KM, Stuart AL, Williamson EJ, Jacka FN, Dodd S, Nicholson G, et al. Annual high-dose vitamin D3 and mental well-being: randomised controlled trial. British Journal of Psychiatry. 2011;198:357-64.
44. Motsingera S, Lazovicha D, MacLehose RF, Torkelson CJ, Robien K. Vitamin D intake and mental health-related quality of life in older women: The Iowa Women's Health Study. Maturitas. 2012;71:267–73.
45. Awad AG. Neurobiological Issues in Autism. Can J Psychiatry. 1984;29(7):609-13.
46. Sanchez-Villegas A, Delgado-Rodriguez M, Alonso A, Schlatter J, Lahortiga F, Majem LS, et al. Association of the Mediterranean dietary pattern with the incidence of depression. Arch Gen Psychiatry. 2009;66(10):1090–8.
47. Jacka FN, Pasco JA, Mykletun A, Williams LJ, Hodge AM, O'Reilly SL, et al. Association of Western and traditional diets with depression and anxiety in women. Am J Psychiatry. 2010;167(3):305–11.

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. 2020;4(9):771-774.
DOI: 10.28982/josam.789704

Research article
Araştırma makalesi

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

Change in expression of NFκb and MUC5AC in nasal mucosa during pregnancy

Gebelik sırasında nazal mukozada NFκb ve MUC5AC ekspresyon düzeylerinin değişimi

Burak Ülkümen [1], Burcu Artunç Ülkümen [2], Muhammet Burak Batır [3], Sırrı Cam [4]

[1] Manisa Celal Bayar University, Faculty of Medicine, Department of Otorhinolaryngology-Head Neck Surgery, Manisa, Turkey
[2] Manisa Celal Bayar University, Faculty of Medicine, Department of Obstetrics and Gynecology, Manisa, Turkey
[3] Manisa Celal Bayar University, Faculty of Science and Letters, Department of Biology, Manisa, Turkey
[4] Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, Manisa, Turkey

ORCID ID of the author(s)
BÜ: 0000-0003-1981-5886
BAÜ: 0000-0002-3128-8751
MBB: 0000-0002-8722-5055
SC: 0000-0002-0972-8896

Corresponding author / Sorumlu yazar:
Burak Ülkümen
Address / Adres: Manisa Celal Bayar Üniversitesi, Kulak Burun Boğaz-Baş Boyun Cerrahisi Anabilim Dalı, Manisa, Türkiye
E-mail: drburak@gmail.com

Ethics Committee Approval: This animal experimental research was approved by the Laboratory Animals Local Ethics Committee of Manisa Celal Bayar University (4/28/2015;77.637.435-29).
Etik Kurul Onayı: Bu hayvan deneysel araştırması, Manisa Celal Bayar Üniversitesi Laboratuvar Hayvanları Yerel Etik Kurulu (28.04.2015;77.637.435-29) tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: Funding: Research funder: Unit of Scientific Research Projects (BAP) of Manisa Celal Bayar University (Grant number: 2014-131).
Finansal Destek: Finansman: Araştırma fonu: Manisa Celal Bayar Üniversitesi Bilimsel Araştırma Projeleri Birimi (BAP) (no: 2014-131).

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: There is very limited information concerning gestational course of chronic inflammatory diseases of the upper airway. In the current study, we tried to reveal biomolecular changes in the nasal mucosa during pregnancy regarding NFκb and MUC5AC. This way, we may have the opportunity to suggest new treatment strategies for pregnancy induced nasal disorders.

Methods: Thirty adult female rats were separated into pregnant and control groups. Serum estradiole (E2) and progesterone (PG) levels were evaluated by ELISA. Nasal expression of NFκb and MUC5AC were analyzed by polymerase chain reaction testing. Relative expression of NFκb and MUC5AC was compared between two groups. In addition, the influences of PG and E2 levels on NFκb and MUC5AC were determined.

Results: NFκb was significantly low (P=0.015), while MUC5AC was significantly high in pregnant rats (P=0.029). Serum PG had a significantly negative effect on NF-κB expression (P=0.027) and a significantly positive effect on MUC5AC expression (P=0.017). There was a positive correlation between estradiol and MUC5AC (P=0.017).

Conclusions: In the current study, the physiological expression of NFκb and MUC5AC was shown for the first time by PCR in rat nasal mucosa. The effect of PG and E2 on the expression of these biomolecules in the context of pregnancy was also revealed. These findings have the potential to elucidate gestational inflammatory alterations in the upper airway.

Keywords: Pregnancy, Immunity, NFκb, MUC5AC, Nasal mucosa

Öz

Amaç: Üst solunum yolunun kronik enflamatuar hastalıklarının gebelikteki seyri konusunda çok sınırlı bilgi mevcuttur. Bu çalışmada, NFκb ve MUC5AC ile ilgili olarak hamilelik sırasında nazal mukozadaki biyomoleküler değişiklikleri ortaya çıkarmaya çalıştık. Bu sayede, gebeliğe bağlı burun rahatsızlıkları için yeni tedavi stratejileri önerme fırsatımız olabilir.

Yöntemler: Sıçanlar üzerinde yapılan bu çalışma, Deney Hayvanları Araştırma ve Uygulama Merkezinde yapılmıştır. Otuz yetişkin Wister albino dişi sıçan, bir kontrol grubu ve bir hamile grubu olarak ayrıldı. Serum estradiole (E2) ve progesteron (PG) düzeyleri ELISA ile değerlendirildi. NFκb ve MUC5AC'nin nazal ekspresyonu, polimeraz zincir reaksiyon testi ile analiz edildi. İstatistiksel analiz, NFkb ve MUC5AC ekspresyonunun grup bazında karşılaştırılması ile yapıldı. Ayrıca E2 ve PG seviyelerinin bu moleküller üzerindeki etkisi de araştırıldı.

Bulgular: Gebe sıçanlarda NFκb anlamlı olarak düşük (P=0,015) bulunurken MUC5AC anlamlı derecede yüksek bulundu (P=0,029). Serum PG ve NF-κB ekspresyonu arasında istatistiksel olarak anlamlı negatif korelasyon (P=0,027), progesteron ile MUC5AC ekspresyonu arasında ise pozitif korelasyon (P=0,017) bulundu. Ek olarak, estradiol ve MUC5AC arasında pozitif korelasyon tespit ettik (P=0.017).

Sonuçlar: Bu çalışmada, sıçan nazal mukozasında NFκb ve MUC5AC'nin fizyolojik ekspresyonu ilk kez PCR ile gösterilmiştir. E' ve PG'nin bu biyomoleküllerin ekspresyonu üzerindeki etkisi de gebelik bağlamında ortaya konmuştur. Bu bulgular, üst solunum yolunun gestasyonel enflamatuar değişikliklerini açıklama potansiyeline sahiptir.

Anahtar kelimeler: Gebelik, Bağışıklık, NFκb, MUC5AC, Nazal mukoza

How to cite/Atıf için: Ülkümen B, Ülkümen BA, Batır MB, Cam S. Change in expression of NFκb and MUC5AC in nasal mucosa during pregnancy. J Surg Med. 2020;4(9):771-774.

Introduction

Nuclear factor kappa B (NFκb) is a key biomolecule taking role in the transcription of many genes associated with inflammation and immune processes via various pro-inflammatory and anti-inflammatory cytokines. Maintenance of a healthy pregnancy is achieved mainly by the maternal immunologic shift with increasing the ratio of T Helper lymphocytes 2 (Th2) to T helper lymphocytes 1 (Th1) [1]. NFκb plays a key role in this immunologic differentiation in pregnancy. Besides, maternal hormones influence NFκb expression in different tissues [2-5]. Estradiol causes suppression of NFκb expression [3,4]; whereas the effect of Progesterone is conflicting [4,5].

AC subclass of Mucin type 5 (MUC5AC) is the main mucin of the upper respiratory system [6-7]. Overproduction of MUC5AC is related to deterioration of mucociliary clearance which paves the way for rhinitis and nasal obstruction [7]. On the other hand, NFκb takes part in the main pathway regulating the MUC5AC secretion. It has been shown that NFκb has an upregulatory effect on nasal MUC5AC [7]. Recent data showed that Estradiol (E2) also enhances mucin production in bronchial epithelial cells. This finding may be the reason for the higher incidence of chronic inflammatory airway diseases in women [8].

Pregnancy is a unique period which is characterized by varying degrees of immunosuppression and immunologic shift from cell-mediated immunity towards humoral immunity. NFκb is known to play a significant role in this pregnancy induced immune regulation during both implantation window and subsequent trimesters [1]. There is still an ongoing debate concerning the prognosis of chronic inflammatory airway diseases (i.e. asthma, allergic rhinitis) in pregnancy. We aimed to find out the change in the expression of NFκb and MUC5AC in nasal mucosa during pregnancy. This may help to elucidate the pathophysiology of chronic inflammatory conditions of the upper airway in pregnancy. To the best of our knowledge, NFκb and MUC5AC expression in nasal mucosa during pregnancy has not been studied before. In the current study, the effect of maternal hormones on the expression of these biomolecules was also evaluated.

Materials and methods

Animals

The current experimental animal study was approved by the Laboratory Animals Ethics Committee of the institution. The experiment was performed in the Experimental Animals Research and Application Center.

Twenty, 12-week-old Wister albino female rats were enrolled in the study. They were kept at 22 (2) °C on a light-dark cycle of 12 hours. Male rats were kept together with female rats with a M:F ratio of 3:1 for 1 night. Female and male rats were separated from each other in the following morning. Sperm exploration was performed in the vaginal smears of female rats. The day sperm was detected was assumed as Day 0 of gestation, as defined before [9-11]. Group A (control) was constituted by the rats with negative vaginal smear whereas Group B included (pregnant) sperm-positive ones. Pregnancy period of Wister albino rat is around 22 (21-26) days [10-12]. For this reason, we sacrificed the animals at 21st day of gestation with sodium-pentobarbitone (400mg/kg) injection, as reported before [11]. Then, 20 ml of blood sample was obtained by a 23 G needle before the pulse disappeared. Blood samples were sent for detection of serum E2 and PG levels by ELISA. Then we shaved the nasal dorsum. We separated the nasal bones from the maxilla in upward direction and exposed the whole nasal cavity superiorly. Cartilaginous part of the septum (Cartilago septi nasi) with its mucoperichondrium was resected and analyzed by real time PCR.

ELISA

Heparin, EDTA and sodium citrate were mixed into the blood samples. The mixture was centrifugated for 10 minutes at 3000 rpm. The supernatant was kept at -80 °C. General Progesterone (PG) ELISA Kit and Rat E2 (estradiol) ELISA Kit were used for quantitative measurement of serum PG and E2 levels, respectively (MyBioSource, Inc.,CA, USA) [11].

Extraction of RNA and Analyses of Quantitative Real-Time PCR (qRT-PCR)

TRIzol® Reagent with the PureLink® RNA Mini Kit (Thermo Fisher Scientific, 12183555) was used for total mucosal RNA extraction from the larynx. QuantiFast SYBR Green qRT-PCR Kit (Qiagen, 204154), NF-kB primers and MUC5AC primers were used for qRT-PCR procedure. QuantiFast SYBR Green, NF-kB primers and MUC5AC primers were prepared separately. Next, analyses for the detection of MUC5AC and NF-kB RNA expression levels was performed in Rotor-Gene Q (Qiagen, Hilden, Germany). We have normalized the expression variations of β-microtubulin (B2M) and hypoxanthine phosphoribosyl transferase (HPRT1) by a housekeeping gene. We synthesized reverse and forward primers (Table 1) by Metabion company (Germany). The first step of thermal cycling conditions of the RT-PCR program was the reverse transcription step at 50°C (10 min) which was followed by the PCR step, including an initial activation/denaturation stage at 95°C for 5 minutes. Then we applied 40 cycles of denaturation at 95°C for 15 seconds, accompanying annealing/extension at 60°C for 30 seconds. For calculation of relative variations in gene expression obtained from Real-Time PCR analysis, the $2^{-\Delta\Delta CT}$ method was used [13].

Table 1: Nucleotide sequences used in Quantitative Real-Time PCR analyses

Gene	Primer	Sequence
NF-kB	Forward	5'-ATGTGGTGGAGGACTTGCTG-3'
	Reverse	5'-GCTGCCTTGCTGTTCTTGAG-3'
MUC5AC	Forward	5'-GTTGGCTCTGACTGTACCACC-3'
	Reverse	5'- CCAGTGTGATGATGGTGAGGA-3'
HPRT1	Forward	5'-CGTCTTGCTCGAGATGTGAT-3'
	Reverse	5'- TTCAGTGCTTTGATGTAATCCAG-3'
B2M	Forward	5'-TCTCTCTTTCTGGCCTGGA-3'
	Reverse	5'-TGTCGGATGGATGAAACCC-3'

Statistical analysis

Relative NF-κB and MUC5AC expressions of group A and B were compared. Shapiro-Wilk test was used for evaluation of data distribution. Independent samples t-test or Mann-Whitney U Test were used for comparison of Group A and B according to the results of Shapiro-Wilk test. Pearson correlation test was used for evaluation of the effect of serum E2 and PG levels on TREK-1 and AQP5. Results were presented as mean (SD). Statistical significance was defined as $P<0.05$. We used

Statistical Package for the Social Sciences (SPSS) Version 21.0 (IBM Corp.; Armonk, NY, USA) for statistical calculations.

Results

Twenty Wister albino female rats were enrolled in the study (10 control, 10 pregnant). The mean relative expression of mRNA of NF-κB in groups A and B were 0.10 (0.03) and 0.08 (0.02), respectively. The mean relative expression of mRNA of MUC5AC in groups A and B were 1.06 (0.01) and 1.17 (0.27), respectively. The mean serum E2 levels in groups A and B were 19.15 (5.36) pg/ml and 73.38 (4.26) pg/ml, respectively. The mean PG levels of groups A and B were 14.14 (1.33) ng/ml and 31.99 (4.43) ng/ml, respectively (Table 2). The PCR data of NF-κB and MUC5AC showed non-normal distribution while ELISA of E2 and PG were normally distributed (P>0.05).

Table 2: Expression of NFκb and MUC5AC in nasal mucosa, and serum E2 and PG levels based on groups

Biomolecules & Sex Hormones	Control (Group A)	Pregnant (Group B)	P-value
Biomolecules			
NF-κB (REV)[a]	0.102 (0.027)	0.76 (0.018)	0.015[b]
MUC5AC (REV)[a]	1.063 (0.013)	1.171 (0.272)	0.029[c]
Serum Sex Hormone Levels			
Estradiol (pg/ml)	19.15 (5.36)	73.38 (4.26)	<0.001[b]
Progesterone (ng/ml)	14.14 (1.33)	31.99 (4.43)	<0.001[b]

[a] Denotes Relative Expression Value, [b] P values obtained by Mann-Whitney U Test, [c] p values obtained by Independent Samples t- test

Comparison of NF-κB between the groups revealed significantly lower expression in Group B (P=0.015). On the other hand, MUC5AC was significantly higher in group B (P=0.029) compared to group A (Figures 1, 2).

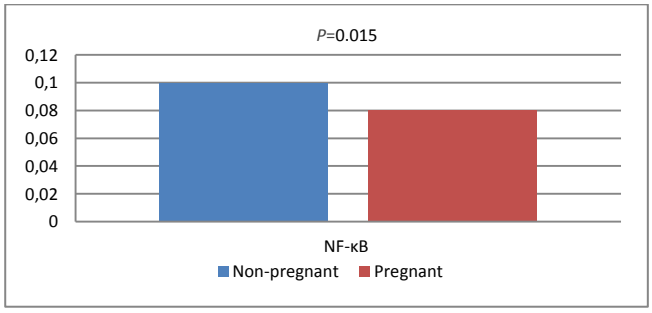


Figure 1: Graphic showing the increase of NF-κB expression in nasal mucosa during pregnancy

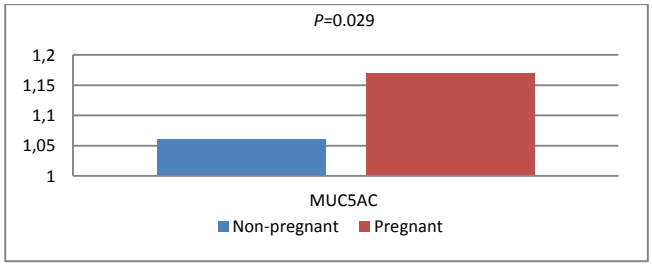


Figure 2: Graphic showing the increment of MUC5AC expression in nasal mucosa during pregnancy

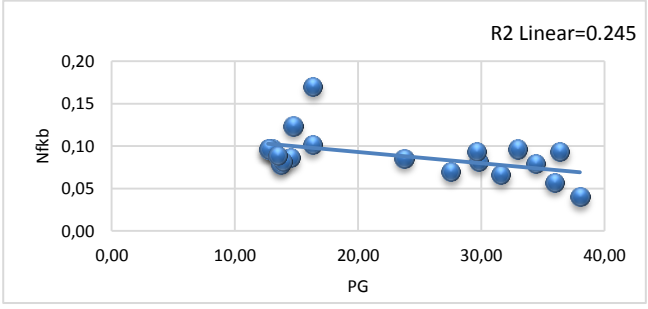


Figure 3: Scatter plot graphic showing the relationship between NF-κB expression and serum PG levels

A statistically significant negative correlation was found between serum PG and NF-κB expression (P=0.027), while a positive correlation was found between PG and MUC5AC expression (P=0.017) (Figure 3, 4). We did not find any correlation between E2 and NF-κB expression (P=0.126); however, E2 and MUC5AC were positively correlated (P=0.017) (Figure 5).

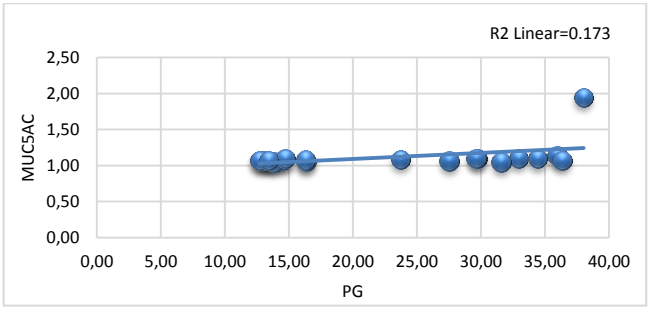


Figure 4: Scatter plot graphic showing the relationship between MUC5AC expression and serum PG levels

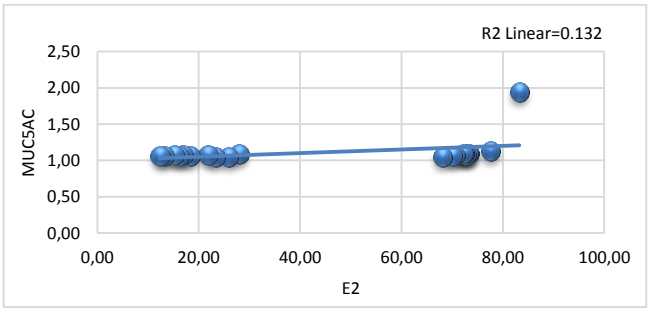


Figure 5: Scatter plot graphic showing the relationship between MUC5AC expression and serum E2 levels

Discussion

Pregnancy is characterized by unique immunomodulation supporting the healthy development and maintenance of the feto-placental unit. The pregnancy related physiological alterations of the immune system raise questions concerning the course of the allergic and other immunologic disorders which already exist before pregnancy [14]. NFκb is well-known with its key role in certain immunologic processes, especially in pregnancy [4-5]. Previous studies showed that NFκb also modulates MUC5AC levels by taking part in certain pathways [7]. As MUC5AC is the main mucin type seen in upper airways, its alterations cause deterioration in mucociliary clearance and transport which lead up to chronic inflammatory airway diseases. From that point of view, we hypothesized that these biomolecules may also play a role in pregnancy related airway diseases and may lead to exacerbation of preexisting chronic airway diseases during pregnancy. In this context, we evaluated whether expressions of nasal MUC5AC and NFκb changed in pregnancy. We also tried to find out whether E2 and PG affected the levels of both biomolecules.

There is a consensus that all pregnant women have a certain level of airway inflammation. Nonetheless, the effect of pregnancy on preexisting chronic inflammatory airway diseases has not been studied comprehensively. As pregnancy is characterized with some degree of immune suppression, deterioration of preexisting inflammatory conditions might be expected. For example, the course of asthma in pregnancy is variable. Namely, one third of patients experience worsening of the symptoms whereas nearly 20% of patients experience

improvement [15]. Allergic rhinitis is also one of these inflammatory conditions which is known to exacerbate in pregnancy. Although the course of allergic rhinitis in pregnancy is still hazy, there are reports concerning adverse outcomes caused by nasal obstruction. Nasal obstruction may lead to maternal hypertension, intrauterine growth restriction, low Apgar scores and increased admission in neonatal intensive care units [16].

Gestational NFκb suppression is particularly important in maternal immunologic differentiation. McCracken et al. revealed downregulation of NFκb in T cells isolated from pregnant women. They suggested that NFκb suppression leads to reduction of cytokine release from T Helper type 1 cells, which is essential for maintaining a healthy pregnancy [17]. NFκb modulates the expression of the genes related to immunity, especially in antigen presenting cells, lymphocytes, and cytokines [1]. On the other hand, MUC5AC is known to be the main mucin constituting a physical barrier in mucosa of nasopharyngeal lymphoid tissues [18]. Thus, it plays a critical role in nasal immunity [19]. Placental NFκb is suppressed in healthy pregnancies while overexpressed in pathological states like preeclampsia [20]. Similarly, we found significant suppression NFκb expression in the nasal mucosa of pregnant rats (Figure 1).

PG is known for its immunomodulatory effect in pregnancy by induction of immune tolerance in favor of Th2 [21]. In the current study, increased PG was associated with suppressed NFκb levels (Figure 2). From that point of view, we suggest that NFκb may take part in immunomodulatory effect of PG. In contrast to PG, E2 levels had no correlation with NFκb in our study. Data about the relationship between E2 and NFκb is controversial. Stice et al. showed that E2 treatment activates protective response via rapid NFκb stimulation in ischemia and trauma cases [22]. However, prior studies showed that prolonged E2 exposure causes inhibition of NFκb expression [23].

We showed that nasal MUC5AC was upregulated by E2 and PG. In contrast, Lange et al found no effect of E2 and PG on MUC5AC expression in ocular epithelial surface of mice [24]. They concluded that regulation of epithelial mucin genes was tissue-specific because previously, mucin in reproductive tract epithelium was found to be regulated by E2 and PG [24,25].

Conclusions

The physiological alteration of NFκb and MUC5AC in nasal mucosa of pregnant rats was shown for the first time. Using real time PCR, we also determined the association of E2 and PG with these biomolecules in rat nasal mucosa. Our findings may partially reveal the biomolecular background of mucosal changes of upper airway during pregnancy. Furthermore, tissue specific regulation of these biomolecules with E2 and PG in nasal mucosa may also elucidate the course of inflammatory airway diseases during pregnancy. Limitation of the current study is that we did not study mucosal expression of NFκb and MUC5AC with immunohistochemistry. Future nasal immunohistochemical studies concerning these biomolecules will elucidate the structural (laminar) localization. By this means, potential influence of topical agents on these biomolecules can be studied in the context of pregnancy.

References

1. Sakowicz A. The role of NFκB in the three stages of pregnancy – implantation, maintenance, and labour: a review article. BJOG. 2018;125(11):1379-87. doi: 10.1111/1471-0528.15172.
2. Dale E, Davis M, Faustman DL. A role for transcription factor NF-kappaB in autoimmunity: possible interactions of genes, sex, and the immune response. Adv Physiol Educ. 2006;30(4):152-8. Review.
3. Santos RS, de Fatima LA, Frank AP, Carneiro EM, Clegg DJ. The effects of 17 alpha-estradiol to inhibit inflammation in vitro. Biol Sex Differ. 2017;8(1):30. doi: 10.1186/s13293-017-0151-9.
4. Fernandez-Valdivia R, Lydon JP. From the ranks of mammary progesterone mediators, RANKL takes the spotlight. Mol Cell Endocrinol. 2012;357(1-2):91-100. doi: 10.1016/j.mce.2011.09.030.
5. Garside H, Stevens A, Farrow S, Normand C, Houle B, Berry A, et al. Glucocorticoid ligands specify different interactions with NF-kappaB by allosteric effects on the glucocorticoid receptor DNA binding domain. J Biol Chem. 2004;279(48):50050-9.
6. Ulkumen B, Artunc Ulkumen B, Batir MB, Pala HG, Vatansever S, Cam S. Impact of Pregnancy and Glucocorticoid Treatment on NF-κB and MUC5AC in Mucosa of Rat Larynx. J Voice. 2019 Dec 2. pii: S0892-1997(19)30470-9. doi: 10.1016/j.jvoice.2019.11.008.
7. Wang W, Zheng M. Mucin 5 subtype AC expression and upregulation in the nasal mucosa of allergic rhinitis rats. Otolaryngol Head Neck Surg. 2012;147(6):1012-9.
8. Tam A, Wadsworth S, Dorscheid D, Man SF, Sin DD. Estradiol increases mucus synthesis in bronchial epithelial cells. PLoS One. 2014;9(6):e100633. doi: 10.1371/journal.pone.0100633.
9. Agematsu Y, Ikadai H, Amao H. Early detection of pregnancy of the rat. Jikken Dobutsu. 1983;32:209-12. doi: 10.1538/expanim1978.32.4_209
10. Lohmiller JJ, Swing SP. Reproduction and Breeding. In: Suckow MA., Weisbroth SH, Franklin CL, editors. The laboratory rat. Boston, United States: Elsevier; 2006. p. 147-165.
11. Ulkumen B, Artunc Ulkumen B, Batir MB, Pala HG, Vatansever S, Cam S. (2019). Impact of Pregnancy and Glucocorticoid Treatment on NF-κB and MUC5AC in Mucosa of Rat Larynx. Journal of Voice, doi: 10.1016/j.jvoice.2019.11.008
12. Witlin AG, Li ZY, Wimalawansa SJ, Grady JJ, Grafe MR, Yallampalli C. Placental and fetal growth and development in late rat gestation is dependent on adrenomedullin. Biol Reprod. 2002; 67:1025-31.
13. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods. 2001;25(4):402-8.
14. Başer Açıkgöz R. Spontaneous vaginal delivery after a pregnancy complicated with Guillain-Barré syndrome. J Surg Med. 2018;2(2):143-4.
15. ACOG Practice Bulletin; Asthma in Pregnancy; Clinical Management Guidelines For Obstetrician-Gynecologists; VOL. 111, NO. 2, PART 1, FEBRUARY 2008.
16. Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. Obstet Gynecol 2003;102:739–52.
17. McCracken SA, Gallery E, Morris JM. Pregnancy- specific down- regulation of NF- kappa B expression in T cells in humans is essential for the maintenance of the cytokine profile required for pregnancy success. J Immunol 2004;172:4583–91.
18. Thibeault SL, Rees L, Pazmany L, Birchall MA. At the crossroads: mucosal immunology of the larynx. Mucosal Immunol. 2009;2(2):122-8.
19. Tacchi, L. et al. Nasal immunity is an ancient arm of the mucosal immune system of vertebrates. Nat Commun. 2014;5:5205. doi: 10.1038/ncomms6205.
20. Armistead B, Kadam L, Drewlo S, Kohan-Ghadr HR. The Role of NFκB in Healthy and Preeclamptic Placenta: Trophoblasts in the Spotlight. Int J Mol Sci. 2020;21(5):1775. doi: 10.3390/ijms21051775
21. Shah NM, Lai PF, Imami N, Johnson MR. Progesterone-Related Immune Modulation of Pregnancy and Labor. Front Endocrinol (Lausanne). 2019;10:198.
22. Stice JP, Mbai FN, Chen L, Knowlton AA. Rapid Activation of Nuclear Factor-κB by 17β-Estradiol and Selective Estrogen Receptor Modulators: Pathways Mediating Cellular Protection. Shock. 2012;38(2):128–36.
23. Simoncini T, Maffei S, Basta G, Barsacchi G, Genazzani AR, Liao JK, et al. Estrogens and Glucocorticoids Inhibit Endothelial Vascular Cell Adhesion Molecule-1 Expression by Different Transcriptional Mechanisms. Circulation Research. 2000 July;87(1):19–25.
24. Lange C, Fernandez J, Shim D, Spurr-Michaud S, Tisdale A, Gipson IK. Mucin gene expression is not regulated by estrogen and/or progesterone in the ocular surface epithelia of mice. Exp Eye Res. 2003;77(1):59- 68.
25. McNeer RR, Carraway CA, Fregien NL, Carraway KL. Characterization of the expression and steroid hormone control of sialomucin complex in the rat uterus: implications for uterine receptivity. J Cell Physiol. 1998;176(1):110-9. doi: 10.1002/(SICI)1097-4652(199807)176:1<110::AID-JCP13>3.0.CO;2-B.

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. 2020;4(9):775-778.
DOI: 10.28982/josam.796153

Research article
Araştırma makalesi

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

A new application of external valvuloplasty using interventional injection of N-butyl cyanoacrylate for malfunctioning venous valves

Venöz kapak yetmezliği için N-butil siyanoakrilatın girişimsel enjeksiyonunu kullanan yeni bir harici valvüloplasti uygulaması

Erhan Hafız [1], Elzem Şen [1]

[1] Gaziantep University Faculty of Medicine, Department of Cardiovascular Surgery Department, Gaziantep, Turkey

ORCID ID of the author(s)
EH: 0000-0002-0801-3194
EŞ: 0000-0003-3001-7324

Corresponding author / Sorumlu yazar:
Erhan Hafız
Address / Adres: Sağlık Bilimleri Üniversitesi, Gaziantep Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi Anabilim Dalı Bölümü, Gaziantep, Türkiye
E-mail: erhantr@yahoo.com

Ethics Committee Approval: The ethic approval of the present the study was obtained from Ethical Committee of Gaziantep University, School of Medicine (Approval number: 2020/288 Date: 9/23/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışmanın etik onayı Gaizantep Üniversitesi Tıp Fakültesi Etik Kurulundan alınmıştır (Onay numarası: 2020/288 Tarih: 23.09.2020). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: Chronic venous insufficiency (CVI) is a common disorder that occurs when the venous valves are not working sufficiently. The treatment strategies depend on ameliorating the function of the valves. The aim of this study was to evaluate the external application of N-Butyl Cyanoacrylate to improve venous valves' functions.

Methods: Thirty patients with CVI who were admitted to the cardiovascular surgery clinic with CVI complaints and underwent extravenous N-Butyl Cyanoacrylate application (extravenous application to the area surrounding the malfunctioning venous valves) between January 2020 and June 2020 were included in this retrospective cohort study. Preoperative and postoperative (third and sixth month) venous Doppler ultrasound findings and complaints were noted, and the results were compared.

Results: The diameter of the great saphenous vein was found to have decreased during the postoperative period (9.27 (1.95 mm) vs. 6.27 (2.16), *P*=0.001). Decremental saphenofemoral reflux durations were detected in postoperative ultrasound evaluations when compared with preoperative data (0.77(0.87) vs. 4.77(0.97) seconds). CVI complaints, including oedema, pigmentation and restless leg syndrome, improved within months after the operation.

Conclusion: The external application of N-Butyl Cyanoacrylate gel seems effective for recovering venous valve function in the medium term.

Keywords: Chronic venous insufficiency, Incompetent venous valve, Treatment, External gel application

Öz

Amaç: Kronik venöz yetmezlik (CVI), venöz kapaklar yeterince çalışmadığında ortaya çıkan yaygın bir hastalıktır. Bu nedenle tedavi stratejileri, kapakların fonksiyonlarının iyileştirilmesine dayanır. Bu çalışmada, venöz kapak fonksiyonlarını iyileştirmek için N-Butil Siyanoakrilat'ın harici uygulamasını değerlendirmeyi amaçladık.

Yöntemler: Ocak 2020-Haziran 2020 tarihleri arasında kardiyovasküler cerrahi kliniğine CVI şikayetleri ile başvuran hastalar geriye dönük olarak kayıt altına alındı. Ekstravenöz N-Butil Siyanoakrilat uygulaması yapılan 30 hasta (fonksiyonu bozulmuş venöz kapak çevresini sarma olarak ekstravenöz uygulama) çalışmaya dahil edildi. Preoperatif ve postoperatif (3. ve 6. ay) venöz Doppler ultrason bulguları ve şikayetleri not edildi ve sonuçlar karşılaştırıldı.

Bulgular: Büyük safen ven çapı postoperatif dönemde geriledi (9,27 (1,95 mm) ve. 6,27 (2,16), *P*=0,001). Preoperatif verilerle karşılaştırıldığında, postoperatif ultrason değerlendirmelerinde azalan safenofemoral reflü süreleri saptandı (0,77 (0,87) ve 4,77 (0,97) saniye). Operasyondan aylar sonra ödem, pigmentasyon, bacakta huzursuzluk vb. şikayetler geriledi.

Sonuç: Sonuçlarımız, N-Butil Siyanoakrilat jelin harici uygulamasının orta vadede venöz kapak fonksiyonlarının iyileştirilmesinde etkili olduğunu gösterdi.

Anahtar kelimeler: Kronik venöz yetmezlik, Venöz kapak yetersizliği, Tedavi, Harici jel uygulaması

How to cite/Atıf için: Hafız E, Şen E. A new application of external valvuloplasty using interventional injection of N-butyl cyanoacrylate for malfunctioning venous valves. J Surg Med. 2020;4(9):775-778.

Introduction

Chronic venous insufficiency (CVI) is a worldwide problem that affects quality of life and can result in high treatment costs for health care systems. It is responsible for almost 70% of all lower extremity vascular ulcers, which lead to prolonged hospital stays and wound care protocols [1,2]. Other CVI symptoms, such as restless leg syndrome, edema and pigmentation, result in further social and psychological problems [1,3].

Most treatment strategies consist of conservative methods, such as compression stockings, food care, exercises and venoactive drugs. However, in patients with advanced failure, these treatments cannot provide sufficient or long-term protection [4,5]. In such cases, microsurgical strategies on venous valves can be used, but they are highly invasive and controversial [5–7]. Recently, some minimally invasive treatment strategies, albeit controversial, have been reported. Banding or wrapping of the incompetent venous valve is one example of these suggested strategies [6]. External valvular stenting is another option for the treatment of venous valve incompetence in patients with CVI [7,8]. Better long-term outcomes were reported in external valvular stenting patients when compared with conventional surgical stripping. However, that also requires surgical incision [8].

Less invasive methods might be superior to surgical external valvular venous applications. Therefore, this study aimed to investigate the outcome of ultrasound-guided external N-Butyl Cyanoacrylate application to incompetent venous valves.

Materials and methods

The retrospective data of 30 CVI patients who underwent ultrasound-guided external venous valvuloplasty with percutaneous N-Butyl Cyanoacrylate gel application were examined. Ethics Approval was obtained from the local ethics committee of Gaziantep University, School of Medicine (Approval number: 2020/01). Power analysis of the study was calculated as follows: A sample size including 30 patients for the extra venous application was enough to detect a clinical significance with a type one error rate (α) of 5% and a (β) power of 0.9644. Patients who had post-phlebitic syndrome or recurrent deep venous thrombosis history were not included in the study. The demographic findings, clinical classification [according to the CEAP classification as described in previous reports [9]] and preoperative and postoperative Doppler ultrasound findings were noted.

Preoperative venous insufficiency and postoperative ultrasound follow-ups were recorded by the same radiologist with the same ultrasound device (Mindray® DP-20 Vet, Shenzhen, China). The evaluation of venous reflux with Doppler ultrasound is shown in Figure 1.

The external application of N-Butyl Cyanoacrylate gel was made with a special medical device (Viniera X™, Noegenix, Ankara, Turkey). This method depends on percutaneous puncture of the inguinal area and ultrasound-guided interventional injection of N-Butyl Cyanoacrylate in the surroundings of the incompetent venous valve (Figure 2). After detection of the saphenofemoral junction (SFJ) and incompetent venous valves with Doppler ultrasound, a 6 F sheath was placed using the Seldinger technique [10]. Thereafter, the surrounding tissue of the SFJ was dissected with a polytetrafluoroethylene catheter. N-Butyl Cyanoacrylate gel was diffusely infused just external to the surroundings of the malfunctioning venous valves of the great saphenous vein (GSV) and deep femoral vein using the Viniera X™ device (Figure 3 A, B).

Statistical analysis

The obtained data were statically analyzed using the SPSS software program (ver. 15.0, Chicago, Illinois, USA). Mean (standard deviation (SD)) was used for continuous variables, and categorical values were expressed as percentages. The preoperative and postoperative values were analyzed with the Mann-Whitney U test. The paired samples t-test was used to evaluate the significance of the difference between two variables. $P<0.05$ was considered statistically significant.

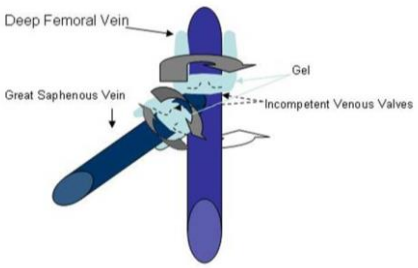


Figure 1: Illustration of N-Butyl Cyanoacrylate gel application on the surrounding area of the incompetent venous valves

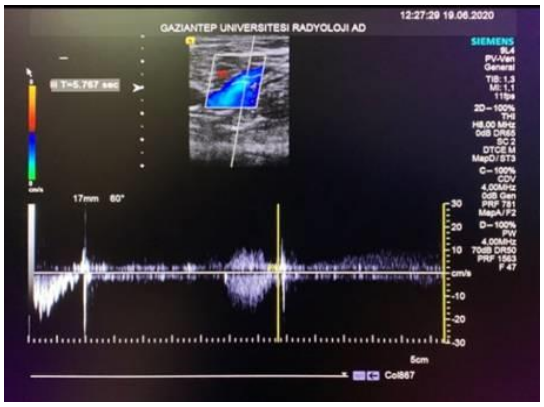


Figure 2: Colored Doppler ultrasound evaluation of venous reflux

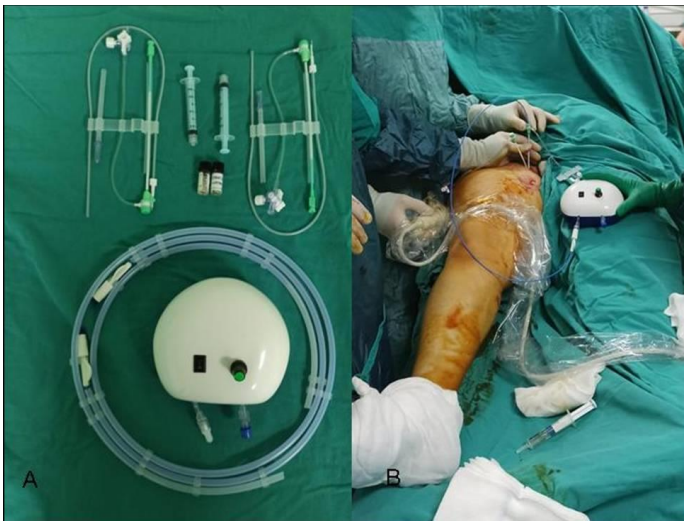


Figure 3: A: The Viniera X™ device and contents of package (Seldinger needle, guide-wire, catheters) B: Ultrasound-guided application of Viniera X™ device in the operating room for treatment of venous reflux

Results

There were 19 (63%) male patients and 11 (37%) female patients. The mean age of all patients was 44.1 years (7.6, range 32–58 years). The accompanying conditions included hypertension (n=12, 40%), hyperlipidemia (n=5, 17%) and smoking (n=21, 70%). There were seven patients (23%) with CEAP 3 class, 11 patients (37%) with CEAP 4 class, nine patients (30%) with CEAP 5 class and three patients (10%) with CEAP 6 class. All patients were discharged uneventfully at the eighth hour of operation.

The preoperatively calculated mean GSV diameter at the level of the SFJ was 9.27mm (1.95, range 6.00–13.20 mm). Postoperatively decremental GSV diameters [6.27 (2.16) mm: range 4.20–9.40 mm] were obtained when compared with preoperative values (P=0.001). The reflux at the SFJ reduced significantly after the operation to 0.77 (0.87) seconds (range 0.15–5.22 seconds) from the preoperative value of 4.77 (0.97) seconds (range 3.12–6.43 seconds) (P<0.001). The preoperative and postoperative values are presented in Table 1. The preoperative and postoperative ultrasonographic examination (three months later) of reflux at the SFJ level is demonstrated in Figure 4.

Table 1: The comparison of preoperative and postoperative values

	Preoperative Mean (SD)	Postoperative Mean (SD)	*P*-value
GSV* diameter, mm	9.27 (1.95)	6.27 (2.16)	0.001
Reflux at SFJ**, sec	0.77 (0.87)	4.77 (0.97)	<0.001

SD: Standard deviation, GSV: Great saphenous vein, SFJ: Saphenofemoral junction

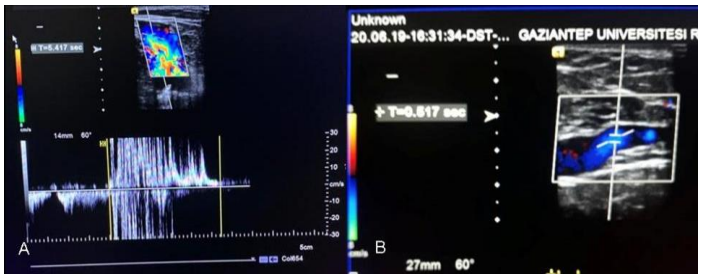


Figure 4: Preoperative and postoperative ultrasonographic examination of reflux at the SFJ level; A: Preoperative reflux; B: Postoperative reduced reflux

Discussion

Interventional treatment of venous valve incompetency seems an effective method with reduced postoperative reflux duration and decreased venous diameter. Moreover, all procedures were completed with local anesthesia, and the treatment was performed without a surgical incision. The results show that the Viniera X™ extravalvular gel application device resulted in short hospital stays and improved medium-term outcomes.

CVI is a progressive disease that can result in disrupted quality of life and socioeconomic problems. It can be easily managed and treated in its early phases; however, it can lead to chronic non-healing wounds and severe limb edema if neglected [9,11]. Conventional treatment modalities involve vasoactive drugs and compression stockings. Wound care and palliative strategies can be applied for recurrent ulcers. However, these strategies are generally directed towards the symptoms and not curative. The more precise treatment strategies consist of surgical methods for remission of complaints and recovery of venous function as much as possible [11]. Direct venous valve repair or venous valve replacement strategies are more invasive and require an experienced center [12]. There is insufficient evidence to recommend these strategies, and the exact methodology is still controversial [12,13]. Therefore, minimally invasive strategies that can be applied with less trauma have been developed. The most common strategies depend on surgically externally banding or wrapping strategies of incompetent venous valves. The long-term data present beneficial outcomes with these strategies [14]. Technically, the vein can be tightened to the desired diameter until competence is achieved, but the result should be confirmed with ultrasonographic evaluation. Valve incompetence is not sufficiently treated if not properly tightened, or venous stenosis, thrombosis or thrombophlebitis can occur [14–16]. Interventional methods without surgical incision allow simultaneous Doppler examination for evaluation of incompetent venous valves during application. External venous shaping utilizing perivenous fluids is a more recently reported technique that offers promising results. However, there is insufficient data to obtain precise evidence regarding long-term results. The ultrasound-guided application of injectable fluids can cover incompetent venous valves and improve valve function via reshaping the enlarged venous structure [17]. N-Butyl Cyanoacrylate was used in this study as an injectable fluid for ultrasound-guided vein shaping. The diameter of the saphenous veins reduced, and reflux durations shortened after the application of N-Butyl Cyanoacrylate with the newly developed medical device Viniera X™. Patient complaints regressed after application, and no operational complications were observed.

Limitations

The main limitations of this study are its small sample size and its single-center design. The findings should be confirmed with larger cohort studies.

Conclusions

Viniera X™ seems a minimally invasive and feasible method to eliminate venous reflux in patients with CVI. The ultrasound-guided application provides simultaneous confirmation of sufficient and anatomically precise injection of perivenous N-Butyl Cyanoacrylate for adequate covering of the enlarged vessels.

References

1. Sándor T. Chronic venous disease. A state of art. Orv Hetil. 2010;151:131-9.
2. Ross DS. Venous stasis ulcers: a review. Northeast Florida Medicine. 2012;63:29-51.
3. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. Circulation. 2005;111:2398-409.
4. Santler B, Goerge T. Chronic venous insufficiency - a review of pathophysiology, diagnosis, and treatment. J Dtsch Dermatol Ges. 2017;15(5):538-56. doi: 10.1111/ddg.13242
5. van Gent WB, Catarinella FS, Lam YL, Nieman FH, Toonder IM, van der Ham AC, et al. Conservative versus surgical treatment of venous leg ulcers: 10-year follow up of a randomized, multicenter trial. Phlebology. 2015;30(1 Suppl):35-41. doi: 10.1177/0268355514568848
6. Derin Çiçek E, Arslan HM. The efficacy of external valvuloplasty with silicone stents (Venocuff™) in the management of focal valvular incompetence as assessed by Doppler ultrasound. Turk J Vasc Surg. 2020;29(3):152-8.
7. Lane RJ, Cuzzilla ML, Coroneos JC, Phillips MN, Platt JT. Recurrence rates following external valvular stenting of the saphenofemoral junction: a comparison with simultaneous contralateral stripping of the great saphenous vein. Eur J Vasc Endovasc Surg. 2007;34(5):595-604. doi:10.1016/j.ejvs.2007.06.021
8. Lane RJ, Graiche JA, Coroneos JC, Cuzzilla ML. Long-term comparison of external valvular stenting and stripping of varicose veins. ANZ J Surg. 2003;73(8):605-9. doi:10.1046/j.1445-2197.2003.02714.x
9. Karahan O, Yavuz C, Kankilic N, Demirtas S, Tezcan O, Caliskan A, et al. Simple blood tests as predictive markers of disease severity and clinical condition in patients with venous insufficiency. Blood Coagul Fibrinolysis. 2016;27(6):684-90. doi:10.1097/MBC.0000000000000478
10. Song IK, Kim EH, Lee JH, Jang YE, Kim HS, Kim JT. Seldinger vs modified Seldinger techniques for ultrasound-guided central venous catheterisation in neonates: a randomised controlled trial. Br J Anaesth. 2018;121(6):1332-7. doi:10.1016/j.bja.2018.08.008
11. Yavuz C, Demirtas S, Guclu O, Karahan O, Yazici S, Caliskan A, et al. An alternative therapy for recurrent stasis ulcers in chronic venous insufficiency: venocuff. Case Rep Vasc Med. 2012;2012:315147. doi:10.1155/2012/315147
12. Goel RR, Abidia A, Hardy SC. Surgery for deep venous incompetence. Cochrane Database Syst Rev. 2015;2015(2):CD001097.
13. Hardy SC, Riding G, Abidia A. Surgery for deep venous incompetence. Cochrane Database Syst Rev. 2004;(3):CD001097. doi:10.1002/14651858.CD001097.pub2

14. Joh JH, Lee KB, Yun WS, Lee BB, Kim YW, Kim DI. External banding valvuloplasty for incompetence of the great saphenous vein: 10-year results. International Journal of Angiology. 2009;18(1):25–8.
15. Sarac A, Jahollari A, Talay S, Ozkaya S, Ozal E. Long-term results of external valvuloplasty in adult patients with isolated great saphenous vein insufficiency. Clin Interv Aging. 2014;9:575-9. doi:10.2147/CIA.S60555
16. Zamboni P, Marcellino MG, Cappelli M, Feo CV, Bresadola V, Vasquez G, et al. Saphenous vein sparing surgery: principles, techniques and results. J Cardiovasc Surg (Torino) 1998;39:151-62.
17. Ragg JC: A New Modality to Shape Enlarged Veins and Restore Valves by Perivenous Injection of Viscous Fluids. J Am Coll Cardiol Intv 2014;7:S33.

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. 2020;4(9):779-783.
DOI: 10.28982/josam.800830

Research article
Araştırma makalesi

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

Sexual dysfunction and associated risk factors in multiple sclerosis

Multipl sklerozda seksüel disfonksiyon ve ilişkili risk fakörleri

Mesrure Köseoğlu [1], Rabia Gökçen Gözübatık Çelik [1], Mesude Tütüncü [1], Ayhan Bingöl [2], Bahar Erbaş [3], Duygu Deringöl [2], Dilek Ataklı [1]

[1] Department of Neurology, Bakirkoy Training and Research Hospital for Psychiatry and Neurological Disorders, University of Health Sciences, Istanbul, Turkey
[2] Behavioral Change Academy, Istanbul, Turkey
[3] Department of Pharmacology, Demiroglu Bilim University Medical Faculty and Neurology Clinic, İstanbul Florence Nightingale Hospital, Istanbul, Turkey

ORCID ID of the author(s)

MK: 0000-0003-0469-0064
RGGÇ: 0000-0002-8186-8703
MÖT: 0000-0002-1176-3156
AB: 0000-0002-6024-6550
BE: 0000-0002-6125-7761
DD: 0000-0002-0921-3905
DA: 0000-0001-6458-8374

Corresponding author / Sorumlu yazar:
Rabia Gökçen Gözübatık Çelik
Address / Adres: Bakırköy Ruh Sağlığı ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi Nöroloji Kliniği, Sağlık Bilimleri Üniversitesi, İstanbul, Türkiye
E-mail: gokcen3@hotmail.com

Ethics Committee Approval: Approval was obtained from the Ethics Committee of Bakirkoy Training and Research Hospital for Psychiatry and Neurological Disorders, University of Health Sciences on 5/7/2019 with a decision number of 318. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma onayı Sağlık Bilimleri Üniversitesi Bakırköy Ruh Sağlığı ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi Etik Kurulu'ndan 318 sayılı karar ile 07.05.2019 tarihinde alınmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: Sexual dysfunction (SD) is quite common in multiple sclerosis (MS), and exhibits a multifactorial pattern. This study was set out to evaluate the frequency of SD and explore the related factors to support the quality of MS patients' lives.

Methods: This cross-sectional study included 96 volunteer RRMS patients between 18 and 60 years of age who were diagnosed with MS according to the Mc Donald criteria between 2018 and 2019 in our hospital. Multiple sclerosis intimacy and sexuality questionnaire-19 (MSISQ-19), Arizona Sexual Experience Scale (ASEX), Multiple Sclerosis Inventory of Cognition (MUSIC) and Beck Depression Inventory (BDI) questionnaires were used.

Results: Mean age of the patients was 38.46 (8.47) (min-max:20 – 60 years) years, and mean disease period was 77.02 (70.62) (3–324 months) months. Mean Extended Disability Status Scale (EDSS) score was 2.1 (1.33) (0-5) with a standard deviation of 80.5%. A negative correlation was observed between MUSIC cognitive and EDSS (P=0.017; r=-0.273), and BDI scores (P=0.003; r=-0.306). A significant and positive correlation was detected between MSISQ score (P<0.001; r=0.476) and BDI (P<0.001; r=0.529) in MUSIC fatigue test results. A negative and poor correlation was found between MUSIC fatigue and MUSIC cognitive score (P<0.001; r=-0.365). In patients with depression, mean MUSIC cognitive scores were lower (P=0.009), while MUSIC fatigue scores were higher (P<0.001). Age, educational status, presence of secondary SD were independent risk factors.

Conclusion: SD, a quite common condition in MS, may be decreased to increase the quality of lives of patients through treatment of psychosocial factors associated with cognitive state.

Keywords: Multiple sclerosis, Sexual dysfunction, Cognitive impairment, Depression

Öz

Amaç: Cinsel işlev bozukluğu (CİB), multipl sklerozda (MS) sık görülen multifaktöryel bir durumdur. Bu çalışma, MS'de CİB sıklığını değerlendirmek ve ilgili faktörleri araştırmak amacıyla düzenlenmiştir.

Yöntemler: Kesitsel özellikteki bu çalışmaya, 2018-2019 yıllarında,18 ile 60 yaşları arasında Mc Donald kriterlerine göre kesin relapsing remitting multipl skleroz (RRMS) tanısı alan 96 hasta gönüllü olarak çalışmaya dahil edildi. Multiple sclerosis intimacy and sexuality questionnaire-19 (MSISQ-19), Arizona Sexual Experience Scale (ASEX), Multiple Sclerosis Inventory of Cognition (MUSIC) ve Beck Depresyon Ölçeği (BDI) anketleri uygulandı.

Bulgular: Hastaların yaş ortalaması 38,46 (8,47) (min-maks: 20 - 60 yıl) yıldı; ortalama hastalık süresi 77,02 (70,62) (3 - 324 ay) aydı. Ortalama Genişletilmiş Özürlülük Durumu Ölçeği (EDSS) puanı 2,1 (1,33) (0-5) ve standart sapma %80,5 idi. MÜZİK bilişsel puanı ile EDSS puanı (P=0,017; r=-0,273) ve MÜZİK bilişsel ve BDÖ puanı arasında (P=0,003; r=-0,306) negatif bir korelasyon görüldü. Müzik yorgunluk testi sonuçlarında MSISQ skoru (P<0,001; r=0,476) ile BDÖ (P<0,001; r=0,529) arasında anlamlı ve pozitif bir ilişki tespit edildi. Müzik yorgunluğu ile müzik bilişsel puanı arasında negatif ve zayıf ilişki bulundu (P<0,001; r=-0,365). Ortalama MUZİK bilişsel puanı depresyonu olanlarda daha düşüktü (P=0,009); MÜZİK yorgunluk puanları depresyon grubunda daha yüksek saptandı (P<0,001). Yaş, eğitim durumu, ikincil seksüel disfonksiyon (SD) varlığı bağımsız risk faktörleriydi.

Sonuç: SD, MS'te çok yaygındır. Kognitif durumla da ilişkili olan psikososyal faktörlerin tedavisi ile SD oranı azaltılarak hastaların yaşam kalitesi arttırılabilir.

Anahtar kelimeler: Multipl skleroz, Seksüel disfonksiyon, Kognitif bozukluk, Depresyon

How to cite/Atıf için: Köseoğlu M, Çelik RGG, Tütüncü M, Bingöl A, Erbaş B, Deringöl D, Ataklı D. Sexual dysfunction and associated risk factors in multiple sclerosis. J Surg Med. 2020;4(9):779-783.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease which usually affects young adults with relapse and remission periods. Although its pathophysiology is not clear, the most important characteristic is axonal demyelination. Relapsing remitting MS (RRMS), which progresses with attacks, is the most common clinical form. Tiredness, cognitive disorder, and physical disability significantly affect the quality of life in younger ages. There are many articles on MS patients in the literature [1]; however, there are limited number of studies investigating sexual dysfunctions. The cause for that may be explained in two forms: First, MS is a chronic disease which affects young adults and causes severe disability. Therefore, clinicians prefer to focus on the main treatments of the patients to reduce disability and increase the quality of life. Also, sexuality is an area of intimacy associated with familial factors, relations between individuals, marriage/partner status, and cultural characteristics. The patient abstains from informing the physician about this subject or the physician is not aware about the importance of the issue. Therefore, each basic treatment to improve the quality of life remains insufficient when other factors are not considered [2,3].

Sexual dysfunction (SD) prevalence in MS is between 16.9% and 95% [4]. This rate varies between 40% and 80% in females, and 50% and 90% in males [3]. The most common complaints for SD include erectile dysfunction and ejaculation problems in male patients, loss of vaginal lubrication and libido in female patients, and orgasm problems in both genders [2,5]. Etiology of SD in MS is not clear. Previous studies suggest primary, secondary, and tertiary SD for classification. Primary SD (PSD) is defined as that caused by the disease, namely, demyelinated plates in the brain and spine; secondary SD (SSD) occurs as a result of indirect causes regarding sexual organs including fatigue, spasticity, coordination dysfunction, and side effects of medications prescribed for MS. Tertiary SD (TSD) is caused by psychosocial and cultural factors such as fear of rejection by sexual partner, problems with partners, and depression [2].

Since SD is a multifactorial disease and there is no objective test to detect it, different results are obtained due to cultural and social factors. For instance, two different studies from two different countries detected that SD is associated with gender difference in MS [2,6]; however, Demirkıran et al. [5] did not detect any gender difference in their study.

Previous studies in the literature state that PSD is prominent in MS, and urinary bladder / bowel dysfunction is more responsible than other causes. [2,5,7] Furthermore, recent reviews report that SD in MS is associated with patient age, lower educational level, unemployment, long lasting marriage, menopause, chronic disease, and unhappiness in relationship [4,8].

The aim of the present study was to reveal causes of SD in MS patients, investigate SD-associated factors, and differently from the literature, its association with cognitive functions.

Materials and methods

The study included 96 volunteer patients with RRMS between 18 and 60 years of age who were diagnosed with MS according to Mc Donald criteria. Patients without any sexual partners, those with sexual dysfunction due to different co-morbidities, and severe neurological / psychiatric diseases were excluded from the study. The Kurtzke Extended Disability Status Scale (EDSS) [9] was used for disability evaluation. The Multiple Sclerosis Intimacy and Sexuality Questionnaire 19 (MSISQ-19), Arizona Sexual Experience Scale (ASEX), Multiple Sclerosis Inventory of Cognition (MUSIC), and Beck Depression Inventory (BDI) of voluntary forms were performed on all participants. Clinical and demographic data of the participants were obtained from the files and recorded in a table format.

Approval was obtained from the Ethics Committee of Bakirkoy Training and Research Hospital for Psychiatry and Neurological Disorders, University of Health Sciences on 07.05.2019 with the decision number of 318.

Tests:

Multiple sclerosis intimacy and sexuality questionnaire-19 (MSISQ-19)

It is a self-report form consisting of 19 Foley and Iverson questions to understand sexual dysfunction in patients with multiple sclerosis. Sexual dysfunction is categorized into three levels: Primary, secondary, and tertiary [10].

Arizona Sexual Experience Scale (ASEX)

The self-reported assessment of McGahey and his friends (2000) is intended to assess sexual changes and disorders in patients using psychotropic medicines. It has two distinct forms, male and female, and consists of five questions. Growing questions in the scale explores sexual motivation, psychological excitement, physiological stimulation, orgasmic potential, and orgasm satisfaction. Each question is scored from 1 to 6, with a total score of 5 to 30. When the overall score is 19 or higher, any item is scored 5 or 6 points, or 3 or more items are scored 4 points, sexual dysfunction is highly related to clinically-defined sexual dysfunctions [11].

Multiple Sclerosis Inventory of Cognition (MUSIC)

Calabrese and his friends developed this test. Developmental MUSIC test, which is based on empirical studies, offers the opportunity of consistency and monitoring of the most commonly affected cognitive performance areas in MS disease in the shortest period (8-10 minutes). The highest possible score is 30 points, and it has a cut-off value of 20 [12]. It consists of two parts: 1. Cognitive activity performance analysis: It covers areas of verbal memory (long-term and short-term), word fluence, attention focus and memory maintenance. 2. Fatigue Scale: Measures fatigue over 7 points by asking people questions. The maximum and minimum scores are 21, and 3, respectively.

Statistical analysis

Data were analyzed through IBM SPSS V23. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate conformity to normal distribution. Chi-square and Fisher's exact test were used to compare categorical variables according to groups (age, gender, educational status, disease period, age of disease onset, EDSS). Independent two sample t test was utilized to compare normally distributed quantitative

data according to binary groups; non-normally distributed data were compared by Mann-Whitney U test. One-way variance analysis was used to compare normally distributed quantitative data in three and more groups. Non-normally distributed data were compared by Kruskal Wallis test. Pearson's correlation coefficient was used to evaluate the association between normally distributed quantitative data. Binary logistic regression analysis was used to review independent risk factors affecting SD. Logistic regression analysis was performed as univariate and multivariate; inclusion of independent risk factors in multivariate model was performed with the Backward: Wald method. Quantitative data were expressed in mean ± standard deviation and median (minimum-maximum) whereas categorical data were expressed in frequency (percentage). Significance level was $P<0.05$.

Sample Size and Power Analysis: Correlation analysis was used for relational analysis for basic hypotheses to be validated in the study, and independent samples t test was utilized in group comparisons. According to the large effect size targeted in the T test (r=.80), with the α error probability of 0.05 and the 1-β error probability of 0.95, the required minimum sample number was calculated with the G-Power 3.0.10 program. For the presence / absence of sexual dysfunction, the group ratios were determined as 1 to 2 (n=non-sexual dysfunction group, 2n= Group with sexual dysfunction) and the critical t in the comparison to be made with groups of 31 to 63 people was determined as 1.986. This is the study of 94 people, which amounts to a power of 95,034. Considering this information, 98 people were included in the study and the rate of sexual dysfunction presence / absence was partially preserved (81,19). According to the number of these groups, the analysis was determined to be at critical t: 1.285 and 87,622 power, and the required and targeted effect / power size was obtained in the two group comparisons.

Results

A total of 96 RRMS patients including 69 (71.9%) females were enrolled in the study. MSIS-Q results revealed that 80.5% of the participant patients had MS.

Mean age of the patients was 38.46(8.47) (min-max:20 – 60 years) years, and mean disease period was 77.02(70.62) (3 – 324 months) months. Mean EDSS score was 2.1(1.33) (0-5). Majority of the patients were elementary school graduates (58.5%); 25.5% of the patients were high-school graduates, and 15.9% were had bachelor's degrees. Mean onset age of the disease was 32.13 years (median: 32 years; min-max.: 14-49). There was no statistically significant difference regarding other sociodemographic characteristics according to educational status ($P>0.05$).

Mean MSISQ score was 39.72 (17.41) (min-max:18 - 82). Mean scores for PSD and SSD were 32.13 (7.81) (min-max:14-49) and 20.44(8.3) (min-max: 9 – 42), respectively. Mean score for TSD was 8.93(5.28) (min-max:5-25). As expected, each three SD types were significantly associated with each other ($P<0.01$). Mean ASEX score was 16.1 (median:16, min-max:0-30); mean MUSIC cognitive score was 16.08 (median 17; min-max: 3-29); and mean MUSIC fatigue score was 12.61 (median 12.5; min-max: 3-21).

PSD, SSD and TSD were detected in 10.42%, 19.84%, and 8.30% of female participants, respectively. Such rates were 10.19%, 21.92%, and 10.50%, respectively in male participants. There was no significant correlation between gender and SD (including sub-types of SD) (38.9% in female vs 42.58% $P=0.324$ *P*-value for primary SD: 0.870, secondary: 0.350, tertiary: 0.124; independent samples T test). The only parameter for gender difference was the onset age of the disease. Mean age of onset was 33.32 years in females, which was higher than the mean age of onset in males (29.11) ($P=0.017$). There was no statistically significant difference between other quantitative parameters with respect to gender ($P>0.05$) (Table 1).

Elaboration of MSISQ scores and sociodemographic characteristics revealed a positive and moderate correlation between disease period and MSISQ score ($P<0.001$; r=0.414). Review of the association between disease period and SD subtypes exposed a significantly positive and poor association between disease period and PSD ($P=0.004$; r=0.303), a significantly positive and moderate association between disease period and SSD ($P<0.001$; r=0.409), and a significantly positive and poor association between disease period and TSD ($P<0.001$; r=0.377). When the SD group (n:70) and non-SD group (n:10) were elaborated, there was no significant differences in age (0.300), gender, EDSS (0.105) ($P=0.005$) (Table 2).

A positive correlation was detected between MUSIC fatigue and MSISQ scores ($P<0.001$; r=0.476). Same correlation was also valid for Arizona test ($P=0.006$; r=0.302). A statistically significant and positive correlation was found between fatigue and PSD ($P=0.008$; r=0.281), SSD ($P<0.001$; r=0.599), and TSD ($P=0.004$; r=0.303) (Table 2).

The patients were divided into two groups depending on presence of depression: Medians of disease period were statistically different with regards to the presence of depression ($P=0.012$). A significant difference was observed in mean EDSS scores ($P=0.018$). In those with depression, the mean MUSIC cognitive score was lower ($P=0.009$), while MUSIC fatigue scores were higher ($P<0.001$) (Table 3).

Table 1: Comparison of quantitative parameters according to the gender

		Female (n=69)	Male (n=27)	Total (n=96)	*P*-value
Age	Mean (SD)	38.96 (8.84)	37.19 (7.44)	38.46(8.47)	0.359*
	Mean (Min-max)	39 (20 - 60)	38 (24 - 52)	38 (20 - 60)	
Disease period	Mean (SD)	69.22 (65.36)	96.67(80.41)	77.02(70.62)	0.088*
	Mean (Min-max)	48 (0 - 240)	84 (0 - 324)	60 (0 - 324)	
EDSS	Mean (SD)	1.94 (1.38)	2.44 (1.19)	2.1(1.33)	0.126*
	Mean (Min-max)	2 (0 - 5)	3 (0 - 5)	2 (0 - 5)	
Beck depression	Mean (SD)	15.91(12.22)	18.48 (13.86)	16.64(12.68)	0.385**
	Mean (Min-max)	13 (0 - 52)	16 (0 - 57)	13 (0 - 57)	
Primary sexual dysfunction	Mean (SD)	10.42 (6.18)	10.19(5.56)	10.36(5.98)	0.826**
	Mean (Min-max)	8.5 (4 - 25)	8 (5 - 25)	8 (4 - 25)	
Secondary sexual dysfunction	Mean (SD)	19.84 (7.43)	21.92(10.14)	20.44(8.3)	0.350*
	Mean (Min-max)	18 (9 - 40)	18.5 (10 - 42)	18 (9 - 42)	
Tertiary sexual dysfunction	Mean (SD)	8.3 (4.6)	10.5(6.5)	8.93(5.28)	0.142**
	Mean (Min-max)	6 (5 - 24)	8 (5 - 25)	6 (5 - 25)	
MSISQ	Mean (SD)	38.56(16.07)	42.58 (20.39)	39.72(17.41)	0.375*
	Mean (Min-max)	33.5 (18 - 82)	34.5 (20 - 82)	33.5 (18 - 82)	
ASEX	Mean (SD)	16.52(6.97)	14.91 (5.07)	16.1 (6.53)	0.323*
	Mean (Min-max)	16 (0 - 30)	14 (9 - 28)	16 (0 - 30)	
Music cognitive	Mean (SD)	16.65 (5.48)	14.58(6.52)	16.08(5.82)	0.122*
	Mean (Min-max)	17 (3 - 29)	13.5 (5 - 29)	17 (3 - 29)	
Music fatigue	Mean (SD)	12.22 (5.42)	13.68 (5.08)	12.61(5.34)	0.243*
	Mean (Min-max)	12 (3 - 21)	15 (3 - 21)	12.5 (3 - 21)	
Disease onset age	Mean(SD)	33.32 (7.88)	29.11 (6.87)	32.13 (7.81)	0.017*
	Mean (Min-max)	33 (16 - 49)	29 (14 - 43)	32 (14 - 49)	

SD: Standard deviation, * Independent two sample t test statistics, ** Mann-Whitney U test

Table 2: The association of sexual dysfunction sub-types with sociodemographic characteristics and test scores

	Primary sexual dysfunction		Secondary sexual dysfunction		Tertiary sexual dysfunction		MSISQ	
	r	*P*-value	r	*P*-value	r	*P*-value	r	*P*-value
Age	0.184	0.082	0.133	0.212	0.117	0.274	0.161	0.128
Disease period	0.303	0.004	0.409	<0.001	0.377	<0.001	0.414	<0.001
EDSS	0.179	0.129	0.224	0.057	0.191	0.105	0.230	0.051
Beck depression	0.457	<0.001	0.687	<0.001	0.571	<0.001	0.658	<0.001
Music cognitive	-0.077	0.472	-0.215	0.043	-0.181	0.089	-0.184	0.084
Music fatigue	0.281	0.008	0.599	<0.001	0.303	0.004	0.476	<0.001
ASEX	0.467	<0.001	0.302	0.006	0.403	<0.001	0.428	<0.001

Table 3: Comparison of quantitative parameters according to the depression

		Absent (n=60)	Present (n=36)	Total (n=96)	*P*-value
Age	Mean (SD)	38.52 (8.2)	38.36 (9.01)	38.46 (8.47)	0.931*
	Mean (Min-max)	38 (21 - 60)	38.5 (20 - 54)	38 (20 - 60)	
Disease period	Mean (SD)	66.34 (70.88)	94.53 (67.55)	77.02 (70.62)	0.012**
	Mean (Min-max)	36 (0 - 324)	60 (3 - 264)	60 (0 - 324)	
EDSS	Mean (SD)	1.8 (1.19)	2.52 (1.42)	2.1 (1.33)	0.018*
	Mean (Min-max)	2 (0 - 4)	3 (0 - 5)	2 (0 - 5)	
Beck depression	Mean (SD)	8.68 (5.07)	29.89 (10.2)	16.64 (12.68)	<0.001*
	Mean (Min-max)	8.5 (0 - 17)	26 (18 - 57)	13 (0 - 57)	
Primary sexual dysfunction	Mean (SD)	8.47(4.9)	13.31(6.38)	10.36(5.98)	<0.001*
	Mean (Min-max)	6 (4 - 25)	12 (5 - 25)	8 (4 - 25)	
Secondary sexual dysfunction	Mean (SD)	17.02 (6.86)	25.83 7.53	20.44 (8.3)	<0.001*
	Mean (Min-max)	16 (9 - 42)	26 (11 - 40)	18 (9 - 42)	*
Tertiary sexual dysfunction	Mean (SD)	6.96 (3.45)	12.03 6.15	8.93 (5.28)	<0.001*
	Mean (Min-max)	5 (5 - 20)	11 (5 - 25)	6 (5 - 25)	*
MSISQ	Mean (SD)	32.44 (13.11)	51.17 17.31	39.72 (17.41)	<0.001*
	Mean (Min-max)	29 (18 - 78)	47 (26 - 82)	33.5 (18 - 82)	*
Music cognitive	Mean (SD)	17.27 (5.55)	14.06 5.8	16.08 (5.82)	0.009*
	Mean (Min-max)	18 (6 - 29)	14 (3 - 27)	17 (3 - 29)	
Music fatigue	Mean (SD)	10.73 (4.63)	15.77 5.01	12.61 (5.34)	<0.001*
	Mean (Min-max)	10 (3 - 21)	16 (3 - 21)	12.5 (3 - 21)	
ASEX	Mean (SD)	14 (6.11)	19.61 5.72	16.1 (6.53)	<0.001*
	Mean (Min-max)	14 (0 - 30)	19 (11 - 30)	16 (0 - 30)	
Disease onset age	Mean (SD)	33.22 (7.52)	30.33 8.05	32.13 (7.81)	0.080*
	Mean (Min-max)	33 (16 - 49)	31 (14 - 44)	32 (14 - 49)	

The association of tests with each other were reviewed (Table 4). According to the results, a negative correlation was observed between MUSIC cognitive and EDSS score (*P*=0.017; r=-0.273), and BDI score (*P*=0.003; r=-0.306). A significant and positive correlation was detected between MSISQ score (*P*<0.001; r=0.476) and BDI (*P*<0.001; r=0.529) scores in MUSIC fatigue test results. A negative and poor association was found between MUSIC fatigue and MUSIC cognitive scores (*P*<0.001; r=-0.365).

The independent risk factors affecting SD were analyzed through binary logistic regression analysis as univariate and multivariate models. Risk of SD was 0.178-fold less in associate graduates than elementary school graduates, based on univariate analysis (*P*=0.042). Age was an independent risk factor according to multivariate analysis; increase of the age increased the risk of SD by 0.9-fold (*P*=0.045). Furthermore, among sub-types of SD, secondary SD was an independent risk factor; and an increase in secondary sexual dysfunction increased the risk of SD by 1.178-fold (*P*=0.038). Other independent risk factors affecting SD were not statistically significant (*P*=0.802, *P*=0.625) (Table 5).

Table 4: Correlation of tests with each other and disease onset age

		MSIASQ	EDSS	Beck depression	Music cognitive	Music fatigue	Acyo
EDSS	r	0.230					
	P-value	0.051					
Beck depression	r	0.658	0.189				
	P-value	<0.001	0.100				
Music cognitive	r	-0.184	-0.273	-0.306			
	P-value	0.084	0.017	0.003			
Music fatigue	r	0.476	0.185	0.529	-0.365		
	P-value	<0.001	0.109	<0.001	<0.001		
ASEX	r	0.428	0.060	0.403	-0.166	0.205	
	P-value	<0.001	0.623	<0.001	0.137	0.065	
Disease onset age	r	-0.146	-0.156	-0.164	-0.086	-0.213	0.188
	P-value	0.173	0.179	0.112	0.409	0.040	0.091

r: Pearson's correlation coefficient

Discussion

The remarkable features of our outcomes were higher SD rates of 80.5% in MS patients regardless of MS. Presence of depression was the most determinant factor for all sub-types of SD in MS. Age, educational level, and presence of SSD were detected as independent risk factors for SD in MS. Cognitive influence was significant, especially in secondary SD. Other factors associated with SD may be summarized as phatic and disease period.

Different outcomes may be obtained in the literature due to diagnostic difficulties with sexual dysfunction and multifactorial influence. For instance, we detected higher SD rates than average in the patients with RRMS compared to previous studies; however, a recent review reported that SD may reach up to 80% in males, and 90% in females [4,13,14]. Another difference is that SD in MS was observed more in females in a similar study conducted on MS patients in a different territory of our country in 2013 [2]. Results of the present study were not significant for SD in MS in terms of gender.

Physical disability may be associated with psychosocial factors and cause SD in MS. Mood disorders may affect emotional and sexual functions in MS patients due to physical disability; and patients experience fear of rejection in sexual intercourse, decreased self-respect image, lack of confidence, and higher stress [5,15]. Rocco et al. [14] suggested in another updated research conducted in 87 patients with RRMS in 2018 that EDSS does not play a leading role for sexual dysfunction. Another longitudinal research performed in Belgrade reported that the factors affecting SD in MS are associated with disease period, depression, anxiety, and fatigue [15,16].

Table 5: Logistic regression analysis of parameters affecting sexual dysfunction

	Univariate				Multivariate			
	Beta	OR (%95 CI)	*P*-value	DSO	Beta	OR (%95 CI)	*P*-value	DSO
Age	-0.036	0.964 (0.9 - 1.033)	0.298	80.5	-0.105	0.9 (0.813 - 0.998)	0.045	87.7
Gender	-0.455	0.635 (0.205 - 1.964)	0.430	80.5				
Education Status (Reference: primary school)								
Education status high school)	0.506	1.658 (0.404 - 6.798)	0.483	81.2				
Education status (university)	-1.728	0.178 (0.034 - 0.938)	0.042					
Education status (undergraduate)	0.351	1.421 (0.152 - 13.325)	0.758					
Duration of disease	0.001	1.001 (0.994 - 1.009)	0.719	80.2				
EDSS	-0.37	0.691 (0.441 - 1.082)	0.106	80.6				
Beck depression score	0.028	1.028 (0.981 - 1.078)	0.246	80.5				
Primary sexual dysfunction	0.058	1.06 (0.951 - 1.18)	0.294	82.9				
Secondary sexual dysfunction	0.069	1.072 (0.986 - 1.165)	0.104	82.9	0.163	1.178 (1.009 - 1.375)	0.038	
Tertiary sexual dysfunction	0.046	1.047 (0.927 - 1.182)	0.462	82.9				
MSIASQ	0.027	1.027 (0.988 - 1.068)	0.178	82.9				
MUSIC cognitive	-0.016	0.985 (0.894 - 1.084)	0.751	81.4				
MUSIC fatigue	0.067	1.069 (0.966 - 1.184)	0.196	81.2				
ASEX	0.072	1.075 (0.976 - 1.183)	0.143	82.7	0.136	1.146 (0.991 - 1.324)	0.065	
Disease onset of age	-0.043	0.958 (0.892 - 1.028)	0.234	80.2				
Diagnosis of depression	1.253	3.5 (0.922 - 13.284)	0.066	80.5				

ACR: Accurate classification rate, independent risk factors were included into the multivariate analysis through Backward: Wald method

Moreover, another study conducted in our country revealed that SSD plays a significant role in MS. It was advocated that SD occurs due to problems in the urinary bladder and intestines, spasticity, exhaustion, pain, and decrease in sexual desire, all of which affect quality of life of the patients during progress of MS. Our results also support this hypothesis; there was no significant correlation between SD and EDSS; EDSS scores were higher in MS patients with depression; and MS patients with depression are more diagnosed with SD. This supports the assumption that EDSS may cause SD through psychosocial diagnoses. Furthermore, we concluded that there is a positive correlation between SD and disease period, fatigue, and depression.

A positive correlation was found between lower educational level and SD in the literature. In line with previous studies, our findings suggested that SD was significantly lower in the associate graduate group [4,8].

Cognitive functions may depend on physical injury such as cortical atrophy occurring during the disease or cognitive loss concomitant to mood disorders may be observed. In addition to the key role of SSD in MS patients, a negative association with cognitive functions was detected. MUSIC cognitive tests were lower in all SD patients who enrolled in the present study; however, other sub-types were not significant. This reminded the importance of SSD and revealed that clinicians should consider it. Moreover, cognitive functions were significantly lower in MS patients with depression when compared with those without. Demirkıran et al. [5] evaluated the cognition of 67 MS patients by the Minomen test and detected lower cognitive scores in the patients with SD. Ashtari et al. [17] demonstrated that memory and concentration problems were higher in MS patients with SD (64%) when compared with those without (39.5%).

Several studies indicated the role of diseases such as depression and anxiety in sexual dysfunction in MS patients [18-20]. In line with the literature, our study showed that the results have been higher compared to the ones who were not diagnosed with depression in the group with SD. Furthermore, MS was also detected as a risk factor for SD. Therefore, physical disability is not the primary cause for SD in MS patients [14]; monitoring and treatment of depressive symptoms in these patients are most important steps during SD counteracting.

Limitation

This is a single-center study and it cannot be generalized. The findings reported for cultural reasons are focused on the individual's own statement, i.e. the results of the survey and objective diagnostic tests have not been carried out on the people because of costs and shyness. Studies conducted with larger patient groups consisting of MS patients in different hospitals and different regions will enable us to better understand the importance of this issue and obtain more information.

Conclusions

SD in MS is a multifactorial condition. Along with unchangeable factors such as age, disease period, and physical disability, psychosocial factors such as depression play a key role in this diagnosis. Furthermore, SD significantly affects cognitive functions and negatively affects the quality of life. The present study serves as the first study that evaluates the SD-associated factors and the association between SD and cognition.

References

1. Chalah MA, Ayache SS. Cognitive behavioral therapies and multiple sclerosis fatigue: A review of literature. Journal of Clinical Neuroscience. 2018;52:1-4.
2. Çelik DB, Poyraz EÇ, Bingöl A, İdiman E, Özakbaş S, Kaya D. Sexual dysfunction in multiple sclerosis: Gender differences. Journal of the Neurological Sciences. 2013;324:17-20.
3. Dupont S. Multiple sclerosis and sexual functioning -a review. Clin Rehabil. 1995;9:135-41.
4. Dunya CP, Tulek Z, Uchiyama T, Haslam C, Panicker JN. Systematic review of the prevalence, symptomatology and management options of sexual dysfunction in women with multiple sclerosis. Neurourology and Urodynamics. 2019;39:83-95.
5. Demirkiran M, Sarica Y, Uguz S, Yerdelen D, Aslan K. Multiple sclerosis patients with and without sexual dysfunction: are there any differences? Mult Scler. 2006;12:209-14.
6. Zorzon M, Zivadinov R, Bosco A, Hocking JS, De Livera AM, Taylor KL, et al. Sexual dysfunction in multiple sclerosis: a case–control study. I. Frequency and comparison of groups. Mult Scler. 1999;5:418-27.
7. Zivadinov R, Zorzon M, Bosco A, Bragadin LM, Moretti R, Bonfigli L, et al. Sexual Disfunction and Associated Risk Factors in Multiple Sclerosis II. Correlation analysis. Mult Scler. 1999;5:428-31.
8. Drulovic J, Kisic Tepavcevic D, Pekmezovic T. Epidemiology, diagnosis and management of sexual dysfunction in multiple sclerosis. Acta Neurologica Belgica. 2020;120:791-7.
9. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded dis- ability status scale (EDSS). Neurology. 1983;33:1444-52.
10. Tudor KI, Panicker JN. Management of erectile dysfunction in neurological patients. In: Minhas S, Mulhall J, editors. Male Sexual Dysfunction: A Clinical Guide: John Wiley & Sons, Ltd;2017.
11. McGahuey CA, Gelenberg AJ, Francisco AL, Delgado PL, McKnight KM, Manber R. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther. 2000;26:25-40.
12. Calabrese P, Kalbe E, Kessler J. Ein neuropsychologisches Screening zur Erfassung kognitiver Störungen bei MS-Patienten: das Sklerose Inventarium Cognition (MUSIC). Neuropsychologia: An International Journal in Behavioural and Cognitive Neuroscience. 2004;30:384-8.
13. Hulter BM, Lundberg PO. Sexual function in women with advanced multiple sclerosis. J Neurol Neurosurg Psychiatry. 1995;59:83-6.
14. Calabro RS, Russo M, Dattola V, Luca RD, Leo A, Grisolaghi J, et al. Sexual Function in Young Individuals with Multiple Sclerosis: Does Disability Matter? J Neurosci Nurs. 2018;50:161-6.
15. Tepavcevic DK, Kostic J, Basuroski ID, Stojsavljevic N, Pekmezovic T, Drulovic J. The impact of sexual dysfunction on the quality of life measured by MSQoL-54 in patients with multiple sclerosis. Mult Scler. 2008;14:1131-6.
16. Kisic-Tepavcevic D, Pekmezovic T, Trajkovic G, Stojsavljevic N, Dujmovic I, Mesaros S, et al. Sexual dysfunction in multiple sclerosis: a 6-year follow-up study. J Neurol Sci. 2015;358:317–23.
17. Ashtari F, Rezvani R, Afshar H. Sexual dysfunction in women with multiple sclerosis: dimensions and contributory factors. J Res Med Sci. 2014;19:228-33.
18. Hösl KM, Deutsch M, Wang R, Roy S, Winder K, Niklewski G, et al. Sexual dysfunction seems to trigger depression in female multiple sclerosis patients. Eur Neurol. 2018;80:34-41.
19. Solmaz V, Ozlece HK, Him A, Güneş A, Cordano C, Aksoy D, et al. Evaluation of the association between sexual dysfunction and demyelinating plaque location and number in female multiple sclerosis patients. Neurol Res. 2018;40:683-8.
20. Gava G, Visconti M, Salvi F, Bartolomei I, Seracchioli R, Meriggiola MC. Prevalence and psychopathological determinants of sexual dysfunction and related distress in women with and without multiple sclerosis. J Sex Med. 2019;16:833-42.

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. 2020;4(9):784-789.
DOI: 10.28982/josam.730332

Research article
Araştırma makalesi

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

Examination of the levels of structures in the thorax in multidetector computerized tomography images

Multidedektör bilgisayarlı tomografi görüntülerinde toraks'daki yapıların seviyelerinin incelenmesi

Güneş Bolatlı [1], Nadire Ünver Doğan [2], Mustafa Koplay [3], Zeliha Fazlıoğulları [2], Ahmet Kağan Karabulut [2]

[1] Siirt University, Faculty of Medicine, Department of Anatomy, Siirt, Turkey
[2] Selcuk University, Faculty of Medicine, Department of Anatomy, Konya, Turkey
[3] Selcuk University, Faculty of Medicine, Department of Radiology, Konya, Turkey

ORCID ID of the author(s)
GB: 0000-0002-7648-0237
NÜD: 0000-0001-5696-5547
MK: 0000-0001-7513-4968
ZF: 0000-0002-5103-090X
AKK: 0000-0002-9635-8829

Corresponding author / Sorumlu yazar:
Güneş Bolatlı
Address / Adres: Siirt Üniversitesi Tıp Fakültesi, Anatomi Anabilim Dalı, Siirt, Türkiye
E-mail: gunesbolatli83@gmail.com

Ethics Committee Approval: Non-Invasive Clinical Research Ethics Committee of Selcuk University, Faculty of Medicine gave approval on 20.02.2017 with the decision numbered 2017/69. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma onayı Selçuk Üniversitesi Tıp Fakültesi, 20.02.2017 tarih ve 2017/69 sayı ile İnvazif Olmayan Klinik Araştırmalar Etik Kurulundan alınmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Previous presentation: Presented at the convention 19th National Anatomy Congress and International Mediterranean Anatomy Congress on 6th and 9th of September 2018.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: Levels of the anatomical structures found in thorax and their relationships are particularly important in terms of surgical procedures. These levels are indicated with reference to the ribs and most are based on cadaver studies. The vertebral level of many structures is not specified. In this study, it was aimed to determine the level changes of some structures in the thorax according to age and gender by referring to the vertebrae. Methods: Multidetector computed tomography images of the thorax region in the PACS archives of Selcuk University Medical Faculty Hospital were used in the study. Images of 700 people, who did not undergo thoracic surgery, were studied in different age groups. The anatomical structures were evaluated with reference to the vertebrae on these images, and the findings were compared according to age groups and genders.

Results: Some of the levels of the investigations were different from the information in the classical books. It was seen that the entrance level of the aorta from the diaphragm was at Th10 level, the entrance level of superior vena cava to the right atrium was Th7 in the 0-9-year age group, Th6 level in the other age groups, and exit level of the pulmonary trunk from the right ventricle and the apex of the heart were Th7 and Th10, respectively.

Conclusion: Most of our current knowledge is based on cadaver studies rather than living human beings and the intercostal spaces are referenced in defining the levels of structures in the thorax. Age and gender distinctions have not been made in cases where most of the structures are not specified. Vertebral reference is important in terms of comparing superficial and deep structures. As the thoracic surgeon is needed in every age group, it is important that surgeons know these differences.

Keywords: Anatomy, Levels, MDCT, Thorax

Öz

Amaç: Torakstaki anatomik yapıların düzeyleri ve aralarındaki ilişki cerrahi işlemler açısından çok önemlidir. Bu seviyeler genel olarak kaburgalar referans alınarak belirtilir ve çoğu kadavra çalışmalarına dayanır. Birçok yapının vertebral seviyesi belirtilmemiştir. Bu çalışmada torakstaki bazı yapıların yaş ve cinsiyete göre düzey değişiklikleri, vertebralar referans alınarak belirlenmek amaçlanmıştır.

Yöntemler: Çalışmada Selçuk Üniversitesi Tıp Fakültesi Hastanesi Pacs arşivindeki toraks bölgesi Çok Dedektörlü Bilgisayarlı Tomografi görüntüleri kullanıldı. Göğüs cerrahisi geçirmemiş farklı yaş gruplarında 700 kişinin görüntüleri incelendi. Bu görüntülerdeki anatomik yapılar omurlara göre değerlendirildi ve bulgular yaş gruplarına ve cinsiyetlere göre karşılaştırıldı.

Bulgular: Araştırmada tespit edilen bazı düzeyleri klasik kitaplardaki bilgilerden farklıydı. Aortun diyaframdan geçişi T10, vena cava süperior'un sağ atriyuma girişi 0-9 yaş grubunda T7, diğer yaş gruplarında T6, turuncus pulmonalis'in sağ ventrikül'den çıkışı T7 ve apeks kordis'in T10 seviyesinde olduğu görüldü.

Sonuç: Mevcut bilgimizin çoğu canlı insanlardan ziyade yapılan kadavra çalışmalarına dayanmaktadır ve genellikle interkostal aralıklar referans alınarak yapıların seviyeleri belirtilmiştir. Yapılan çalışmaların çoğunda yaş ve cinsiyet ayrımı yapılmamıştır. Vertebraların referans alınması yüzeysel ve derin yapıların karşılaştırılması açısından önemlidir. Göğüs cerrahisinde yaş grupları arasındaki seviye farklılıklarının bilinmesi cerrahlar için son derece önemlidir.

Anahtar kelimeler: Anatomi, Seviyeler, MDBT, Toraks

How to cite/Atıf için: Bolatlı G, Doğan NÜ, Koplay M, Fazlıoğulları Z, Karabulut AK. Examination of the levels of structures in the thorax in multidetector computerized tomography images. J Surg Med. 2020;4(9):784-789.

Introduction

The thorax (chest) is the part of the body between the neck and the abdomen. There are several organs in the thorax that are the primary organs of the respiratory and cardiovascular systems, as well as components of the digestive, endocrine and lymphatic systems [1,2]. Therefore, it is particularly important to know the anatomy of this part of the body.

The level of structures in the thorax is indicated with reference to ribs and most of them are based on cadaver studies. The vertebral level of many structures is not specified. Multidetector computed tomography (MDCT) method can be used to do several measurements (change of bone formation according to age and gender, level of structures relative to vertebras) about the structures in the thorax. Measurements based on vertebras are important for clinical applications to compare deep and superficial structures [3]. It also makes it easier for radiologists to diagnose images [4].

The anatomy of the thorax varies from person to person. The levels of anatomic structures and their relationship with each other are very important for surgical procedures [3,4]. In this study, by using the MDCT method, it was aimed to investigate the levels of some formations in the thorax compared to the vertebral bodies on patients who had not undergone thoracic trauma or operation.

Materials and methods

The study was started with the approval of the Non-Invasive Clinical Research Ethics Committee of Selcuk University, Faculty of Medicine dated 20.02.2017 and numbered 2017/69.

A total of 897 images of thin-slice thorax MDCT were examined between January 2016 and May 2017. The images of 78 cases were excluded due to intervention in the region and the images of 119 cases were excluded due to low resolution. 700 cases without thoracic trauma and operation history were included in the study (Figure 1). The MDCT images of 1 mm cross-sectional thickness in the axial plane were transferred to the workstation, along with sagittal and coronal reformat images.

The 700 cases that were measured were grouped according to gender and 7 different age ranges (0-9 years, 10-19 years, 20-29 years, 30-39 years, 40-49 years, 50-60 years, over 60 years) and results were evaluated (Table 1).

Levels of anatomically and surgically important structures were examined with reference to vertebrae. These structures are the level of passage of the aorta through the diaphragm (ADL), the entry level of the superior vena cava into the right atrium (SVCL), the entry level of the inferior vena cava into the right atrium (IVCL), the exit level of the pulmonary trunk from the right ventricle (PTL), aortic arch level (AAL), cardiac apex level (CAL), carina level (CL), right principal bronchus level of separation to segmental bronchus (RPBL), left principal bronchus level of separation to segmental bronchus (LPBL), level of sternoclavicular joint (SCJL), jugular notch level (JNL), manubriosternal joint level (MSJL) and xiphosternal joint level (XSJL) (Figure 2).

Figure 1: Number of cases according to inclusion and exclusion criteria

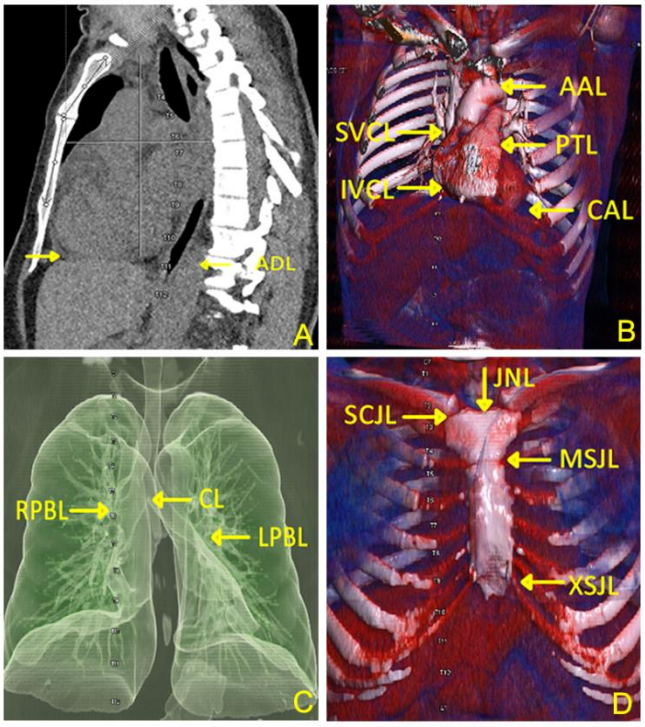


Figure 2: A: ADL level, B: AAL, SVCL, IVCL, PTL, CAL level, C: CL, RPBL, LPBL level, D: JNL, SCJL, MSJL, XSJL level

Statistical analysis

The data obtained in the study were analyzed using SPSS (Statistical Package for Social Sciences) for Windows 22.0 program. Number, percentage, mean, and standard deviation were used as descriptive statistical methods in the evaluation of the data. The relationship between grouped variables was analyzed by Chi-square analysis. The t-test was used to compare the quantitative continuous data between two independent groups, and One-way Anova test was used to compare the quantitative continuous data between more than two independent groups.

Table 1: Distribution of cases by age and gender

Age	0-9	10-19	20-29	30-39	40-49	50-59	Over 60	Total
Female	9	22	32	45	56	46	127	337
Male	16	25	41	53	41	45	142	363

Results

Levels of important anatomical structures were examined, and differences were found according to gender and age. ADL was most commonly at the T10 level in all age groups. A significant correlation was found between ADL and age groups (P<0.05). It was most commonly at the T10-11 level in individuals between the ages of 40-59 years and at the T10 level in individuals under 40 and over 60 years of age. T10-11 level was the highest (25.6%) in males (P<0.05) and T10 level was the highest (28.2%) in females (Table 2).

A significant relationship was found between SVCL age groups and gender groups (P<0.05). T7 level was the most

prominent in the 0-9-year age group while the T6 level was higher in other age groups (Table 3), and T6 level was more commonly found in women (45.4%) than men (39.7%) (P<0.05).

There was a significant difference between the age groups of IVCL. Although it was highly observed at the T9 level in all age groups, the level slightly lowered (T10 level) with increasing age. However, it was found that the probability of being seen at the T9 level increased in individuals over 60 years of age (Table 4). There was no significant difference between the genders in terms of IVCL (P>0.05). The T9 level was the most common among men and women.

There was a significant difference between the age groups with regards to PTL (P<0.05). PTL was at the T7 level the most and the rate PTL being detected at the T8 level increased with age (Table 5). The rate of PTL being at the level of T7 was significantly higher in women (42.1%) than men (38%) (P<0.05).

AAL was most frequently observed in the T4 level in all age groups (Table 6), and the rate of being seen at the T5 level significantly increased with age (P<0.05). It was found that it was significantly more commonly found at the T4 level in women (61.4%) compared to men (56.5%) (P<0.05).

CAL was most frequently observed at the T10 level in all age groups, but the frequency of it being detected at T11 significantly increased with age (P<0.05). It was significantly more at the T10 level in women (41.2% T10 level, 26.1% T9 level) compared to men (34.7% T10 level, 22.9% T11 level) (Table 7) (P<0.05).

CL was most frequently observed at the T5 level in all age groups, but the frequency of observation at the T6 level significantly increased with age (P<0.05). T5 level was significantly higher in women (59.9% T5 level, 15.7% T6 level) than men (48.8% T15 level, 29.5% T6 level) (Table 8) (P<0.05).

RPBL was most frequently observed at the T5-6 level in all age groups, but the frequency of observation at the T6-7 level significantly increased with age (P<0.05). It was located significantly higher in women (52.2% T5-6 level, 10.4% T6-7 level) compared to men (39.9% T5-6 level, 28.7% T6-7 level) (Table 9) (P<0.05).

LPBL was most frequently observed at the T6 level in all age groups, but the frequency of observation at the T7 level significantly increased with age (except over 60 years old) (P<0.05). It was significantly higher in women (52.5% T6 level, 14.5% T7 level) compared to men (39.1% T6 level, 29.8% T7 level) (Table 10) (P<0.05).

SCJL was most frequently observed at the T2 level in all age groups, but the frequency of observation at the T1 level significantly increased with age (P<0.05). There was no significant relationship between SCJL and gender (P<0.05) (Table 11).

JNL was most frequently observed at the T2 level in all age groups, but the frequency of observation at the T1 level significantly increased with age (P<0.05). There was no significant relationship between JNL and gender (Table 12) (P<0.05).

MSJL was most frequently observed at the T3 level between the ages of 0-9 years and at the T4 level in all other age groups, but the frequency of observation at the T4 level significantly increased with age (P<0.05). There is no significant relationship between MSJL and gender (Table 13) (P<0.05).

XSJL was most frequently observed at the T7 level between the ages of 0-9 years and at the T9 level in all other age groups, but the frequency of observation at the lower levels significantly increased with age (P<0.05). There was no significant relationship between XSJL and gender (Table 14) (P<0.05).

Table 2: The relationship between ADL& age and gender

ADL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
T7	8	0	0	0	0	0	0.4	0.4	<0.001	0.6	0.3	0.002
T7-8	0	0	0	0	1	1.1	0.4	0.4		0	0.9	
T8	20	4.3	0	1	1	2.2	0	1.6		1.1	2.1	
T8-9	4	4.3	2.7	6.1	1	3.3	2.2	3		2.8	3.3	
T9	20	10.6	2.7	8.2	8.2	2.2	4.8	6.1		4.7	7.7	
T9-10	0	14.9	16.4	18.4	15.5	19.8	14.9	15.7		12.1	19.6	
T10	36	23.4	32.9	25.5	19.6	23.1	29	26.7		25.3	28.2	
T10-11	0	27.7	28.8	20.4	29.9	30.8	21.2	24		25.6	22.3	
T11	12	8.5	11	11.2	17.5	9.9	11.2	11.7		13.8	9.5	
T11-12	0	6.4	4.1	6.1	6.2	6.6	11.5	7.9		11	4.5	
T12	0	0	1.4	3.1	0	1.1	4.5	2.4		3	1.8	

ADL: These structures are the level of passage of the aorta through the diaphragm

Table 3: The relationship between SVCL& age and gender

SVCL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
T3	12	0	0	0	0	0	0	0.4	<0.001	0.6	0.4	0.014
T4	0	0	0	4.1	0	0	0.4	0.7		0.8	0.7	
T4-5	4	0	0	0	0	0	0	0.1		0.3	0.1	
T5	16	8.5	12.3	16.3	9.3	7.7	7.4	9.9		6.1	9.9	
T5-6	4	0	0	0	0	1.1	0.4	0.4		0.6	0.4	
T6	24	48.9	42.5	45.9	42.3	39.6	42.8	42.4		39.7	42.4	
T6-7	0	2.1	1.4	0	1	2.2	0.7	1.0		0.8	1	
T7	40	31.9	37	25.5	37.1	31.9	34.6	33.6		38	33.6	
T8	0	8.5	6.8	7.1	10.3	16.5	10.8	10		11.6	10	
T9	0	0	0	1	0	1.1	3	1.4		1.7	1.4	

SVCL: The entry level of superior vena cava into the right atrium

Table 4: The relationship between IVCL& age and gender

IVCL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
T5	12	0	0	0	0	0	0	0.4	<0.001	0.6	0.3	0.158
T6	0	0	0	2	0	0	0.4	0.4		0.3	0.6	
T7	8	0	1.4	3.1	3.1	2.2	2.6	2.6		1.4	3.9	
T8	32	23.4	19.2	27.6	19.6	20.9	19.7	21.6		18.5	24.9	
T8-9	0	0	0	0	0	1.1	0.4	0.3		0.3	0.3	
T9	44	38.3	47.9	41.8	38.1	36.3	47.6	43.3		43.3	43.3	
T9-10	0	4.3	0	0	0	0	0	0.3		0.8	0.3	
T10	4	25.5	27.4	17.3	30.9	30.8	18.6	22.6		25.6	19.3	
T10-11	0	0	0	1	0	0	0.4	0.3		0.6	0	
T11	0	8.5	1.4	7.1	8.2	7.7	8.6	7.1		8	6.2	
T12	0	0	2.7	0	0	1.1	1.9	1.1		1.4	0.9	

IVCL: The entry level of inferior vena cava into the right atrium

Table 5: The relationship between PTL& age and gender

PTL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
T4	12	0	0	2	0	0	0	0.7	<0.001	0.8	0.6	0.023
T5	8	4.3	1.4	7.1	3.1	0	3	3.3		1.7	5	
T6	32	12.8	19.2	24.5	21.6	16.5	19	19.9		17.6	22.3	
T6-7	0	0	0	1	0	1.1	0.4	0.4		0.6	0.3	
T7	36	46.8	46.6	36.7	36.1	40.7	39.8	40		38	42.1	
T7-8	0	2.1	0	2	1	1.1	0.7	1		1.7	0.3	
T8	12	29.8	26	20.4	34	28.6	28.6	27.4		30.3	24.3	
T8-9	0	0	0	1	1	0	0.7	0.6		0.8	0.3	
T9	0	4.3	6.8	5.1	3.1	12.1	4.5	5.4		6.9	3.9	
T10	0	0	0	2	0	0	3.3	1.3		1.7	0.9	

PTL: The exit level of the pulmonary trunk from the right ventricle

Table 6: The relationship between AAL& age and gender

AAL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
T2	12	0	0	4.1	0	0	0.7	1.3	0.001	1.1	1.3	0.001
T3	8	10.6	17.8	13.3	23.7	18.7	19.7	18		13.8	18	
T3-4	0	0	0	0	1	0	1.5	0.7		1.1	0.7	
T4	72	74.5	58.9	65.3	51.5	53.8	56.9	58.9		56.5	58.9	
T4-5	0	0	0	0	1	0	0.4	0.3		0.6	0.3	
T5	8	10.6	23.3	14.3	20.6	26.4	16.0	17.9		23.1	17.9	
T5-6	0	0	0	1	0	0	0	0.1		0.3	0.1	
T6	0	4.3	0	1	2.1	1.1	4.8	2.7		3.6	2.7	
T7	0	0	0	1	0	0	0	0.1		0	0.1	

AAL: Aortic arch

Table 7: The relationship between CAL& age and gender

CAL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
T7	12	0	0	4.1	0	0	0.4	1.1	0.007	1.4	0.9	0.003
T8	12	4.3	4.1	10.2	9.3	3.3	5.9	6.6		3.9	9.5	
T8-9	0	0	0	0	1.	0	0.7	0.4		0.3	0.6	
T9	28	25.5	24.7	29.6	21.6	27.5	21.9	24.4		22.9	26.1	
T9-10	0	0	0	1	2.1	3.3	1.5	1.4		1.9	0.9	
T10	44	42.6	41.1	34.7	37.1	30.8	39.4	37.9		34.7	41.2	
T10-11	0	4.3	5.5	1	7.2	1.1	3	3.3		4.4	2.1	
T11	4	17	21.9	15.3	17.5	7.5	18.6	18.9		22.9	14.5	
T11-12	0	2.1	0	0	3.1	1.1	1.1	1.1		1.4	0.9	
T12	0	4.3	2.7	4.1	1	5.5	7.1	4.7		6.1	3.3	
T12-l1	0	0	0	0	0	0	0.4	0.1		0.3	0	

CAL: Level cardiac apex level

Table 8: The relationship between CL& age and gender

CL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
T3	4	0	1.4	3.1	0	0	0	0.7	<0.001	0.6	0.9	<0.001
T4	40	12.8	13.7	12.2	11.3	7.7	8.9	11.4		7.7	15.4	
T4-5	0	2.1	4.1	1	1	3.3	2.2	2.1		1.7	2.7	
T5	52	68.1	53.4	63.3	55.7	49.5	49.8	54.1		48.8	59.9	
T5-6	0	6.4	6.8	4.1	5.2	3.3	3.3	4.1		5.2	3	
T6	4	10.6	20.5	12.2	26.8	34.1	26	22.9		29.5	15.7	
T6-7	0	0	0	2	0	0	2.2	1.1		2.2	0	
T7	0	0	0	2	0	2.2	7.1	3.3		4.4	2.1	
T8	0	0	0	0	0	0	0.4	0.1		0	0.3	

CL: Carina level

Table 9: The relationship between RPBL& age and gender

RPBL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
T3-4	4	0	1.4	1	0	0	0	0.4	<0.001	0.6	0.3	<0.001
T4	0	0	0	1	0	0	0	0.1		0	0.3	
T4-5	20	8.5	8.2	8.2	10.3	6.6	6.3	8		5.2	11	
T5	20	4.3	9.6	5.1	2.1	4.4	4.1	5.1		3.6	6.8	
T5-6	36	48.9	39.7	52	53.6	45.1	43.1	45.9		39.9	52.2	
T6	16	25.5	19.2	16.3	7.2	7.7	10	12.4		14.3	10.4	
T6-7	0	12.8	20.5	11.2	26.8	31.9	25.3	22.1		28.7	15.1	
T7	4	0	1.4	4.1	0	2.2	1.9	1.9		1.9	1.8	
T7-8	0	0	0	1	0	2.2	9.3	4		5.8	2.1	

RPBL: Right principal bronchus level of separation to segmental bronchus

Table 10: The relationship between LPBL& age and gender

LPBL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
T4	4	0	1.4	1	0	0	0	0.4	<0.001	0.6	0.3	<0.001
T4-5	0	0	0	1	0	0	0	0.1		0	0.3	
T5	8	6.4	8.2	8.2	9.3	6.6	6.3	7.3		4.7	10.1	
T5-6	20	6.4	9.6	5.1	3.1	4.4	4.1	5.4		3.6	7.4	
T6	44	48.9	39.7	51	51.5	45.1	42.8	45.6		39.1	52.5	
T6-7	16	25.5	19.2	16.3	8.2	7.7	10	12.6		14.3	10.7	
T7	4	12.8	20.5	11.2	27.8	31.9	25.3	22.4		29.8	14.5	
T7-8	4	0	1.4	3.1	0	1.1	2.6	1.9		1.9	1.8	
T8	0	0	0	3.1	0	3.3	8.6	4.1		6.1	2.1	
T9	0	0	0	0	0	0	0.4	0.1		0	0.3	

LPBL: Left principal bronchus level of separation to segmental bronchus

Table 11: The relationship between SCJL& age and gender

SCJL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
C7	0	0	0	1	0	2.2	1.1	0.9	<0.001	1.1	0.6	0.085
C7-T1	0	0	0	0	1	0	0.4	0.3		0	0.6	
T1	4	19.1	23.3	29.6	32	37.4	40.1	32.7		29.8	35.9	
T1-2	0	2.1	4.1	1	4.1	2.2	3.7	3		4.1	1.8	
T2	72	55.3	60.3	54.1	47.4	42.9	44.2	49.3		49	49.6	
T2-3	0	4.3	0	3.1	3.1	1.1	1.5	1.9		2.8	0.9	
T3	4	19.1	12.3	9.2	12.4	14.3	8.2	10.7		11.6	9.8	
T4	20	0	0	2	0	0	0.7	1.3		1.7	0.9	

SCJL: Level of sternoclavicular joint

Table 12: The relationship between JNL& age and gender

JNL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
C7	0	0	0	1	2.1	4.4	1.5	1.6	<0.001	1.7	1.5	0.208
C7-T1	0	0	0	0	1	1.1	1.1	0.7		0.6	0.9	
T1	0	19.1	23.3	30.6	29.9	35.2	41.3	32.7		30.6	35	
T1-2	0	2.1	2.7	1	4.1	2.2	3	2.6		3.3	1.8	
T1-3	0	0	0	0	0	0	0.4	0.1		0	0.3	
T2	72	57.4	61.6	53.1	49.5	41.8	43.1	49.1		48.5	49.9	
T2-3	0	4.3	0	3.1	2.1	2.2	1.5	1.9		3.0	0.6	
T3	4	17	12.3	9.2	11.3	13.2	7.4	10		10.7	9.2	
T4	20	0	0	2	0	0	0.7	1.3		1.7	0.9	

JNL: Jugular notch level

Table 13: The relationship between MSJL& age and gender

MSJL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
T2	20	2.1	1.4	4.1	1	2.2	5.6	4.1	<0.001	4.1	4.2	0.382
T2-3	0	0	0	0	2.1	3.3	2.6	1.7		2.2	1.2	
T3	40	12.8	12.3	23.5	17.5	28.6	26	23		20.7	25.5	
T3-4	0	4.3	9.6	7.1	7.2	18.7	10.4	9.7		11.3	8	
T4	36	40.4	39.7	34.7	43.3	29.7	40.9	38.6		37.7	39.5	
T4-5	0	4.3	9.6	7.1	13.4	9.9	3.3	6.7		8.3	5	
T5	4	25.5	23.3	19.4	11.3	4.4	7.1	11.9		11.	12.8	
T5-6	0	4.3	1.4	2	1	2.2	1.1	1.6		1.9	1.2	
T6	0	6.4	1.4	2	3.1	1.1	2.6	2.4		2.5	2.4	
T6-7	0	0	0	0	0	0	0.4	0.1		0	0.3	
T7	0	0	1.4	0	0	0	0	0.1		0.3	0	

MSJL: Manubriosternal joint level

Table 14: The relationship between XSJL& age and gender

XSJL	Age 0-9 (%)	10-19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	Over 60 (%)	Total (%)	*P*	Male (%)	Female (%)	*P*
T4	0	0	0	1	0	0	0	0.1	0.002	0	0.3	0.081
T5	0	0	0	0	0	0	0.4	0.1		0	0.3	
T5-6	0	0	0	0	0	0	0.4	0.1		0.3	0	
T6	20	0	2.7	1.	0	0	2.6	2.1		1.7	2.7	
T7	28	8.5	0	12.2	9.3	11	14.9	11.7		10.5	13.1	
T7-8	0	0	1.4	3.1	1	3.3	0.7	1.4		1.7	1.2	
T8	24	21.3	31.5	25.5	26.8	28.6	26	26.6		24.8	28.5	
T8-9	0	2.1	5.5	3.1	5.2	13.2	4.8	5.4		4.1	6.8	
T9	24	29.8	35.6	32.7	30.9	25.3	26.8	29		29.2	28.8	
T9-10	0	6.4	5.5	3.1	8.2	6.6	4.1	5		6.9	3	
T10	4	25.5	15.1	17.3	16.5	7.7	15.6	15.1		16.3	13.9	
T10-11	0	0	0	0	1	2.2	1.1	0.9		1.1	0.6	
T11	0	6.4	2.7	1	1	2.2	2.2	2.1		3.3	0.9	
T12	0	0	0	0	0	0	0.4	0.1		0.3	0	

XSJL: Xiphosternal joint level

Discussion

The surface anatomy must be known for safe clinical and practical implementations. The current information is based on textbooks. In anatomy textbooks, surface marks are generally made with reference to costae, and the level of many structures is not included. Most of the included ones are based on cadaver work. In our study, we examined some of the structures in the thorax by reference to the vertebras according to gender and age groups. Reference to the vertebras is important for comparison of superficial and deep structures and facilitating clinical evaluation on radiological images [4]. Knowing the changes in levels according to age group and gender will facilitate surgical procedures.

ADL was found at the T12 level [3,5-7] in some studies and at the T11 [3,4] level in others. In another study, it was determined at the T11 level in the 0-1 year age group, at the T12 level in the age group of 1-4 years, and at the T11 level in the 4-12 years age group [3]. In our study, although there are differences between age groups, it is mostly at the T10 level, and when we evaluate it according to gender, the rates of it being found at the T10 level in women and T10-11 levels in men are high. While performing surgical interventions, level differences between age groups and genders should be taken into consideration.

It was stated that SVCL was at the right third cartilage costae level [8,9] in some anatomy books and at the T6 level [4,10] in some other studies. In our study, it was seen that T7 was the most common level in the 0-9 year-age group and T6 was most common in other age groups. In terms of gender, the rate of it being found at the T6 level was significantly higher in women. Superior vena cava catheterization may be required to feed clinically severe patients or for other purposes. Therefore, it is very important to know the surface anatomy of this vein [11]. We think that the possibility of SVCL being at the T6 level in

men and children should be considered in interventional practices.

IVCL is reportedly between the T8-T9 levels or at the level of right sixth costae [8]. In this study, it was observed that the IVCL was highly found at the T9 level in all age groups, but significant differences were found between the age groups as well (Table 4). We believe that the level at which this vein can be found should be evaluated according to the age of the patient.

Anatomy books indicate that PTL is at the level of the third cartilage rib [9]. In our study, although there was a significant difference between PTL levels between age groups, it was mostly seen at the T7 level in all age groups, followed by the T6 level in the 0-9 age group and the T8 level in the other age groups. Pulmonary thromboembolism is a common clinical problem in the world, often difficult to diagnose, and mortality can be quite high if not treated appropriately. In pulmonary thromboembolism, the rate of embolism in pulmonary trunk is high [12,13]. It is especially important to know PTL in radiological and interventional procedures.

Studies have reported that AAL is at the T4 level [4,5,9,14]. In another study, it was found over the T4 level in the age group of 0-1 year and under the T4 level in the age groups of 1-4 and 4-12 years [15]. In our study, although there was a significant difference between the age groups, it was generally found at the T4 level, which was followed by T2 in the 0-9 year-age group and the T5 level among all other age groups. Similar to the literature, AAL was located lower with increasing age. It is important to know the AAL in the head, neck, and thorax region in radiological and surgical procedures.

CAL is known to be at the level of the 5^{th} intercostal space [1,9,11] and in a study based on vertebral reference, CAL was found at the T9 level [4]. In our study, although there was a significant difference between the age groups, it was determined that the T10 level was the most common in all age groups. The rate of it being observed in lower levels increased in older age (except for the individuals over 60 years of age) and in males. Knowing the level of the cardiac apex is especially important in the accurate evaluation of the dimensions of the heart and in the diagnosis of hypertrophy [4].

In anatomy books, CL was found at the T5 level [8] and in the literature it is recorded at the T4-5 level [3,5,6,16]. In another study, it was higher than the T4 level in the 0-1-year age group and below T5 in the 1-4 and 4-12-year age groups [15]. In our study, although there was a significant difference between the age groups, it was generally at the T5 level. Similar to the literature, it was determined that with the progression of age, the probability of being observed at a lower level increased. The T4 level was the second most common in the 0-9-year age group and in older ages, the T6 level was the second most common. Normally the carina is in the sagittal plane and has almost sharp borders. If tracheobronchial lymph nodes at the angle between the main bronchi grows due to the bronchogenic cancer metastasis, the carina breaks down, expands posteriorly, and becomes immobilized. Therefore, changes in carina level are important in the differential diagnosis of respiratory diseases [9].

In previous studies, it was stated that RPBL was at T5 level and LPBL was at T6 level [8]. In our study, RPBL was most commonly at the T5-6 level and LPBL was most commonly at the T6 level. Both were found to be significantly lower in older age and in men.

SCJL is known to be at the level of the first cartilage rib [2,9]. In our study, SCJL was most commonly found at the T2 level. Also, it significantly relocated to the T1 level with increasing age. The internal jugular vein and subclavian vein join next to the sternoclavicular joint to form the brachiocephalic vein [2]. It is important to know the level of sternoclavicular joint in terms of its proximity to these vessels.

In the literature, JNL is mostly found at the T2 level [9,11]. We also observed JNL most frequently at the T2 level in all age groups and it was significantly observed at the T1 level as age increased. Left brachiocephalic vein is located behind the upper half of the manubrium. In the first years of life, this vein could be observed at a higher level to be over jugular notch. This should be taken into consideration when performing a tracheotomy in children [1,2]. Median sternotomy is one of the most common procedures in cardiac surgery. Surgeons cut the sternum from jugular notch to the lower end of xiphoid process and try to reach the heart and large vessels. Sternal dehiscence is the separation of the sternum halves. It is very rare, but it is a serious and mortal condition [17,18]. Jugular notch is therefore a clinically important reference point.

In the literature, it is stated that MSJL is at the T4-5 level [1,9,11]. In the study done by Fischer et al. (2017), it was found above T4 in 0-1-year and 1-4-years age group and below T4 in the age group of 4-12 years [15]. It was at the T5 level in the study of Badshah et al. [4] and above T5 level in the study of Chukwuemeka et al. [19]. In our study, MSJL was most commonly at the T3 level in the age group of 0-9 years and at the T4 level in all other age groups. The level of MSJL was found to increase significantly with age.

Xiphosternal joint (XSJL) is located at the T9 level, as stated in the anatomy books [9, 11] and the literature [3-5,14]. In our study, XSJL was most commonly found at the T7 level in the 0-9-year age group and at the T9 level in all other age groups. It was also determined that the incidence of it being observed at lower levels was significantly higher with increasing age. Xiphosternal joint is an important reference point and determines the lower edge of the heart and the upper limit of the liver [11].

Manubriosternal joint anomalies are usually unidentified causes of chest pain. The joint should be evaluated in rheumatoid diseases and in patients with non-arthritic chest or shoulder pain [20]. In this respect, it is important to know the Louis angle, the normal anatomy of manubriosternalis joint and xiphosternalis joint. In addition, bone marrow biopsy examinations are mostly performed from the manubrium, and it is also important to know the level at which the manubrium and corpus make joints [21].

Limitations

As our study is a retrospective study, there is no information about the height, weight, occupation, and sports activities of the patients. In addition, all level measurements belong to patients reclined in the supine position. It would be beneficial to conduct a similar study by knowing the height and weight of the patients.

Conclusion

Much of our current surface anatomy knowledge is based on cadaver studies rather than living humans. The levels of most structures are not specified by vertebras, and there is also no age group and gender distinction for many of them. Our study examining the images of 700 women and men in different age groups may be the basis for defining the levels of the structures in the thorax according to age group and gender. Radiological imaging is especially important in the evaluation of the levels. Thoracic intervention can be performed in any age group. Therefore, it is important to know the differences in the anatomy of this region according to age and gender. In this sense, our study results contain important reference information. Using modern imaging techniques, reviewing human anatomy, and adding findings to anatomical and clinical sources, and comparing them to medical textbooks will help in interventional interference.

References

1. D'Antoni AV. Gray's Anatomy, the Anatomical Basis of Clinical Practice, 41st edition. Clin Anat. 2016;29(2):264-5. doi: 10.1002/ca.22677. PubMed PMID: WOS:000370613000022.
2. Drake L, Vogl A, Mitchell A. Gray's anatomy for students. 2016 Mar 15. 456- p.
3. Mirjalili SA, Hale SJ, Buckenham T, Wilson B, Stringer MD. A reappraisal of adult thoracic surface anatomy. Clin Anat. 2012;25(7):827-34. Epub 2012/05/12. doi: 10.1002/ca.22091. PubMed PMID: 22576938.
4. Badshah M, Soames R, Khan MJ, Ibrahim M, Khan A. Revisiting thoracic surface anatomy in an adult population: A computed tomography evaluation of vertebral level. Clin Anat. 2017;30(2):227-36. Epub 2016/12/10. doi: 10.1002/ca.22817. PubMed PMID: 27935171.
5. Shen XH, Su BY, Liu JJ, Zhang GM, Xue HD, Jin ZY, et al. A reappraisal of adult thoracic and abdominal surface anatomy via CT scan in Chinese population. Clin Anat. 2016;29(2):165-74. Epub 2015/06/03. doi: 10.1002/ca.22556. PubMed PMID: 26032163.
6. Keough N, Mirjalili SA, Suleman FE, Lockhat ZI, van Schoor A. The thoracic surface anatomy of adult black South Africans: A reappraisal from CT scans. Clin Anat. 2016;29(8):1018-24. Epub 2016/10/21. doi: 10.1002/ca.22776. PubMed PMID: 27571396.
7. Mirjalili SA, McFadden SL, Buckenham T, Stringer MD. A reappraisal of adult abdominal surface anatomy. Clin Anat. 2012;25(7):844-50. Epub 2012/06/30. doi: 10.1002/ca.22119. PubMed PMID: 22744875.
8. Drake RL. VA, Mitchell AWM. Gray's Anatomy for Student. New York: Elsevier; 2017.
9. Moore K, Dalley A. Clinically Oriented Anatomy: Lipincot; 2005. 114 p.
10. Connolly B, Mawson JB, MacDonald CE, Chait P, Mikailian H. Fluoroscopic landmark for SVC-RA junction for central venous catheter placement in children. Pediatr Radiol. 2000;30(10):692-5. Epub 2000/11/15. doi: 10.1007/s002470000297. PubMed PMID: 11075603.
11. Snell RS. Cninical Anatomy: Lipincot; 2013. 62 p.
12. Karwinski B, Svendsen E. Comparison of Clinical and Postmortem Diagnosis of Pulmonary-Embolism. J Clin Pathol. 1989;42(2):135-9. doi: 10.1136/jcp.42.2.135. PubMed PMID: WOS:A1989T235200005.
13. Goldhaber SZ, Visani L, De Rosa M, Icoper. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353(9162):1386-9. doi: 10.1016/S0140-6736(98)07534-5. PubMed PMID: WOS:000080020800010.
14. Pak N, Patel SG, Hashemi Taheri AP, Hashemi F, Eftekhari Vaghefi R, Naybandi Atashi S, et al. A reappraisal of adult thoracic and abdominal surface anatomy in Iranians in vivo using computed tomography. Clin Anat. 2016;29(2):191-6. Epub 2015/11/18. doi: 10.1002/ca.22669. PubMed PMID: 26575429.
15. Fischer NJ, Morreau J, Sugunesegran R, Taghavi K, Mirjalili SA. A reappraisal of pediatric thoracic surface anatomy. Clin Anat. 2017;30(6):788-94. doi: 10.1002/ca.22913. PubMed PMID: WOS:000407689500014.
16. Uzun C, Atman ED, Ustuner E, Mirjalili SA, Oztuna D, Esmer TS. Surface anatomy and anatomical planes in the adult turkish population. Clin Anat. 2016;29(2):183-90. Epub 2015/09/26. doi: 10.1002/ca.22634. PubMed PMID: 26403267.
17. Jutley RS, Shepherd DET, Hukins DWL, Jeffrey RR. Preliminary evaluation of the Sternum Screw: a novel method for improved sternal closure to prevent dehiscence. Cardiovasc Surg. 2003;11(1):85-9. doi: 10.1016/S0967-2109(02)00118-7. PubMed PMID: WOS:000180732800016.
18. Stahle E, Tammelin A, Bergstrom R, Hambreus A, Nystrom SO, Hansson HE. Sternal wound complications - Incidence, microbiology and risk factors'. Eur J Cardio-Thorac. 1997;11(6):1146-53. doi: 10.1016/S1010-7940(97)01210-4. PubMed PMID: WOS:A1997XK71400037.
19. Chukwuemeka A, Currie L, Ellis H. CT anatomy of the mediastinal structures at the level of the manubriosternal angle. Clin Anat. 1997;10(6):405-8. doi: 10.1002/(Sici)1098-2353(1997)10:6<405::Aid-Ca6>3.0.Co;2-N. PubMed PMID: WOS:A1997YF22100006.
20. Sebes JI, Salazar JE. The Manubriosternal Joint in Rheumatoid Disease. Am J Roentgenol. 1983;140(1):117-21. doi: 10.2214/ajr.140.1.117. PubMed PMID: WOS:A1983PW07900025.
21. Malempati S, Joshi S, Lai S, Braner DAV, Tegtmeyer K. Bone Marrow Aspiration and Biopsy. New Engl J Med. 2009;361(15). PubMed PMID: WOS:000270540000010.

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. 2020;4(9):790-793.
DOI: 10.28982/josam.792221

Research article
Araştırma makalesi

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

Thyroid fine needle aspiration biopsy: The effect of radiological features of nodules on cytological adequacy

Tiroid ince iğne aspirasyon biyopsisi: Nodüllerin radyolojik özelliklerinin sitolojik yeterlilik oranına etkisi

Cennet Şahin [1], Bade Von Bodelschwingh [1]

[1] University of Health Sciences, Istanbul Sisli Hamidiye Etfal Training and Research Hospital, Radiology Clinic, Sisli, Istanbul, Turkey

ORCID ID of the author(s)
CŞ: 0000-0002-8695-327X
BVB: 0000-0002-4049-0222

Corresponding author / Sorumlu yazar:
Cennet Şahin
Address / Adres: Sağlık Bilimleri Üniversitesi, İstanbul Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi, Radyoloji Kliniği, Şişli, İstanbul, Türkiye
E-mail: cennetsahin2@hotmail.com

Ethics Committee Approval: This study was approved by the Ethics Committee of Sisli Hamidiye Etfal Training and Research Hospital (Date: 12/4/2018; Number: 2193). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından onaylandı (Tarih: 04.12.2018; Sayı: 2193). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: Thyroid fine needle aspiration biopsy (FNAB) is an inexpensive and microinvasive procedure used in the diagnosis of thyroid nodules. However, cytology may be insufficient in up to 40% of biopsies. This study aimed to assess the effect of radiological features of thyroid nodules on cytological adequacy.

Methods: The patients who underwent thyroid FNAB between 2016 and 2019 in our clinic were reviewed in this retrospective cohort study. Diagnostic adequacy rate and radiological features of nodules (size, cystic component, calcification content, echogenicity, margin feature) were noted and their relationship was investigated.

Results: A total of 525 patients (77% female, 23% male; mean age 53.3 years; age range 14-87) had FNAB for 595 nodules. Mean diameter of the nodules was 20.1 mm (min: 4mm; max: 60 mm). Of the all biopsies, 25% were inadequate for diagnosis. Adequacy was significantly low in nodules containing macrocalcification (P=0.036). There was no significant relationship between adequacy and echogenicity, margin feature, solid structure or size of the nodules (P>0.05 for each).

Conclusion: Some radiological features may be predictive of inadequate sampling. Nevertheless, varied extrinsic factors affect cytopathological adequacy besides radiological features. Additional techniques may be required in these nodules.

Keywords: Thyroid nodule, Ultrasound, Biopsy, Radiology

Öz

Amaç: Tiroid ince iğne aspirasyon biyopsisi (İİAB), tiroid nodüllerinin tanısında kullanılan ucuz ve mikroinvaziv bir işlemdir. Bununla birlikte, biyopsilerin % 40'ına kadarında sitoloji yetersiz gelebilir. Bu çalışma, tiroid nodüllerinin radyolojik özelliklerinin sitolojik yeterlilik oranına etkisini değerlendirmeyi amaçlamıştır.

Yöntemler: Kliniğimizde, 2016-2019 yılları arasında tiroid nodul İİAB'si yapılan hastalar bu retrospektif kohort çalışmada incelendi. Nodüllerin tanısal yeterlilik oranı ve radyolojik özellikleri (boyut, kistik komponent, kalsifikasyon içeriği, ekojenite, sınır özelliği) not edildi ve aralarındaki ilişki araştırıldı.

Bulgular: Toplam 525 hastada (%77 kadın, %23 erkek; ortalama yaş 53,3; yaş aralığı 14-87) 595 nodüle İİAB yapıldı. Nodüllerin ortalama çapı 20,1 mm (min: 4 mm; maks: 60 mm) idi. Biyopsilerin %25'inde tanısal yetersizlik saptandı. Makrokalsifikasyon içeren nodüllerde yeterlilik anlamlı olarak düşüktü (P=0,036). Nodüllerin yeterlilik oranları ile ekojenite, sınır özelliği, solid yapısı veya boyutu arasında anlamlı bir ilişki yoktu (her biri için P>0,05).

Sonuç: Bazı radyolojik özellikler, yetersiz örneklemenin habercisi olabilir. Bununla birlikte, radyolojik özelliklerin yanı sıra çeşitli dış faktörler de sitopatolojik yeterliliği etkiler. Bu nodüllerde ek teknikler gerekebilir.

Anahtar kelimeler: Tiroid nodülü, Ultrason, Biyopsi, Radyoloji

How to cite/Atıf için: Şahin C, Bodelschwingh BV. Thyroid fine needle aspiration biopsy: The effect of radiological features of nodules on cytological adequacy. J Surg Med. 2020;4(9):790-793.

Introduction

Fine needle aspiration biopsy (FNAB) of thyroid nodules is a microinvasive, cost-effective and safe procedure that is mostly performed on an outpatient basis. The Bethesda system for reporting thyroid cytopathology has been used to classify nodules since 2007 [1,2]. FNAB findings are reported based on the risk of malignancy using 6 general diagnostic categories according to Bethesda. These categories are as follows: I: Nondiagnostic; II: Benign; III: Atypia of Undetermined Significance or Follicular Lesion of Undetermined significance; IV: Follicular Neoplasm or Suspicious for a follicular Neoplasm; V: Suspicious for malignancy; VI: Malignant according to Bethesda classification.

Approximately 5-15% of detected nodules are surgically confirmed to be malignant. Thus, US-guided FNAB is recommended as standard care by all guidelines to differentiate malignant and benign thyroid nodules, since results significantly affect treatment. However, about 0.4–40.7% of FNA results are insufficient for diagnosis [3]. Ultrasound (US) guidance allows the needle to be imaged real-time within the lesion, providing accurate biopsy of nodules [4]. Factors affecting material adequacy may be associated with intrinsic factors of the thyroid nodules such as echogenicity, structure (presence of macro or microcystic component), size, calcification content, margin features. Adequacy is not solely affected by intrinsic factors, it also depends on some extrinsic factors such as the experience of the radiologist and cytopathologist, presence of an onsite cytopathologist, number of needle passes during biopsy, type and size of the biopsy needle, biopsy technique (aspiration or capillary technique), poor specimen fixation or presence of an additional liquid-based cytology affect adequacy [5].

In this study, we aimed to assess the effect of intrinsic features of thyroid nodules on cytological adequacy rate.

Materials and methods

This retrospective cohort study was approved by the Ethics Committee of Sisli Hamidiye Etfal Training and Research Hospital (Date: 04.12.2018; Number: 2193). The patients who underwent thyroid FNAB between 2016 and 2018 were reviewed. Intrinsic factors of the nodules were noted. Echogenicity of the nodules were classified into four groups as isoechogenic, hyperechogenic, hypoechogenic, heterogeneous. Structure of the nodules was classified as ‘’solid’’ and ‘’semisolid’’ according to predominant internal component. Nodules containing micro or macrocystic areas were classified as semisolid. Pure cystic nodules were excluded from the study. Calcification content were classified into three groups as ‘’no calcification’’, ‘’micro‘’ and ‘’macrocalcification’’. Nodules were divided into 4 groups according to size as ‘’<10mm’’, ‘’11-20mm’’, ‘’21-40mm’’, ‘’41-60mm’’. The largest diameter of the nodules was considered as size. Margin of the nodules were classified into three groups as ‘’smooth-distinct’’, ‘’macro lobulated,’’ ‘’micro lobulated’’ (or indistinct).

Biopsy procedures were performed by two radiologists (with 10 and 2 years of experience). Informed patient consents were obtained before the biopsies from all patients. All patients were questioned about anticoagulant medication usage and appropriate procedures were applied before the biopsy if the patient had been under medication. All biopsies were performed under US (Mindray, China) guidance with a 14 MHZ linear array transducer. Local anesthetic medication was not routinely used except of a few patients who had high anxiety. Biopsies were performed under aseptic precautions. Twenty-two, 23- or 27-gauge needles were used as necessary according to the size and depth of the nodules; and aspiration technique was used during biopsy. Two needle passes were performed for each nodule. After biopsy, specimens were fixed in liquid-based cytology solution according to advice of our cytopathologists. Rapid onsite adequacy assessment by a cytopathologist was not available in our institution. Biopsy specimens were assessed by different cytopathologists in the pathology department, considering the radiological features of the nodules.

Cytopathological results were classified into 6 groups according to Bethesda (National Cancer Institute, Fourth Thyroid FNAB Guideline Committee) classification system [1]. Diagnostic adequacy rates and radiological features (echogenicity, structure, size, calcification content, margin feature) of the nodules were noted and the relationship between diagnostic inadequacy and radiological features of the nodules was investigated retrospectively.

Statistical analysis

For statistical analysis, Statistical Package for the Social Sciences (SPSS) for Windows (Version 21.0, Chicago, SPSS Inc.) program was used. The Pearson Chi-square test was used to analyze the specimen adequacy ratio. A *P*-value of 0.05 or less was considered statistically significant.

Results

A total of 525 patients (77% female and 23% male; mean age 53.3; age range 14-87) had 595 FNABs in our institution. Of the all biopsies, 75% were reported as adequate while 25% were inadequate (Bethesda I).

Mean diameter of the nodules was 20.1 mm (min: 4mm; max: 60 mm). Of all, 50% of the nodules were solid in structure. Thirty-one percent (31%) were isoechogenic, 13% hyperechogenic, 32% hypoechogenic and 24% were heterogeneous. Ratios of nodules in size groups of ‘’<10mm’’, ‘’11-20mm’’, ‘’21-40mm’’, ‘’41-60mm’’ were 9%, 52%, 35% and 4% respectively. Seventy-five percent (75%) of the nodules did not contain calcification while 12% had micro and 13% had macrocalcifications. Eighty-five percent (85%) had smooth-distinct margins, while 11% had macro-lobulated and 4% had micro-lobulated (or irregular) margins.

Isoechogenic nodules were more likely, while hyperechogenic nodules were less likely to be insufficient; but no statistical significance was found between echogenicity and inadequacy (P=0.05). Those with macrocalcifications had a higher rate of inadequacy (P<0.05). There was no statistically significant relationship between inadequacy rates and cystic-solid structure, size or border features of the nodules (P>0.05). The relationships between radiological features of the nodules and inadequate diagnostic sampling are listed in Table 1. There were no significant procedure-related complications according to Cardiovascular and Interventional Radiology Society of Europe (CIRSE) guidelines [6].

Table 1: Influence of echogenicity, internal structure (solid proportion), size, calcification, and margins on cytological inadequacy

	Inadequate sample n (%)	Adequate sample n (%)	Total n (%)	*P*-value
Echogenicity				
Isoechogenic	58 (31.2)	128 (68.8)	186 (100.0)	0.051
Hyperechogenic	13 (16.7)	65 (83.3)	78 (100.0)	
Hypoechogenic	46 (24.1)	145 (75.9)	191 (100.0)	
Heterogenous	30 (21.4)	110 (78.6)	140 (100.0)	
Structure				
Solid	76 (25.5)	222 (74.5)	298 (100.0)	0.651
Semisolid	71 (23.9)	226 (76.1)	297 (100.0)	
Size				
<10mm	8 (14.3)	48 (85.7)	56 (100.0)	0.210
11-20mm	83 (27.0)	224 (73.0)	307 (100.0)	
21-40mm	52 (24.6)	159 (75.4)	211 (100.0)	
41-60mm	4 (19.0)	17 (81.0)	21 (100.0)	
Calcification				
No calcification	104 (23.2)	345 (76.8)	449 (100.0)	0.036
Microcalcification	16 (22.5)	55 (77.5)	71 (100.0)	
Macrocalcification	27 (36.0)	48 (64.0)	75 (100.0)	
Margin				
Smooth-distinctive	129 (25.5)	377 (74.5)	506 (100.0)	0.160
Macrolobulated	11 (16.2)	57 (83.8)	68 (100.0)	
Microlobulated-indistinctive	7 (33.3)	14 (66.7)	21 (100.0)	

Categorical variables were compared using Qui square test.

Discussion

US-guided FNAB of thyroid nodules are recommended by all guidelines to differentiate malignant nodules from benign ones for management of thyroid nodules [7-10]. However, inadequate results of US guided FNAB are reported in about 0.4-40.7% of biopsies [3]. US guidance decreased the inadequacy rate compared to palpation-guided biopsies due to selective targeting of specific nodules and real time sampling. Nevertheless, inadequacy rate in US-guided biopsy is also reported up to 40% [5]. Since the Italian Societies of Endocrinology and Pathology (SIAPEC-IAP) consensus statement recommends that non-diagnostic results should not exceed 20% of the reports, being aware of the factors affecting adequacy is particularly important for the operators who perform the biopsies [11]. In the current study we aimed to demonstrate the intrinsic factors that affect diagnostic adequacy for achieving a successful biopsy.

Many of the studies have reported that specimen adequacy is not dependent on the echogenicity of the biopsied nodule [4,15]. In contrary to these studies, some other studies have reported that hypoechogenicity has a negative effect on adequacy [13,16]. Hypoechogenic nodules are more likely fibrotic in nature, which makes needle movement harder during aspiration. There was no negative correlation between hypoechogenicity and inadequate sampling rate in our study. On the other hand, we have demonstrated that hyperechogenic nodules were more frequently diagnostic compared to hypoechogenic and heterogenous nodules.

FNAB of solid nodules are expected to be more frequently adequate compared to cystic ones due to cellularity [12-14]. On the other hand, cystic areas may be related to hemorrhage in semisolid nodules which cause blood contamination and more frequently inadequate cytology. However, in our study, there was no significant relationship between the nodule structure and inadequacy rates. This may be due to exclusion of pure cystic nodules from the study. We included the nodules which the solid component composed at least one third of the nodule volume.

According to some studies, frequency of nondiagnostic cytology increases in nodules larger than 3 cm and smaller than 5 mm [12]. Although sampling of large nodules is easier than smaller ones, cytopathological results may be nondiagnostic. Large nodules tend to comprise necrotic-cystic-acellular areas. On the other hand, some studies have reported that size does not affect adequacy of biopsies [13,14]. American Thyroid Association (ATA) guidelines recommend the 1 cm cut-off size for nodules that are highly suspicious, since smaller nodules yield inadequate results more frequently. Nevertheless, smaller nodules should be sampled in case of high suspicion of malignancy [7]. In the current study, 56 (9%) nodules were smaller than 10 mm. In contrast with the results in some of these studies, we demonstrated no significant relationship between nodule size and inadequacy rate in our study.

Presence of an intra-nodular macrocalcification increases the possibility of inadequate results regarding the coarse structure of the nodules and restriction of the needle movement during FNAB [17-19]. As opposed to this, according to Moon et al. [13] and Grani et al. [16], presence of calcification is not associated with inadequate cytology. Consistent with Yi et al. [17], we demonstrated that there was a negative correlation with macrocalcification and diagnostic adequacy rate. However, it was not the case for presence of microcalcification.

Although it is known that irregular margins in a nodule is most likely related to malignancy, we could not find any study reports which reveal the relationship between specimen adequacy and margin features. In our study, there was no significant relationship between margin features of the nodules and specimen adequacy, either.

There are many extrinsic factors affecting the adequacy rates in FNAB of thyroid nodules. It is reported in the literature that rapid onsite adequacy assessment of thyroid FNABs have yielded conflicting results. [20-22]. Some studies have reported that rapid onsite adequacy assessment of thyroid FNABs reduce the frequency of nondiagnostic aspirates and thereby avoid the need for a re-biopsy [20]. However, some have reported that rapid onsite adequacy assessment does not provide a significant increase in the diagnostic adequacy rate of aspirates [21]. Since rapid onsite adequacy assessment was not available in our institution, we performed all the biopsies without an onsite cytopathologist. We think that rapid onsite adequacy assessment would reduce the rate of inadequacy, but it would require more needle passes and prolong the procedure time.

The experience of the operator in FNAB is another extrinsic factor affecting diagnostic yield. In their study, Ghofrani et al. [23] reported that the experience of the operator is a determining factor. They have noted that inadequacy rates may significantly reduce from 13.0% to 4.5% by an experienced operator. Nevertheless, we were not able to compare diagnostic yield rates between both the experienced and less-experienced operators in our study due to lack of information about the performing operator for each biopsy.

In the reported studies, a wide range of needle sizes between 20-25 Gauge were frequently used for thyroid FNABs [15]. Thinner needles such as 25 and 27 G were suggested to increase the diagnostic adequacy rate [24]. In the current study, 22, 23 and 27 Gauge needle were used as necessary, according to the size and depth of the nodules. Since 27 G needles tend to bend and get obstructed quickly, we preferred such a thin needle in limited number of cases, mostly for semisolid nodules with a

prominent cystic component or nodules that were smaller than 10 mm. We could not compare the role of needle size since we used them randomly. In our experience, we agree that thinner needles provide a higher diagnostic yield due to less contamination with blood.

Most of the studies recommend at least three needle passes per nodule to increase diagnostic yield rate [5,15,25]. Due to busy schedule of our outpatient clinic and the prominent level of anxiety of the patients, we performed two needle passes per nodule. The adequacy rate in the current study was 25% which was slightly higher than the suggested level in some reports [11]. This result might be due to performing less than 3 needle passes in our study. We agree that increase in the number of needle passes will result in an increase in adequacy rate.

Limitations

The most important limitation in this study was its retrospective design. Further research is needed to analyze the effect of radiological features of the nodules with combining more optimal extrinsic factors to investigate its presumed relation to the adequacy rate in our clinic.

Conclusion

Some radiological features may be predictive of inadequate sampling. Macrocalcification content increased the frequency of inadequate cytological result. On the other hand, echogenicity, inner structure (solid vs cystic), size and margin features of the nodules did not affect the yield of adequate sampling rate. Nevertheless, varied intrinsic and extrinsic factors affect cytopathological adequacy. None of them alone is enough to have a high diagnostic sampling. Some additional methods may be required in these nodules such as sampling with higher number of needle passes and using thinner needles. Patients must be notified that their biopsy report might be concluded as inadequate sampling or nondiagnostic before the biopsy.

References

1. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. Thyroid. 2009;19(11):1159–65.
2. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda system for reporting thyroid cytopathology: a meta-analysis. Acta Cytologica. 2012;56(4):333–9.
3. Lee YH, Baek JH, Jung SL, Kwak JY, Kim JH, Shin JH. Ultrasound-guided fine needle aspiration of thyroid nodules: a consensus statement by the korean society of thyroid radiology. Korean J Radiol. 2015;16(2):391-401. doi: 10.3348/kjr.2015.16.2.391.
4. Kim MJ, Kim EK, Park SI, Kim BM, Kwak JK, Kim SJ, et al. US-guided fine-needle aspiration of thyroid nodules: indications, techniques, results. Radiographics. 2008;28(7):1869-87. doi: 10.1148/rg.287085033.
5. de Koster EJ, Kist JW, Vriens MR, Borel Rinkes IH, Valk GD, de Keizer B. Thyroid Ultrasound-Guided Fine-Needle Aspiration: The Positive Influence of On-Site Adequacy Assessment and Number of Needle Passes on Diagnostic Cytology Rate. Acta Cytol. 2016;60(1):39-45. doi: 10.1159/000444917.
6. Veltri A, Bargellini I, Giorgi L, Almeida PAMS, Akhan O. CIRSE Guidelines on Percutaneous Needle Biopsy (PNB). Cardiovasc Intervent Radiol. 2017;40(10):1501-13. doi: 10.1007/s00270-017-1658-5.
7. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L et al. American Association of Clinical Endocrinologists, American College of endocrinology and Associazione Medici Endocrinologi. Medical Guidelines for clinical practice for the diagnosis and management of thyroid nodules. 2016;22(5):622-39. doi: 10.4158/EP161208.G.L.
8. Çayır D, Kulah B. Effects of preoperative fine needle aspiration biopsy on surgical strategy in patients with papillary thyroid carcinomas. J Surg Med. 2019;3(9):655-658.
9. Baloch ZW, Cibas ES, Clark DP, Layfield LJ, Ljung BM, Pitman MB, et al. The National Cancer Institute Thyroid fine needle aspiration state of the science conference: a summation. Cytojournal. 2008;5:6.
10. Pitman MB, Abele J, Ali SZ, Duick D, Elsheikh TM, Jeffrey RB, et al. Techniques for thyroid FNA: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol 2008;36:407-24.
11. Fadda G, Basolo F, Bondi A, Bussolati G, Crescenzi A, Nappi O. Cytological classifi- cation of thyroid nodules. Proposal of the SIAPEC-IAP Italian Consensus Working Group. Pathologica. 2010;102,:405–8.
12. Richards, ML, Bohnenblust E., Sirinek K. Bingener J. Nondiagnostic thyroid fine-needle aspiration biopsies are no longer a dilemma. American Journal of Surgery. 2008;196:398–402.
13. Moon HJ, Kwak JY, Kim EK, Kim MJ. Ultrasonographic characteristics predictive of nondiagnostic results for fine-needle aspiration biopsies of thyroid nodules. Ultrasound in Medicine and Biology. 2011;37:549–55.
14. Alexander EK, Heering JP, Benson CB, Frates MC, Doubilet PM, Cibas ES, et al: Assessment of nondiagnostic ultrasound-guided fine needle aspirations of thyroid nodules. J Clin Endocrinol Metab. 2002;87:4924–7.
15. Degirmenci B, Haktanir A, Albayrak R, Acar M, Sahin DA, Sahin O et al. Sonographically guided fine-needle biopsy of thyroid nodules: the effects of nodule characteristics, sampling technique, and needle size on the adequacy of cytological material. Clin Radiol. 2007;62(8):798-803. doi: 10.1016/j.crad.2007.01.024.
16. Grani G, Calvanese A, Carbotta G, D'Alessandri M, Nesca A, Bianchini M et al. Intrinsic factors affecting adequacy of thyroid nodule fine-needle aspiration cytology. Clin Endocrinol (Oxf). 2013;78(1):141-4. doi: 10.1111/j.1365-2265.2012.04507.x.
17. Yi KS, Kim JH, Na DG, Seo H, Min HS, Won JK et al. Usefulness of core needle biopsy for thyroid nodules with macrocalcifications: comparison with fine-needle aspiration. Thyroid. 2015;25(6):657-64. doi: 10.1089/thy.2014.0596.
18. Choi SH, Han KH, Yoon JH, Moon HJ, Son EJ, Youk JH, et al. Factors affecting inadequate sampling of ultrasound-guided fine-needle aspiration biopsy of thyroid nodules. Clin Endocrinol (Oxf). 2011;74:776–82.
19. Belfiore A, La Rosa GL. Fine-needle aspiration biopsy of the thyroid. Endocrinol Metab Clin North Am. 2001;30:361–400.
20. Nasuti JF, Gupta PK, Baloch ZW. Diagnostic value and cost-effectiveness of on-site evaluation of fine-needle aspiration specimens: review of 5,688 cases. Diagn Cytopathol. 2002;27:1–4.
21. O'Malley ME, Weir MM, Hahn PF, Misdraji J, Wood BJ, Mueller PR. US-guided fine-needle aspiration biopsy of thyroid nodules: adequacy of cytologic material and procedure time with and without immediate cytologic analysis. Radiology. 2002;222:383–7.
22. Eedes CR, Wang HH. Cost-effectiveness of immediate specimen adequacy assessment of thyroid fine-needle aspirations. Am J Clin Pathol. 2004;121:64–9.
23. Ghofrani M, Beckman D, Rimm DL. The value of onsite adequacy assessment of thyroid fine-needle aspirations is a function of operator experience. Cancer. 2006;108:110–3.
24. Gümüş M, Cay N, Algin O, Ipek A, Ersoy RÜ, Belenli O, et al. Comparison of 21 and 27 gauge needles for determining sample adequacy in the aspiration biopsy of thyroid nodules. Diagn Interv Radiol. 2012;18(1):102-5. doi: 10.4261/1305-3825.DIR.4340-11.1.
25. Rausch P, Nowels K, Jeffrey Jr RB. Ultrasonographically guided thyroid biopsy: a review with emphasis on technique. J Ultrasound Med. 2001;20:79e85.

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. 2020;4(9):794-797.
DOI: 10.28982/josam.800175

Research article
Araştırma makalesi

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

Is Bethesda classification sufficient to predict thyroid cancer in endemic regions?

Endemik bölgelerde Bethesda sınıflaması tiroid kanserini ön gördürmede yeterli midir?

Gamze Çıtlak [1], Bahar Canbay Torun [1]

[1] Haseki Education and Research Hospital, Department of General Surgery, Istanbul, Turkey

ORCID ID of the author(s)
GÇ: 0000-0001-9483-6105
BCT: 0000-0002-6353-6692

Corresponding author / Sorumlu yazar:
Bahar Canbay Torun
Address / Adres: Haseki Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İstanbul, Türkiye
E-mail: baharcanbay@gmail.com

Ethics Committee Approval: This study was approved by Non-pharmacological Clinical Research Ethics Committee of Haseki Training and Research Hospital (569-2017). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Haseki Eğitim ve Araştırma Hastanesi Etik Kurulu (569/18.10.2017) tarafından onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: Bethesda classification is widely used to determine the risk of malignancy of thyroid nodules and in many guidelines, treatment algorithms are determined according to this classification. We aimed to investigate the accuracy of malignancy predictions of Bethesda classification in patients who underwent surgery.

Methods: In this retrospective cohort study, the medical records of patients who underwent thyroidectomy between 2013 and 2017 were analyzed. Patients' demographic characteristics, fine needle aspiration biopsy (FNAB) results, ultrasonographic findings, number of nodules, diameter of nodules, type of surgeries performed, and the terminal pathology results were recorded. Malignancies that were detected in Bethesda 1-2 patients and in nodules other than the nodule to which FNAB was performed in other Bethesda categories were defined as incidental cancer.

Results: Nine hundred sixty-seven patients were included in the study. The mean age of the patients was 46.9 (12.4) years and 82.4 % (n=797) were female. Mean nodule diameter was 29.7(13.9) mm and 64.3% (n=622) of the patients had 3 or more nodules. In our series, the rate of malignancy was 24.2% for Bethesda 1, 24.7% for Bethesda 2, 35% for Bethesda 3, 52.1% for Bethesda 4, 91.2% for Bethesda 5 and 100% for Bethesda 6. In all categories, the malignancy rate was higher than the expected range, but statistical significance was determined in Bethesda 1, 2, 4 and 5 groups. When compared to the whole series, rate of incidental cancer was 18.2%, whereas the incidental cancer rate was 49.5% of all cancers. The tumor was multicentric in 34.6% of malignant cases.

Conclusion: In endemic regions, higher rates of malignancy are detected than that predicted by the Bethesda classification. Therefore, updates on guidelines in patient selection for surgery and in choosing the surgical technique may be necessary for endemic areas.

Keywords: Bethesda classification, Incidental thyroid cancer, Endemic region, Thyroid nodule

Öz

Amaç: Tiroid nodüllerinin malignite riskinin belirlenmesinde Bethesda sınıflaması yaygın olarak kullanılmakta ve birçok kılavuzda bu sınıflamaya göre tedavi algoritmaları belirlenmektedir. Bethesda sınıflamasının malignite öngörülerinin cerrahi uygulanmış hastalarda doğruluğunu araştırmayı amaçladık.

Yöntemler: Bu retrospektif kohort çalışmada 2013-2017 yılları arasında tiroidektomi uygulanan hastaların dosyaları incelendi. Hastaların demografik özellikleri, İnce İğne Aspirasyon Biyopsisi(İİAB) sonuçları, ultrasonografik bulguları, nodül sayıları, nodül çapları, yapılan ameliyat ve terminal patoloji sonuçları kaydedildi. İİAB sonucu Bethesda 1 ve 2 olan hastalarda saptanan maligniteler ve diğer Bethesda gruplarında İİAB yapılan nodül dışında saptanan maligniteler insidental kanser olarak tanımlandı.

Bulgular: Dokuzyüzaltmışyedi hasta çalışmaya dahil edildi. Hastaların yaş ortalaması 46,9(12,4) saptandı ve hastaların %82,4'ü (n=797) kadındı. Ortalama nodül çapı 29,7(13,9) mm idi ve hastaların %64,3'ünde (n=622) 3 ve üzeri sayıda nodül mevcuttu. Serimizde malignite oranları Bethesda 1 için %24,2, Bethesda 2 için %24,7, Bethesda 3 için %35, Bethesda 4 için %52,1, Bethesda 5 için %91,2 ve Bethesda 6 için %100 olarak saptandı. Tüm kategorilerde malignite oranları beklenen aralıkların üstünde saptanmasına rağmen bu fark Bethesda 1, 2, 4 ve 5 gruplarında istatistiksel olarak anlamlı saptandı. Tüm seriye göre kıyaslandığında insidental kanser oranı %18,2 iken tüm kanserler içinde insidental kanser oranı %49,5 saptandı. Malignite saptanan olguların %34,6'sında tümör multisentrikti.

Sonuç: Endemik bölgelerde Bethesda klasifikasyonun öngörülerinden yüksek oranda malignite saptanabilmektedir. Bu nedenle cerrahi uygulanacak hastaların seçiminde ve cerrahi teknik tercihinde kılavuz önerilerinin güncellenmesi gerekebilir.

Anahtar kelimeler: Bethesda sınıflaması, İnsidental tiroid kanseri, Endemik bölge, Tiroid nodülü

How to cite/Atıf için: Çıtlak G, Torun BC. Is Bethesda classification sufficient to predict thyroid cancer in endemic regions? J Surg Med. 2020;4(9):794-797.

Introduction

Thyroid nodules are the most common diseases of the thyroid gland [1]. While the prevalence of thyroid nodules varies according to the method of detection, age, gender, and exposure to radiation, it is between 28.3 to 42.4 percent [1,2].

Ultrasound (US) and fine needle aspiration biopsy (FNAB) are used to evaluate the risk of malignancy of thyroid nodules. All relevant guidelines have defined ultrasonographic risk factors and classified FNAB recommendations [1,3].

Cytological evaluation is the gold standard method for detection of risk of malignancy for thyroid nodules. FNAB results have been standardized by the widely used Bethesda classification system which was defined in 2009 and updated in 2017 [1,3,4]. According to this classification, FNAB results have been divided into six categories, for each of which the risk of malignancy was determined. Recommendations for surgery and follow-up are present in national and international guidelines based on ultrasonographic and cytologic results [1,3].

The aim of this study is to compare the cancer predictions of Bethesda classification with terminal pathology results of the patients who were operated according to the recommendations of the guideline and investigate whether the recommendations of the guideline are sufficient.

Materials and methods

Medical records of patients who had undergone thyroidectomy for thyroid nodules between 2013 and 2017 were retrospectively analyzed, after approval of Non-pharmacological Clinical Research Ethics Committee of Haseki Training and Research Hospital (569-2017) was obtained. Patients operated for hyperthyroidism, whose diagnosis of malignancy was definite before surgery and for whom neck dissection was planned, who had undergone secondary surgery for completion thyroidectomy, for whom sufficient clinical data could not be obtained and who had a cancer other than differentiated thyroid cancer in their terminal pathology were excluded from the study. Thyroidectomy indications were based on ATA guidelines in Bethesda group 3-4-5-6 patients. In Bethesda group 1-2 patients, nodule sizes greater than 3 cm in diameter, grade 2-3 multinodular goiter, compression symptoms and patient preference were operation indications.

Demographic characteristics of the patients, ultrasonographic findings, FNAB results, number of nodules, diameters of nodules, the type of surgery performed, and the terminal pathology results were recorded.

The malignancies that were detected in patients whose FNAB result was Bethesda 1 and 2 were defined as incidental cancer. In patients whose FNAB result were consistent with Bethesda 3, 4, 5 and 6, if malignancy was detected in another nodule while the nodule to which FNAB was performed was benign, that case was also defined as incidental cancer. In patients whose FNAB result were consistent with Bethesda 3, 4, 5 and 6 and if malignancy was detected in that nodule, it was defined as non-incidental cancer. Patients were classified into three groups: Benign, incidental cancer and non-incidental cancer. Indications for surgery were divided into 3 groups according to FNAB as Bethesda 1-2, Bethesda 3-4 and Bethesda 5-6.

Statistical analysis

Descriptive statistics were expressed as number and percent for categorical variables, and as mean, standard deviation, minimum and maximum for numerical variables. The ratios in independent groups were compared using the chi-square test. Since multiple group comparisons did not demonstrate a normal distribution, Kruskal Wallis test was used. Frequency analysis, single ratio test and independent double ratio test were used for data analysis. *P*-value less than 0.05 was considered statistically significant. Applications were prepared using R Project (R Core Team, 2019) and IBM SPSS 20 (IBM Corp. 2011).

Results

Medical records of 1132 patients were retrospectively analyzed, and 967 patients were included in the study. Among all, 82.4 percent of the patients were female. Mean age of the patients was 46.97 (12.49) years. Diameter of the largest nodule was 29.7(13.9) mm and the mean tumor diameter was 17(14.6) mm. 64.3% of patients had 3 or more nodules. Rate of malignancy was 36.7 percent in the entire series. Patients' demographic characteristics and related information is summarized in Table 1.

FNAB results demonstrated that 10.2 percent of patients was classified as Bethesda 1, 44.5 percent of patients was classified as Bethesda 2, 22.1 percent of patients, as Bethesda 3, 14.7 percent, as Bethesda 4, 7 percent, as Bethesda 5 and 1.4 percent, as Bethesda 7. The rate of malignancy in each Bethesda group was 24.2%, 24.7%, 35%, 52.1%, 91.2% and 100% respectively. The 2017 Bethesda classification update presented two different cancer risk predictions based on whether noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFT-P) is considered cancer or not. When NIFT-P is considered cancer and the single ratio comparison test is performed by taking the upper limit of risk ratios, there was a statistically significant difference in Bethesda 1,2,4 and 5 groups (Table 2) ($P<0.001$). When NIFT-P is not considered cancer, the difference in Bethesda 3 category is also statistically significant ($P<0.001$).

While the ratio of incidental cancer was 18.2 % in the whole series, incidental cancers made up 49.5 % of patients with malignancy. 34.6 % of all cancers was multicentric. Patients were classified into three groups: Those with incidental cancer, non-incidental cancer, and benign pathology. Comparison of three groups demonstrated that the mean diameter of largest nodule was 29.7 (14) mm in the incidental cancer group, 22.4 (13.7) mm in the non-incidental cancer group and 31.8(13.2) mm in the benign group. The differences between incidental and non-incidental cancer groups ($P<0.001$) and between non-incidental cancer and benign groups were statistically significant ($P<0.001$) (Figure 1). Mean age of the patients in the incidental cancer, non-incidental cancer and benign groups were 47.6 (11.5) years, 44.8 (13.5) years and 47.3 (12.3) years, respectively. The difference between non-incidental cancer and benign groups was statistically significant ($P=0.047$).

Largest nodule diameter and tumor diameter were significantly smaller in incidental cancers compared to non-incidental cancers (P<0.001). The mean age of the patients in the incidental cancer group was significantly higher than those in the non-incidental cancer group (P=0.024).

Incidental cancers and non-incidental cancers were compared according to multicentricity, tumor capsule invasion, lymphovascular invasion, invasion of thyroid capsule and tumor diameter being larger than 10 mm. 40.3% of incidental cancers and 29.1% of non-incidental cancers were multicentric, the difference between which was statistically significant (P=0.026). There was no statistical significance between the two groups in terms of lymphovascular invasion (p>0.05). However, non-incidental cancers had a significantly higher rate of tumor capsule invasion and invasion of thyroid capsule (P<0.001 and P=0.012 respectively). Tumor diameter was ≥10 mm in 48.9% of incidental cancers and in 72.1% in non-incidental cancers. This difference was also statistically significant (P<0.001) (Table 3).

The diameter of the largest nodule in the non-incidental cancer group was significantly smaller than that in the other 2 groups (P<0.001). There was no difference between the incidental cancer and benign groups (Figure 1).

Table 1: Characteristics of the patients

		n	%
Gender	Female	797	82.4
	Male	170	17.6
Mean age(standard deviation)		46.97(12.49)	
Type of Surgery	Bilateral total thyroidectomy (BTT)	606	62.7
	Lobectomy	361	37.3
Pathology	Thyroid Papillary Cancer	206	21.3
	Papillary Microcancer	143	14.8
	Follicular	6	0.6
	Benign	612	63.3
Indication	Bethesda 1-2	529	54.7
	Bethesda 3-4	356	36.8
	Bethesda 5-6	82	8.5
Number of nodules	1	237	24.5
	2	108	11.2
	3 and more	622	64.3
Diameter of the largest nodule (mm) Mean(SD)		29.7(13.9)	
Tumor diameter (mm) Mean(SD)		17(14.6)	

Table 2: Comparison of ratio of malignancy according to Bethesda groups (If NIFT-P is accepted as cancer)

Bethesda	Reference (%)	Ratio (%)	Z-statistic	*P*-value
1	10	24.244	-5.067	<0.001
2	3	24.707	-26.437	<0.001
3	30	35.033	-1.672	0.095
4	40	52.106	-3.191	0.001
5	75	91.254	-3.652	<0.001
6	99	100.000	0.376	0.707

Table 3: Comparison of histopathologic characteristics of incidental cancers and non-incidental cancers

	Incidental cancers	Non-incidental cancers	*P*-value
Multicentricity	40.3%	29.1%	0.026
Tumor capsule invasion	11.9%	27.4%	<0.001
Lymphovascular invasion	4%	8.9%	0.083
Thyroid capsule invasion	4.5%	12.3%	0.012
Tumor diameter ≥10mm	48.9%	72.1%	<0.001

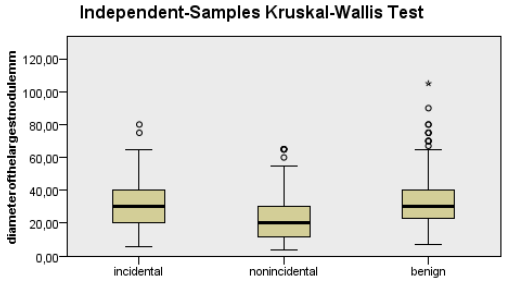


Figure 1: The comparison of three groups according to diameter of the largest nodule

Discussion

Thyroid nodules continue to be the most common disease of thyroid gland. In a patient presenting with thyroid nodule, thyroid function tests, ultrasonography, scintigraphy, fine needle aspiration biopsy are used as indicated to evaluate the nodule. Many guidelines have similar suggestions regarding this approach. For these patients it is important to determine the necessity of surgical treatment and avoid over-treatment. For this purpose, international guidelines have defined certain diagnostic and therapeutic algorithms. According to these algorithms, patients with a thyroid nodule and a normal serum TSH have FNAB indications that are based on ultrasonographic characteristics and size of nodule. FNAB results are widely categorized according to Bethesda classification.

In a meta-analysis performed by Bongiovanni et al. [5], the distribution of patients who had undergone surgery according to different Bethesda categories was 8.3 %, 24.6%, 15%, 28.2%, 7.9% and 16%, respectively and the total rate of cancer was 33.8%. In our series 10.2 % of patients were Bethesda 1, 44.5% were Bethesda 2, 22.1% was Bethesda 3, 14.7% were Bethesda 4, 7% were Bethesda 5 and 1.4% was Bethesda 6 and the total rate of cancer was 36.7%. We believe that the high prevalence of multinodular goiter in our country, the large diameter of nodules and the patients who were treated surgically due to multiple nodules has caused the high rate of patients in benign group. However, in the whole series, the rate of cancer was comparable with the rates reported in the literature.

Bethesda classification was first defined in 2009 and updated in 2017. In the updated classification, malignancy predictions have been determined separately according to whether NIFT-P is considered cancer or not. Accordingly, in cases where NIFT-P is considered cancer, malignancy prediction is 5-10 % for Bethesda 1, 0-3% for Bethesda 2, 10-30% for Bethesda 3, 25-40% for Bethesda 4, 50-75% for Bethesda 5 and 97-99% for Bethesda 6 [4]. In our series, the rate of malignancy was 24.2 % in Bethesda 1 group, 24.7 % in Bethesda 2 group, 35 % in Bethesda 3 group, 52.1% in Bethesda 4 group, 92.1 % in Bethesda 5 group and 100% in Bethesda 6 group. When the rate of malignancy in our series was compared with the upper limits of rates of malignancy where NIFT-P was considered cancer in the 2017 update, the rate of malignancy was significantly higher in our patients in Bethesda 1, 2, 4 and 5 groups. Even though the rate of malignancy in Bethesda 3 group was higher than the predicted upper limit, there was no statistical significance. We used the reference values that considered NIFT-P cancer because our study retrospectively analyzed the data of patients that were treated between 2013 and 2017 and in that period, NIFT-P was not histopathologically reported in our center.

Many studies in the literature report different percentages of malignancy than the rates of cancer that were foreseen in the literature [5-10]. In a meta-analysis by Bongiovanni et al, the percentage of malignancy in Bethesda categories were 16.8%, 3.7%, 15.9%, 26.1%, 75.2 and 98.6% respectively [5]. In 2015 ATA guideline, the actual cancer risk of surgically resected nodules was calculated based on this study and found as 20% (9-32), 2.5% (1-10), 14% (6-48), 25% (14-34), 70% (53-97) and 99% (94-100) respectively [3]. In our series we compared the cancer risk by considering NIFT-P cancer in the

2017 revision of Bethesda classification and by taking the upper limit of predicted cancer risk percentages. There was a statistically significant difference in Bethesda groups 1,2,4 and 5. When evaluated according to actual risk percentages of ATA guideline, the rate of cancer in Bethesda 2 (24.7%) and 4 (52.1%) were above reference values.

In a meta-analysis performed by Huy Gia Vuong et al. [10], the rate of malignancy in Western and Eastern countries was compared according to Bethesda categories. Cancer rates in for Bethesda categories 1, 2,3, 4, 5 and 6 were 13.2 %, 4.1 %, 21.5 %, 27.3%, 75.1% and 99.2%, respectively, in the Western countries, and 26.5%, 13.8%, 45%, 32.8%, 88.1% and 98.6%, respectively, in the Eastern countries. In Eastern countries, the rates of cancer in Bethesda 2, 3 and 5 categories were significantly higher. The malignancy rates in Eastern countries was generally higher. In our series, in all categories, cancer rates were higher than that in the Western countries. When compared with Eastern countries, cancer rates were higher in Bethesda groups 2 and 4 and lower in Bethesda group 3.

Incidental thyroid cancer is reported in up to 12 % of clinical series and in up to 36 % autopsy series in the literature [11]. In our study, rate of incidental cancer was 18.2% of the whole series and 49.5% of all cancers were evaluated as incidental cancer. A study by Evranos et al. detected incidental cancer in 326 (36 %) of 906 patients who were operated and determined to have a malignancy [12].

A study performed by Can et al. [13] compared the incidental and non-incidental thyroid cancers (NITC) according to the histopathologic data and detected findings which demonstrated that NITC could have a more aggressive course. Proximity to surgical margin, positive surgical margin, capsule invasion, lymphovascular invasion, extrathyroidal dissemination, multifocal tumor and lymph node metastasis were significantly higher in NITC. 94.7% bilateral tumors were non-incidental. BRAF V 600 gene mutation was detected in 94 % of NITC. In our series multicentricity was significantly higher in patients with incidental cancer. Tumor capsule invasion, and thyroid capsule invasion were significantly higher in patients with NITC. In our series 48.9 % of incidental cancers were larger than 1 cm, while in NITC, this rate was 72.1%. Incidental cancers are reported to possess less aggressive histopathologic characteristics and our findings are compatible with literature [13,14]. However, nearly half of the incidental cancers are larger than 1 cm and their clinical significance cannot be denied.

In a study that retrospectively analyzed 308 patients with papillary thyroid cancer, 63.6 % of patients that had coexisting chronic lymphocytic thyroiditis in the pathological specimen were incidental. In the same series 88.9 % of patients with multinodular hyperplasia were incidental and 11.1% were non-incidental [13]. Our country is endemic for thyroid diseases, therefore lymphocytic thyroiditis and multinodular hyperplasia are frequently detected. In our series, 64.3% patients had 3 and more nodules, only 24.5 % of patients had a single nodule.

Limitations

The limitations of this study are its retrospective design and that the patients only included those who underwent surgery. Another limitation of this study is that although all patients were operated with an indication according to the guideline recommendations, the study was retrospective and some of the patients had to be excluded from the study due to insufficient data.

Conclusion

Ultrasonographic evaluation and FNAB are gold standard for evaluation of thyroid nodules. Bethesda classification is widely used and a useful and instructive classification. Most guidelines suggest follow-up and treatment algorithms based on this classification. However, in endemic countries such as ours, most of the patients have more than 3 nodules. Guidelines usually make suggestions for a solitary nodule and recommend each nodule to be separately evaluated for risk of malignancy. There are similar studies to our series in the literature. Results of our retrospective study demonstrated higher rates of malignancy than predicted for each Bethesda category. Based on our results we believe that patients in endemic regions should be managed according to the suggestions of guidelines but situations that are unique for endemic regions should also be considered in the decision making. We believe that decisions should be made according to clinical findings, number of nodules, diameter of nodules and radiologic signs, especially for Bethesda 1 and 2 categories. Guidelines recommend lobectomy for Bethesda 3 and 4 categories. In these groups of patients, the dissemination of the disease should be considered and the need for more extensive surgeries should be kept in mind.

References

1. Erdoğan MF. Tiroid Hastalıkları Tanı ve Tedavi Kılavuzu. Türkiye Klinikleri; 2019.
2. Moon JH, Hyun MK, Lee JY, Shim JI, Kim TH, Choi HS, et al. Prevalence of thyroid nodules and their associated clinical parameters: a large-scale, multicenter-based health checkup study. Korean J Intern Med. 2018 Jul;33(4):753–62.
3. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1–133.
4. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. J Am Soc Cytopathol. 2017;6(6):217–22. doi: 10.1016/j.jasc.2017.09.002
5. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda system for reporting thyroid cytopathology: A meta-analysis. Acta Cytol. 2012;56(4):333–9.
6. Ke J, Jianyong L, Ying L, Genpeng L, Linlin S, Zhihui L, et al. The use of The Bethesda System for Reporting Thyroid Cytopathology in a Chinese population: An analysis of 13,351 specimens. Diagn Cytopathol. 2019 Sep;47(9):876–80.
7. Kumari KA, Jadhav PD, Prasad C, Smitha NV, Jojo A, Manjula VD. Diagnostic Efficacy of Ultrasound-Guided Fine Needle Aspiration Combined with the Bethesda System of Reporting. J Cytol. 2019;36(2):101–5.
8. Kim M, Park HJ, Min HS, Kwon HJ, Jung CK, Chae SW, et al. The Use of the Bethesda System for Reporting Thyroid Cytopathology in Korea: A Nationwide Multicenter Survey by the Korean Society of Endocrine Pathologists. J Pathol Transl Med. 2017 Jul;51(4):410–7.
9. Zarif HA, Ghandurah SE, Al-Garni MA, Binmahfooz SK, Alsaywid BS, Satti MB. Thyroid Nodules Cytopathology Applying the Bethesda System with Histopathological Correlation. Saudi J Med Med Sci. 2018;6(3):143–8.
10. Vuong HG, Ngo HTT, Bychkov A, Jung CK, Vu TH, Lu KB, et al. Differences in surgical resection rate and risk of malignancy in thyroid cytopathology practice between Western and Asian countries: A systematic review and meta-analysis. Cancer Cytopathol. 2020 Apr;128(4):238-249. doi: 10.1002/cncy.22228.
11. Bradly DP, Reddy V, Prinz RA, Gattuso P. Incidental papillary carcinoma in patients treated surgically for benign thyroid diseases. Surgery. 2009;146(6):1099–104. doi: 10.1016/j.surg.2009.09.025
12. Evranos B, Polat SB, Cuhaci FN, Baser H, Topaloglu O, Kilicarslan A, et al. A cancer of undetermined significance: Incidental thyroid carcinoma. Diagn Cytopathol. 2019 May;47(5):412–6.
13. Can N, Ozyilmaz F, Celik M, Sezer AY, Sut N, Tastekin E, et al. Comparison of clinico pathological features in incidental and nonincidental papillary thyroid carcinomas in 308 patients. Polish J Pathol. 2017;68(3):197-209. doi: 10.5114/pjp.2017.71527.
14. Çayır D, Kulah B. Effects of preoperative fine needle aspiration biopsy on surgical strategy in patients with papillary thyroid carcinomas. J Surg Med. 2019;3(9):655-8.

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. 2020;4(9):798-802.
DOI: 10.28982/josam.711490

Research article
Araştırma makalesi

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

The relationship between different upper extremity patterns and independence level in individuals with spastic cerebral palsy from the ICF perspective

Spastik serebral palsili bireylerde farklı üst ekstremite patternleri ve bağımsızlık seviyesi arasındaki ilişkinin ICF perspektifine göre incelenmesi

Hasan Bingöl [1,2], Hikmet Kocaman [2,3], Mintaze Kerem Günel [4]

[1] Vocational School of Health, Mus Alparslan University, Muş, Turkey
[2] Department of Physiotherapy and Rehabilitation, Institute of Health Sciences, Hacettepe University, Ankara, Turkey
[3] Research Assistant, PT, MSc, Faculty of Health Science, Karamanoğlu Mehmetbey University, Karaman, Turkey
[4] Faculty of Physiotherapy and Rehabilitation, Hacettepe University, Ankara, Turkey

ORCID ID of the author(s)

HB: 0000-0003-3185-866X
HK: 0000-0001-5971-7274
MKG: 0000-0001-6895-2495

Corresponding author / Sorumlu yazar:
Hasan Bingöl
Address / Adres: Muş Alparslan Üniversitesi Sağlık Hizmetleri MYO, Kulp Yolu 7. Km. Muş, Türkiye
E-mail: hesenbingol@gmail.com

Ethics Committee Approval: This study was approved by the Scientific Research and Publication Ethics Committee of Muş Alparslan University on 2/13/2018 with the decision numbered E.2065. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma 13.02.2018 tarihinde E.2065 sayılı kararla Muş Alparslan Üniversitesi Bilimsel Araştırma ve Yayın Etiği Kurulu tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Previous presentation: The study is presented at 7th National Physiotherapy and Rehabilitation Congress. Date: 4/18/2019, Ankara, Turkey

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: Although various upper limb and hand involvement patterns in individuals with cerebral palsy (CP) have been defined, our knowledge about their functionality in daily life is still insufficient. The purpose of this study was to investigate upper extremity involvement patterns concerning the level of functionality in individuals with spastic CP.

Methods: A total of 101 individuals, aged 7 to 21 years, with spastic cerebral palsy (30% unilateral CP, 70% bilateral CP), and a total of 172 hand and upper limb patterns were evaluated in this study. To identify different spastic upper extremity patterns, two classification systems, one for the upper limb and one for the hand (Classification of Upper Limbs and Hand Patterns), were used separately. Then, the Manual Ability Classification System [MACS] and Functional Independency Measure [Wee-FIM] were utilized to quantify hand functions and functional independency level, respectively, in the activities of daily living.

Results: A strong correlation was found between MACSI and Simple Flex of Hand Pattern (r=0.72) while a moderate correlation was detected between MACSII and Simple Flex of Hand Pattern (r_2=0.57). Besides, the level of independence in daily living activities was consistent with Type Ia and Type Ic patterns of the upper limb (r_1=0.56 and r_2=0.44)

Conclusion: It was concluded in the light of the obtained data that Type Ia and Type Ic patterns of the upper limb, as well as Simple Flex of the hand pattern, are very efficient for functionality. Additionally, the pattern of Simple Flex Plus and Intrinsic Punching Hand were significantly related to bad capacity in hand functioning. The various upper limb and hand patterns affect the functionality or functional independence in daily living. Consequently, abnormal upper limb and hand patterns, which commonly occur in the upper extremities of children with CP, are quite different from each other in terms of functionality. Hence, it is recommended that before the application of BoNT-A or orthopedic surgery in managing spasticity, the client should be comprehensively evaluated in both terms of rigidity and functionality.

Keywords: Cerebral Palsy, Upper Limb, Pattern, ICF, ADL, Independency

Öz

Amaç: Serebral palsili (SP) bireylerde şu ana kadar çeşitli el ve kol tutulum patternleri tanımlanmış olsa da, günlük yaşamdaki işlevsellikleri hakkındaki bilgilerimiz hala yetersizdir. Bu çalışmanın amacı, spastik SP'li bireylerde üst ekstremite tutulum patternlerini işlevsellik düzeyine göre araştırmaktı.

Yöntemler: Çalışmaya yaşları 7-21 yıl arasından değişen toplam 101 spastik SP'li tanılı birey (%30 unilateral SP, %70 bilateral SP; toplam 172 el ve kol patterni) dahil edildi. Anormal el ve kol patternlerini tanımlamak için El ve Kol Pattenleri Sınıflandırma Sistemleri ayrı ayrı kullanıldı. Sonrasında, çalışmaya dahil edilen hastaların el işlevsellikleri ve günlük yaşam aktivitelerindeki bağımsızlık düzeyleri El Becerileri Sınıflandırma Sistemi (EBSS) ve Fonksiyonel Bağımsızlık Ölçütü (FBÖ) kullanılarak belirlendi

Bulgular: EBSS I ve Simple Flex el patterni arasında yüksek düzeyde bir ilişki bulunurken r=0,72) ve EBSS II ve Simple Flex el patterni arasında orta düzeyde bir ilişki tanımlanmıştır (r=0,57). Ayrıca, Tip Ia ve Tip Ic kol patternleri ile günlük yaşam aktivitelerindeki bağımsızlık seviyesi arasında orta derecede bir ilişki saptandı (r_1=0,56 ve r_2=0,44)

Sonuç: Elde edilen verilerin ışığında; bir yandan Tip Ia ve Tip Ic kol patternlerinin diğer yandan Simple Flex el patterninin fonksiyonellik açısından verimli olduğu sonucuna varıldı. Ek olarak, Simple Flex Plus ve Intrinsic Punching Hand el patternlerinin el işlevselliği açısından verimli olmadıkları bulundu. Sonuç olarak SP'li çocuklarda yaygın olarak görülen farklı kol ve el patternlerinin işlevsellik açısından birbirlerinden farklıdırlar. Bundan Ötürü spastisite yönetiminde sıklıkla başvurulan yöntemlerden biri olan BoNT-A tedavisine karar vermeden önce hasta hem rijit hem de fonksiyonel açıdan kapsamlı bir şekilde değerlendirilmelidir.

Anahtar kelimeler: Serebral palsi, Üst esktremite, Pattern, ICF, GYA, Bağımsızlık

How to cite/Atıf için: Bingöl H, Kocaman H, Günel MK. The relationship between different upper extremity patterns and independence level in individuals with spastic cerebral palsy from the ICF perspective. J Surg Med. 2020;4(9):798-802.

Introduction

Cerebral Palsy (CP) is a non-progressive yet permanent condition that occurs as a result of damage to the developing brain and is characterized by postural and movement disorders as well as activity limitations [1]. Upper motor neuron (UMN) lesion results in several forms of motor impairment ranging from neural-related ones, such as spasticity, to non-neural related ones, due to changes in the mechanical properties of muscles. These two interact with each other, causing muscle hypertonia, leading to increased resistance to passive motion in the upper limb [2]. Consequently, muscle hypertonia increases energy consumption during activities by interference with voluntary muscle movements [3].

Studies have shown that the increase of tone in upper limbs of children with CP, which occurs around the age of 10 years [4], and is mainly predominant in the shoulder (adductors and internal rotators), forearm (pronators), elbow, wrist and finger (flexors), leads to structural and functional contractures [5,6]. Hyperactivity of different muscle combinations in CP forces the affected extremity into abnormal posture and movement patterns [7]. Chaleat-Valayer et al. [8] developed two different classification systems by identifying different upper limb and hand patterns that were common in patients with CP. These abnormal postures or movement patterns that occur as a result of spasticity adversely affect upper extremity functions such as reaching, grasping-releasing and manipulating objects [7, 9]. Secondary body structure-function problems in children with CP affect their manual ability and have a direct impact on their performance in daily living such as feeding, dressing, toilet-bathing; and an indirect effect on their participation in the social environment, school and home activities.

The International Classification of Functioning, Disability and Health (ICF) is a conceptual framework that describes the effects of disability on individuals' daily living and social participation beyond physical injury and disability. In general, the ICF model is a conceptual framework that gives a dynamic idea about evaluation, goals and interventions [10]. Various rehabilitation approaches focus on ICF's activity and participation domains rather than on body structure/function domain. However, the relationship between the main domains of ICF is not yet fully understood [11]. The relationship between the main domains of ICF mostly relies on evaluation and is based on cross-sectional studies published previously [7,12,13]. In contrast, several clinical studies have shown that the relationship between different domains of ICF is complicated, and the improvements in activity and participation related to intervention are also influenced by individual and environmental factors [11,14,15]. These results make it difficult to think of the ICF framework for treatment and goals planning.

In their study, Kim and Park tried to show the results of spasticity on the main domains of ICF by using path analysis [12]. Since BoNT-A is a popular intervention to manage pediatric upper limb hypertonia and improving function in the spastic upper extremity [7], the professionals working in this field must have detailed information on all the spectrum of upper extremity impairment (related to all areas of ICF). Patterns caused by muscle hypertonia should be evaluated precisely before deciding on BoNT-A injection as an adjunctive treatment method [16-18]. Also, according to the current consensus published in 2009, in non-focal conditions such as CP, body structures and functions (contracture and decreased range of motion), as well as the severity of the functional level (Gross Motor Classification System, Manual Ability Classification System) should be taken into account. The use of BoNT-A in children with CP must target a muscle group rather than a single muscle [19].

Based on the above premise, the present study aimed to examine different upper limb and hand patterns in children with spastic CP and investigate these patterns concerning functionality in daily living. The hypothesis of this study was that in children with spastic CP, upper limb and hand patterns differentiate depending on the severity of involvement and these abnormal patterns adversely affect the functionality of the upper limbs and hands.

Materials and methods

The study protocol was approved by the Scientific Research and Ethical Board of Mus Alparslan University with the decision number E.2065 on 2/13/2018. Before inclusion into the study, informed consent was obtained from the parents or participants. A total of 101 patients (children and adults) with unilateral and bilateral CP (aged 7-21 years) were enrolled in this current study to investigate the relationship between the independence in daily living and the abnormal upper limb and hand patterns. The study also aimed to establish a resource document to serve for decision making of BoNT-A injection in the spastic upper limb(s) of the patients. The inclusion criteria included (1) being diagnosed with spastic CP, (2) having had no previous surgical interventions such as muscle lengthening, (3) having had no previous BoNT-A treatment, and (4) being older than seven years of age. Based on the static posture positions of the upper limbs and hands, patterns of each were classified according to the Classification of Upper Limb Patterns and Classification of Hand Patterns (with the permission of R. Bard-Pondarre), respectively. Considering the unilateral or bilateral involvement of participants enrolled in this study, a total of 172 upper limb and hand patterns were evaluated. Detailed clinical observations and classification of abnormal spastic patterns of the patients were performed while the subjects were in sitting or standing positions without being exposed to any activity. In patients with bilateral spastic CP, patterns of each upper extremity were evaluated separately considering the asymmetric involvement.

Manual performance of each subject was measured based on how the children (CP) use their hands in daily life or children's designated hand function of capacity in a clinical setting. Functional ability in daily living (what a child with a disability does) were exhibited for the tasks of such as self-care, eating, dressing, mobility, and communication skills.

Outcome Measures

Upper Limb and Hand Patterns Classification System

This is based on a previous study on the classification of spastic upper limb and hand patterns in adult stroke patients [16]. Chaleat-Valayer et al. [8] developed a similar classification for

patients with CP. In their study on intra- and inter-rater reliability of both classification systems, the same researchers concluded that both these classification systems had good reproducibility in children with CP [8].

Manual Ability Classification System

The Manual Ability Classification System (MACS) is used to quantify the severity of upper limb involvement. It classifies how children with cerebral palsy use their hands to handle objects in daily activities [20]. This system includes five levels of hand function, from Level I, indicating that the child is capable of easily manipulating objects without restrictions in daily living activities, to Level V, indicating that the child requires full assistance to handle objects. [21]

Functional Independence Measure

Functional Independence Measure (Wee-FIM) comprises rating that best describes the child's level of function related to self-care, mobility and cognitive skills and can be used for all children with developmental disorders ranging from 6 months to 21 years of age. It consists of 18 items, and each item is scored between 1 and 7. Of these scores, 6 and 7 represent "INDEPENDENT", 3 to 5 represent "ASSISTANCE REQUIRED", and 1 and 2 indicate "DEPENDENT". Taking this classification into consideration, we can sub-categorize the total scores as following: Any score between 18-36 represents "DEPENDENT", between 37-90 represents "ASSISTANCE REQUIRED", and between 91-126 indicates "INDEPENDENT".

Mapping Instruments by Using ICF-CY as A Reference Framework

ICF is a classification system or framework in which tools that assess body structure and functionality, as well as activity and participation are mapped. This broad framework organizes assessments based on their content and enables them to focus on selecting relevant aspects of functionality and disability during evaluation [22]. The outcome measures were categorized according to ICF main domains consisting of components from body structure/impairment, activity and participation [10]

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics v.22. Hand patterns, according to upper limb patterns, manual ability level according to hand patterns, and upper limb patterns according to Wee-FIM levels, were given using cross-tabulations. The calculated correlation coefficient (r) or the strength of the relationship was related to how similar the values of the two variables were. In contrast, the direction of the association was determined by analyzing whether the increase or decrease in the values of one variable was in the same direction with the increase or decrease in the values of the other variable. The relationship between the two variables –in percentage– was interpreted as follows: Values of <20% were considered small, 40-59% were deemed moderate, and 60- 79% and above were considered large [23].

Results

Age, gender, type of CP, GMFCS and MACS levels of the participants are presented in Table 1.

Type Ia (36.04%) and Type Ib (17.6%) accounted for the majority of the upper limb patterns of 172 included in the study, and a small proportion showed Type III b (2.3%) pattern. Besides, Simple Flex and Simple Flex Plus yielded proportions of 41.1% and 22.3%, respectively (Table 2).

When we look at the distribution between manual ability levels (MACS) and hand patterns of the participants (See Table 3), the majority of 18 hand patterns with MACS level I were associated with Simple Flex hand pattern (72.2%), whereas 5.5% and 22.2% were related to Total Flex and Intrinsic Punching Hand patterns, respectively. According to these results, there was a strong relationship between MACS level I and Simple Flex Hand pattern. Likewise, there was a moderate relationship between MACS level II (somewhat reduced quality of handling objects) and MACS level III and the Simple Flex Hand pattern (56.9% and 50% respectively). As a result, MACS levels I and II, in which manual ability does not limit independence in daily living activities, are associated with high and moderate levels of Simple Flex Hand pattern. On the other hand, there was a very weak relationship between MACS levels IV and V, and Simple Flex Hand pattern (13.6% and 12.2% respectively).

Table 1: Characteristics of the Participants

Age	Gender		Type of CP		GMFCS					MACS				
	Female	Male	Bilateral Dominant	Unilateral Dominant	I	II	III	IV	V	I	II	III	IV	V
11.62 (4)	45	56	71	30	22	19	26	24	10	10	39	11	12	29

MACS: Manual Ability Classification System, GMFCS: Gross Motor Classification Systems

Table 2: Upper Extremity Pattern Distributionsn, number of upper limb or hand patterns; %, percent for each pattern

Type of Upper Limb Patterns	n	%	Type of Hand Patterns	n	%
Type Ia	62	36.04	Simple Flex	70	41.1
Type Ib	30	17.6	Total Flex	12	7.01
Type Ic	10	5.2	Simple Flex Plus	38	22.3
Type IIa	21	12.2	Total Flex Plus	8	5.2
Type IIb	32	18	Intrinsic Punching Hand	32	18.8
Type IIc	6	3.4	Superficial Punching Hand	3	1.7
Type IIIa	7	4.06	Profound Punching Hand	9	5.2
Type IIIb	4	2.3	-	-	
Total	172	100		172	100

Table 3: The Relationship between Manual Ability Level and Hand Patterns

MACS Levels	Hand Patterns							n
	Simple Flex	Total Flex	Simple Flex Plus	Total Flex Plus	Intrinsic Punching Hand	Superficial Punching Hand	Profound Punching Hand	
I	13(%72.2)	1(%5.5)	-	-	4(%22.2)	-	-	18
II	37(%56.9)	3(%4.6)	9(%13.8)	3(%4.6)	11(%16.9)	-	2 (%3)	65
III	9 (%50)	2(%11.1)	3(%16.6)	1(%5.5)	2 (%11.1)	-	1(%5.5)	18
IV	3(%13.6)	2(%9)	9(%40.9)	1(%4.5)	3(%13.6)	2(%9)	2(%9)	22
V	6 (%12.2)	4(%8.1)	17(%34.6)	4(%8.1)	12(%24.4)	2(%4)	4 (%8.1)	49

MACS: Manual Ability Classification System, n: number of hand patterns for each MACS level, % percentage of each defined hand patterns

The majority of the total of 49 patterns related to MACS level V, which corresponds to the bad capacity associated with the manual ability where objects cannot be grasped, or total help is required, are associated with Simple Flex Plus and Intrinsic Punching Hand patterns (34.6% and 24.4% respectively). The relationship between MACS level I, II, III and Total Flex hand pattern is remarkably close to 0. More patterns are needed to determine the relationship between these variables.

Table 4 and Figure 1 show the distributions of upper limb patterns at different levels of independence in daily life and the Wee-FIM score range of each upper limb pattern, respectively. According to Table 4, while there was a moderate relationship between Type Ia and Type Ic upper limb patterns and the "INDEPENDENT" level in daily life (56.4% and 44.4% respectively), Type Ib, Type IIb, Type IIc and Type IIIb upper limb patterns had a weak correlation with the level of independence in ADL. In contrast, there is no relationship between Type IIa and Type IIIa upper limb patterns and the

"INDEPENDENT" level in daily life. More patterns are needed to determine the relationship. While the relationship between "ASSISTED" level in daily living and Type IIc of upper limb pattern was very strong (83.3%), Type IIb had a lower than moderate relationship (41.9%), and Type Ia had a weak relationship (35.4%).

Table 4: The relationship between Upper Limb Patterns and Wee-FIM Levels

Upper Limb Patterns		Wee-FIM Levels			Total
		INDEPENDENT	ASSISSTED	DEPENDENT	
Type Ia	n	35	22	5	62
	%	56.4%	35.4%	8.06%	43.2%
Type Ib	n	8	8	14	30
	%	26.6%	26.6%	46.6%	21.6%
Type Ic	n	4	2	3	9
	%	44.4%	22.2%	33.3%	5.7%
Type IIa	n	1	4	16	21
	%	4.7%	19.04%	76.1%	11.4%
Type IIb	n	5	13	13	31
	%	16.1%	41.9%	41.9%	12.5%
Type IIc	n	1	5	0	6
	%	16.6%	83.3%	0.0%	2.3%
Type IIIa	n	0	2	5	7
	%	0.0%	28.5%	71.4%	2.3%
Type IIIb	n	1	2	3	6
	%	16.6%	33.3%	50%	1.1%
Total	n	55	58	59	172
	%	100.0%	100.0%	100.0%	100.0%

n: number of upper limb patterns for each independency level, % percent; Wee-FIM: Functional Independency Measure

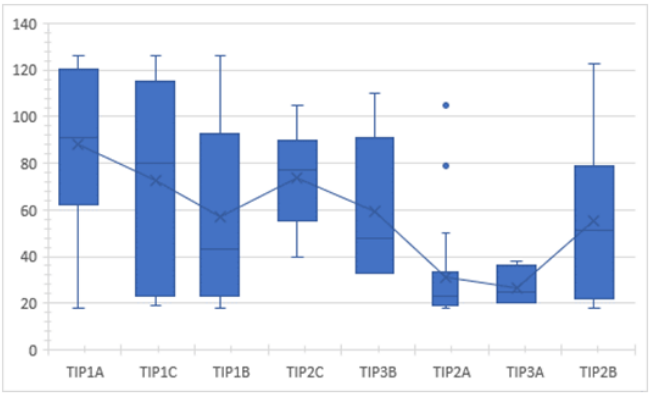


Figure 1: Wee-FIM score distribution according to upper limb patterns

Discussion

This study sought to explore different upper limb and hand involvement patterns observed in children with spastic CP concerning functionality in daily activities. Overall, MACS I, MACS II, and MACS III were associated with Simple Flex Hand pattern. That is, MACS I-III levels corresponding to moderate-minor problems in hand function were compatible with the Simple Flex Hand pattern at a decreasing rate. Based on these distributions, it can be concluded that Simple Flex Hand pattern is efficient in daily activities. Besides, a moderate correlation was found between Type Ia and Type Ic patterns of the upper limb and functional independence in daily living.

On the other hand, a moderate-high relationship was found between Type IIa, Type IIIa, and Type IIIb of upper limb patterns and dependent level in daily living. Additionally, our results indicated that Type Ia of upper limb pattern was moderately functional; instead, Type Ic upper limb pattern is slightly functional. Conversely, it was found out that Type IIa and Type IIIa upper limb patterns were associated with significantly poor functionality.

Considering the sub-classification of upper limb patterns made according to elbow postures [8], it can be observed that the pronator teres and biceps brachii muscles are mainly affected. Studies have shown that these muscles or supination-pronation movements of forearm affect hand patterns and therefore, manual ability [7]. According to the results of the study conducted by Kane et al. [24], wrist movements are positively associated with the complex bone-soft tissue structures, forearm rotations influence carpal kinematics, effective use of wrist and hand requires good coordination of the wrist and forearm, and rotation of forearm around its long axis for various degrees of pronation or supination need normal range of motion of the wrist and forearm (This is essential in nearly all daily activities, from simple movements such as turning keys and opening doors to complex movements such as throwing a baseball).

MACS Level I and II, which correspond to the effective use of the hand, were more compatible with the Simple Flex Hand pattern. Studies have shown that such a posture is consistent with the functional use of the hand [25]. MACS Level IV and V, which require continuous or total help to perform part of the activity, are often associated with "Simple Flex Plus" and "Intrinsic Punching Hand" patterns. This can be explained based on the fact that these two patterns are more complex postures where both the intrinsic and extrinsic structures of the hand are affected, according to the definition of the related classification resources: "Wrist flexion is associated with swan neck deformity or dinosaur hand (exclusion of the index finger during grasping)". Studies investigating hand patterns have concluded that the atypical posture in hand is often accompanied by ulnar deviation and that the increased wrist-finger flexion prevents functional use of the hand [26].

Normal selective hand and finger movements, free from the arm movements, which enhance the development of graduated movements required for the high quality of grasping and releasing objects, are not easy to perform. As some authors have suggested, hand functions do not consist solely of the functional sensory activation or intrinsic structures of the hand, so it can be concluded that the effective use of the hand in daily life is related with the upper limb posture as well as hand postures. It is in this context that rehabilitation approaches focusing on proximal segments such as the elbow and forearm responsible for positioning and orientation of the hand, or rehabilitation approaches focusing on increasing active ROM, may improve hand functions.

Considering the data on the relationship between upper limb patterns and independency levels in daily living, the highest level of independence in daily living was associated with Type Ia pattern. In contrast, the highest dependency was more related to Type IIa. In this regard, our results about the suitability of these two different patterns in terms of functional use are supported by several studies. In this context, various researchers examining the relationship between manual ability and the upper limb concluded that the maximum reach amount was directly related to the joint range of motion in the shoulder [27]. Another study reported that when there was not enough movement in the shoulder joint, a significant increase in trunk movements was observed during reaching as a compensation mechanism [28]. Similarly, the relationship between the amount of supination and pronation of the forearm and hand functions was examined in another study, and it was concluded that while the forearm rotates around its long axis, various degrees of pronation or

supination allows the orientation of movements leading to the effective use of the hand [24].

Limitations

A limitation of our study was the lack of CP population with similar topographic involvement. Although considered, creating a homogenous group would have caused a smaller sample size. Thus, further research is needed to investigate the functionality of the upper limb and hand involvement patterns in a more homogenous and larger population. However, despite this limitation, our study results are the first and precious because of its unique findings.

Conclusion

One of the primary purposes of orthopedic surgeons working with CP is to improve muscle hypertonia based on the assumption that this will increase motor functions. Now the question is whether spasticity is a problem and whether it always needs to be treated. This question can be answered based on the fact that in any case of muscle weakness in the lower extremities, the factor that enhances standing upright is skeletal muscle spasticity in favor of extension. However, the situation may be slightly different for the upper extremities, which often exhibit functionality in the open kinetic chain. Here, muscle weakness associated with spasticity should also be considered. As a result, both hypertonia and hypotonia in upper extremity muscles compromise the effectiveness of hand use in daily activities (e.g. eating, bathing, and dressing). Therefore, before deciding on BoNT-A injection or orthopedic surgery for the upper limb muscles, which are the most frequently used methods in the management of spasticity, the patient should be evaluated comprehensively in terms of rigidity and functionality. That is, when deciding on BoNT-A injection or orthopedic surgery for the upper limb muscles, it would be more appropriate to evaluate the patient' s activity or participation estimation as well as a range of motion, estimated muscle tone, and pain. Otherwise, the injection may adversely affect the level of independence in daily living by disrupting the existing upper extremity posture, which is already functional for the patient. Consequently, it was concluded that Type Ia and Type Ic patterns for the upper limb, and Simple Flex Hand pattern for the hand were the most convenient patterns in terms of functional use.

References

1. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Developmental medicine and child neurology Supplement. 2007;109:8-14.
2. Bar-On L, Molenaers G, Aertbeliën E, Van Campenhout A, Feys H, Nuttin B, et al. Spasticity and its contribution to hypertonia in cerebral palsy. BioMed Research International. 2015;2015.
3. Gage JR, Schwartz MH, Koop SE, Novacheck TF. The identification and treatment of gait problems in cerebral palsy. John Wiley & Sons; 2009.
4. Pontén E. Contracture formation in the upper limb in cerebral palsy starts early. Developmental Medicine & Child Neurology. 2019;61:117-8.
5. Sugiyama T, Taguchi T, Kawai S. Spontaneous fractures and quality of life in cerebral palsy. The Lancet. 2004;364:28.
6. Klingels K, Demeyere I, Jaspers E, De Cock P, Molenaers G, Boyd R, et al. Upper limb impairments and their impact on activity measures in children with unilateral cerebral palsy. European Journal of Paediatric Neurology. 2012;16:475-84.
7. Park ES, Sim EG, Rha D-w. Effect of upper limb deformities on gross motor and upper limb functions in children with spastic cerebral palsy. Research in Developmental Disabilities. 2011; 32: 2389-97.
8. Chaleat-Valayer E, Bard-Pondarre R, Bernard J, Roumenoff F, Lucet A, Denis A, et al. Upper limb and hand patterns in cerebral palsy: Reliability of two new classifications. European Journal of Paediatric Neurology 2017;21:754-62.
9. McConnell K, Johnston L, Kerr C. Upper limb function and deformity in cerebral palsy: a review of classification systems. Developmental Medicine & Child Neurology. 2011;53:799-805.
10. Rosenbaum P, Stewart D. The World Health Organization International Classification of Functioning, Disability, and Health: a model to guide clinical thinking, practice and research in the field of cerebral palsy. In: Seminars in Pediatric Neurology. 2004; Elsevier; p.5-10.
11. Hermann KM, Reese CS. Relationships among selected measures of impairment, functional limitation, and disability in patients with cervical spine disorders. Physical Therapy 2001;81:903-12.
12. Park E-Y. Path analysis of strength, spasticity, gross motor function, and health-related quality of life in children with spastic cerebral palsy. Health and Quality of Life Outcomes. 2018;16:70.
13. Abel MF, Damiano DL, Blanco JS, Conaway M, Miller F, Dabney K, et al. Relationships among musculoskeletal impairments and functional health status in ambulatory cerebral palsy. Journal of Pediatric Orthopaedics. 2003;23:535-41.
14. Wright FV, Rosenbaum PL, Goldsmith CH, Law M, Fehlings DL. How do changes in body functions and structures, activity, and participation relate in children with cerebral palsy? Developmental Medicine & Child Neurology. 2008;50:283-9.
15. Love S, Valentine J, Blair E, Price C, Cole J, Chauvel P. The effect of botulinum toxin type A on the functional ability of the child with spastic hemiplegia a randomized controlled trial. European Journal of Neurology 2001; 8: 50-8.
16. Hefter H, Jost WH, Reissig A, Zakine B, Bakheit AM, Wissel J. Classification of posture in poststroke upper limb spasticity: a potential decision tool for botulinum toxin A treatment? International Journal of Rehabilitation Research 2012; 35: 227-33.
17. Wasiak J, Hoare BJ, Wallen MM. Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy. Cochrane Database of Systematic Reviews. 2004;(3):CD003469. doi: 10.1002/14651858.CD003469.pub2..
18. Fehlings D, Novak I, Berweck S, Hoare B, Stott N, Russo RN. Botulinum toxin assessment, intervention and follow-up for paediatric upper limb hypertonicity: international consensus statement. European Journal of Neurology. 2010;17:38-56.
19. Heinen F, Desloovere K, Schroeder AS, Berweck S, Borggraefe I, van Campenhout A, et al. The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy. European Journal of Paediatric neurology. 2010;14:45-66.
20. Compagnone E, Maniglio J, Camposeo S, Vespino T, Losito L, De Rinaldis M, et al. Functional classifications for cerebral palsy: correlations between the gross motor function classification system (GMFCS), the manual ability classification system (MACS) and the communication function classification system (CFCS). Research in Developmental Disabilities. 2014;35:2651-7.
21. Öhrvall A-M, Krumlinde-Sundholm L, Eliasson A-C. Exploration of the relationship between the Manual Ability Classification System and hand-function measures of capacity and performance. Disability and Rehabilitation. 2013;35:913-8.
22. Organization WH. The World Health Report 2001: Mental health: new understanding, new hope. World Health Organization; 2001.
23. Cohen J. Statistical power analysis for the behavioral sciences. Routledge; 2013.
24. Kane PM, Vopat BG, Got C, Mansuripur K, Akelman E. The effect of supination and pronation on wrist range of motion. Journal of Wrist Surgery 2014;3:187-91.
25. Brumfield RH, Champoux JA. A biomechanical study of normal functional wrist motion. Clinical Orthopaedics and Related Research. 1984:23-5.
26. Arnould C, Penta M, Thonnard J-L. Hand impairments and their relationship with manual ability in children with cerebral palsy. Journal of Rehabilitation Medicine. 2008;39:708-14.
27. Hung J-W, Chang Y-J, Chou C-X, Wu W-C, Howell S, Lu W-P. Developing a Suite of Motion-Controlled Games for Upper Extremity Training in Children with Cerebral Palsy: A Proof-of-Concept Study. Games for Health Journal. 2018;7:327-34.
28. Furuya M, Ohata K, Izumi K, Matsubayashi J, Tominaga W, Mitani A. Effect of the angle of shoulder flexion on the reach trajectory of children with spastic cerebral palsy. Research in Developmental Disabilities. 2015;36:413-8.

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. 2020;4(9):803-807.
DOI: 10.28982/josam.789516

Research article
Araştırma makalesi

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

Long-term follow-up results of patients with sarcomatoid RCC: A retrospective evaluation of a single center experience

Sarkomatoid RHK tanılı hastaların uzun dönemli takip sonuçları: Tek merkez deneyiminin retrospektif değerlendirmesi

Emrah Eraslan [1], Ülkü Yalçıntaş Arslan [1]

[1] University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Health Practice and Research Center, Department of Medical Oncology, Ankara, Turkey

ORCID ID of the author(s)

EE: 0000-0003-2497-5913
ÜYA: 0000-0001-5279-0903

Corresponding author / Sorumlu yazar:
Emrah Eraslan
Address / Adres: Sağlık Bilimleri Üniversitesi, Dr. Abdurrahman Yurtaslan Ankara Onkoloji Sağlık Uygulama ve Araştırma Merkezi, Tıbbi Onkoloji Anabilim Dalı, Mehmet Akif Ersoy Mahallesi 13. Cadde No: 56, Yenimahalle, Ankara, Türkiye
E-mail: dremraheraslan@gmail.com

Ethics Committee Approval: University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Health Practice and Research Center Clinical Research Ethics Committee (No: 220-08/755, Date: 8/26/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Sağlık Bilimleri Üniversitesi Dr. Abdurrahman Yurtaslan Ankara Onkoloji Sağlık Uygulama ve Araştırma Merkezi Klinik Araştırmalar Etik Kurulu (No: 220-08/755, Tarih: 26.08.2020). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: Sarcomatoid renal cell cancer (sRCC) is an extremely rare condition, and literature on disease management is limited. There are no treatment recommendations based on high-quality data. Our aim in this study is to reveal our long-term experience with patients diagnosed with sRCC.

Methods: Patients who were followed up with a diagnosis of sRCC between January 2010 and December 2019 were retrospectively evaluated in terms of main disease characteristics, treatments, treatment responses and survival times.

Results: Twenty-five (8.0%) of 311 RCC patients had sarcomatoid differentiation. The median age of the 25 patients included in the study was 58.1 (26.3-78.0) years, and the vast majority were male (n=18, 72%). Distant organ metastasis was present in 11 (44.0%) patients at the time of diagnosis. In 10 (71.4%) out of 14 patients who underwent curative surgery, recurrence was observed with distant organ metastasis. Thirteen (61.9%) of 21 metastatic patients received tyrosine kinase inhibitor (pazopanib or sunitinib) in second-line treatment. The progression-free survival for the second line treatment of these 13 patients was 6.1 months (95% CI: 3.8-8.4). Long-term disease control was achieved in one of the two patients who received nivolumab treatment. Cytoreductive nephrectomy was performed in seven (63.6%) of the 11 patients who were in metastatic stage at the time of diagnosis. Pulmonary metastasectomy was performed in two patients with lung metastasis. One of these two patients was still followed up without recurrence at the 112th month after metastasectomy. Overall survival was 10.8 months (85% CI: 8.9-12.6) for 21 patients in the metastatic stage.

Conclusion: sRCC is a rare disease with a poor prognosis. Systemic treatment efficacy is low with frequent distant metastases. Tyrosine kinase inhibitors are prominent among current treatment methods. Immune checkpoint inhibitors, one of the new generation treatment options, is promising in terms of treatment success. The addition of cytoreductive nephrectomy and metastasectomy to the treatment process may provide additional benefits.

Keywords: RCC, Sarcomatoid differentiation, sRCC, TKI, Nivolumab, Cytoreductive nephrectomy

Öz

Amaç: Sarkomatoid renal hücreli kanser (sRHK) oldukça nadir bir durum olup, hastalık yönetimi ile ilgili literatür verisi kısıtlıdır. Yüksek kalitede veriye dayanan tedavi önerileri yoktur. Bu çalışmadaki amacımız, sRHK tanılı hastalarımızdaki uzun süreli tecrübemizi ortaya koymaktır.

Yöntemler: sRHK tanısıyla Ocak 2010-Aralık 2019 arasında takip edilen hastalar, genel hastalık özellikleri, verilen tedaviler, tedavi yanıtları ve sağ kalım süreleri açısından retrospektif olarak değerlendirildi.

Bulgular: Üç yüz on bir RCC hastasının 25'inde (%8,0) sarkomatoid farklılaşma gözlendi. Çalışmaya dahil edilen 25 hastanın ortanca yaşları 58,1 (26,3-78,0)'di ve büyük çoğunluğu erkekti (n=18, 72%). Tanı anında 11 (%44,0) hastada uzak organ metastazı vardı. Küratif cerrahi yapılan 14 hastanın 10'unda (%71,4) uzak organ metastazı ile nüks izlendi. Metastatik 21 hastanın 13 (%61,9)'ü ikinci basamak tedavide tirozin kinaz inhibitörü (pazopanib veya sunitinib) aldı. Bu 13 hastanın ikinci basamak tedavisi için progresyonsuz sağ kalım süresi 6,1 aydı (%95 CI: 3,8-8,4). Nivolumab tedavisi alan 2 hastadan birinde uzun süreli hastalık kontrolü sağlandı. Tanı anında metastatik evrede olan 11 hastanın 7 (%63,6)'sinde sitoredüktif cerrahi uygulandı. Pulmoner metastazektomi yapılan 2 hastadan biri metastazektomi sonrası 112.ayda hala nükssüz izlenmekteydi. Metastatik evredeki toplam 21 hasta için genel sağ kalım süresi 10,8 aydı (%85 CI: 8,9-12,6).

Sonuç: Sarkomatoid RCC oldukça nadir görülen ve kötü prognoza sahip bir hastalıktır. Hastaların çoğunda uzak organ metastazı gözlenmekle birlikte sistemik tedavi etkinliği düşüktür. Güncel tedavi yöntemleri içinde tirozin kinaz inhibitörleri ön plandadır. Yeni nesil tedavi seçeneklerinden olan immun kontol noktası inhibitörleri tedavi başarısı açısından ümit vaat etmektedir. Sitoredüktif nefrektomi ve metastazektominin tedaviye eklenmesi ek faydalar sağlayabilir.

Anahtar kelimeler: RHK, Sarkomatoid diferansiyasyon, sRHK, TKİ, Nivolumab, Sitoredüktif nefrektomi

How to cite/Atıf için: Eraslan E, Arslan ÜY. Long-term follow-up results of patients with sarcomatoid RCC: A retrospective evaluation of a single center experience. J Surg Med. 2020;4(9):803-807.

Introduction

Sarcomatoid renal cell cancer (sRCC) is defined as the tumor exhibiting pronounced cytological atypia and containing malignant spindle cells resembling sarcoma [1]. Sarcomatoid differentiation may accompany many subtypes of RCC. It refers to a high-grade transformation rather than a different histological entity. In 2012, it was redefined as dedifferentiation characterized by the loss of epithelial features [2]. Although it varies according to histological subtypes, it is seen in approximately 5-8% in all RCCs [3,4]. However, when metastatic cases are considered, sarcomatoid differentiation can be seen in nearly 20% [5]. sRCC has a very aggressive clinical course, and stage IV cases are frequently encountered [3, 4]. In a study involving patients diagnosed with metastatic RCC, the overall survival (OS) was 22.2 months in patients without sarcomatoid differentiation. In contrast, it was 10.0 months in patients with sRCC [6]. Metastatic RCC treatment has improved significantly in recent years with targeted treatment options, but the effectiveness of these drugs against sRCC is limited [7]. Objective tumor response was detected with doxorubicin-gemcitabine combination chemotherapy to treat metastatic sRCC [8]. However, the results of phase II studies evaluating the effectiveness of chemotherapy on survival in the treatment of metastatic sRCC are inconsistent [9]. Since it is rare, it could not find enough place in extensive prospective studies in clinical course, treatment, and survival evaluations. Therefore, although the clinical features are different from conventional RCC, in international treatment guidelines, there are not enough additional recommendations for sRCC treatment [10,11]. Our current study aimed to share our experiences in sarcomatoid RCC, where clinical data are usually based on small or retrospective studies.

Materials and methods

The data of patients treated and followed up with the diagnosis of RCC between January 2010 and December 2019 in the medical oncology clinic of the University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital were retrospectively evaluated. Patients diagnosed with RCC with sarcomatoid differentiation were included in the study. Patients with insufficient data in terms of histopathological evaluation and medical records were excluded from the study. Patients who had a baseline visit but had no follow-up visits were excluded. Patients' demographic characteristics, stages at the time of diagnosis, surgical modalities, recurrence, metastatic sites, systemic treatments, systemic treatment response rates, progression-free survival (PFS), and OS times were evaluated, which were compared with the literature data. Local ethics committee approval was obtained, and the study was conducted in accordance with the principles of the Helsinki Declaration.

Statistical analysis

Descriptive statistics were used to show the distribution of the main characteristics of the population. PFS was defined as the time interval between the initiation of systemic treatment and progression. OS was defined as the time interval between histological diagnosis and time of death or last follow-up. Survival rates were estimated with the use of the Kaplan–Meier method. A comparison was made using the log-rank test to evaluate the difference in survival between groups. Analyses were performed using IBM SPSS Statistics version 24.0 software (SPSS Inc., Chicago, IL, USA).

Results

Sarcomatoid differentiation was observed in 25 (8.0%) of 311 RCC patients. The main patient and tumor characteristics in the study population of 25 patients with a median age of 58.1 (26.3-78.0) years and mostly males (n=18, 72%) are displayed in Table 1. The median follow-up period of the patients in the study was 13.7 (0.7-138.5) months.

Among the 25 patients included in the study, 14 (56%) patients who did not have distant metastases underwent curative surgery at the time of diagnosis. Cytoreductive nephrectomy was performed in 7 (63.6%) of 11 patients who were metastatic at the time of diagnosis. There were a total of 21 metastatic patients. Two of metastatic patients (9.5%) had lung metastasectomy. One of the patients was being followed up in remission at the 112th month after metastasectomy. While 3 (14.3%) of 21 metastatic patients could not receive any systemic treatment, 18 (85.7%) patients received various systemic therapies. Findings related to treatments are displayed in table 2.

Table 1: Patient and tumor characteristics (n=25)

Characteristic	Number	%
Age-Median (range)	58.1 (26.3-78.0)	
Gender		
Male	18	72.0
Female	7	28.0
Tumor Grade		
Grade II	8	32.0
Grade III	9	36.0
Unknown	8	32.0
Stage at Diagnosis		
Stage I	3	12.0
Stage III	9	36.0
Stage IV	13	52.0
Distant Metastasis at Diagnosis		
Yes	11	44.0
No	14	56.0
Recurrence *	10	71.4
All Metastatic Patients	21	84.0
Metastatic Sites **		
Lung	14	66.7
Bone	13	61.9
Lymph Node	6	28.6
Liver	4	19.0
Brain	1	4.8

* Calculated by proportioning to patients without distant metastases at diagnosis, ** Calculated by proportioning to all metastatic patients

Table 2: Treatment-related characteristics (n=25)

Characteristics	Number	%
Curative Surgery	14	56.0
Cytoreductive Nephrectomy *	7	63.6
Metastasectomy**	2	9.5
Systemic Treatments **		
First Line	18	85.7
Interferon	14	66.7
Pazopanib	1	4.8
Chemotherapy	3	14.3
Second Line	13	61.9
Pazopanib	10	47.6
Sunitinib	3	14.3
Third Line	4	19.1
Axitinib	2	9.5
Everolimus	1	4.8
Nivolumab	1	4.8
Fourth Line	1	4.8
Nivolumab	1	4.8
No systemic treatment	3	14.3

* Calculated by proportioning to patients with distant metastases at diagnosis, ** Calculated by proportioning to all metastatic patients

Three patients in the study received chemotherapy (1 patient gemcitabine, one patient gemcitabine-doxorubicin, one patient gemcitabine-docetaxel) as the first-line therapy. One patient who received chemotherapy developed SD after three cycles and PD after six cycles. At the same time, PD was observed after three cycles of chemotherapy in the other two patients. Three patients who received chemotherapy did not receive any treatment afterwards. Fourteen patients had received interferon-alpha (IFN) as first-line therapy. In 12 (85.7%) of 14 patients who received interferon, treatment could not be continued due to intolerance. The median time of IFN therapy in 12 patients with intolerance was 6 (1-38) days. Partial remission (PR) was achieved in 1 (50%) of the 2 patients who could tolerate IFN, and the duration of PFS with IFN for this patient was 13.0 months. The other 1 (50%) patient also developed PD at the first control in the 3rd month. Response rates to treatment agents are shown in Table 3.

The median OS was 19.7 months (95% CI: 9.9-29.6) when the entire patient group was considered. The median OS for patients at the metastatic stage was 10.8 months (95% CI: 8.9-12.6). The survival plot is displayed in Figure 1. Median OS was 10.8 months (95% CI: 9.8-11.7) for those who underwent cytoreductive nephrectomy and 8.7 months (95% CI: 0.0-18.0) for those who did not (P=0.493).

The median PFS was 6.1 months (95% CI: 3.8-8.4) for those who received tyrosine kinase inhibitor (TKI) (pazopanib or sunitinib) as second-line therapy, and the survival plot is displayed in Figure 2.

Table 3: Treatment response rates

Treatment Agent (n)	PR, n (%)	SD, n (%)	PD, n (%)
Chemotherapy (3)		1 (33.3%)	2 (66.7%)
Interferon (2)	1 (50.0%)		1 (50.0%)
Sunitinib (3)		2 (66.7%)	1 (33.3%)
Pazopanib (11)	2 (18.2%)	5 (45.4%)	4 (36.4%)
Axitinib (2)	1 (50.0%)		1 (50.0%)
Everolimus (1)			1 (100.0%)
Nivolumab (2)		1 (50.0%)	1 (50.0%)

PR: Partial Remission, SD: Stable Disease, PD: Progressive Disease

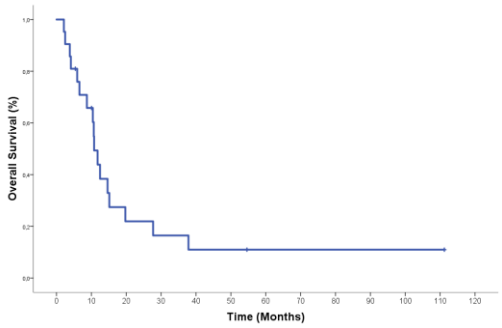


Figure 1: Overall survival for patients in the metastatic stage

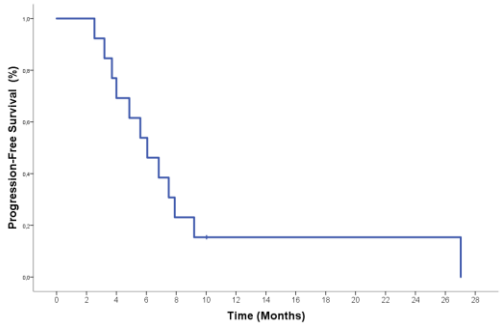


Figure 2: Progression-free survival for patients receiving tyrosine kinase inhibitors as second-line therapy

Discussion

In our current study, we shared our clinical experience in patients diagnosed with RCC with sarcomatoid differentiation. Sarcomatoid differentiation is not a common condition in RCC and is observed around 5-8% [3, 4]. In our study, we saw that 8% of the patients with RCC who were followed up in our clinic over 10 years had sarcomatoid differentiation. Albeit rare, it represents a major clinical challenge. It has been demonstrated to be an independent adverse prognostic factor for RCC [12, 13]. In a retrospective analysis involving sRCC patients who underwent curative surgery, 77% of distant metastases developed after approximately 26 months of follow-up [14]. In our study, the recurrence rate was 71.4% in patients who underwent curative surgery in accordance with the literature.

Systemic chemotherapy was considered one of the options that could provide efficacy in treating metastatic sRCC. Doxorubicin-gemcitabine combination therapy appears to be a relatively prominent option in this area. In the ECOG 8802 study, 16% of 39 patients who received doxorubicin-gemcitabine combination chemotherapy with a diagnosis of sRCC had an objective response, and 26% had stable disease. [8]. Nanus et al. reported CR in 2 and PR in 5 of 18 patients who received gemcitabine-doxorubicin [15]. Few patients in our study received gemcitabine-based chemotherapy as first-line therapy. However, all of them progressed, and none received second-line treatment due to deterioration in their performance status. Our study's poor chemotherapy outcomes and the inconsistent literature data [9] caused us to think negatively about chemotherapy.

In the first-line treatment of metastatic RCC, the primary current treatment options for clear cell histological subtype are anti-VEGF (vascular endothelial growth factor) TKI (sunitinib, pazopanib, tivozanib), anti-c-Met TKI (cabozantinib), anti-VEGF TKI and immune checkpoint inhibitor combination (axitinib-pembrolizumab), immune checkpoint inhibitor combination (nivolumab-ipilimumab) and anti-VEGF antibody and cytokine combination (bevacizumab-IFN) [10, 11]. There is no high-evidence recommendation for a different treatment option for patients with sarcomatoid differentiation in these guidelines. Although it is not recommended in international treatment guidelines according to Turkey's health insurance system's rules, to apply anti-VEGF TKI therapy, IFN must be used in first-line treatment. Therefore, most of our patients had received IFN treatment in first-line treatment. However, treatment could not be continued due to intolerance in most patients. One of the two patients who could continue with IFN therapy had an objective treatment response, and the other patient progressed. Treatment guideline recommendations and our findings led us to think negatively about the use of IFN.

There are robust data on anti-VEGF TKI, which forms the basis of metastatic RCC treatment. In a phase III study in patients with cytokine pretreated or treatment-naive metastatic RCC, a PFS of 9.2 months was achieved with pazopanib, significantly better than placebo [16]. In the long-term follow-up analysis, it was observed that OS was 22.9 months for these patients [17]. In the phase III study in which sunitinib's effectiveness was evaluated compared to IFN, PFS was significantly better in favor of sunitinib at five months versus 11 months [18]. Although sunitinib and pazopanib's significant

efficacy was demonstrated in these studies, sRCC is not included in subgroup analyses. In a retrospective analysis involving 230 sRCC patients, PFS (4.5 months vs. 7.8 months) and OS (10.4 months vs. 22.5 months) were significantly worse for sRCC compared to non-sRCC histological type [13]. Similar to this study, in our research, PFS was 6.1 months for patients who received pazopanib or sunitinib, and the OS was 10.8 months for patients in the metastatic stage. Although disease control (PR or SD) was achieved in approximately two-thirds of the patients with pazopanib and sunitinib in our study, survival times were significantly worse than patients' literature data without sarcomatoid differentiation. Our study results and literature data suggest that pazopanib and sunitinib can be beneficial in treating sRCC, but this may be limited.

In a randomized controlled trial, the non-inferiority of sunitinib treatment to sunitinib and cytoreductive nephrectomy was demonstrated [19]. However, the presence of an intense poor-risk group in this study makes it difficult to generalize the study results. Therefore, cytoreductive nephrectomy may be an option for patients with sRCC for whom systemic treatments are insufficient in terms of effectiveness. In a retrospective study evaluating cytoreductive nephrectomies performed for three decades, it was observed that the contribution of cytoreductive surgery to OS in patients with sRCC improved with chronological progress, but did not reach statistical significance. The same study could not clearly explain whether the improvement in survival contribution is due to cytoreductive nephrectomy or the advances in systemic treatments over time [20]. In our study, the OS of seven patients who underwent cytoreductive nephrectomy was approximately two months better, but it was not statistically significant. The low number of patients who underwent nephrectomy prevents us from making a definite interpretation. Another important point in terms of surgical treatments is metastasectomy. It has been stated that complete pulmonary metastasectomy may be beneficial in RCC patients with pulmonary metastasis [21]. In a study involving three patients with sRCC who underwent pulmonary metastasectomy, one patient's disease-free survival was seven months. It was stated that metastasectomy should be a component of the treatment of RCC patients with sarcomatoid differentiation [22]. One patient in our study who underwent pulmonary metastasectomy had no recurrence at the 112th month. Therefore, it should be kept in mind in all patients who are eligible for metastasectomy in the management of sRCC.

It has been determined that sRCC may express PD-1 / PDL-1 at a higher percentage compared to RCC without sarcomatoid differentiation [23]. It was stated in an earlier study that high PDL-1 expression is an independent factor associated with poor prognosis for RCC [24]. High PDL-1 expression may explain the poor prognosis of sRCC and indicate that immune checkpoint inhibitors will benefit in treating sRCC. A 53% ORR for sRCC was observed in a recent phase II study with atezolizumab-bevacizumab combination therapy [25]. Similarly, in the CheckMate 214 study, an exploratory analysis of sRCC cohort, an ORR of 56.7% was detected using a combination of ipilimumab-nivolumab [26]. Current immunotherapy options show promise in the treatment of sRCC. In our study, only two patients were able to receive nivolumab. Although one of them received treatment in the fourth line, stable response and survival of around 20 months were obtained. This time was longer than the total time for this patient on the 3-line treatment before nivolumab.

Limitations

The study's main limitations are its retrospective design and the small number of patients, although it was conducted in a rare patient group. Also, the percentage of sarcomatoid differentiation could not be obtained in pathological evaluation. Another limitation is the requirement to have used IFN before anti-VEGF TKI.

Conclusion

RCC with sarcomatoid differentiation shows a poor prognosis characterized by a high rate of recurrence and short survival. Current treatment options have limited efficacy in the treatment of sRCC. New generation immunotherapeutic drugs may contribute positively to survival. The addition of cytoreductive nephrectomy and metastasectomy to the treatment process may provide additional benefits. Prospective randomized studies are needed to optimize systemic therapies and surgical interventions in the management of sRCC.

References

1. Farrow GM, Harrison Jr EG, Utz DC. Sarcomas and sarcomatoid and mixed malignant tumors of the kidney in adults—part III. Cancer. 1968;22(3):556-63.
2. Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. The American journal of surgical pathology. 2013;37(10):1490-504.
3. de Peralta-Venturina M, Moch H, Amin M, Tamboli P, Hailemariam S, Mihatsch M, et al. Sarcomatoid differentiation in renal cell carcinoma: a study of 101 cases. The American journal of surgical pathology. 2001;25(3):275-84.
4. Cheville JC, Lohse CM, Zincke H, Weaver AL, Leibovich BC, Frank I, et al. Sarcomatoid renal cell carcinoma: an examination of underlying histologic subtype and an analysis of associations with patient outcome. The American journal of surgical pathology. 2004;28(4):435-41.
5. Shuch B, Said J, LaRochelle JC, Zhou Y, Li G, Klatte T, et al. Histologic evaluation of metastases in renal cell carcinoma with sarcomatoid transformation and its implications for systemic therapy. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2010;116(3):616-24.
6. Kwak C, Park YH, Jeong CW, Jeong H, Lee SE, Moon KC, et al. Sarcomatoid differentiation as a prognostic factor for immunotherapy in metastatic renal cell carcinoma. Journal of surgical oncology. 2007;95(4):317-23.
7. Keskin SK, Msaouel P, Hess KR, Yu K-J, Matin SF, Sircar K, et al. Outcomes of patients with renal cell carcinoma and sarcomatoid dedifferentiation treated with nephrectomy and systemic therapies: comparison between the cytokine and targeted therapy eras. The Journal of urology. 2017;198(3):530-7.
8. Haas NB, Lin X, Manola J, Pins M, Liu G, McDermott D, et al. A phase II trial of doxorubicin and gemcitabine in renal cell carcinoma with sarcomatoid features: ECOG 8802. Medical Oncology. 2012;29(2):761-7.
9. Lebacle C, Pooli A, Bessede T, Irani J, Pantuck AJ, Drakaki A. Epidemiology, biology and treatment of sarcomatoid RCC: current state of the art. World journal of urology. 2019;37(1):115-23.
10. National Comprehensive Cancer Network: NCCN Practice Guidelines in Oncology.Kidney Cancer. Version 1.2021.
11. Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2016;27(suppl_5):v58-v68.
12. Mian BM, Bhadkamkar N, Slaton JW, Pisters PW, Daliani D, Swanson DA, et al. Prognostic factors and survival of patients with sarcomatoid renal cell carcinoma. The Journal of urology. 2002;167(1):65-70.
13. Kyriakopoulos CE, Chittoria N, Choueiri TK, Kroeger N, Lee J-L, Srinivas S, et al. Outcome of patients with metastatic sarcomatoid renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. Clinical genitourinary cancer. 2015;13(2):e79-e85.
14. Merrill MM, Wood CG, Tannir NM, Slack RS, Babaian KN, Jonasch E, et al., editors. Clinically nonmetastatic renal cell carcinoma with sarcomatoid dedifferentiation: Natural history and outcomes after surgical resection with curative intent. Urologic Oncology: Seminars and Original Investigations; 2015: Elsevier.
15. Nanus DM, Garino A, Milowsky MI, Larkin M, Dutcher JP. Active chemotherapy for sarcomatoid and rapidly progressing renal cell carcinoma. Cancer. 2004;101(7):1545-51.
16. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Wagstaff J, Salman P, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. Journal of clinical oncology. 2010.
17. Sternberg CN, Hawkins RE, Wagstaff J, Salman P, Mardiak J, Barrios CH, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. European journal of cancer. 2013;49(6):1287-96.
18. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. New England Journal of Medicine. 2007;356(2):115-24.
19. Méjean A, Ravaud A, Thezenas S, Colas S, Beauval J-B, Bensalah K, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. New England Journal of Medicine. 2018;379(5):417-27.
20. Silagy AW, Mano R, Blum KA, DiNatale RG, Marcon J, Tickoo SK, et al. The Role of Cytoreductive Nephrectomy for Sarcomatoid Renal Cell Carcinoma: A 29-Year Institutional Experience. Urology. 2020;136:169-75.

21. Hofmann H-S, Neef H, Krohe K, Andreev P, Silber R-E. Prognostic factors and survival after pulmonary resection of metastatic renal cell carcinoma. European urology. 2005;48(1):77-82.
22. Ueno T, Yamashita M, Sawada S, Sugimoto R, Nishijima N, Sugawara Y, et al. Pulmonary metastasectomy from renal cell carcinoma including 3 cases with sarcomatoid component. General thoracic and cardiovascular surgery. 2016;64(3):149-52.
23. Joseph RW, Millis SZ, Carballido EM, Bryant D, Gatalica Z, Reddy S, et al. PD-1 and PD-L1 expression in renal cell carcinoma with sarcomatoid differentiation. Cancer immunology research. 2015;3(12):1303-7.
24. Thompson RH, Kuntz SM, Leibovich BC, Dong H, Lohse CM, Webster WS, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer research. 2006;66(7):3381-5.
25. McKay RR, McGregor BA, Gray K, Steinharter JA, Walsh MK, Braun DA, et al. Results of a phase II study of atezolizumab and bevacizumab in non-clear cell renal cell carcinoma (nccRCC) and clear cell renal cell carcinoma with sarcomatoid differentiation (sccRCC). Journal of Clinical Oncology. 2019;37(7_suppl):548-8.
26. McDermott DF, Choueiri TK, Motzer RJ, Aren OR, George S, Powles T, et al. CheckMate 214 post-hoc analyses of nivolumab plus ipilimumab or sunitinib in IMDC intermediate/poor-risk patients with previously untreated advanced renal cell carcinoma with sarcomatoid features. Journal of Clinical Oncology. 2019;37(15_suppl):4513.

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. 2020;4(9):808-811.
DOI: 10.28982/josam.710076

Research article
Araştırma makalesi

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

A public health concern: Chronic low back pain and the relationship between pain, quality of life, depression, anxiety, and sleep quality

Bir halk sağlığı sorunu: Kronik bel ağrısı, ağrı, depresyon, anksiyete ve uyku bozukluğu ilişkisi

Tariyel Mammadov [1], Hüma Bölük Şenlikci [1], Şehri Ayaş [1]

[1] Başkent University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Ankara, Turkey

ORCID ID of the author(s)

TM: 0000-0001-9624-5827
HBŞ: 0000-0001-6771-3265
ŞA: 0000-0002-5078-6529

Corresponding author / Sorumlu yazar:
Hüma Bölük Şenlikci
Address / Adres: Başkent Üniversitesi Tıp Fakültesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, Ankara, Türkiye
E-mail: humaboluk@gmail.com

Ethics Committee Approval: Approval for the study was granted by the Ethics Committee of Başkent University School of Medicine (Approved on 06.12.2017, decision number 17/99). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma için onay Başkent Üniversitesi Tıp Fakültesi Etik Kurulu tarafından verildi (06.12.2017 tarihinde onaylandı, karar no: 17/99). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: Chronic low back pain (CLBP) is a common condition of the musculoskeletal system and a public health concern. CLBP patients suffer from conditions such as muscle weakness and numbness, resulting in diminished quality of life (QoL), poor functioning, psychological disorders and sleep disorders related to disabling pain. The aim of the current study was to reveal relationship between CLBP and patients' health related QoL, anxiety, depression, and sleep disturbances.

Methods: Seventy-three patients with CLBP and 73 healthy controls participated in this questionnaire-based cross-sectional study. The Short form McGill Pain Questionnaire, Roland-Morris disability, Short form-36 (SF-36), Beck Depression (BDI) and anxiety inventory (BAI) and the Pittsburgh Sleep Quality Index (PSQI) were used in the study group, and SF-36, BDI, BAI and PSQI were used in the control group. The relationships between QoL, depression, anxiety, and sleep disorders were examined in the two groups.

Results: Two groups did not differ in terms of demographic characteristics ($P>0.05$). In the sub-scales of SF-36, except vitality and mental health, a significant difference was detected between the study and control groups ($P<0.001$). The depression, anxiety and PSQI scores did not differ between the two groups ($P>0.05$).

Conclusion: CLBP affects QoL negatively. This should be considered when managing CLBP.

Keywords: Chronic low back pain, sleep disorders, Quality of life

Öz

Amaç: Kronik bel ağrısı (KBA) sık görülen ve bir halk sağlığı sorunu olan kas iskelet sistemi bozukluğudur. KBA hastaları kuvvetsizlik, uyuşma, yaşam kalitesinde azalma, fonksiyonellikte azalma, depresyon ve anksiyete gibi psikolojik bozukluklar ve uyku bozukluğuna neden olan ağrı gibi semptomlardan şikayetçidir. Bu çalışmanın amacı, KBA ile hastalarda yaşam kalitesi, anksiyete, depresyon ve uyku bozuklukları arasındaki ilişkiyi ortaya koymaktır.

Yöntemler: Yetmiş-üç KBA olan hasta ve 73 sağlıklı kontrol bu anket bazlı kesitsel çalışmaya dahil edildi. Çalışma grubunda Kısa form McGill ağrı anketi, Roland-Morris özürlülük anketi, Kısa Form-36 S(F-36), Beck depresyon ve anksiyete ölçekleri ve Pittsburgh uyku kalitesi indeksi, SF-36, Beck depresyon ve anksiyete ölçekleri ve Pittsburgh uyku kalitesi indeksi ise kontrol grubunda uygulanmıştır. Yaşam kalitesi, depresyon, anksiyete ve uyku bozuklukları ilişkisi her iki grupta araştırılmıştır.

Bulgular: İki grup demografik özellikler açısından farklılık göstermemiştir ($P<0,05$). SF-36 altgruplarında canlılık ve mental sağlık dışındaki alt gruplarda anlamlı farklılık saptanmıştır ($P<0,001$). Depresyon, anksiyete ve Pittsburgh uyku kalitesi skorları iki grup arasında herhangi bir farklılık gösterilmemiştir ($P>0,05$).

Sonuç: KBA yaşam kalitesini negatif olarak etkilemektedir. KBA hastalara yaklaşımda gözönünde bulundurulması gereken bir durumdur.

Anahtar kelimeler: Kronik bel ağrısı, Uyku bozuklukları, Yaşam kalitesi

How to cite/Atıf için: Mammadov T, Şenlikci HB, Ayaş Ş. A public health concern: Chronic low back pain and the relationship between pain, quality of life, depression, anxiety, and sleep quality. J Surg Med. 2020;4(9):808-811.

Introduction

Chronic low back pain (CLBP) is an important and common public health condition that leads to impairment, depression, and labor loss. Management of CLBP is also complicated and difficult. In the adult population, low back pain prevalence has been reported as 28.8% [1]. Sleep disorders such as irregular sleep and insomnia are not uncommon symptoms in CLBP patients. Uchmanowicz et al. [2] reported a relationship between CLBP and sleep disorders, with insomnia seen in 83% and daytime sleepiness in 29% of individuals with CLBP. Additionally, sleep disorders may be accompanied by anxiety and depressive symptoms in individuals with CLBP. Increased pain scores and decreased health related QoL scores have been determined in these patients with depressive symptoms [3]. CLBP is thought to decrease QoL and increase disability. In a study of 200 subjects, Panahi et al. [4] determined CLBP in 60.3%, and 80% of those with CLBP experienced disability according to the Roland-Morris disability questionnaire. The results of that study revealed that CLBP affects the physical dimension of health related QoL, along with exerting psychosocial effects. In the study of Uçurum et al. [5], CLBP was reported to affect QoL negatively due to pain and functional outcome. As shown in that study, CLBP is a psychosocial health problem that diminishes QoL. Anxiety in CLBP patients exacerbates depressive symptoms and sleep disorders, which leads to a deterioration in health-related life quality, social life, and labor loss.

In the light of this information, we aimed to reveal relationship between CLBP and QoL, depressive and anxiety symptoms and sleep disturbances in Turkish population by taking a different approach to these patients.

Materials and methods

Subjects

This cross-sectional study included 73 healthy controls and 73 CLBP patients with complaints for at least 6 months, who were referred to Başkent University Physical Medicine and Rehabilitation Outpatients Clinic. Patients who met the criteria between January-June 2018 aged between 18-65 years were included in the study. No gender difference was taken into consideration. Exclusion criteria were determined as low back pain with inflammatory characteristics, a history of lumbar stabilization surgery, infection, pregnancy, or a diagnosis of depression, anxiety, or psychosis. Approval for the study was granted by the Ethics Committee of Başkent University School of Medicine with the project number of KA17/319 prior to commencement (Approved on 06.12.2017, decision number 17/99). All participants signed informed consents.

Evaluation

The demographic and clinical characteristics were obtained in a face-to-face interview and recorded. The history of the chronic low back pain including the time of onset, characteristics (mechanical or inflammatory), dissemination, and factors that increased the pain were examined. A detailed motor and sensory examination were performed to all the patients by the same physician. The spinal mobility examination was performed with finger-to-floor distance measurement and the modified Schober test. Following detailed examination, the same physician applied all the questionnaires to the participants.

Short form of McGill Pain Questionnaire: Pain was evaluated using the Short form of the McGill Pain Questionnaire. The first part includes 15 descriptors, 11 sensory and 4 affective. Second part consists of visual analog scale (VAS) and the last part contains evaluative words that subjectively report the severity of the pain they experienced [6].

Roland Morris Disability Index: This index evaluates disability due to low back pain. It consists of 24 items related to physical activity, rest/sleep, psychosocial outcomes, home management, feeding and pain frequency. Higher scores indicate increased disability [7].

Beck Depression Inventory: The Beck Depression Inventory (BDI) was utilized to assess depressive symptoms and anxiety. The BDI contains 21 items with higher scores indicating increased severity of depressive symptoms [8].

Beck Anxiety Inventory: The Beck Anxiety Inventory (BAI) is a subjective and self-reporting scale that is used to assess the anxiety. The BAI contains 21 items with higher scores indicating severe anxiety symptoms [9].

Pittsburgh Sleep Quality Index (PSQI): This index is used to assess sleep quality, sleep latency, and sleep duration. Symptoms experienced in the previous 4 weeks are questioned with higher scores indicating poor sleep quality [10].

Short Form-36 (SF-36): The Short form 36 (SF-36) is a scale that consists of questions containing items that measure the QoL. It contains 36 items in 2 parts; mental and physical. Points range from 0-100, with higher points indicating a better health related QoL [11].

Statistical analysis

IBM SPSS statistics v20 software program was used for statistical analyses. Power analysis was performed, and the sample size was determined as a minimum of 73 participants per group. Kolmogorov-Smirnov test was used to determine the normality of the distribution of the continuous variables. Normally distributed quantitative data were expressed as mean (standard deviation) (SD) and non-normally distributed quantitative data were shown as median (min-max) values. Categorical variables were stated as number and percentage. The Student's t-test was used to determine correlations between normally distributed data and the Mann Whitney U-test was applied to non-normally distributed data. Nominal variables were compared using the Chi-square and Fischer's Exact test. Pearson/Spearman correlation analyses were used on quantitative data. The level of statistical significance was set at $P<0.05$.

Results

No statistically significant difference was determined between the study and the control groups in terms of age, gender, or male/female ratio ($P>0.05$ for all) (Table 1).

The study and control groups showed a statistically difference with respect to the sub-scales of SF-36, including physical functioning, physical role, bodily pain, general health, social functioning and emotional role ($P<0.001$), However, no significant difference was determined regarding the sub-scales of vitality and mental health ($P=0.218$, $P=0.444$) (Table 2).

In the comparison of the BDI, BAI, and PSQI scores, there were no significant differences between the two groups (P>0.05).

With exception of the mental health sub-scale, a negative correlation was determined between the other sub-scales of SF-36 and the short form McGill pain scores. The mental health sub-scale scores did not show any correlation with the short form McGill pain scores (r=-0.195, P>0.05).

A negative correlation was determined between the Roland-Morris scores and the SF-36 total and sub-scale scores of physical functioning, role physical, emotional role, vitality, social functioning, bodily pain and general health (r=-0.646, P<0.001; r=-0.392, P<0.01; r=0-.310, P<0.01; r=-0.313, P<0.01; r=-0.474, P<0.001; r=-0.568, P<0.001; r=-0.233, P<0.05, respectively). No significant correlation was determined with respect to mental health scores (r=-0.292, P>0.05).

A positive correlation was determined between the PSQI scores and BDI, BAI, Short form McGill pain, and the Roland Morris scores (r=0.556, P<0.001; r=0.477, P<0.001; r=0387, P<0.01; r=0.300, P<0.05, respectively). The Short form McGill scores were correlated with the BDI, BAI and the Roland-Morris scores positively (r=0.392, P<0.01; r=0.336, P<0.01; r=0.369 P<0.01, respectively). The Roland-Morris scores showed a positive correlation with the BDI and BAI scores (r=0.322, P<0.01; r=0.195, P<0.01, respectively). Finally, a positive correlation was determined between the BDI and BAI scores (r=0.679, P<0.001).

Table 1: Demographic characteristics of the subjects

	Study group	Control group	*P*-value
Age, mean (SD)	43.00 (9.90)	43.22 (11.87)	0.904
Gender, n(%)			
Female	45 (61.6)	45 (61.6)	1.000
Male	28 (38.4)	28 (38.4)	

Table 2: Comparison of scores SF-36 subgroups in study and control groups

SF-36	Study group		Control group		Test	*P*-value
	Mean (SD)	Median (Min-max)	Mean (SD)	Median (Min-max)	Statistics	
Physical Functioning	55.00(21.24)	50 (5-100)	77.46(20.92)	80 (20-100)	U=1189.5	<0.001
Role physical	29.79(37.65)	0 (0-100)	67.82(35.47)	75 (0-100)	U=1323.0	<0.001
Role emotional	49.77(42.35)	33.3(0-100)	79.91(30.80)	100 (0-100)	U=1624.0	<0.001
Vitality	44.73(16.49)	45 (5-80)	47.81(21.92)	50 (0-100)	U=2351.0	0.218
Mental Health	64.66(14.77)	68 (28-92)	66.30(15.52)	72 (8-96)	U=2469.5	0.444
Social Functioning	54.11(26.36)	50 (0-100)	62.50(20.62)	62.5(0-100)	U=2084.5	0.021
Bodily pain	45.89(22.05)	45 (0-90)	57.10(24.26)	55 (0-100)	U=1963.5	0.006
General Health	52.88(18.56)	55 (10-85)	66.44(17.96)	70 (10-100)	U=1568.5	<0.001
Beck Depression Inventory	10.86(8.54)	10 (0-36)	10.94(8.75)	9 (0-34)	U=2653.0	0.964
Beck Anxiety Inventory	13.94(9.99)	11 (0-40)	11.05(9.39)	8 (0-32)	U=2190.5	0.063
Pittsburgh sleep Quality Index	6.52(3.49)	6 (0-16)	5.81(2.96)	5 (2-16)	U=2352.0	0.218

Discussion

CLBP is the most common musculoskeletal pain and a serious public health condition that can lead to workforce loss, disability, sleep disorders, depression, and anxiety [12]. Management of this condition may be more difficult than expected. The goal of the current study was to reveal the correlation between depression, pain, disability and QoL in patients suffering from CLBP.

No significant differences were detected between the mean age of the two groups (43.00 (9.90) years vs. 43.22 (11.87) years). It has been previously shown that low back pain is a musculoskeletal disorder, mostly affecting middle-aged individuals [2,6,14,15]. Currently, findings were coherent with the literature.

Chronic low back pain is a widespread, public (65%) problem which has a negative effect on both physical and mental functioning [12,13]. The SF-36 is utilized to reveal QoL in 8 sub-scales [11]. Similarly, Mutubuki et al. [12] reported poor QoL in patients with CLBP. Another study that used a different questionnaire, reported poor QoL among CLBP subjects [14]. According to the findings of current study, no significant correlation was detected in the comparison of the two groups in terms of the vitality and mental health sub-scales of the SF-36. The other sub-scale scores (social functioning, general health, and pain) were worse in the study group. These findings were similar to the findings obtained in the comparison of the depression scores of the two groups. Depression scores did not differ between two groups.

The effect of chronic pain on depression has always been remarkable [14]. It has been reported that CLBP patients suffer from depression and anxiety more than their healthy counterparts [13,15]. Namgwave et al. [16] detected depression at a rate of 39.5% in a cross-sectional study of 114 CLBP patients. Similarly, in a controlled study, Sribastav et al. [17] reported increased depressive symptoms in patients with CLBP. High depression scores were reported not only in CLBP patients but also in comparison with patients with and without subacute low back pain [18]. In contrast, the present study found no difference in respect of BDI scores.

One of the non-organic causes of chronic low back pain is psychosomatic spinal pain. Physiological muscle stiffness due to anxiety is thought to be one of the most significant reasons for this spinal pain [14]. Oliveira et al. [19] reported anxiety in 72% of patients with CLBP. Another study revealed similar anxiety scores in the same patient group [13]. In the current study, anxiety scores of the patients did not show any differences between the subjects (P>0.05). These findings may contradict many findings in previous studies in literature. Some studies have stated that comorbidities such as hypertension or previously received health care are other risk factors for depression in patients with CLBP [20]. Comorbidities and prior treatment/health care were not evaluated in the current study, so the difference in results could be related to this lack of data.

Many previous studies have evaluated the relationship between CLBP and sleep disorders [21]. CLBP seemed to have a negative effect on sleep quality [22]. Sleep disorders have been shown to accompany depression and anxiety [17]. However, although another study reported that depressive and anxiety symptoms were highly seen in patients with CLBP, we did not detect any significant differences between two groups with respect to sleep quality. However, in that study, patients highly had spinal stenosis and no pain in supine position [23]. Currently, there was not any correlation between the scores of depression and anxiety in the two groups, but the findings showed that sleep disorders were related to depression, anxiety, pain, and disability. Sleep disorders might be related to nocturnal pain, however, in the current study, patients were not questioned about whether they experienced nocturnal pain. Our study group was mostly composed of patients with no night pain. This contradiction might be related to the sample size.

Currently, both VAS and Short form McGill pain questionnaire is used to evaluate pain. A negative correlation was determined between the Short form McGill pain and SF-36 scores. Apart from the mental health scores, all the other SF-36

sub-scales were correlated with the Short form McGill pain questionnaire scores. A negative correlation was also determined between VAS and SF-36 scores.

With the exception of the mental health scores, a negative relationship was detected between the other QoL sub-scales and the Roland Morris disability index scores.

Previous studies investigating the correlation between pain and disability in patients with CLBP have revealed that pain affects disability scores [22]. A similar positive correlation was determined between disability and pain scores in the current study.

There were some limitations to this study, primarily that the patients included had symptoms ongoing for at least 6 months, but the exact duration was not known. Therefore, disease duration could not be linked with depression, anxiety, QoL or sleep disorders. In addition, any correlation of sleep disorder and pain could not be evaluated due to the lack of night pain data. Although the exclusion criteria consisted of diagnosed psychological disorders, undiagnosed disorders may have been missed. While clinical and demographic characteristics of the patients were recorded, previous treatment, medication or conventional physical therapy were not questioned. The records did not include any etiology inquiry so etiological factors could not be evaluated. Depression and anxiety were evaluated according to the patients' own reports.

Conclusion

CLBP negatively effects individuals' QoL. This finding might be important in the treatment and management of chronic low back pain.

References

1. Bento TPF, Genebra CVDS, Maciel NM, Cornelio GP, Simeão SFAP, Vitta A. Low back pain and some associated factors: is there any difference between genders? Braz J Phys Ther. 2020;24(1):79-87.
2. Uchmanowicz I, Kołtuniuk A, Stępień A, Uchmanowicz B, Rosińczuk J. The influence of sleep disorders on the QoL in patients with chronic low back pain. Scand J Caring Sci. 2019;33(1):119-27.
3. Tsuji T, Matsudaira K, Sato H, Vietri J. The impact of depression among chronic low back pain patients in Japan. BMC Musculoskel Disord. 2016;17(1):447-55.
4. Panahi R, Mohammadi B, Kazemi SS, Geshti MRSN. Low Back Pain, Disability and QoL among University Students. International Journal of Muscoloskeletal Pain Prevention 2016;1(4):173-77.
5. Ucurum SG, Kalkan AC. Relationship between pain, kinesiophobia an quality of life in patients with low back pain [Article in Turkish] Ege Tıp Derg. 2018;57(3):131-35.
6. Yakut Y, Yakut E, Bayar K, Uygur F. Reliability and validity of the Turkish version short-form McGill pain questionnaire in patients with rheumatoid arthritis. Clin Rheumatol. 2007;26(7):1083-7.
7. Kucukdeveci AA, Tennant A, Elhan AH, Niyazoglu H. Validation of the Turkish version of the Roland-Morris Disability Questionnaire for use in low back pain. Spine. 2001;26(24):2738-43.
8. Hisli N. Validation of the Beck Depression Inventory: Turkish sample of Psychiatric Outpatients. J Turk Physcol. 1987;6:118-22.
9. Ulusoy M, Sahin NH, Erkmen H. Turkish version of the Beck Anxiety Inventory: Psychometric properties. J Cogn Psychother. 1998;12:163-72.
10. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pitts¬burgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193-213.
11. Kocyigit H, Aydemir O, Fisek G, Olmez N, Memiş A. Validity and reliability of Turkish version of Short form 36: A study of a patients with rheumatoid disorder. [Article in Turkish] J Drug Ther. 1999;12:102–6.
12. Mutubuki EN, Beljon Y, Maas ET, Huygen FJPM, Ostelo RWJG, van Tulder MW, et al. The longitudinal relationships between pain severity and disability versus health-related QoL and costs among chronic low back pain patients. Qual Life Res. 2020;29(1):275-87.
13. Fernandez M, MChiro, Colodro-Conde L, Hartvigsen J, Ferreira ML, Refshauge KM, et al. Chronic low back pain and the risk of depression or anxiety symptoms: insights from a longitudinal twin study. Spine J. 2017;17(7):905-12.
14. Ünal Ö, Akyol Y, Tander B, Ulus Y, Terzi Y, Kuru Ö. The relationship of illness perceptions with demographic features, pain severity, functional capacity, disability, depression, and QoL in patients with chronic low back pain. Turk J Phys Med Rehabil. 2019;65(4):301-8.
15. Park SM, Kim HJ, Jang S, Kim H, Chang BS, Lee CK, et al. Depression is Closely Associated With Chronic Low Back Pain in Patients Over 50 Years of Age: A Cross-sectional Study Using the Sixth Korea National Health and Nutrition Examination Survey (KNHANES VI-2). Spine. 2018;43(18):1281-87.
16. Namgwa KJ, Terkura A, William Y, Daniel MD, Cornilius EI. Depression in patients with chronic low back pain: Ahospital-based study. Niger J Surg Res 2016;17(1):1-4.
17. Sribastav SS, Peiheng H, Jun L, Zemin L, Fuxin W, Jianru, et al. Interplay among pain intensity, sleep disturbance and emotion in patients with non-specific low back pain. PeerJ. 2017;5:e3282.
18. Calvo Lobo C, Vilar-Fernández JM, Losa-Iglesias ME, López-López D, Rodríguez-Sanz D, Palomo-López P, et al. Depression Symptoms Among Older Adults With and Without Subacute Low Back Pain. Rehabil Nurs. 2019;44(1):47-51.
19. Oliveira DS, Vélia Ferreira Mendonça L, Sofia Monteiro Sampaio R, Manuel Pereira Dias de Castro-Lopes J, Ribeiro de Azevedo LF. The Impact of Anxiety and Depression on the Outcomes of Chronic Low Back Pain Multidisciplinary Pain Management-A Multicenter Prospective Cohort Study in Pain Clinics with One-Year Follow-up. Pain Med. 2019;20(4):736-46.
20. Omoke NI, Igwe MN. Analysis of risk factors for depression among patients with chronic low back pain in an orthopaedic clinic of a Nigerian teaching hospital. Afr Health Sci. 2019;19(1):1727-35.
21. Gokçek E, Akelma H, Kaydu A. Assessment of Sleep and Life Qualities of Patient with Chronic Low Back Pain; Single-Centered, Prospective Observational Study. Int J Med Sci Clin Inven. 2019;6:4251-7.
22. Sezgin M, Hasanefendioğlu EZ, Sungur MA, Incel NA, Çimen ÖB, Kanık A, et al. Sleep quality in patients with chronic low back pain: a cross-sectional study assesing its relations with pain, functional status and QoL. J Back Musculoskelet Rehabil. 2015;28(3):433-41.
23. Hong JH, Kim HD, Shin HH, Huh B. Assessment of depression, anxiety, sleep disturbance, and QoL in patients with chronic low back pain in Korea. Korean J Anesthesiol. 2014;66(6):444-50.

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. 2020;4(9):812-816.
DOI: 10.28982/josam.780127

Research article
Araştırma makalesi

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

Do early neutrophil to eosinophil ratio and the levels of neutrophil and white blood cells predict intra-hospital mortality in patients with spontaneous intracerebral hemorrhages?

Erken nötrofil/eozinofil oranı ile nötrofil ve beyaz kan hücrelerinin seviyeleri spontan intraserebral hemorajili hastalarda hastane içi mortaliteyi öngörüyor mu?

Ersin Özeren [1], Muzaffer Güneş [2]

[1] Aksaray University Training and Research Hospital, Neurosurgery Department, Aksaray, Turkey
[2] Aksaray University Training and Research Hospital, Neurology Department, Aksaray, Turkey

ORCID ID of the author(s)
EÖ: 0000-0001-9861-274X
MG: 0000-0002-9325-1292

Corresponding author / Sorumlu yazar:
Muzaffer Güneş
Address / Adres: Aksaray Üniversitesi Eğitim ve Araştırma Hastanesi, Nöroloji Bölümü, Aksaray, Türkiye
E-mail: drmuzaffergunes@gmail.com

Ethics Committee Approval: The study was approved by the Aksaray University Human Research Ethics Committee (6/22/2020, 2020/06-57). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Aksaray Üniversitesi İnsan Araştırmaları Etik Kurulu tarafından onaylandı (22.06.2020, 2020/06-57). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: In recent years, inflammatory markers such as red blood cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), and C-reactive protein to albumin ratio (CAR) have been investigated in spontaneous intracerebral hemorrhage (ICH). However, they were not analyzed together in ICH. In the present study, we examined whether neutrophil, neutrophil to eosinophil ratio (NER), and white blood cell (WBC) levels along with the above-mentioned markers predict the intrahospital mortality in patients diagnosed with spontaneous ICH at admission.

Methods: We conducted this retrospective cohort study by examining spontaneous ICH patients hospitalized in our clinic between April 2015 and March 2019. We divided patients into two groups, as survivors and non-survivors. The receiver operating characteristics (ROC) curve analysis test was used to evaluate the predictive value of laboratory variables for mortality and to calculate cut-off values.

Results: A total of 130 patients, 82 survivors and 48 non-survivors, were included in the study. The patients who were non-survivors at the hospital had significantly higher median hemorrhage volume, WBC, and neutrophil levels compared to those of survivors (P<0.001, P=0.001 and P=0.003, respectively). There was no significant difference between the two groups in terms of median CAR, NLR, NER, and RDW-SD values (P=0.216, P=0.237, P=0.229, and P=0.215, respectively). The area under the ROC curve was 0.676 (95% CI, 0.57-0.78) for WBC and 0.659 (95% CI, 0.56-0.76) for neutrophil.

Conclusion: Our results showed that the elevated neutrophil and WBC levels at the acute phase of spontaneous ICH predict the intrahospital mortality of the patients. Further studies are required for the predictive value of NER.

Keywords: White blood cell, Spontaneous intracerebral hemorrhage, Neutrophil, Inflammatory parameters, Red blood cell distribution width, Neutrophil to lymphocyte ratio, Neutrophil to eosinophil ratio

Öz

Amaç: Son yıllarda, spontan intraserebral hemorajide (ICH) kırmızı kan hücresi dağılım genişliği (RDW), nötrofil/lenfosit oranı (NLO) ve C-reaktif protein/albümin oranı (CAO) gibi inflamatuar belirteçler araştırılmıştır. Ancak, bunlar ICH'de birlikte incelenmemiştir. Bu çalışmada, spontan ICH tanısı alan hastalarda başvuru sırasında yukarıda belirtilen belirteçlerle birlikte nötrofil, nötrofil/eozinofil oranı (NEO) ve beyaz kan hücresi (WBC) düzeylerinin hastane içi mortaliteyi tahmin edip etmediğini araştırdık.

Yöntemler: Bu retrospektif kohort çalışmasını, Nisan 2015 - Mart 2019 tarihleri arasında kliniğimizde yatan spontan ICH hastalarını inceleyerek gerçekleştirdik. Hastaları hayatta kalanlar ve hayatta kalmayanlar olarak iki gruba ayırdık. Mortalite için laboratuvar değişkenlerinin prediktif değerini değerlendirmek ve kesme değerlerini hesaplamak için, alıcı çalışma karakteristikleri (ROC) eğrisi analizi kullanılmıştır.

Bulgular: Çalışmaya, 82'si hayatta kalan ve 48'i hayatta kalmayan olmak üzere 130 hasta dahil edildi. Hastanede ölen hastaların medyan hemoraji hacmi, WBC ve nötrofil değerleri yaşayanlara göre anlamlı olarak yüksekti (sırasıyla P<0,001; P=0,001 ve P=0,003). Medyan CAO, NLO, NEO ve RDW-SD değerleri açısından iki grup arasında fark yoktu (sırasıyla P=0,216; P=0,237; P=0,229 ve P=0,215). ROC eğrisi altındaki alan: WBC için 0,676 (% 95 CI; 0,57-0,78) ve nötrofil için 0,659 (% 95 CI; 0,56-0,76) idi.

Sonuç: Sonuçlarımız, spontan ICH'nin akut evresinde daha yüksek nötrofil ve WBC düzeyleri hastaların hastane içi mortalitesini öngörmüştür. NEO'nın predikdif değeri için ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Beyaz kan hücresi, Spontan intraserebral hemoraji, Nötrofil, İnflamatuvar parametreler, Kırmızı kan hücresi dağılım genişliği, Nötrofil/lenfosit oranı, Nötrofil/eozinofil oranı

How to cite/Atıf için: Özeren E, Güneş M. Do early neutrophil to eosinophil ratio and the levels of neutrophil and white blood cells predict intra-hospital mortality in patients with spontaneous intracerebral hemorrhages? J Surg Med. 2020;4(9):812-816.

Introduction

Stroke is still one of the major causes of death around the world [1]. Although the spontaneous intracerebral hemorrhages (ICH) account for the 10-20% of all strokes, mortality and disability risk of spontaneous ICH can be much higher than ischemic stroke type [2]. Unfortunately, spontaneous ICH patients are not as lucky as ischemic stroke patients as there are few therapeutic strategies for ICH treatment, and their benefits are limited [3]. Factors such as age, hemorrhage volume, infratentorial localization, intraventricular hemorrhage, and initial Glasgow Coma Scale score are important indicators of the prognosis in spontaneous ICH [4]. High arterial blood pressure in the early phase was also associated with the prognosis of ICH [5]. Surely, it is important to know the prognostic factors not only for fighting against the neurological and systemic complications of ICH (e.g., antibiotic treatment in case of a systemic infection, decompression surgery and/or evacuating hemorrhage if shift develops, external ventricle drainage for ventricle hemorrhages, etc.) but also for informing the patients' relatives properly. Knowing the prognostic factors may contribute to clinician's ICH management. Therefore, researchers have been trying to identify new prognostic factors that may affect the prognosis of ICH. In recent years, neutrophil to lymphocyte ratio (NLR) [6,7], C-reactive protein (CRP) [8], C-reactive protein to albumin ratio (CAR) [9], and red blood cell distribution width (RDW) have been investigated in ICH [10]. However, these markers were not investigated together in spontaneous ICH. In our study, we aimed to investigate whether neutrophil to eosinophil ratio (NER), neutrophil, and white blood cell (WBC) levels, along with the abovementioned inflammatory markers, predict the intrahospital mortality. To that end, we carried out the present study based on the laboratory results of patients collected during the first admission to the hospital.

Materials and methods

Study population

We retrospectively identified the spontaneous ICH patients who were followed and treated at the Aksaray University Education and Research Hospital between April 2015 and March 2019. The patients included in the study were those who applied to the hospital within 24 hours from the onset of symptoms and either died in hospital while being treated for spontaneous ICH or discharged upon a partial or complete recovery. Patients older than 18 years were included in the study. Patients who have subarachnoid hemorrhage and secondary ICHs (trauma, vascular malformation, brain tumor, etc.), acute or chronic infection, blood disease, liver and renal failure, electrolyte abnormalities, receive immunomodulatory or immunosuppressive therapy, had a hemorrhagic infarction, and are younger than 18 years of age were excluded.

Initially, the medical history of the patients, who are brought to the emergency room of our hospital with stroke pre-diagnosis, was collected from themselves or their relatives. Vital signs (pulse, blood pressure, arterial oxygen saturation, fever, etc.) are quickly recorded; blood sugar level is measured from a finger. During the rapid neurological examination, blood samples are collected for hemogram, international normalized ratio, activated partial thromboplastin time, and biochemical evaluation. Brain computed tomography (brain CT) or magnetic resonance imaging (brain MRI) for parenchymal imaging, and vascular imaging of the brain (brain CT angiography or brain MR angiography) for vascular abnormalities were performed routinely. The location and the volume of the hematoma are determined based on the parenchymal and vascular imaging results and treatment is planned accordingly. All the included patients received standard treatment according to up to date stroke guidelines [3]. Laboratory analysis was conducted in the hematology laboratory of our institution. Venous blood samples were taken from patients, centrifuged, and blood cell counts were performed at our hematology center using an autoanalyzer (Sysmex XN-1000 hematology analyzer, Kobe, Japan). NER was calculated by dividing the neutrophil count by eosinophil count, while CAR was calculated by dividing the amount of C-reactive protein (mg/dL) by albumin amount (g/L), and NLR was calculated by dividing the neutrophil count by lymphocyte count.

Clinical findings and laboratory results, brain parenchymal and vascular imaging results, risk factors, and other demographic characteristics of patients during the initial emergency room admission was collected from our database and used for statistical analysis. The study was approved by the Aksaray University Human Research Ethics Committee (6/22/2020, 2020/06-57) and carried out in accordance with the Helsinki Declaration.

Statistical analysis

The results are presented as mean (standard deviation) for normally distributed data, median (min-max) for non-normally distributed data and percentage (%). Kolmogorov-Smirnov normality test was used to investigate the distribution pattern. Red blood cell (RBC) and platelet data, which distributed normally, were compared using Student's independent samples T test. The other blood test parameters with non-normal distribution, were compared using Mann Whitney U test. Categorical variables were investigated using the Chi- square test. The factors affecting mortality were investigated using univariate and multivariate logistic regression analysis. The variables with a *P* value of primary comparison under 0.25 were included in the univariate logistic regression model and the variables with a *P* value of univariate logistic regression analysis under 0.1 were included in the multivariate logistic regression model. The model fit was assessed using Hosmer-Lemeshow goodness of fit statistics. The assessment of consistency between the variables was performed using Cox and Snell pseudo-R^2 and Nagelkerke pseudo-R^2 tests. To evaluate the predictive value of variables, and to calculate the cut- off values, receiver operating characteristics (ROC) curve analysis test was used. If the area under the ROC curve is 0.5, the model does not discriminate; 0.5-0.7, the model has poor to fair discrimination; 0.7-0.8, the model has acceptable discrimination; 0.8-0.9, the model has excellent discrimination; and 0.9-1.0, is a very rare outcome [11]. For statistical analysis of all data, we used SPSS 23.0 software for Windows (SPSS Inc., Chicago, IL, USA). A *P* value of less than 0.05 was considered statistically significant.

Results

130 patients with spontaneous ICH were included in the study. There were 82 survivors [43 males and 39 females, median age: 69 (25-89) years] and non-survivors consisted of 48 patients [20 males and 28 females, median age: 68.5 (42-93)]. The median age (P=0.334) and gender distribution (P=0.236, X^2=1407) were not different between the non-survivors and survivors.

The comparison of hematological parameters between the groups (survivors and non-survivors) is given in detail in Table 1. According to the Student's T test, the mean RBC was not significantly different between the non-survivors and survivors (P=0.674). Mann Whitney U test revealed that the median CRP, albumin, CAR, lymphocyte, NLR, eosinophil, NER, hemoglobin, hematocrit, RDW-CV, RDW-SD and mean corpuscular volume (MCV) values did not significantly differ between the non-survivors and survivors (P=0.377, P=0.396, P=0.216, P=0.739, P=0.237, P=0.708, P=0.229, P=0.504, P=0.94, P=0.43, P=0.215 and P=0.152, respectively). However, the median volume of hemorrhage, WBC and neutrophil values were significantly higher in non-survivors, compared with the survivors (P<0.001, P=0.001 and P=0.003, respectively).

The Chi-square test revealed that in terms of shift, opening to the ventricle and the presence of congestive heart failure were significantly higher in non-survivors, compared with the survivors (P<0.001, P=0.001 and P<0.011, respectively) (Table 2). However, the rates of diabetes mellitus, arterial hypertension, hyperlipidemia, and coronary artery disease did not significantly differ between the non-survivors and survivors (P=0.132, P=0.579, P=0.396, and P=0.834, respectively).

Table 3 represents the distribution of hemorrhage localizations, which were similar between the non-survivors and survivors (P=0.783, X^2=3.97).

In Table 4, the univariate and multivariate logistic regression analysis results were presented. The univariate logistic regression model revealed that the volume of hemorrhage, WBC, neutrophil, the presence of shift, ventricular opening, and congestive heart failure were found to affect mortality (P=0.002, P=0.002, P=0.003, P<0.001, P=0.003 and P=0.017, respectively). However, the multivariate logistic regression model revealed that only the presence of ventricular opening affected mortality (P=0.006).

Table 1: Comparison of routine hematological parameters between survivors and non-survivors

	Survivor patients (n=82)	Non-survivor patients (n=48)	P-value
Age, year	69 (26-89)	68.5 (42-93)	0.334
Red blood cell (10^{12}/L)	4.36 (5.55)	4.67 (6.85)	0.674
The volume of hemorrhage (cm^3)	7.16 (0.28-142.2)	26.14 (0.6-170)	<0.001
C- reactive protein (mg/dL)	5.07 (0.27-297)	7.15 (0.29-190)	0.377
Albumin (g/L)	41.15 (24.3-50.1)	40.3 (4.37-51)	0.396
CAR	0.16 (0.1-8.48)	0.21 (0.1-10.58)	0.216
WBC (10^9/L)	8.63 (3.70-22.37)	10.72 (1.88-20.31)	0.001
Neutrophil (10^9/L)	5.54 (2.41-17.95)	7.22 (1.16-18.1)	0.003
Lymphocyte (10^9/L)	1.83 (0.32-5.63)	1.52 (0.23-7.74)	0.739
NLR	3.28 (0.6-82.4)	3.93 (0.7-44.39)	0.237
Eosinophil (10^9/L)	0.1 (0.005-2.16)	0.085 (0.01-0.55)	0.708
NER	50.14 (1.70-1795)	61.43 (5.4-1709)	0.229
Hemoglobin (g/dL)	13.85 (7.5-19.6)	13.8 (5.18-18.7)	0.504
Hematocrit (%)	41.3 (25.6-56.4)	41.05 (22.9-80.4)	0.94
RDW-CV (%)	13.5 (1.8-19.1)	13.56 (11.20-44.6)	0.43
RDW-SD (fL)	42.6 (27.8-63.7)	43.8 (13.9-65.8)	0.215
MCV (fL)	86.05 (30.2-114)	87.55 (77.7-98.6)	0.152

NLR: Neutrophil to lymphocyte ratio, CAR: C- reactive protein to albumin ratio, NER: Neutrophil to eosinophil ratio, RDW: Red blood cell distribution width, WBC: White blood cell, MCV: Mean corpuscular volume

Table 2: Comparison of categorical variables between survivors and non-survivors

	Survivor patients (n=82)	Non-survivor patients (n=48)	P-value	X^2-value
Gender (M/F)	43/39	20/28	0.236	1.407
Presence of shift	21 (25.6%)	28 (58.3%)	<0.001	13.805
IVH (cm^3)	20 (24.4%)	25 (52.1%)	0.001	10.259
DM, n (%)	24 (29.3%)	22 (45.8%)	0.132	4.05
HT, n (%)	56 (68.3%)	35 (72.9%)	0.579	0.308
HL, n (%)	4 (4.9%)	3 (6.25%)	0.396	1.853
CHF, n (%)	4 (4.9%)	9 (18.75%)	0.011	6.474
CAD, n (%)	6 (7.3%)	4 (8.3%)	0.834	0.044

IVH: Intraventricular hemorrhage, DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, CHF: Congestive heart failure, CAD: Coronary artery disease

Table 3: The distribution of hemorrhage localizations

Localization	Survivor patients	Non-survivor patients
Pons	3 (3.66%)	4 (8.3%)
Mesencephalon	1 (1.22%)	0 (0%)
Cerebellum	10 (12.2%)	6 (12.5%)
Basal Ganglia	13 (15.85%)	6 (12.5)
Thalamus	22 (26.8%)	13 (26.8%)
Caudate nucleus	0 (0%)	1 (2.08)
Putamino- capsular	9 (10.97%)	4 (8.3%)
Lobar	24 (29.3%)	14 (29.16%)
Total	82 (%100)	48 (100%)

Table 4: The logistic regression analysis results of the study

	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
The volume of hemorrhage	1.029 (1.011-1.048)	0.002	1.015 (0.995-1.036)	0.139
CAR	1.186 (0.963-1.46)	0.109	-	-
WBC	1.192 (1.067-1.331)	0.002	1.089 (0.811-1.464)	0.57
Neutrophil	1.186 (1.058-1.329)	0.003	1.104 (0.788-1.546)	0.566
NLR	1.01 (0.971-1.051)	0.609		
NER	1.001 (1-1.002)	0.092	1 (0.999-1.002)	0.436
RDW-SD	1.024 (0.972-1.079)	0.37	-	-
MCV	1.037 (0.981-1.098)	0.202	-	-
Gender	1.544 (0.752-3.168)	0.237	-	-
Shift	4.067 (1.905-8.682)	<0.001	1.93 (0.712-5.231)	0.196
Ventricular opening	3.157 (1.487-6.702)	0.003	3.479 (1.418-8.535)	0.006
Diabetes Mellitus	1.929 (0.923- 4.032)	0.081	1.826 (0.723-4.612)	0.202
Congestive Heart Failure	4.5 (1.304- 15.534)	0.017	2.988 (0.679-13.154)	0.148
			Cox and Snell pseudo-R^2 = 0.258	
			Nagelkerke pseudo-R^2 = 0.352	
			Hosmer- Lemeshow P = 0.305	

Figure 1 shows the ROC curve representing the predictive value of WBC and neutrophil for mortality. The area under the ROC curve was 0.676 (95% CI, 0.57-0.78) for WBC and 0.659 (95% CI, 0.56-0.76) for neutrophil. The cut-off value of WBC and neutrophil were 9.63 (sensitivity: 66% and specificity: 67%) and 6.67 (sensitivity: 58% and specificity: 65%), respectively.

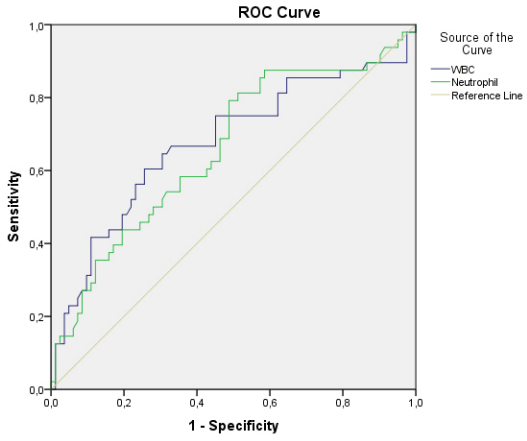


Figure 1: The receiver operating characteristic (ROC) curve expressing the ability of white blood cell (WBC) and neutrophil to predict in-hospital mortality

Discussion

The significant findings of our study were that the elevated neutrophil and WBC levels at the hospital admission have a predictive value for intrahospital mortality in spontaneous

ICH patients. These results suggest that neutrophil-mediated severe inflammation during the acute phase of ICH increases mortality by contributing to secondary brain damage.

An increase in the neutrophil, NLR, CAR, RDW, CRP, and WBC levels reflects systemic inflammation. In recent years, the significance of these parameters has been emphasized in ICH prognosis [6-10]. However, NER has not been investigated together with these parameters. Therefore, we analyzed all these parameters together to examine their predictive value for ICH mortality.

It is emphasized that high neutrophil levels at the time of application are associated with poor prognosis in ICH [12]. In our study, we found that elevated neutrophil levels during admission (acute phase) predict intrahospital mortality in ICH patients. Secondary brain damage in ICH occurs with a chain of inflammatory pathophysiological events. Neutrophils play an important role in this type of damage [13,14]. Immediately after the stroke onset, microglia activation starts with hematoma components within minutes [13,15,16]. Free oxygen radicals, chemokines, and pro-inflammatory cytokines released by the excessive microglia activation initiate inflammatory signaling [13]. Then, the neutrophils produced in the blood begin to accumulate around the hematoma approximately 4 hours after the ICH, reaching peak within 2-3 days [13,14]. Neutrophils, accumulated around and within the hematoma in the brain, lead to excessive regulation of the matrix metalloproteinase-9 (MMP-9), macrophage activation, and the secretion of pro-inflammatory cytokines such as IL-1beta and TNF-alpha [13,17]. The result of this chain of pathophysiological events is secondary brain damage caused by the blood-brain barrier (BBB) breakdown, hemorrhage growth, and increased edema around hemorrhage [17,18]. It was shown in a neutrophil depletion study carried out with the anti-polymorphonuclear leukocyte antibody that the BBB breakdown, MMP-9 expression in perihematomal neutrophils, axon injuries, the number of perihematomal microglia/macrophages, and glial scar formation was reduced with the reduced neutrophil levels [18]. These findings reveal the significant role played by neutrophils in secondary brain damage developed in ICH. In the present study, we aimed to emphasize the significance of neutrophils in ICH once more.

WBC is considered a reliable biomarker for inflammation [19]. It was found that the elevated WBC count in blood predicts the poor outcome occurring within the first 3 days after ICH [20]. Similarly, we found that high WBC levels at hospital admission predict the intrahospital mortality in ICH patients.

In previous studies, NLR, CAR, and RDW-SD were associated with mortality in spontaneous ICH patients. These markers also reflect the systemic inflammation, just as neutrophils [6,9,10]. In the present study, deceased patients had higher NLR, CAR, RDW-SD, and NER levels than alive patients, yet the difference between the two groups was not statistically significant. The reason for this might be the fact that the study groups consisted of a small number of patients or that we analyzed the patients' laboratory parameters obtained during the acute phase. NER, which expresses the increase of neutrophils and the decrease of eosinophils in the blood, can be easily calculated by dividing the number of neutrophils by the number of eosinophils. As we analyzed the blood parameters obtained in the acute phase of ICH in the present study, the changes in these blood parameters may have not been reflected in NER yet. Analyzing the laboratory parameters collected after the 4th or, ideally, the 24th hour of ICH may reflect changes to NER better. The significance of NER in ICH can be clarified in the future with more detailed and extensive studies by addressing the current findings and issues.

Limitations

Although the present study was carried out to determine whether hematological inflammatory parameters at the time of admission have a predictive value for the intrahospital mortality of spontaneous ICH patients and emphasize the significance of neutrophils in ICH, it has some limitations. These include small number of patients, working with laboratory parameters obtained during the acute phase of the disease (at the admission), and carrying out a retrospective analysis can be considered as the limitations of the present study.

Conclusion

As a result, elevated neutrophil and WBC levels at the hospital admission predicted the intrahospital mortality of patients in the acute phase of ICH. Further studies with larger patient groups are needed to define NER as a new inflammation parameter.

Acknowledgments

The authors would like to thank Assoc. Prof. Dr. Ö. Hızlı and Assist. Prof. Dr. P. Güneş for their assistance with the statistical analysis.

References

1. Sarti C, Rastenyte D, Cepaitis Z, Tuomilehto J. International trends in mortality from stroke, 1968 to 1994. Stroke. 2000;31(7):1588-601. doi: 10.1161/01.str.31.7.1588
2. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol. 2003;2(1):43-53. doi: 10.1016/s1474-4422(03)00266-7
3. Hemphill JC, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke. 2015;46:2032-60. doi: 10.1161/STR.0000000000000069
4. Schmidt FA, Liotta EM, Prabhakaran S, Naidech AM, Maas MB. Assessment and comparison of the max-ICH score and ICH score by external validation. Neurology. 2018;91(10):e939-e946. doi: 10.1212/WNL.0000000000006117.
5. Lattanzi S, Silvestrini M, Provinciali L. Elevated blood pressure in the acute phase of stroke and the role of Angiotensin receptor blockers. Int J Hypertens. 2013;2013:941783. doi: 10.1155/2013/941783.
6. Lattanzi S, Cagnetti C, Rinaldi C, Angelocola S, Provinciali L, Silvestrini M. Neutrophil-to-lymphocyte ratio improves outcome prediction of acute intracerebral hemorrhage. J Neurol Sci. 2018;387:98-102. doi: 10.1016/j.jns.2018.01.038.
7. Zhang J, Cai L, Song Y, et al. Prognostic role of neutrophil lymphocyte ratio in patients with spontaneous intracerebral hemorrhage. Oncotarget. 2017;8(44):77752-60. doi: 10.18632/oncotarget.20776.
8. Di Napoli M, Parry-Jones AR, Smith CJ, et al. C-reactive protein predicts hematoma growth in intracerebral hemorrhage. Stroke. 2014;45(1):59-65. doi: 10.1161/STROKEAHA.113.001721.
9. Bender M, Haferkorn K, Friedrich M, Uhl E, Stein M. Impact of Early C-Reactive Protein/Albumin Ratio on Intra-Hospital Mortality Among Patients with Spontaneous Intracerebral Hemorrhage. J Clin Med. 2020 Apr 24;9(4). pii: E1236. doi: 10.3390/jcm9041236.
10. Altintas O, Duruyen H, Baran G, et al. The Relationship of Hematoma Growth to Red Blood Cell Distribution Width in Patients with Hypertensive Intracerebral Hemorrhage. Turk Neurosurg. 2017;27(3):368-73. doi: 10.5137/1019-5149.JTN.16136-15.1.
11. Forthofer RN, Lee ES, Hernandez M. Biostatistics: A Guide to Design, Analysis and Discovery. 2nd Ed. United States of America: Elsevier Academic Press; 2007. doi: 10.1016/C2009-0-03861-6.
12. Leira R, Dávalos A, Silva Y, et al; Stroke Project, Cerebrovascular Diseases Group of the Spanish Neurological Society. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. Neurology. 2004;63(3):461-7. doi: 10.1212/01.wnl.0000133204.81153.ac
13. Lattanzi S, Brigo F, Trinka E, Cagnetti C, Di Napoli M, Silvestrini M. Neutrophil-to-Lymphocyte Ratio in Acute Cerebral Hemorrhage: a System Review. Transl Stroke Res. 2019;10(2):137-45. doi: 10.1007/s12975-018-0649-4.
14. Wang J, Doré S. Inflammation after intracerebral hemorrhage. J Cereb Blood Flow Metab. 2007;27(5):894-908. doi: 10.1038/sj.jcbfm.9600403.
15. Aronowski J, Hall CE. New horizons for primary intracerebral hemorrhage treatment: experience from preclinical studies. Neurol Res. 2005;27(3):268-79. doi: 10.1179/016164105X25225
16. Zhou Y, Wang Y, Wang J, Anne Stetler R, Yang QW. Inflammation in intracerebral hemorrhage: from mechanisms to clinical translation. Prog Neurobiol. 2014;115:25-44. doi: 10.1016/j.pneurobio.2013.11.003.
17. Chen S, Yang Q, Chen G, Zhang JH. An update on inflammation in the acute phase of intracerebral hemorrhage. Transl Stroke Res. 2015;6(1):4-8. doi: 10.1007/s12975-014-0384-4.

18. Moxon-Emre I, Schlichter LC. Neutrophil depletion is lower-brain barrier breakdown, axon injury, and inflammation after intracerebral hemorrhage. J Neuropathol Exp Neurol. 2011;70(3):218-35. doi: 10.1097/NEN.0b013e31820d94a5.
19. Wirth MD, Sevoyan M, Hofseth L, Shivappa N, Hurley TG, Hébert JR. The Dietary Inflammatory Index is associated with elevated white blood cell counts in the National Health and Nutrition Examination Survey. Brain Behav Immun. 2018;69:296-303. doi: 10.1016/j.bbi.2017.12.003.
20. Sun W, Peacock A, Becker J, Phillips-Bute B, Laskowitz DT, James ML. Correlation of leukocytosis with early neurological deterioration following supratentorial intracerebral hemorrhage. J Clin Neurosci. 2012;19(8):1096-100. doi: 10.1016/j.jocn.2011.11.020.

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. 2020;4(9):817-821.
DOI: 10.28982/josam.782307

Research article
Araştırma makalesi

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

Annexin-2, pentraxin-3, and osteopontin expressions in the endometrium of women with idiopathic recurrent pregnancy loss during the implantation window

İdiyopatik tekrarlayan gebelik kaybı olan kadınların endometriyumunda implantasyon penceresi sırasında Annexin-2, Pentraxin-3 ve Osteopontin ekspresyonları

Banuhan Şahin [1], Erkan Alataş [2], Sevgi Özkan [3]

[1] Amasya University Sabuncuoglu Serefeddin Training and Reseach Hospital, Department of Gynecology and Obstetrics, Amasya, Turkey
[2] Pamukkale University Medical School, Department of Gynecology and Obstetrics, Denizli, Turkey
[3] Pamukkale University, Health School, Denizli, Turkey

ORCID ID of the author(s)
BŞ: 0000-0002-8711-1584
EA: 0000-0001-6423-5106
SÖ: 0000-0002-5933-5441

Corresponding author / Sorumlu yazar:
Banuhan Şahin
Address / Adres: Amasya Üniversitesi Sabuncuoğlu Şerefeddin Araştırma ve Eğitim Hastanesi, Kadın Hastalıkları ve Doğum Bölümü, 05000, Amasya, Türkiye
E-mail: banuhansahin@gmail.com

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Medical School of Pamukkale University, with the number 11/04/2014-TPF012. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Pamukkale Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından 11/04/2014-TPF012 numarası ile onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The study was financially supported by the Scientific Research Projects and Funds of Pamukkale University (No: 2014TPF012).
Finansal Destek: Çalışma, Pamukkale Üniversitesi Bilimsel Araştırma Projeleri ve Fonları tarafından finansal olarak desteklenmiştir (No: 2014TPF012).

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: Failed expression of endometrial receptivity molecules and genes during the implantation window may lead to idiopathic recurrent pregnancy loss (IRPL). The aim of this study was to investigate annexin-2 (ANXA-2), pentraxin-3 (PTX-3) and osteopontin (OPN) expressions in the endometrium of women with IRPL.

Methods: A total of 34 women with IRPL and 34 age-matched healthy women were recruited in this case control study. Serum samples were collected in the mid-luteal phase of the menstrual cycle and endometrial biopsies were harvested in the window of implantation days. The expressions of ANXA-2, PTX-3, and OPN in the endometrial biopsies according to localizations were examined by immunohistochemistry. The H-score method was used to evaluate the intensity of endometrial ANXA-2, PTX-3, and OPN immune-reactivity.

Results: The mean PTX-3 score was significantly higher in the epithelial endometrium of women with IRPL compared with control cases (2.47 (0.56) vs 1.44 (0.50), $P<0.001$). Both luminal and glandular epithelial and stromal components of the endometrium showed increased staining for PTX-3 in women with IRPL. The increase of PTX-3 expression in the epithelial endometrium correlated with the decrease of serum progesterone level ($P=0.016$). When ANXA-2 and OPN expressions in the epithelial endometrium of IRPL samples were compared with the age-matched control subjects, although there was lower expression, no statistically significant difference was observed (1.97 (0.71) vs 2.21 (0.59), $P=0.145$ and 1.97 (0.79) vs 2.12 (0.68), $P=0.418$).

Conclusion: PTX-3 expression increases in the epithelial and stromal endometrium of women with IRPL during the implantation window. As the serum progesterone level decreases, endometrial PTX-3 expression increases in glandular and luminal epithelium in women with IRPL. Endometrial PTX-3 may be a potential molecular target for IRPL.

Keywords: Annexin-2, Endometrium, Osteopontin, Pentraxin-3, Pregnancy loss

Öz

Amaç: İmplantasyon penceresi sırasında endometriyal reseptivite moleküllerinin ve genlerinin başarısız ekspresyonu, idiyopatik tekrarlayan gebelik kaybına (ITGK) yol açabilir. Bu çalışmanın amacı, ITGK'li kadınlarda endometriumda annexin-2 (ANXA-2), pentraxin-3 (PTX-3) ve osteopontin (OPN) ekspresyonlarını incelemekti.

Yöntemler: Bu vaka kontrol çalışmasına ITGK'li toplam 34 kadın ve yaşları eşleştirilmiş 34 sağlıklı kadın dahil edilmiştir. Menstruel döngüsünün orta luteal fazında serum örnekleri toplandı ve implantasyon penceresi günlerinde endometriyal biyopsiler alındı. Endometriyal biyopsilerde lokalizasyonlara göre ANXA-2, PTX-3 ve OPN ekspresyonları immunohistokimya ile incelendi. Endometriyal ANXA-2, PTX-3 ve OPN immün reaktivitesinin yoğunluğunu değerlendirmek için H-skor yöntemi kullanıldı.

Bulgular: Ortalama PTX-3 skoru, ITGK'li kadınların epitel endometriyumunda kontrol vakalarına göre anlamlı olarak daha yüksekti (2,47 (0,56)'ya karşı 1,44 (0,50), $P<0,001$). ITGK 'li kadınlarda endometriyumun hem luminal hem de glandüler epitel ve stromal bölümleri, PTX-3 için artmış boyanma gösterdi. Epitelyal endometriyumda PTX-3 ekspresyonundaki artış, serum progesteron seviyesindeki düşüş ile korelasyon gösterdi ($P=0,016$). ITGK örneklerinin epitel endometriyumundaki ANXA-2 ve OPN ekspresyonları yaşa uygun kontrol denekleriyle karşılaştırıldığında daha düşük ekspresyon görülmesine rağmen istatistiksel olarak anlamlı bir fark gözlenmedi (1,97 (0,71)'e karşı 2,21 (0,59), $P=0,145$ ve 1,97 (0,79)'a karşı 2,12 (0,68), $P=0,418$).

Sonuç: İmplantasyon penceresi sırasında ITGK'li kadınların epitel ve stromal endometriyumunda PTX-3 ekspresyonu artmaktadır. ITGK'li kadınlarda serum progesteron seviyesi düştükçe glandüler ve lüminal epitelde endometrial PTX-3 ekspresyonu artmaktadır. Endometriyal PTX-3, ITGK için potansiyel bir moleküler hedef olabilir.

Anahtar kelimeler: Annexin-2, Endometrium, Osteopontin, Pentraxin-3, Gebelik kaybı

How to cite/Atıf için: Şahin B, Alataş E, Özkan S. Annexin-2, pentraxin-3, and osteopontin expressions in the endometrium of women with idiopathic recurrent pregnancy loss during the implantation window. J Surg Med. 2020;4(9):817-821.

Introduction

Recurrent pregnancy loss (RPL) is defined as two or more consecutive failed pregnancies [1]. In obstetric practice, systematic evaluation is generally recommended after the second consecutive pregnancy loss [2]. Although anatomic, genetic, immunological, thrombophilic or endocrinological factors play a role in the development of RPL, half of cases have an unclear pathogenesis and are diagnosed with idiopathic RPL (IRPL) [3]. Couples are mostly disappointed with the process of the diagnosis of this situation, since the etiology continues to remain mostly unclear and there is a lack of evidence regarding effective treatment.

Implantation of the human embryo into the maternal endometrium is the main step in the establishment of a successful pregnancy [4]. Blastocyst adhesion in the uterine epithelium depends on endometrial receptivity, which is driven by ovarian steroids during the mid-luteal phase of the menstrual cycle [5]. The appearance of some molecules, such as integrin b3, leukemia inhibitor factor and mucin-1, in the luminal epithelium during the implantation window has been proposed as a biomarker of uterine receptivity [6]. A number of earlier studies suggested that failure of the endometrium to express a receptive phenotype is thought to be one of the causes of IRPL [7,8].

Annexins have a significant impact on the physiological and pathological processes involved in cell growth, differentiation, apoptosis, and signal transduction [9]. During the human implantation process, annexin-2 (ANXA-2) increases embryo adhesiveness, endometrial epithelial cell migration, and trophoblast overgrowth [10]. This protein has been identified as a major contributor to the human receptive endometrium [11]. ANXA-2 is strongly expressed in endometrial glands and the luminal epithelium in the mid- and late-secretory endometria for embryo adhesiveness [12].

Pentraxin-3 (PTX-3) is an acute-phase reactant and a member of the pentraxin protein family [13]. Several studies have demonstrated that PTX-3 has an important role in innate immunity, inflammation, implantation, decidualization, and placentation [14,15,16]. It has been determined that PTX-3 is expressed in the receptive endometrium, and trophoblasts have been found to affect PTX- expression in decidua [17]. PTX-3 has been proposed as a novel biomarker for the prediction of placental failure [18].

Osteopontin (OPN) is mainly involved in cell proliferation, adhesion, migration, and angiogenesis in the endometrium [19]. OPN and its receptor avB3 integrin are expressed in increasing concentrations in glandular and luminal epithelium during the secretory phase, as markers of endometrial receptivity [20]. It has been demonstrated that OPN expression is regulated by progesterone and reduces significantly in RPL patients [21].

The aim of this study was to examine the expressions of ANXA-2, PTX-3 and OPN in the endometrium of patients with IRPL and to compare these with those in a control group of subjects with a history of healthy live births.

Materials and methods

In this case-control study, 34 women were enrolled with a history of IRPL in the Infertility Clinic of Pamukkale University Hospital from June 2013 to June 2014. A control group was formed of 34 healthy and fertile, reproductive-aged women volunteers. The staining intensities of ANXA-2, PTX-3 and OPN in the endometrium during the mid-secretory phase were investigated; the serum progesterone level was measured on the same day. The study protocol was approved by the Clinical Research Ethics Committee of Medical School of Pamukkale University, with the number 11/04/2014-TPF012 and all the participants were informed about the study. The guidelines of the Declaration of Helsinki were followed.

Patients had a minimum of two consecutive pregnancy losses during the first trimester and the control subjects had at least one previous uneventful pregnancy with healthy obstetric histories. To understand the etiology of miscarriage, the patients visited the Infertility Clinic in the Medical School of Pamukkale University and underwent a full examination. They were diagnosed as IRPL with no underlying anatomic, genetic, immunological, thrombophilic, or endocrine factors. All the participants were required to meet the following inclusion criteria: Between 18–35 years of age, regular menstrual cycles (25–35 days), and no use of hormonal supplementation within the last 6 months. Cases were excluded if they had an endometrial pathology such as Asherman syndrome, endometrial polyp, and/or sub-mucous fibroids, or a diagnosis of pelvic inflammatory disease.

Each woman was followed for one menstrual cycle. Ovulation was monitored with transvaginal ultrasonography (GE Voluson® E6, IC5-9-D/GYN transducer; GE Healthcare, Zipf, Austria). The day when the luteinizing hormone (LH) surge occurred was identified by measuring LH levels in the blood samples. Endometrial biopsies were performed seven days after ovulation, during the mid-secretory phase. The endometrial samples were collected from the uterine cavity via a Karman cannula. For immunohistochemical examination, tissues were fixed in 4% formalin and finally embedded in paraffin. Histological dating was evaluated according to the criteria of Noyes [22]. All biopsies were found to be in the correct phase.

Overall, 68 biopsy samples were analyzed. Three serial sections were prepared from each biopsy sample. The 3 μm paraffin embedded sections were incubated overnight at 60°C for deparaffinization. Concentrated polyclonal antibodies against Annexin-2 (ANXA-2, Thermo Fisher, Co Ltd, US), Pentraxin-3 (PTX-3, Thermo Fisher, Co Ltd, US), and Osteopontin (OPN, Thermo Fisher, Co Ltd, US) were diluted 1:500, 1:25, and 1:50, respectively. All the immunohistochemical steps were carried out in the fully automated closed system of Ventana Benchmark XT (Roche Groups, Switzerland). Following washing with distilled water, rehydrating in xylene and a series of graded ethanol solutions at room temperature, slides were mounted with Entellan® (Merck, Darmstadt, Germany). All slides were exposed to amino ethylcarbazole chromogen, counterstained with hematoxylin, and mounted with aqueous mount. The term human placenta was used as positive control. Slides were selected at random and were examined by a single pathologist blinded to the group origin of the slide. The stained sections were

observed under a microscope (Nikon Ecclipse E200, Nikon, Japan) (10x ocular and 4x objective lenses). To evaluate the intensity of endometrial ANXA-2, PTX-3 and OPN immunoreactivity, the H-score method was used [23]. The reactivity of each antibody with the luminal epithelium, glandular epithelium, and stromal cells was assessed carefully. This is a semi quantitative method measuring the percentages of positively stained cells multiplied by a weighted intensity of staining: H-Score=Pi (i + 1), where Pi is the percentage of ANXA-2, PTX-3 and OPN stained endometrial cells in each intensity category (0–100%), and i is the intensity indicating weak (i=1), moderate (i=2), or strong staining (i=3) [24].

Serum progesterone levels were assessed using a chemiluminescent immunoassay (Liaison Assay; Diasorin, Italy). In the analysis, the day-to-day variation in progesterone level was excluded by collecting samples at a fixed time (11:00 am).

Statistical analysis

No clear data could be found in literature of ANXA-2, PTX-3 and OPN staining in the endometrial biopsy samples of patients with IRPL. Therefore, to define the sample size of a pilot study, 34 patients and 34 control subjects were selected based on the available number of cases. Data were analyzed using the Statistics Package for Social Science version 17.0 software (SPSS Inc, Chicago, IL, USA). Continuous variables were presented as mean (standard deviation (SD)) values. Differences were analyzed using the parametric Student's t-test. Correlation analysis was applied for multiple comparisons. A value of $P<0.05$ was considered statistically significant. The package used generated significant small round off errors, which had an estimated effect on the results in the order of 103.

Results

Overall, the data of 68 women (34 with IRPL and 34 without IRPL) were analyzed in this study. All menstrual cycles were ovulatory according to ultrasonographic criteria and mid-luteal serum progesterone concentration >10 ng/ml. The clinical characteristics of the women in the patient and control groups are summarized in Table 1. The mean age was 26.94 (4.57) years in the patient group and 28.82 (4.60) years in the control group ($P=0.096$). No statistically significant difference was determined between the groups with respect of body mass index (BMI), as 25.26 (2.84) kg/m^2 in the patient group and 25.74 (2.84) kg/m^2 in the control group ($P=0.497$). Women in the patient group were found to have a median of 3 previous miscarriages.

The comparisons of H-score of immunohistochemical ANXA-2, PTX-3 and OPN expression in women with IRPL and without IRPL are presented in Table 1.

In the patient group, the mean H-score of the endometrial epithelial and stromal ANXA-2 expression was similar to that of the control group (1.97 (0.71) vs 2.21 (0.59), $P=0.145$ and 1.91 (0.62) vs 2.18 (0.57), $P=0.073$, respectively). Both the glandular and luminal components of the epithelial endometrium showed decreased staining for ANXA-2 without statistical significance. The decreased ANXA-2 immunoreactivity was predominantly localized to the luminal epithelial cells (Figure 1a, 1b, 1c).

The mean H-score of the endometrial epithelial PTX-3 expression was significantly increased in the patient group compared to the control group (2.47 (0.56) vs 1.44 (0.50), $P<0.001$). Increased PTX-3 expression was detected in the cytoplasmic and membranous parts of glandular and luminal epithelial cells of the endometrium in women with IRPL. The stromal component of the endometrium showed the most increased staining for PTX-3 in women with IRPL (Figure 1d, 1e, 1f).

The mean H-scores of the endometrial epithelial and stromal OPN expressions of groups were similar (1.97 (0.79) vs 2.12 (0.68), $P=0.418$ and 1.79 (0.64) vs 2.06 (0.69), $P=0.107$). The greatest difference between the groups in OPN staining was detected in the glandular epithelium without statistical significance (Figure 1g, 1h, 1i).

The correlations between serum progesterone level and PTX-3 staining intensity scores in the patient and control groups are presented in Table 2. A negative correlation was detected between serum progesterone level and staining intensity for PTX-3 in epithelial endometrium in women with IRPL ($P=0.016$). This negative correlation was determined in both the glandular and luminal epithelium of the endometrium ($P=0.038$ and $P=0.002$). No correlation was found between serum progesterone level and stromal PTX-3 expression in women with IRPL.

Table 1: Demographic characteristics and the H-scores of the endometrial ANXA-2, PTX-3 and OPN expressions in women with IRPL and without IRPL

	Women with IRPL n=(34)	Women without IRPL n=(34)	*P*-value
Age (year)	26.94 (4.57)	28.82 (4.60)	0.096
BMI (kg/m^2)	25.26 (2.84)	25.74 (2.84)	0.497
Epithelial ANXA-2 score	1.97 (0.71)	2.21 (0.59)	0.145
Glandular	2.06 (0.64)	2.18 (0.57)	0.432
Luminal	1.79 (0.72)	2.09 (0.51)	0.060
Stromal ANXA-2 score	1.91 (0.62)	2.18 (0.57)	0.073
Epithelial PTX-3 score	2.47 (0.56)	1.44 (0.50)	<0.001*
Glandular	2.44 (0.61)	1.38 (0.49)	<0.001*
Luminal	2.50 (0.56)	1.41 (0.50)	<0.001*
Stromal PTX-3 score	2.38 (0.55)	1.38 (0.49)	<0.001*
Epithelial OPN score	1.97 (0.79)	2.12 (0.68)	0.418
Glandular	2.00 (0.77)	2.29 (0.52)	0.072
Luminal	1.74 (0.75)	1.97 (0.75)	0.203
Stromal OPN score	1.79 (0.64)	2.06 (0.69)	0.107
Progesterone (mg/dl)	11.56 (3.65)	11.97 (2.94)	0.611

ANXA-2: Annexin-2, PTX-3: Pentraxin-3, OPN: Osteopontin. Variables presented as mean (standard deviation).

Table 2: Correlations between serum progesterone level and PTX-3 scores in women with IRPL and without IRPL

	Serum progesterone level (mg/dl)	
PTX-3 scores in women with IRPL	r	*P*-value
Epithelial	-0.411	0.016*
Glandular	-0.357	0.038*
Luminal	-0.507	0.002*
Stromal	-0.200	0.258
PTX-3 scores in women without IRPL	r	*P*-value
Epithelial	0.111	0.532
Glandular	0.050	0.780
Luminal	0.111	0.531
Stromal	0.050	0.780

ANXA-2: Annexin-2, PTX-3: Pentraxin-3, OPN: Osteopontin

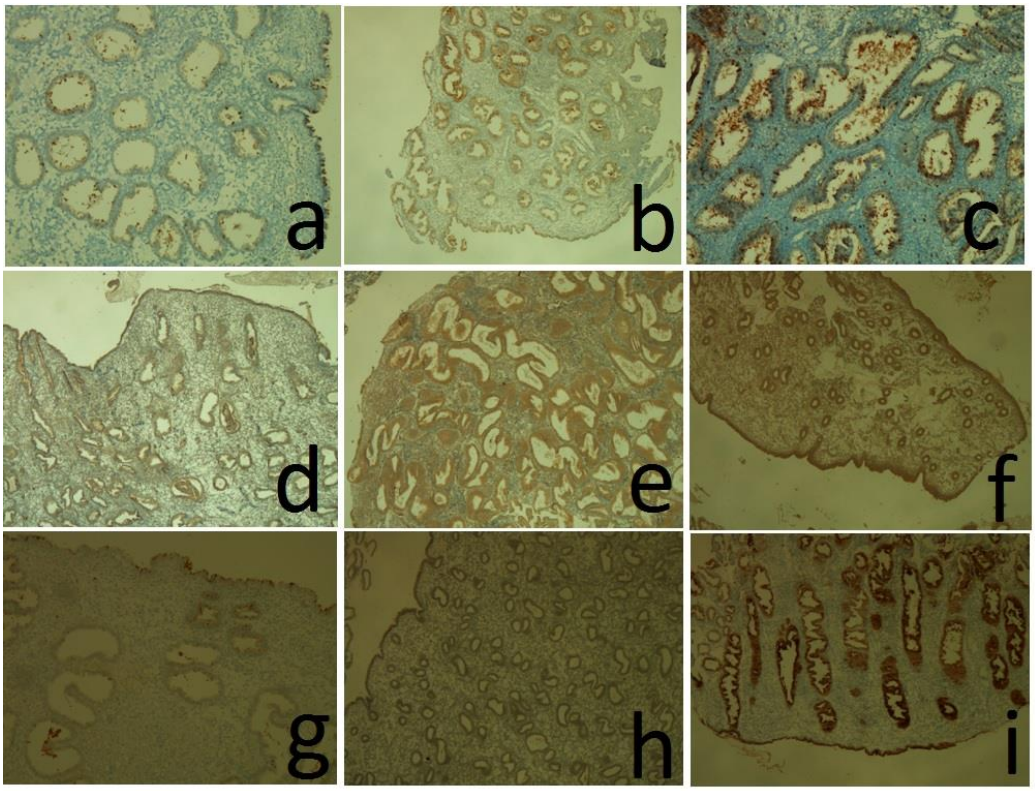


Figure 1: Antibody staining scores for endometrial localizations (ANXA-2 staining: a: score 1, luminal epithelium; b: score 2, luminal and glandular epithelium; c: score 3, glandular epithelium and stroma. ax4, bx4, cx10, PTX-3 staining: d: score 1, luminal and glandular epithelium; e: score 2, glandular epithelium; f: score 3, luminal and glandular epithelium and stroma. dx10, ex10, fx4, OPN staining: g: score 1, luminal epithelium; h: score 2, luminal and glandular epithelium; I: score 3, luminal and glandular epithelium and stroma. gx4, hx4, ix4)

Discussion

The results of the current study demonstrate that the PTX-3 expression increases in the mid-secretory endometrium of women with IRPL during the implantation window. Increased PTX-3 expression was detected in both the epithelial and stromal endometrium. However, ANXA-2 and OPN expressions in the IRPL group were similar to those of the control group. A mild negative correlation was detected between serum progesterone level and staining intensity for PTX-3 in glandular and luminal epithelial cells of mid-luteal endometrial biopsies in women with IRPL. One of the mechanisms responsible for IRPL in this study group may have been the increased PTX-3 expression in all areas of the endometrium.

Pregnancy is a well-programmed physiological process that involves a dynamic maternal and fetal crosstalk [25]. Local immune tolerance, angiogenesis, cytokine and integrin balance, cellular, and molecular trafficking are initiated with implantation and continue throughout the gestation period; deregulation of any of these processes may result in a miscarriage [26]. The proteins produced locally in the endometrial epithelium play an indisputable role in the continuity of a successful pregnancy [27]. However, the prognostic value of these proteins as biomarkers in patients with IRPL remains unclear. Therefore, with the use of immunohistochemistry, we aimed to assess the endometrium during the implantation window in the mid-secretory phase to identify a prognostic marker for IRPL diagnosis and management.

Trophoblasts and stromal cells secrete many substances into the endometrium for a successful implantation, which involves the development of placental vasculature and anchoring, while preventing rejection of semi-allograft [28,29]. The PTX-3 gene is up-regulated during the immune response in early pregnancy [30]. However, an abnormally exaggerated endometrial inflammatory response could cause RPL [31]. A recent study revealed that the level of PTX-3 in maternal serum and placenta were elevated in pre-eclampsia and intrauterine growth restriction (IUGR) [32]. In the present study, increased expression of PTX-3 in the epithelial endometrium was determined in patients with IRPL compared with the control group. Secondly, the localization of strong PTX-3 staining was detected equally in all areas of the endometrial biopsy specimens including the luminal epithelium, glandular epithelium, and stroma. In addition, all the control specimens showed weak staining with PTX-3. It reflects an exaggerated local inflammatory reaction in the whole endometrium of patients with IRPL. The third finding was that PTX-3 staining of patient samples increased with the fall in the progesterone level. Progesterone could directly affect PTX-3 expression in the implantation window or it could regulate the expression and synthesis of several integrins and cytokines indirectly. Further studies are required to clarify the exact mechanism of these interactions.

Annexins are present in the secretory luminal epithelium of endometrium and regulate the receptivity and implantation process. Fowler et al. identified annexins among the irregular proteins in women with endometriosis [33]. Genetic studies have shown that alterations of annexin haplotypes are related to RPL, IUGR, and pre-eclampsia [34,35]. It has been proven that pregnant women with anti-phospholipid syndrome often exhibit autoantibodies against ANXA-5 and the fetus is lost

spontaneously during the early stages of the pregnancy [36]. It has been postulated that ANXA-5 could be a significant auto-antigen for pregnancy loss, acting as an anti-thrombotic agent during pregnancy [37]. In the current study, the weak intensity of ANXA-2 staining in the endometrial biopsy specimens from patients with IRPL compared with the control subjects could be attributed to defective implantation, immunoregulation, or coagulation. Slightly lower ANXA-2 staining was detected in the endometrial biopsies of patients with IRPL than without IRPL, and the localization of ANXA-2 staining was the same in both groups. Despite the findings of several previous studies, these results suggest that ANXA-2 is not a distinctive protein for the pathogenesis of recurrent miscarriages.

Osteopontins are the most upregulated extracellular matrix adhesion molecules in the endometrium as it becomes receptive to implantation [38]. It was hypothesized in this study that the endometrium in the luteal phase of IRPL patients would show weak staining intensity for OPN compared with the control group because blockage of the OPN entity inhibits embryo adhesion, implantation, and the angiogenesis stage. In the immunohistochemical analysis, although the difference was not statistically significant, a slightly lower intensity of OPN staining was observed in samples from patients with IRPL compared to those of the control group. No difference was detected between the localizations of OPN staining in the specimens. In this context, the immunohistochemical examinations in a previous animal study showed that the cellular localization of OPN was mainly restricted to glandular epithelium [39]. The results obtained from the current study do not confirm that OPN deficiency in the endometrium in the luteal phase causes pregnancy loss.

Limitation

In this study, the IRPL group was considered as patients with two or more consecutive pregnancy losses. However, if patients with three and more consecutive pregnancy losses had been included, some outcomes may have been different.

Conclusion

The results of the current study demonstrated that the PTX-3 expression increases in the endometrium of women with IRPL during the implantation window. As serum progesterone level decreases, PTX-3 expression increases in the glandular and luminal epithelium and stroma. ANXA-2 and OPN expressions in the endometrium of women with IRPL are almost similar to those of women without IRPL. PTX-3 staining of endometrial biopsies can be used as a prognostic marker for IRPL and as a specific target for therapeutic implications of IRPL during the implantation window.

References

1. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion, Fertil Steril. 2020;113(3):533-5. doi: 10.1016/j.fertnstert.2019.11.025
2. Hong Li Y, Marren A. Recurrent pregnancy loss: A summary of international evidence-based guidelines and practice. Aust J Gen Pract. 2018;47(7):432-6.
3. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion, Fertil Steril, 2012;98(5):1103-11. doi: 10.1016/j.fertnstert.2012.06.048
4. Dominguez F, Yáñez-Mó M, Sanchez-Madrid F, Simón C. Embryonic implantation and leukocyte transendothelial migration: different processes with similar players? FASEB J. 2005;19(9):1056-60.
5. Lessey BA, Young SL. What exactly is endometrial receptivity? Fertil Steril. 2019;111(4):611-7.
6. Wu F, Chen X, Liu Y, Liang B, Xu H, Li TC, et al. Decreased MUC1 in endometrium is an independent receptivity marker in recurrent implantation failure during implantation window. Reprod Biol Endocrinol. 2018;16(1):60.
7. Huang J, Qin H, Yang Y, Chen X, Zhang J, Laird S, et al. A comparison of transcriptomic profiles in endometrium during window of implantation between women with unexplained recurrent implantation failure and recurrent miscarriage. Reproduction. 2017;153:749-58.
8. Dhaenens L, Lierman S, De Clerck L, Govaert E, Deforce D, Tilleman K, et al. Endometrial stromal cell proteome mapping in repeated implantation failure and recurrent pregnancy loss cases and fertile women. Reprod Biomed Online. 2019;38(3):442-54.
9. Gerke V, Moss S E. Annexins and membrane dynamics. Biochim Biophys Acta. 1997;1357:129-54.
10. Filipenko NR, Waisman DM. The C terminus of annexin II mediates binding to F-actin. J Biol Chem. 2001;276:5310-5.
11. Dominguez F, Garrido-Gomez T, Lopez JA, Camafeita E, Quinonero A, Pellicer A, et al. Proteomic analysis of the human receptive versus non-receptive endometrium using differential in-gel electrophoresis and MALDI-MS unveils stathmin 1 and annexin A2 as differentially regulated. Human Reprod. 2009;24:2607-17.
12. Garrido-Gómez T, Dominguez F, Quiñonero A, Estella C, Vilella F, Pellicer A, et al. Annexin A2 is critical for embryo adhesiveness to the human endometrium by RhoA activation through F-actin regulation. FASEB J. 2012;26(9):3715-27.
13. Bottazzi B, Garlanda C, Cotena A, Moalli F, Jaillon S, Deban L, et al. The long pentraxin PTX3 as a prototypic humoral pattern recognition receptor: interplay with cellular innate immunity. Immunological Reviews. 2009;227: 9-18.
14. Garlanda C, Bottazzi B, Bastone A, Mantovani A. Pentraxins at the crossroads between innate immunity, inflammation, matrix deposition, and female fertility. Annu Rev Immunol. 2005;23:337-66.
15. Garlanda C, Maina V, Martinez de la Torre Y, Nebuloni M, Locati M. Inflammatory reaction and implantation: the new entries PTX3 and D6. Placenta. 2008;29:129-34.
16. Freis A, Von Horn K, Göggl T, Hecht S, Roesner S, Strowitzki T, et al. Serum levels of Pentraxin 3 differ significantly at the time of blastocyst transfer depending on implantation success: a pilot study. Arch Gynecol Obstet. 2018;297(6):1565-70.
17. Larsson A, Palm M, Helmersson J, Axelsson O. Pentraxin 3 values during normal pregnancy. Inflammation. 2011;34:448-51.
18. Zhou P, Luo X, Qi HB, Zong WJ, Zhang H, Liu DD, et al. The expression of pentraxin 3 and tumor necrosis factor-alpha is increased in preeclamptic placental tissue and maternal serum. Inflamm Res. 2012;61(9):1005-12.
19. Johnson GA, Burghardt RC, Bazer FW, Spencer TE. Osteopontin: roles in implantation and placentation. Biol Reprod. 2003;69:1458-71.
20. Casals G, Ordi J, Creus M, Fábregues F, Carmona F, Casamitjana R, et al. Osteopontin and alphavbeta3 integrin as markers of endometrial receptivity: the effect of different hormone therapies. Reprod Biomed Online. 2010;21(3):349-59.
21. Qu X, Yang M, Zhang W, Liang L, Yang Y, Zhang Y, et al. Osteopontin expression in human decidua is associated with decidual natural killer cells recruitment and regulated by progesterone. In Vivo. 2008;22(1):55-61.
22. Noyes RW, Hertig AT, Rock J. Reprint of: Dating the Endometrial Biopsy. Fertil Steril. 2019;112:93-115.
23. Budwit-Novotny DA, McCarty KS, Cox EB, Soper JT, Mutch DG, Creasman WT, et al. Immunohistochemical analyses of estrogen receptor in endometrial adenocarcinoma using a monoclonal antibody. Cancer Res. 1986,46(10):5419-25.
24. Creus M, Ordi J, Fábregues F, Casamitjana R, Ferrer B, Coll E, et al. alphavbeta3 integrin expression and pinopod formation in normal and out-of-phase endometria of fertile and infertile women. Hum Reprod. 2002;17(9):2279-86.
25. Hemberger M. Immune balance at the foeto-maternal interface as the fulcrum of reproductive success. J Reprod Immunol. 2012;97:36-42.
26. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol. 2010;63:425-33.
27. Apparao KB, Murray MJ, Fritz MA, Meye, WR, Chambers AF, Truong PR, et al. Osteopontin and its receptor alphav beta (3) integrin are coexpressed in the human endometrium during the menstrual cycle but regulated differentially. J Clin Endocrinol Metab. 2001;86:4991-5000.
28. Aplin JD, Kimber SJ. Trophoblast-uterine interactions at implantation. Reprod Biol Endocrinol. 2004;2: 48.
29. Hess AP, Hamilton AE, Talbi S, Dosiou C, Nyegaard M, Nayak N, et al. Decidual stromal cell response to paracrine signals from the trophoblast: amplification of immune and angiogenic modulators. Biol Reprod. 2007;76:102-17.
30. Popovici RM, Betzler NK, Krause MS, Luo M, Jauckus J, Germeyer A, et al. Gene expression profiling of human endometrial–trophoblast interaction in a coculture model. Endocrinology. 2006;147:5662-75.
31. Doni A, Michela M, Bottazzi B, Peri G, Valentino S, Polentarutti N, et al. Regulation of PTX3, a key component of humoral innate immunity in human dendritic cells: stimulation by IL-10 and inhibition by IFN-gamma. J Leukoc Biol. 2006;79:797-802.
32. Cetin I, Cozzi V, Pasqualini F, Nebuloni M, Garlanda C, Vago L, et al. Elevated maternal levels of the long pentraxin 3 (PTX3) in preeclampsia and intrauterine growth restriction. Am J Obstet Gynecol. 2006;194:1347-53.
33. Fowler PA, Tattum J, Bhattacharya S, Klonisch T, Hombach-Klonisch S, Gazvani R, et al. An investigation of the effects of endometriosis on the proteome of human eutopic endometrium: a heterogeneous tissue with a complex disease. Proteomics. 2007;7:130-42.
34. Brachvogel B, Moch H, Pausch F. Perivascular cells expressing annexin A5 define a novel mesenchymal stem cell-like population with the capacity to differentiate into multiple mesenchymal lineages. Development. 2005;132:2657-68.
35. Udry S, Aranda F, Latino O. Annexins and recurrent pregnancy loss. Medicina (B Aires). 2013;73(5):495-500.
36. Gris JC, Perneger TV, Quere I. Antiphospholipid/antiprotein antibodies, hemostasis-related autoantibodies, and plasma homocysteine as risk factors for a first early pregnancy loss: a matched case-control study. Blood. 2003;102:3504-13.
37. Ueki H, Mizushina T, Laoharatchatathanin T, Terashima R, Nishimura Y, Rieanrakwong D, et al. Loss of maternal annexin A5 increases the likelihood placental thrombosis and foetal loss. Sci Rep. 2012;2:827.
38. Makker A, Singh MM. Endometrial receptivity: clinical assessment in relation to fertility, infertility, and antifertility. Med Res Rev. 2006;26:699-746.
39. Peyghambari F, Salehnia M, Forouzandeh Moghadam M, Rezazadeh Valujerdi M, Hajizadeh E. The correlation between the endometrial integrins and osteopontin expression with pinopodes development in ovariectomized mice in response to exogenous steroids hormone. Iran Biomed J. 2010;14(3):109-19.

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. 2020;4(9):822-825.
DOI: 10.28982/josam.783286

Research article
Araştırma makalesi

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

Are small bore thorax catheters effective in the treatment of primary spontaneous pneumothorax?

Primer spontan pnömotoraks tedavisinde küçük çaplı toraks kateterleri etkili midir?

Cenk Balta [1], İsmail Can Karacaoğlu [2], Duygu Mergan İliklerden [3], Ali Cem Yekdeş [4]

[1] Department of Thoracic Surgery, Balıkesir University Health Application and Research Hospital, Balıkesir, Turkey
[2] Department of Thoracic Surgery, Van State Health Application and Research Hospital, Van, Turkey.
[3] Department of Thoracic Surgery, Yüzüncü Yıl University Health Application and Research Hospital. Van, Turkey.
[4] Department of Internal Medicine, Balıkesir University Health Application and Research Hospital, Balıkesir, Turkey

ORCID ID of the author(s)
CB: 0000-0002-4073-8101
İCK: 0000-0002-2273-5097
DMİ: 0000-0001-8203-3946
ACY: 0000-0002-8928-2053

Corresponding author / Sorumlu yazar:
Cenk Balta
Address / Adres: Balıkesir Üniversitesi Sağlık Uygulama ve Araştırma Hastanesi Göğüs Cerrahisi Kliniği, 10145 Balıkesir, Türkiye
E-mail: drcenkbalta@gmail.com

Ethics Committee Approval: This study was approved by Balıkesir University Faculty of Medicine Clinical Research Ethics Committee (Decision No: 2019/1127, Date: 9/25/2019). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Balıkesir Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından onaylanmıştır (Karar No: 2019/1127, Tarih: 25.09.2019). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: The first option in the treatment of primary spontaneous pneumothorax (PSP) is still controversial. Large bore thoracic drains (LBTD) are generally preferred by clinicians. However, the use of small-bore thorax catheters (SBTC) has increased in recent years. In our study, we aimed to compare the treatment efficacy, clinical outcomes and pain levels of small and large diameter thoracic catheters used in PSP treatment.

Methods: Patients over the age of 18 who presented with a diagnosis of PSP between August 2017 and August 2019 were included in the study. The patients were divided into two groups according to the application of small and large bore thorax drain. Demographic information, clinical results and pain levels of the groups were analyzed retrospectively. The duration of hospitalization, duration of drainage and Visual Analogue Scale (VAS) results were evaluated comparatively.

Results: 95 male and 10 female patients with a median age of 26 (22-33) were included in the study. LBTD was applied to 47 (44.8%) and SBTC was applied to 58 (55.2%) of the patients. Recurrence was observed in 6 (12.8%) of LBTD group and in 4 (6.9%) SBTC group. VAS scores, drainage time, hospital stay were significantly less in patients with small-sized drainage.

Conclusion: SBTC application is easy to apply, causes less pain, has shorter drainage time and duration of hospital stay. It is as effective as traditional thoracic drains in the treatment of PSP.

Keywords: Pneumothorax, Thoracic drain, Small bore thoracic catheter, Primary spontaneous pneumothorax

Öz

Amaç: Primer spontan pnömotoraks (PSP) tedavisinde ilk seçenek hala tartışmalıdır. Klinisyenler tarafından genellikle geniş çaplı toraks drenleri tercih edilmektedir. Fakat son yıllarda da küçük boyutlu kateterlerin kullanımı artmıştır. Çalışmamızda PSP tedavisinde kullanılan küçük ve geniş çaplı toraks kateterlerinin tedavi etkinliği, klinik sonuçları ve oluşturdukları ağrı seviyeleri karşılaştırılması amaçlandı.

Yöntemler: Ağustos 2017 ve Ağustos 2019 arasında PSP tanısıyla başvuran 18 yaş üstü hastalar çalışmaya dahil edildi. Hastalar küçük ve geniş çalı toraks dreni uygulanmasına göre iki gruba ayrıldı. Grupların demografik bilgileri, klinik sonuçları ve ağrı seviyeleri geriye dönük olarak incelendi. Hastanede yatış süresi, drenaj süresi ve Görsel Analog Skala sonuçları karşılaştırmalı olarak değerlendirildi. Elde edilen veriler istatistiksel olarak incelendi.

Bulgular: Ortanca yaşları 26 (22-33) olan 95 erkek ve 10 kadın hasta çalışmaya dahil edildi. Hastaların 47(%44,8)'ine geniş çaplı, 58(%55,2)'sine küçük çaplı drenaj uygulandı. İki grupta da başarısızlıkla sonuçlanan tedavi olmadı. Geniş çaplı drenaj uygulananların 6(%12,8)'sında, küçük çaplı drenaj uygulananların 4(%6,9)'sinde nüks izlendi. Gruplar arasında yaş, cinsiyet, hastalık yönü, sigara durumu, nüks oranı açısından istatistiksel olarak anlamlı fark saptanmadı. Görsel Analog Skala sonuçları, drenaj süresi, hastane yatış süresi küçük boyutlu drenaj uygulanan hastalarda anlamlı olarak daha az bulundu.

Sonuç: Daha az ağrı oluşturan, kolay uygulanan, daha kısa drenaj ve hastanede yatış süreleri sahip küçük çaplı toraks kateteri uygulamasının geleneksel toraks drenleri kadar PSP tedavisinde etkilidir.

Anahtar kelimeler: Pnömotoraks, Toraks dreni, Küçük çalı toraks kateteri, Primer spontan pnömotoraks

How to cite/Atıf için: Balta C, Karacaoğlu İC, İliklerden DM, Yekdeş AC. Are small bore thorax catheters effective in the treatment of primary spontaneous pneumothorax? J Surg Med. 2020;4(9):822-825.

Introduction

Pneumothorax is defined as the collection of air in the intrapleural space [1]. The spontaneous pneumothorax without any underlying lung disease is known as primary spontaneous pneumothorax (PSP). Although the etiology is still not clear, the most common cause of PSP is the rupture of pulmonary bullae and blebs [2,3]. The frequency of this disease is 18-28 / 100000 in men and 1.2-6 / 100000 in women. PSP makes up approximately 20% of hospitalizations in thoracic surgery clinics [4].

The most common symptoms are chest pain while resting, cough and dyspnea. Physical examination and chest radiography are sufficient for the diagnosis; whereas thorax computed tomography is the gold standard in diagnosis of minimal pneumothoraxes [5].

Conservative treatment is effective in minimal and asymptomatic PSPs. The main purpose for the treatment of larger and symptomatic cases is to extract the air from the intrapleural space and relieve the symptoms [6]. For this purpose, simple needle aspiration, small bore thoracic catheter (SBTC) or large bore thoracic drain (LBTD) insertion, surgical interventions by thoracoscopy or thoracotomy can be performed. Nevertheless, the initial treatment option in PSP is still unclear.

Traditionally, chest tubes have been the first treatment option for pleural conditions such as pneumothorax, pleural effusion, hemothorax and empyema. But the importance of SBTC has increased in the last 2 decades [7]. The use of SBTC has become more popular among surgeons, pulmonologists and oncologists due to its easy application with the Seldinger technique and better pain outcomes [8].

In our study, we evaluated the patients who were admitted to our clinic with the first episode of PSP and who underwent LBTD or SBTC insertion. We aimed to compare clinical outcomes in terms of pain, recurrence, drainage time and hospital stay.

Materials and methods

Patient selection

Patients over the age of 18 who were underwent SBTC and LBTD insertion due to primary spontaneous pneumothorax between August 2017 and August 2019 were included in the study. Patients under 18 years of age or who were treated conservatively for minimal pneumothorax, or diagnosed as secondary spontaneous pneumothorax, iatrogenic and traumatic pneumothorax were excluded.

Prospectively recorded demographic data (age, gender, smoking status, size of pneumothorax) and clinical features (type of drainage, visual analog scale -VAS, drain termination time, hospital stay, and recurrence rates) of the patients were analyzed retrospectively.

Pneumothorax sizes of the patients were evaluated by using Light Index [9] (% pneumothorax = 100 x [1–(lung diameter/hemithorax diameter)]) on the chest X-ray. Pneumothorax size which were 20% and below were evaluated as minimal, 20-40% as partial, 40-60% as subtotal, and 60% and above as total.

The patients who were admitted between August 2017 and August 2018 underwent LBTD (20-28 French- F) insertion. SBTC (8F) insertion was applied to patients who were admitted between August 2018 and August 2019. Patients with minimal PSP were treated conservatively (bed rest, high flow oxygen inhalation and analgesic medication).

This study was approved by Local Ethics Committee (Decision No:20l9/ll27, Date:25/09/2019). This study was carried out in accordance with the principles of the Helsinki Declaration (Version: B.10.4.ISM.4.06.68.48 / 184).

Surgical technique

Surgical procedures were performed under local anesthesia (Prilocaine HCl). To perform LBTD insertion, local anesthesia was injected to the 5th intercostal space after skin disinfection and a 2 cm skin incision was made. Following muscle and pleural dissection by a Kelly clamp, LBTD was placed into the intrapleural space. The drain was fixed to skin using silk No. 0 and LBTD was connected to the underwater seal drainage. To insert SBTC, a 3 mm incision was made after anesthesia injection into the the 3rd intercostal space, following skin disinfection. The catheter was inserted into the intrapleural space by passing through the muscle and pleura with the help of a metal cannula and fixed to the skin with No. 2/0 silk suture. The air in the intrapleural space was removed by negative aspiration with a 60 cc syringe. When the aspiration was finished, the one-way valve on the catheter tip was connected to a urine bag. Cefazolin sodium was administered to all patients before the procedure.

After the procedures, the location of the SBTC or LBTD was confirmed by Chest X-rays in all patients. For pain management, intramuscular diclofenac sodium (75 mg, 2 times a day), and paracetamol 500 mg oral tablet (3 times a day) were given to all patients after the procedure. VAS was applied to patients 4 times: Immediately after the procedure, at the 1st, 6th and 12th hours of drainage. Patients were asked to choose a number between 0-10 (0: no pain, 10: worst pain). LBTD and SBTC were terminated after 24 hours when the lung was fully expanded, and the air leak stopped. Patients were followed up with chest X-rays on the 10th day, 1st month and 3rd month after discharge.

Statistical analysis

Statistical analyses were performed by SPSS (Statistical Package for the Social Sciences Version 22.0; SPSS Inc. Chicago, IL, USA) software package. The normal distribution of the data was assessed with the Shapiro-Wilk test. Categorical data were recorded as frequency and percentage. Non-parametric values were given as median (25.-75. percentiles). The relationship between the categorical variables was examined with the Chi-square and Fisher's exact tests and the relationship between the nonparametric data and continuous variables with the Mann-Whitney U test. For all analyses, $P<0.05$ was considered statistically significant.

Results

There were 134 patient admissions to our clinic with PSP diagnosis. Twenty-nine patients with minimal PSP who were treated conservatively without surgical intervention were excluded from the study.

The median age of 95 (90.5%) male and 10 (9.5%) female patients was 26 (22-33). 85 (81%) of the patients were smoking. 56 (53.3%) of the PSPs were right sided, 49 (46.7%) were left sided. 61 (58.1%) of the patients had total, 12 (11.4%) had subtotal, 32 (30.5%) had partial pneumothorax by Light Index [9] evaluation. Recurrences were detected in 10 (9.5%) patients after discharge (Table 1).

No significant difference was found between the groups in terms of age, gender, smoking status and pneumothorax side (0.661, 0.337, 0.634, and 0.675, respectively). The size of pneumothorax which was evaluated by Light Index (9) was found to be significantly higher in patients who underwent SBTC insertion (P<0.001) (Table 1).

The median drainage time was 5 (4-6) days in the LBTD group and 3.5 (3-4.25) days in the SBCT group. The median time of hospitalization were 7 (5-8) days in the LBTD group and 3.5 (3-4.25) days in the SBCT group. Patients who underwent SBCT insertion had statistically significantly shorter catheter lengths and hospital stays (P<0.001) (Table 1). Pain severity, evaluated by VAS scores, right after the procedure, at the 1st, 6th and 12th hours were significantly lower in the SBCT group (Table 2) (P<0.001). Pneumothoraxes were treated successfully in all patients. Recurrence was detected in 4 (6.9%) patients who underwent SBTC and 6 (12.8%) patients who underwent LBTD insertions. There was no statistically significant difference between the two applications (P=0.337).

Table 1: Comparative evaluation of the LBTD and SBTC

		LBTD n:47(44.8%)	SBTC n:58(55.2%)	Total n:105	*P*-value
Age Median (25-75)		25.00 (21.00-34.00)	27.00 (22.00-32.25)	26.00 (22.00-33.00)	0.661
Gender n (%)	Male	41(87.2%)	54 (93.1%)	95 (90.5%)	0.337
	Female	6(12.8%)	4 (6.9%)	10 (%9.5)	
Smokers n (%)		39(83.0%)	46 (79.3%)	85 (81.0%)	0.634
Pneumothorax Size, n (%)	Minimal	0 (0%)	0 (0%)	0(0%)	<0.001
	Partial	30 (63.8%)	2 (3.4%)	32 (30.5%)	
	Subtotal	4 (8.5%)	8 (13.8%)	12(11.4%)	
	Total	13 (27.7%)	48 (82.8%)	61(58.1%)	
Pneumothorax side, n (%)	Left	23 (48.9%)	26 (44.8%)	49(46.7%)	0.675
	Right	24 (51.1%)	32 (55.2%)	56(53.3%)	
Drain termination (day) median (25-75)		5.00 (4.00-6.00)	3.50 (3.00-4.25)	4.00 (3.00-5.50)	<0.001
Hospital Stay (day) median (25-75)		7.00 (5.00-8.00)	3.50 (3.00-4.25)	4.00 (3.00-7.00)	<0.001
Recurrence n (%)		6 (12.8%)	4 (6.9%)	10 (9.5%)	0.337

n: number, LBTD: large bore thorax drain, SBTC: small bore thorax catheter

Table 2: Visual Analog Scale of LBTD and SBTC groups

	LBTD	SBTC	*P*-value
VAS (0th hour) median(25-75)	8.00 (7.00-8.00)	4.00 (3.00-4.00)	<0.001
VAS (1st Hour) median(25-75)	6.00 (5.00-7.00)	3.00 (2.00-3.00)	<0.001
VAS (6th hour) median(25-75)	6.00 (5.00-6.00)	2.00 (2.00-3.00)	<0.001
VAS (12th hour) median(25-75)	4.00 (4.00-5.00)	2.00 (1.00-2.00)	<0.001

LBTD: large bore thorax drain, SBTC: small bore thorax catheter, VAS: Visual Analog Scale

Discussion

The first thoracic drainage was performed 2400 years ago by Hippocrates in the treatment of empyema. In terms of size, drains are categorized as a "large bore" for those larger than 20 F and a "small bore" for those smaller than 20 F. In an *in vivo* study of Park et al., no significant difference was found according to the amount of fluid drainage between catheters 8F and above. However, they found that there was a significant difference between catheters larger and smaller than 8F [10].

British Thoracic Society guidelines suggests needle aspiration and immediate discharge after the procedure as the first treatment option. It states that needle aspiration with quick discharge decreases the length of hospital stay and health expenses [11]. However, The American College of Chest Physicians recommends hospitalization after LBTD insertion for the initial treatment [12]. There is still no consensus on the initial treatment of pneumothorax in Turkey. In our study, all patients who underwent surgical intervention were hospitalized. We found that SBTC insertion resulted in shorter hospitalization periods compared to LBTD (median: 7 days vs 3.5 days respectively). Çardak et al. [13] determined the hospitalization period of the SBTC group as 3.5 days and the LBTD group as 4.5 days in their study. They found no significant difference between the two groups for time of hospital stay. In another study, similarly, it was observed that the SBTC group had shorter time of hospital stay than LBTD group (median: 4 vs 7 days, respectively) [14].

Complications such as infection, malposition of the drain, hemorrhage, hypotension, and pulmonary edema may develop after pleural drainage [15]. In our study, no complications were observed in each size of drain application. According to the study of Tsai et al., there is a significant relationship between the size of pneumothorax and treatment failure. It stated that treatment failure increases for pneumothoraxes sized above 40% [16]. Although the median size of PSP in our study was significantly higher in the SBTC group, no treatment failure was observed in each group.

Prevention of recurrence is also another important treatment goal in pneumothorax patients. The second attack after discharge usually occurs within the first six months. In the study of Çardak et al. [13] no significant difference between two groups was observed in terms of recurrence rates. In a study published in Korea, patients who underwent SBTC insertion were discharged after the procedure and called after a week. The patients who underwent LBTD insertion were hospitalized. Although the drain termination time was shorter in LBTD group, the medical expenses were higher when compared with the SBTC group [17].

Chest tube application is associated with high pain and anxiety that may require intense analgesics or opioids [18]. Fang et al. [19] reported that patients who underwent LBTD insertion needed more analgesic than SBTC. In the study of Çardak et al. [13], after SBTC and LBTD procedures, patients' pain intensities were measured in the 1st, 4th, 12th and 24th hours. They found that pain levels were lower only in the 4th hour in the SBTC group. In addition, the authors observed more anxiety in patients during LBTD removal. Rahman et al. [20] found a relation between the drain size and the pain intensity during the drain insertion in their study. However, there was no significant difference between the drain size and pain intensity during drain removal. In our study, we observed less pain scores in all measurement times at the SBTC group.

Limitations

The limitations of our study are as follows: 1) The retrospective design; 2) Small study sample; 3) Short follow-up period. Using a scale to determine the pain levels at multiple times after the procedure and the comparative analysis of the homogenous intervention groups in terms of age, gender, smoking status, side of PSP are the strengths of our study.

Conclusions

Our study showed that SBTC usage in the treatment of PSP is more advantageous in terms of pain, tube determination time, and hospitalization time compared to LBTD. There is no difference in terms of effectiveness and recurrence rate. In addition, easy applicability, faster wound healing and better long-term cosmetic results are other advantages of SBTC.

References

1. Shields TW, Cicero JL, Ponn RB, RuschVW, editors. General Thoracic Surgery. 6th ed. Philadelphia: Lippincott Williams&Wilkins; 2005.
2. Sahn SA, Heffner JE. Spontaneous pneumothorax. N Engl J Med. 2000 Mar 23;342(12):868-74. doi: 10.1056/NEJM200003233421207.
3. Donahue DM, Wright CD, Viale G, Mathisen DJ. Resection of pulmonary blebs and pleurodesis for spontaneous pneumothorax. Chest. 1993;104(6):1767-9. doi: 10.1378/chest.104.6.1767.
4. Rivas de Andrés JJ, Jiménez López MF, Molins López-Rodó L, Pérez Trullén A, Torres Lanzas J; Spanish Society of Pulmonology and Thoracic Surgery. Normativa sobre el diagnóstico y tratamiento del neumotórax espontáneo [Guidelines for the diagnosis and treatment of spontaneous pneumothorax]. Arch Bronconeumol. 2008;44(8):437-48. Spanish. doi: 10.1016/s1579-2129(08)60077-4.
5. Melton LJ 3rd, Hepper NG, Offord KP. Incidence of spontaneous pneumothorax in Olmsted County, Minnesota: 1950 to 1974. Am Rev Respir Dis. 1979;120(6):1379-82. doi: 10.1164/arrd.1979.120.6.1379.
6. Balta C, Kuzucuoglu M. Conservative Treatment Approach in Primary Spontaneous Pneumothorax. J Coll Physicians Surg Pak. 2020;30(2):168-71. doi: 10.29271/jcpsp.2020.02.168.
7. Cho S, Lee EB. Management of primary and secondary pneumothorax using a small-bore thoracic catheter. Interact Cardiovasc Thorac Surg. 2010;11(2):146-9. doi: 10.1510/icvts.2009.226589.
8. Filosso PL, Sandri A, Guerrera F, Ferraris A, Marchisio F, Bora G, et al. When size matters: changing opinion in the management of pleural space—the rise of small-bore pleural catheters. J Thorac Dis. 2016;8(7):E503-E510. doi: 10.21037/jtd.2016.06.25.
9. Light RW. Pneumothorax. In: Pleural diseases. Baltimore: Williams & Wilkins; 2007. p. 306–39.
10. Park JK, Kraus FC, Haaga JR. Fluid flow during percutaneous drainage procedures: an in vitro study of the effects of fluid viscosity, catheter size, and adjunctive urokinase. AJR Am J Roentgenol. 1993;160(1):165-9. doi: 10.2214/ajr.160.1.8416618
11. MacDuff A, Arnold A, Harvey J; BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii18-31. doi: 10.1136/thx.2010.136986.
12. Baumann MH, Strange C, Heffner JE, Light R, Kirby TJ, Klein J, et al, ;AACP Pneumothorax Consensus Group. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. Chest. 2001;119(2):590-602. doi: 10.1378/chest.119.2.590.
13. Çardak ME, Özer KB, Cesur EE, Özdemir A, Evman RS, Demirhan R. Small Bore Thoracic Catheter Versus Chest Tube in Treatment of Primary Spontaneous Pneumothorax. SCIE. 2019;30(4):301-5. doi: 10.14744/scie.2019.84429.
14. Korczyński P, Górska K, Nasiłowski J, Chazan R, Krenke R. Comparison of Small Bore Catheter Aspiration and Chest Tube Drainage in the Management of Spontaneous Pneumothorax. Adv Exp Med Biol. 2015;866:15-23. doi:10.1007/5584_2015_146.
15. Rozenman J, Yellin A, Simansky DA, Shiner RJ. Re-expansion pulmonary oedema following spontaneous pneumothorax. Respir Med. 1996;90(4):235-8. doi: 10.1016/s0954-6111(96)90293-0.
16. Tsai TM, Lin MW, Li YJ, Chang CH, Liao HC, Liu CY, et al. The Size of Spontaneous Pneumothorax is a Predictor of Unsuccessful Catheter Drainage. Sci Rep. 2017:15;7(1):181. doi: 10.1038/s41598-017-00284-8.
17. Joh HK, Moon DH, Lee S. Efficacy and Cost-Effectiveness of Portable Small-Bore Chest Tube (Thoracic Egg Catheter) in Spontaneous Pneumothorax. Korean J Thorac Cardiovasc Surg. 2020;5;53(2):49-52. doi: 10.5090/kjtcs.2020.53.2.49. PMID: 32309202.
18. Luketich JD, Kiss M, Hershey J, Urso GK, Wilson J, Bookbinder M, et al. Chest tube insertion: a prospective evaluation of pain management. Clin J Pain. 1998;14(2):152-4. doi: 10.1097/00002508-199806000-00011.
19. Fang M, Liu G, Luo G, Wu T. Does pigtail catheters relieve pneumothorax?: A PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2018;97(47):e13255. doi: 10.1097/MD.0000000000013255.
20. Rahman NM, Maskell NA, Davies CW, Hedley EL, Nunn AJ, Gleeson FV, et al. The relationship between chest tube size and clinical outcome in pleural infection. Chest. 2010;137(3):536-43. doi: 10.1378/chest.09-1044.

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. 2020;4(9):826-829.
DOI: 10.28982/josam.790445

Research article
Araştırma makalesi

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

Enteral feed based gradual improvement of body mass index and normalization of micronutrients in children with malnutrition

Malnutrisyonlu çocuklarda enteral beslemeye dayalı vücut kitle indeksi'nin kademeli iyileştirilmesi ve mikrobesinlerin normalleşmesi

Meryem Keçeli Başaran [1], Nur Şeyma Zengin [2], Ali Evrim Doğan [3], Alihan Sürsal [4], Fatih Özdener [5]

[1] Gaziosmanpaşa Training and Resource Hospital, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Istanbul, Turkey
[2] Gaziosmanpaşa Training and Resource Hospital, Department of General Pediatrics, Istanbul, Turkey
[3] Nutricia, Advanced Medical Nutrition, Medical Department, Istanbul, Turkey
[4] Bahcesehir University, School of Medicine, Department of Neuroscience, Istanbul, Turkey
[5] Bahcesehir University, School of Medicine, Department of Pharmacology, Istanbul, Turkey

ORCID ID of the author(s)

MKB: 0000-0001-8362-8618
NŞZ: 0000-0001-7926-0064
AED: 0000-0002-9040-2737
AS: 0000-0001-8073-3033
FÖ: 0000-0002-0163-318X

Corresponding author / Sorumlu yazar:
Meryem Keçeli Başaran
Address / Adres: Gaziosmanpaşa Eğitim ve Araştırma Hastanesi, Çocuk Gastroenteroloji, Hepatoloji ve Beslenme Bölümü, Karayolları mah. Osmanbey Cad. 621 sok. Posta Kodu: 34255, Gaziosmanpaşa, İstanbul, Türkiye
E-mail: meryem.keceli07@yahoo.com

Ethics Committee Approval: Ethics approval was obtained from the Ethics Committee of Taksim Eğitim ve Araştırma Hastanesi on 02/10/2019 with session number 141. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Taksim Eğitim ve Araştırma Hastanesi Etik Kurulundan 02/10/2019 tarihinde 141 numaralı oturum ile alınmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: Malnutrition is a serious and frequently encountered condition affecting more than 900 million individuals worldwide. Its relationship with negative clinical outcome, bad prognosis and susceptibility to diseases has been demonstrated in numerous studies alongside with the importance of early nutritional intervention. The aim of this study was to define the beneficial influence of a hypercaloric enteral supplement on body mass index (BMI) z-score as well as ferritin, vitamin B12 and vitamin D micronutrients.

Methods: This study is a retrospective observational study. Records of patients who were diagnosed with malnutrition via a physician by having height and weight scores below -2 standard deviation were collected from Gaziosmanpaşa Training and Resource Hospital, Istanbul, Turkey. A comparative statistical analysis was performed on 205 pediatric malnutrition patients (ages 1 to 16) by gathering their BMI, ferritin, b12 and vitamin D at baseline with their measurements at 2 follow-up visits after the administration of hypercaloric (1.5kcal/mL) enteral supplement over 6 months.

Results: There was a significant inverse correlation between BMI z-scores and the duration of enteral supplement administration, reflected by a 33.2% reduction of the mean BMI z-scores from -2.11 to -0.7 over 6 months ($Z=-12.4$, $P<0.001$). Additionally, there was a reduction in the number of patients with excessive or insufficient amounts of ferritin, b12 and vitamin D concentrations with 80%, 41.7% and 39.3% respectively over six months.

Conclusions: Hypercaloric enteral supplementation is a short-acting and highly beneficial nutritional intervention in pediatric patients diagnosed with malnutrition, which provides a robust improvement in the BMI z-scores as well as a 2-tailed improvement of aforementioned micronutrients after six months of supplementation.

Keywords: Pediatrics, Malnutrition, Gastroenterology, Therapeutics

Öz

Amaç: Malnutrisyon, dünya çapında 900 milyondan fazla insanı etkileyen ciddi ve sık karşılaşılan bir durumdur. Malnutrisyon; olumsuz klinik sonuç, kötü prognoz ve hastalıklara yatkınlık ile yakından ilişkilidir, bu yüzden erken müdahalenin öneminin altını çizen çok sayıda çalışma yapılmıştır. Bu çalışmanın amacı, hiperkalorik enteral beslenme tedavisinin vücut kitle indeksi (VKİ) z-skorunun yanı sıra ferritin, B12 vitamini ve D vitamini mikro-besinlerinin üzerindeki yararlı etkilerini tanımlamaktır.

Yöntemler: Bu çalışma geriye dönük gözlemsel bir çalışmadır. Doktor tarafından boy ve kilo ölçümleri -2 standart deviasyonun altında olarak malnütrisyon tanısı almış hastaların kayıtları, Türkiye'nin İstanbul ilinde bulunan Gaziosmanpaşa Eğitim ve Araştırma Hastanesinden toplanmıştır. Toplamda 205 pediatrik malnutrisyon hastasının (1-16 yaş) ilk ziyaretine ait VKİ, ferritin, B12 vitamini ve D vitamini kayıtları, hiperkalorik (1,5 kcal/mL) müdahaleye başlandıktan 6 ay sonrasına kadar yapılan 2 vizite ölçümleri ile karşılaştırılarak istatistiksel olarak analiz edilmiştir.

Bulgular: VKİ z-skorları ile enteral beslenme tedavisi uygulama süresi arasında görsel ve istatistiksel olarak ek hastalık durumları farketmeksizin anlamlı bir ters korelasyon görülmüştür ($Z=-12,4$, $P<0,001$). Ortalama VKİ z-skoru %33,2'lik bir düzelme ile 6 aylık müdahale sonrası -2,11'den -0,7'ye yükselmiştir. Ek olarak, altı ay boyunca ferritin, B12 vitamini ve D vitamini konsantrasyonları gereğinden fazla veya yetersiz olan hasta sayısında sırasıyla %80, %41,7 ve %39,3 oranında azalma görülmüştür.

Sonuçlar: Hiperkalorik beslenme tedavisi, malnutrisyon teşhisi konan pediyatrik hastalarda hızlı, etkili ve oldukça faydalı bir beslenme müdahalesi olup, altı aylık takviye sonrası BMI z-skorlarında anlamlı düzelme ve yukarıda bahsedilen mikro besinlerde 2-taraflı iyileşme sağlamıştır.

Anahtar kelimeler: Pediatri, Malnutrisyon, Gastroenteroloji, Tedavi

How to cite/Atıf için: Başaran MK, Zengin NŞ, Doğan AE, Sürsal A, Özdener F. Enteral feed based gradual improvement of body mass index and normalization of micronutrients in children with malnutrition. J Surg Med. 2020;4(9):826-829.

Introduction

Malnourishment negatively affects the therapeutic outcome from infectious and malignant diseases and delays wound healing because it weakens the bodily functions and affects >900 million individuals worldwide [1]. Thus, malnutrition is a sign of poor outcome and is not always reversible after recovering from the malnourishment state, especially in cancer patients with disturbed energy metabolism [2]. Protein energy malnutrition (PEM) is an undernourishment state that increases susceptibility to various infectious diseases [3]. Undernourishment is a worldwide health problem that affects all age groups and is caused by various factors related to underdevelopment and poor nutrition in developed countries [4]. Malnutrition in childhood is a significant problem and during early childhood, it has a significantly negative effect on all aspects of development.

Despite the importance of a healthy diet for positive treatment outcomes and maintaining resistance to numerous diseases, congenital and acquired conditions, such as allergies, type I diabetes mellitus, inflammatory bowel disease (IBD), and congenital heart disease (CHD), can alter the dietary requirements or results in an immune reaction to food [5]. Especially in patients with accompanying diseases such as patients with Ulcerative colitis (UC) or celiac disease (CD), food allergy is a common consequence, among which 64% and 66% of the patients, respectively, have been reported to have food intolerance [6]. Moreover, the prevalence of CD increases in patients with diabetes mellitus and other autoimmune disorders, which highlights the importance of timely intervention [7].

The present study aimed to determine the effects of a novel prescription enteral nutritional supplement in pediatric patients with such underlying diseases as primary and secondary malnutrition. Study parameters were measured at baseline and then at two follow-ups during 6 months of enteral nutritional supplementation.

Materials and methods

Sample

The study included 205 pediatric patients (ages 1 to 16) diagnosed with malnutrition after presenting to the gastroenterology outpatient clinic of Gaziosmanpaşa Training and Resource Hospital due to inability to gain weight. Patients with height and weight below -2 standard deviation scores (SDS) and who were prescribed with nutritionally complete, dietary fiber-containing hypercaloric (1.5 kcal mL^{-1}) enteral supplement were included in the study. Patients' chronic diseases, biochemical scores, and nutrient requirements were recorded. Laboratory values, height and weight, and BMI were measured at baseline, and compared with measurements obtained after 3 and 6 months of the administration of aforementioned enteral supplement. Weight, height, and BMI z-scores were compared between time points to evaluate clinical improvement.

Observation

The results were obtained via comparing the vitamin D, B12, and ferritin levels, and BMI over the course of 6 months of enteral supplementation, according to posology calculations, which were dependent on the calculated energy requirements in each patient. Baseline measurements were obtained, and then measured again after 3 and 6 months of enteral supplementation. The patients were grouped according to age, as follows: 0-2 years; 3-5 years; 6-8 years; 9-12 years; 13-16 years. Additionally, as primary malnutrition was the most common condition (77%) in the cohort, followed by CD, UC, Familial Mediterranean Fever (FMF), food allergy, Crohn's disease, CHD, and asthma, these diseases were divided into 2 groups—primary malnutrition and secondary malnutrition.

Standardization and reference ranges

Optimal micronutrient reference ranges were obtained from Gaziosmanpaşa Training and Resource Hospital, as follows: Ferritin: 20-200 ng m L^{-1}, B12: 126.5-505 pg mL^{-1}, vitamin D: 30-100 ng mL^{-1}. Vitamin D values <20 ng mL^{-1} were considered as deficient, 20-30 ng mL^{-1} insufficient, and >100 ng mL^{-1}, excessive. Standardization of BMI values was maintained according to lambda (L), mu (M), and sigma (S) parameters, which refer to power in the Box-Cox transformation for skewness, median, and generalized coefficient of variation, respectively [8]. LMS parameters for each age group and gender were obtained from Centers for Disease Control and Prevention website [9]. To calculate each BMI z-score (BMIz) according to LMS parameters, the following formula [10] was used:

$$BMIz = \left[\left(\frac{BMI}{M}\right)^{L} - 1\right] \div (L \times S)$$

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.20.0 (IBM Corp., Armonk, NY, US). Descriptive statistical range values are indicated, and Friedman's test was used for all statistical calculations due to non-normally distributed datasets. In order to determine the significance of the non-parametric subgroup trends, the Wilcoxon test was used separately for each relationship. The level of statistical significance was set at $P<0.05$.

Ethical approval

The authors state that they have obtained the ethical approval from the ethics committee of Taksim Eğitim ve Araştırma Hastanesi on 02/10/2019 with session number 141. In addition, all patients signed the informed consent forms prior to inclusion in the study.

Results

The improvement in BMIz over the course of 6 months of enteral supplementation can be seen in Figure 1. This improvement was based on the difference in BMIz between baseline and the 6^{th}-month values (–2.11 and –0.7, respectively), which indicated a mean 1.41 (33.2%) improvement. The greatest improvement in BMIz was in the 1-2 years age group, followed by 3-5 years, 6-8 years, 9-12 years, and 13-16 years. There was a significant improvement in BMIz during the first 3 months of enteral supplementation, but very little from 3-6 months in the 13-16 years age group (Figure 1). Overall, the BMIz improved significantly over the course of 6 months of enteral supplementation ($P<0.001$). The comparative improvement in BMIz between each measurement time point was also significant ($P<0.001$) (Table 1). Both patient groups (primary malnutrition and secondary malnutrition) had a significant decrease in BMIz

during the 6 months of enteral supplement use based on Friedman's test (P<0.001) (Figure 2).

Ferritin values increased significantly over the course of 6 months of enteral supplementation (Figure 3a and Table 1). Moreover, the mean baseline ferritin level was 22.60 ng mL^{-1}, which is close to the minimum required level, but increased to 28.71 ng mL^{-1} after 6 months after enteral supplement usage. Baseline ferritin values showed that 40 patients had a level below the required minimum of 20 ng mL^{-1}, whereas 24 patients at 3 months and 8 patients at 6 months had a level below the required minimum level.

Table 1: Significance of the improvement in the study parameters after 3 and 6 months of enteral supplement use, as compared to baseline values given as descriptive statistics

	Mean (SD)	Median (Min-Max)	*P*-value
BMIz (baseline)	–2.12 (1.88)	-1.67 (–11.32-0.97)	<0.001*
BMIz (3rd month)	–1.29 (1.55)	-0.98 (–9.74-2.12)	
BMIz (6th month)	–0.71 (1.34)	-0.51 (–6.52-2.99)	
BMIz (3rd month)-BMIz (baseline)			<0.001**
BMIz (6the month)-BMIz (baseline)			<0.001**
BMIz (6th month)-BMIz (3rd month)			<0.001**
Ferritin (baseline) ng mL^{-1}	22.60 (19.44)	17.00 (2-190)	<0.001*
Ferritin (3rd month) ng mL^{-1}	24.88 (13.45)	21.00 (8-118)	
Ferritin (6th month) ng mL^{-1}	28.71 (12.53)	26.00 (13-124)	
Ferritin (3rd month)-ferritin (baseline)			<0.001**
Ferritin (6th month)-ferritin (baseline)			<0.001**
Ferritin (6th month)-ferritin (3rd month)			<0.001**
B12 (baseline) pg/ml	340.64 (194.75)	290.00 (126-1500)	0.447*
B12 (3rd month) pg/ml	320.39 (129.46)	284.00 (140-872)	
B12 (6th month) pg/ml	312.20 (99.54)	291.00 (149-670)	
Vitamin D (baseline) ng/mL	24.34 (17.14)	22.00 (8-213)	<0.001*
Vitamin D (3rd month) ng/mL	26.39 (7.56)	26.00 (13-62)	
Vitamin D (6th month) ng/mL	29.37 (7.1)	28.00 (14-49)	
Vitamin D (3rd month)-vitamin D (baseline)			<0.001**
Vitamin D (6th month)-vitamin D (baseline)			<0.001**
Vitamin D (6th month)-vitamin D (3rd month)			<0.001**

* Friedman's test, ** Wilcoxon signed-rank test, SD: Standard deviation

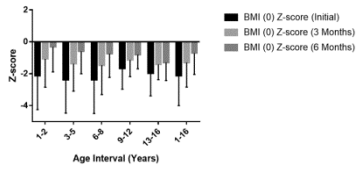


Figure 1: BMIz values at baseline, and after 3 and 6 months of enteral supplement use. Standard deviations for each age group, as well as all patients are indicated over each column.

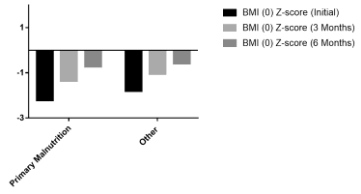


Figure 2: BMIz values in the patients with primary malnutrition and secondary malnutrition at baseline, and after 3 and 6 months of enteral supplementation.

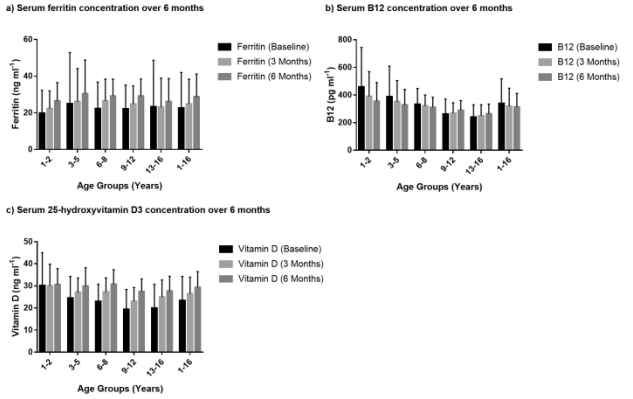


Figure 3: Ferritin, B12 and 25-hydroxyvitamin D3 values at baseline, and after 3 and 6 months of enteral supplementation. Standard deviations for each age group are indicated over each column.

There was not a significant change in the vitamin B12 level (Figure 3b and Table); however, the number of patients with a high B12 level decreased significantly over the course of 6 months. At baseline, 12 patients had a high B12 level (>505 pg mL^{-1}), versus 10 and 7 patients at 3 and 6 months, respectively. The highest B12 levels were 1500 pg mL^{-1}at baseline, 872 pg mL^{-1}at 3 months, and 670 pg mL^{-1} at 6 months, which indicated enteral supplementation stabilized the B12 level.

There was a significant increase in the vitamin D level over the course of 6 months of enteral supplement use (Figure 3c and Table 1); however, the increase in the 1-2 years age group was lower than in the other age groups (Figure 3c). Baseline values indicate that 56 patients had an insufficient vitamin D level (<30 ng mL^{-1}), but after 3 months of enteral supplementation 53 patients had an insufficient level, and after 6 months only 34 patients had an insufficient level, indicating that there was on overall improvement in the vitamin D level over the course of 6 months of enteral supplementation.

Discussion

Malnutrition and undernourishment occur due to multiple causes in all countries. In developing countries and underdeveloped countries, undernourishment is the primary cause of nutritional disorders [11], whereas in developed countries malnutrition is the primary cause of nutritional disorders, including DM and obesity [12]. The spectrum of nutritional disorders occur in all age groups [13].

It was reported that malnutrition negatively affects the immune system, wound healing, and drug metabolism, which have serious negative effects on the prognosis of such diseases as cancer, cardiovascular diseases and infectious diseases [14]. Pediatric malnutrition and undernourishment can have very serious consequences, negatively affecting development, as well as long-term negative effects via epigenetic modifications [1,13]. These serious consequences include poor quality of life, high healthcare costs, and poor response to cancer treatments and treatments for infectious diseases [14,15]. In developed countries, the prevalence of malnutrition can be as high as 50% of the population and even higher in developing or underdeveloped countries [16].

Timely treatment is very important for all diseases, including malnutrition due to the above-mentioned negative cascade of reactions that develop over time. Most importantly, cachexia, which is a syndrome that causes continuous consumption of energy combined with metabolic disorders such as anorexia during a chronic inflammatory condition or cancer [17], should be diagnosed and treated as early as possible [18]. Diagnosis should signal the initiation of nutritional intervention due to the fact that the longer the body is exposed to the stress of inadequate nutrition, the higher the probability of long-term negative effects [18, 19]. Early nutritional intervention aims to support normal growth and eating behavior, which ameliorate malnutrition and/or prevent the risk of having malnutrition in the future, enhancing patient quality of life [20].

The Quetelet index, also known as BVMI, is used to evaluate the nutritional status of patients and is based on the relationship between weight and height [21]. In addition to BMI, ideal body weight (IBW) and weight-for-height (WFH) can be used to evaluate nutritional status [22]; however, WHO accepts BMI as the measurement of nutritional status [23]. Despite some

controversies about BMI [24], alongside with the insufficiencies of BMI upon informing the analyzer about specific localizations of fat around the body [25], in overall measures, BMI maintains its clinical significance on tracing obesity and it's as valuable as more expensive methods for adiposity calculations. In the present study, BMI was the measurement used to determine the effectiveness of enteral nutritional supplementation.

There was an insignificant decrease in BMIz values after 3 months of enteral supplementation usage in the present study's 13-16 years age group, which might have been because this age group included only 23 patients, whereas the other age groups included in the study comprised 35-51 patients. Similarly, the significant decrease in BMIz values in the 1-2 years age group, which included 35 patients, might have been due to the same reason; however, there was an overall significant decrease in BMIz values. Both the patients with primary malnutrition and secondary malnutrition had a significant decrease in BMIz over the course of 6 months of enteral supplementation, which may indicate the benefits of hypercaloric supplement are not dependent on the type of malnutrition. Additionally, the baseline BMIz in the patients with primary malnutrition was worse (–2.21) than in the patients with secondary malnutrition (–1.80), which improved to –0.73 and –0.61, respectively at 6th month. The patients with primary malnutrition might have had greater improvement in the BMIz because their baseline BMIz values were worse.

The overall decrease in the percentage of the patients in the present study with excessive or insufficient ferritin, B12, and vitamin D levels with observed improvement of 80%, 41.7%, and 39.3%, respectively, is an indication of the beneficial effect of the enteral supplement. Enteral supplementation clearly improved the ferritin and vitamin D levels in the patients during the course of 6 months, except in the 1-2 years group in the case of vitamin D, whereas there wasn't a significant overall increase or decrease in B12 levels.

Vitamin D is a crucial micronutrient, and an inhibitory stimulant in tumor cells via activation of an apoptotic cascade in malignant cells. It decreases the rate of tumor progression by preventing their uncontrolled proliferation, and limiting angiogenesis and migration [26, 27]. Vitamin D insufficiency is a signal of tumor progression, but it is also inversely correlated with obesity due to limited adipose tissue formation [28]. Additionally, low ferritin and B12 levels of 46.6% and 21.1, respectively, was reported in a cohort of 1252 pediatric and adult patients with morbid obesity [29]. An inverse correlation between the B12 level and BMI has also been reported [30]. As such, in addition to the improvement in BMIz observed in the present study, the increase in the number of patients within the reference range for ferritin, B12, and vitamin D after 6 months of enteral supplementation is another clear indication of the effectiveness of the nutritional intervention described herein.

Limitations

A cohort of patients more than 200 for each primary and secondary malnutrition should be observed to indicate no difference between effectiveness of hypercaloric supplement more confidently. Additionally, more follow-ups covering more than a year should be added to this kind of analysis to observe the long-term effectiveness of our nutritional intervention.

Conclusions

Enteral nutritional supplementation is an effective nutritional intervention that significantly improves BMIz values and yields a 2-tailed improvement in micronutrient levels after 6 months of administration, regardless of diagnosed disease.

References

1. Martins VJB, Toledo Florêncio TMM, Grillo LP, do Carmo P Franco M, Martins PA, Clemente APG, et al. Long-lasting effects of undernutrition. Int J Environ Res Public Health. 2011;8(6):1817-46. Epub 05/26. doi: 10.3390/ijerph8061817. PubMed PMID: 21776204.
2. Kim DH. Nutritional issues in patients with cancer. Intestinal research. 2019;17(4):455-62. Epub 10/14. doi: 10.5217/ir.2019.00076. PubMed PMID: 31597414.
3. Schaible UE, Kaufmann SH. Malnutrition and infection: complex mechanisms and global impacts. PLoS medicine. 2007;4(5):e115. Epub 2007/05/03. doi: 10.1371/journal.pmed.0040115. PubMed PMID: 17472433; PubMed Central PMCID: PMCPmc1858706.
4. Amoroso L. The Second International Conference on Nutrition: Implications for Hidden Hunger. World Rev Nutr Diet. 2016;115:142-52. Epub 2016/05/21. doi: 10.1159/000442100. PubMed PMID: 27197665.
5. Fakhoury M, Negrulj R, Mooranian A, Al-Salami H. Inflammatory bowel disease: clinical aspects and treatments. J Inflamm Res. 2014;7:113-20. doi: 10.2147/JIR.S65979. PubMed PMID: 25075198.
6. Kotlyar DS, Shum M, Hsieh J, Blonski W, Greenwald DA. Non-pulmonary allergic diseases and inflammatory bowel disease: a qualitative review. World J Gastroenterol. 2014;20(32):11023-32. doi: 10.3748/wjg.v20.i32.11023. PubMed PMID: 25170192.
7. Ludvigsson JF, Ludvigsson J, Ekbom A, Montgomery SM. Celiac Disease and Risk of Subsequent Type 1 Diabetes. A general population cohort study of children and adolescents. 2006;29(11):2483-8. doi: 10.2337/dc06-0794.
8. Cole TJ. The LMS method for constructing normalized growth standards. Eur J Clin Nutr. 1990;44(1):45-60. Epub 1990/01/01. PubMed PMID: 2354692.
9. Statistics NCfH. Percentile Data Files with LMS Values August 4, 2009 [cited 2019 July 3]. Available from: https://www.cdc.gov/growthcharts/percentile_data_files.htm.
10. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. Bmj. 2000;320(7244):1240-3. doi: 10.1136/bmj.320.7244.1240. PubMed PMID: 10797032.
11. Barr RD, Gomez-Almaguer D, Jaime-Perez JC, Ruiz-Argüelles GJ. Importance of Nutrition in the Treatment of Leukemia in Children and Adolescents. Arch Med Res. 2016;47(8):585-92. doi: 10.1016/j.arcmed.2016.11.013. PubMed PMID: 28476186.
12. Mathers CD, Lopez AD, Murray CJL. The Burden of Disease and Mortality by Condition: Data, Methods, and Results for 2001. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, editors. Global Burden of Disease and Risk Factors. Washington (DC): World Bank, The International Bank for Reconstruction and Development/The World Bank Group.; 2006.
13. Bundy DAP, de Silva N, Horton S, Patton GC, Schultz L, Jamison DT. Investment in child and adolescent health and development: key messages from Disease Control Priorities, 3rd Edition. Lancet (London, England). 2018;391(10121):687-99. Epub 2017/11/21. doi: 10.1016/s0140-6736(17)32417-0. PubMed PMID: 29153316.
14. Bauer J, Jürgens H, Frühwald MC. Important aspects of nutrition in children with cancer. Adv Nutr. 2011;2(2):67-77. Epub 03/10. doi: 10.3945/an.110.000141. PubMed PMID: 22332035.
15. van Eys J. Effect of nutritional status on responses to therapy. Cancer Res. 1982;42(2 Suppl):747s-53s. Epub 1982/01/01. PubMed PMID: 6799193.
16. Sala A, Pencharz P, Barr RD. Children, cancer, and nutrition—A dynamic triangle in review. Cancer. 2004;100(4):677-87. doi: 10.1002/cncr.11833.
17. Dhanapal R, Saraswathi T, Govind RN. Cancer cachexia. J Oral Maxillofac Pathol. 2011;15(3):257-60. doi: 10.4103/0973-029X.86670. PubMed PMID: 22144825.
18. Nursing RCo, Fellow FGRCN. Nutrition in Children and Young People with Cancer: RCN Guidance: RCN; 2014.
19. Schoeman J, Dannhauser A, Kruger M. Malnutrition in paediatric oncology patients2010.
20. Nieuwoudt CH. Nutrition and the child with cancer: Where do we stand and where do we need to go? South Afr J Clin Nutr. 2011;24. doi: 10.1080/16070658.2011.11734376.
21. Keys A, Fidanza F, Karvonen MJ, Kimura N, Taylor HL. Indices of relative weight and obesity. J Chronic Dis. 1972;25(6):329-43. Epub 1972/07/01. PubMed PMID: 4650929.
22. Brinksma A, Huizinga G, Sulkers E, Kamps W, Roodbol P, Tissing W. Malnutrition in childhood cancer patients: a review on its prevalence and possible causes. Crit Rev Oncol/Hematol. 2012;83(2):249-75. Epub 2012/01/24. doi: 10.1016/j.critrevonc.2011.12.003. PubMed PMID: 22264939.
23. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organization technical report series. 1995;854:1-452. Epub 1995/01/01. PubMed PMID: 8594834.
24. Rahman M, Berenson AB. Accuracy of current body mass index obesity classification for white, black, and Hispanic reproductive-age women. Obstet Gynecol. 2010;115(5):982-8. doi: 10.1097/AOG.0b013e3181da9423. PubMed PMID: 20410772.
25. Nuttall FQ. Body Mass Index: Obesity, BMI, and Health: A Critical Review. Nutr Today. 2015;50(3):117-28. Epub 04/07. doi: 10.1097/NT.0000000000000092. PubMed PMID: 27340299.
26. Krishnan AV, Trump DL, Johnson CS, Feldman D. The role of vitamin D in cancer prevention and treatment. Endocrinol Metab Clin North Am. 2010;39(2):401-18, table of contents. Epub 2010/06/01. doi: 10.1016/j.ecl.2010.02.011. PubMed PMID: 20511060; PubMed Central PMCID: PMCPmc5788175.
27. Fleet JC. Molecular actions of vitamin D contributing to cancer prevention. Mol Aspects Med. 2008;29(6):388-96. Epub 2008/08/30. doi: 10.1016/j.mam.2008.07.003. PubMed PMID: 18755215; PubMed Central PMCID: PMCPmc2613446.
28. Kong J, Li YC. Molecular mechanism of 1,25-dihydroxyvitamin D3 inhibition of adipogenesis in 3T3-L1 cells. Am J Physiol Endocrinol Metabol. 2006;290(5):E916-24. Epub 2005/12/22. doi: 10.1152/ajpendo.00410.2005. PubMed PMID: 16368784.
29. Arshad M, Rezvandoost N, Pazouki A, Riazi S, Aghababa Rangraz M, Mokhber S. Assessment of the Serum Levels of Hemoglobin, Ferritin, and Vitamin B12 in a Sample of Iranian Population with Morbid Obesity. J Minim Invasive Surg Sci. 2016;Inpress. doi: 10.17795/minsurgery-37637.
30. Baltaci D, Kutlucan A, Turker Y, Yilmaz A, Karacam S, Deler H, et al. Association of vitamin B12 with obesity, overweight, insulin resistance and metabolic syndrome, and body fat composition; primary care-based study. Medicinski glasnik : official publication of the Medical Association of Zenica-Doboj Canton, Bosnia and Herzegovina. 2013;10(2):203-10. Epub 2013/07/31. PubMed PMID: 23892832.

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. 2020;4(9):830-834.
DOI: 10.28982/josam.799157

Research article
Araştırma makalesi

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

Evaluation of pressure ulcer risk in hospitalized patients after metabolic surgery

Metabolik cerrahi sonrası hospitalize hastalarda bası yarası riskinin değerlendirilmesi

Fatih Can Karaca [1], Kıvılcım Ulusan [2]

[1] Bilgi University, Department of Health Sciences, Istanbul, Turkey
[2] University of Health Sciences, Istanbul Education and Research Hospital, Department of General Surgery, Istanbul, Turkey

ORCID ID of the author(s)
FCK: 0000-0001-8959-0294
KU: 0000-0002-4793-5714

Corresponding author / Sorumlu yazar:
Fatih Can Karaca
Address / Adres: Bilgi Üniversitesi, Sağlık Bilimleri Bölümü, İstanbul, Türkiye
E-mail: drckaraca@yahoo.com

Ethics Committee Approval: The study was approved by the ethics committee of the University of Health Sciences, Istanbul Education and Research Hospital on 8/21/2020 with the approval number 2502. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma 21.08.2020 tarihinde Sağlık Bilimleri Üniversitesi İstanbul Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından 2502 onay numarası ile onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract

Aim: Patients who underwent surgery are in the risk group for development of pressure ulcers (PU) due to several factors including surgery time, immobilization and preexisting comorbidities. We aimed to evaluate the PU risk using The Braden Scale in patients during their hospitalization after sleeve gastrectomy with transit bipartition (SG+TB) surgery.

Methods: This is a retrospective cohort study evaluating the PU risk using The Braden Scale, which consists of six subscales including sensory perception, moisture, activity, mobility, nutrition, and friction/shear. The patients were sub-grouped in terms of PU risk based on total Braden score.

Results: The study group consisted of 33 patients who underwent SG+TB. The mean Braden score was 19.2(2.77) (range 12-23) during the hospitalization period. The Braden scores of the patients were lower on the 2nd (P<0.001), 3rd (P<0.001), 4th (P=0.005), and 5th (P=0.004) postoperative days compared to postoperative day 1, and on the 3rd, 4th, 5th, and 6th postoperative days compared to postoperative day 2 (P<0.001 for each). According to our data, the PU risk was significantly different between the 1st postoperative day and the 2nd, 3rd, 4th, and 5th postoperative days (P<0.001 for each).

Conclusion: Metabolic surgery patients have an elevated risk for PU during the hospitalization period. Protein supplementation is among the factors that might improve the nutritional status of patients and decrease PU risk during hospitalization.

Keywords: Pressure ulcer risk, Metabolic surgery, The Braden scale

Öz

Amaç: Operasyon geçiren hastalar, ameliyat süresi, immobilizasyon ve varolan komorbiditeleri nedeniyele bası yarası gelişimi için risk grubunda bulunmaktadır. Bu çalışmada sleeve gastrektomi ve transit bipartisyon (SG+TB) ameliyatı sonrası hastanede yatış sırasında bası yarası riskini Braden Ölçeği ile değerlendirmeyi amaçladık.

Yöntemler: Bu retrospektif kohort çalışmada, Braden Ölçeği değerlendirmesi, duyusal algılama, nem, aktivite, hareketlilik, beslenme ve sürtünme/yırtılma olmak üzere altı alt ölçekten oluşan çizelge ile hastanede yatış süresince günlük olarak yapıldı. Hastalar bası yarası riski açısından toplam Braden skoruna göre alt gruplara ayrıldı.

Bulgular: Çalışma grubu SG+TB uygulanan 33 hastadan oluşturuldu. Ortalama Braden skoru hastanede kalış süresi boyunca 19,2(2,77) idi (12-23 arası). Hastaların Braden skorları postoperatif 2. (P<0,001), 3. (P<0,001), 4. (P=0,005) ve 5. (P=0,004) günlerde postoperatif 1. güne göre anlamlı olarak düşüktü. Braden skorları postoperatif 3., 4., 5. ve 6. günlerde postoperatif 2. güne göre anlamlı olarak düşüktü (her biri için P<0.001). Verilerimize göre PU riski açısından oranlar ameliyat sonrası 2., 3., 4. ve 5. günlerde 1. güne göre anlamlı olarak farklıydı (her biri için P<0,001).

Sonuç: Metabolik cerrahi hastaları, hastanede kaldıkları süre boyunca yüksek bası yarası riski taşır. Protein takviyesi, hastaların beslenme durumlarını iyileştirebilecek ve hastanede yatış sırasında bası yarası riskini azaltabilecek faktörler arasındadır.

Anahtar kelimeler: Bası yarası riski, Metabolik cerrahi, Braden skalası

How to cite/Atıf için: Karaca FC, Ulusan K. Evaluation of pressure ulcer risk in hospitalized patients after metabolic surgery. J Surg Med. 2020;4(9):830-834.

Introduction

The definition of pressure ulcer (PU) is made by The National Pressure Ulcer Advisory Panel (NPUAP) as "localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear" [1]. A large variety of factors including nutritional imbalance and/or insufficiency, skin moisture, disturbed circulation, obesity, prolonged bed rest, improper positioning, and chronic diseases have been associated with PU development [2-4].

Patients who underwent surgery are also prone to PU particularly during the early postoperative period as a result of restricted mobility and prolonged bed rest due to pain and discomfort, and PU is a significant morbidity factor related to longer hospitalization and increased medical costs [5].

Patients who underwent bariatric and metabolic surgery procedures for the resolution of obesity and type 2 diabetes mellitus (T2DM) are at the high-risk group for the development of PU as a result of their preexisting comorbidities, difficulty in frequent position changes, folded skin regions, increased pressure of the muscle and fat tissue on the bony prominences, all of which negatively affect the circulation in these areas.

The Braden Scale is a universal PU risk evaluation tool consisting of six subcategories [6]. According to this scale, patients are evaluated in terms of their sensory perception, skin moisture, activity level, and mobility, nutrition, and friction/shear, and high-risk patients are determined and appropriate care or treatment are given in order to increase patient's life quality and decrease morbidity.

Since patients who underwent metabolic surgery are a special group of patients with impaired vascular structure and circulation as a result of T2DM, we aimed to evaluate The Braden Scale in this group of patients during their hospitalization after sleeve gastrectomy with transit bipartition (SG+TB) surgery.

Materials and methods

This is a retrospective cohort study evaluating The Braden Score data charts of patients who underwent SG+TB surgery for the resolution of T2DM. The data were collected in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from each patient. The study was approved by the ethical committee of the University of Health Sciences, Istanbul Education and Research Hospital on 21.08.2020 with the approval number 2502.

Exclusion criteria included a previous presence of PU and a BMI of 40 kg/m^2 in order to eliminate patients with Class III obesity. From the remaining patients, the study group consisted of 33 T2DM patients who had undergone metabolic surgery. All patients had a hospitalization duration of four days after the surgery, two patients had been discharged on postoperative day 5, and 26 patients had been discharged on the 6th postoperative day.

SG+TB was indicated for obese patients with T2DM [7]. Our inclusion criteria were patients with a BMI between 30-35 kg/m2 with comorbidities and/or with a glycated hemoglobin (HbA1c) level of >7.5% despite optimum anti-diabetic therapy, or a BMI greater than 35 kg/m2 with a history of T2DM, and being obese for ≥5 years despite conservative weight loss therapy and a lifestyle modification.

All patients had been evaluated prior to surgery and confirmed for the absence of a PU that might interfere with the study data.

All patients had started multivitamin supplements two weeks before the operation, and a liquid diet was started 48 days before the procedure. All patients underwent SG+TB surgery laparoscopically between January 2018 and June 2020. In brief, the surgery procedure consisted of sleeve gastrectomy, followed by a gastroileal and jejunoileal anastomoses [8].

In the postoperative period, the patients were mobilized as early as they are available for ambulation, and encouraged to mobilize during their hospitalization. All patients were provided with air mattresses, and frequent repositioning was provided by medical staff every two hours.

Patients were given little amounts of water six hours after the surgery and consumed a liquid diet without solid particles for four-weeks post-operatively starting from the next postoperative day. All patients were initiated protein supplement with a dose of 27 g/day (Barifit, Barifit Health Products, Istanbul, Turkey).

The Braden Scale evaluation was performed every day during the hospitalization using the chart developed in the Turkish language and filled with the help of the ward nurse.

The scale consisted of six categories, and categories assessing sensory perception, moisture, activity, mobility, and nutrition status have four steps, while friction/shear is evaluated in three subscale points (Table 1). A total Braden score ranges between 6 and 23, and the patients were subgrouped in terms of PU risk as follows: Severe risk: total score ≤9; High risk: total score 10-12; Moderate risk: total score 13-14; Mild risk: total score 15-18; no risk: total score 19-23.

Statistical analysis

GraphPad Prism 8.0 software for Windows (California, USA) was used for statistical analyses. The data were presented as mean (standard deviation). Minimum and maximum values were provided for Braden scores. One-way ANOVA with Sidak's multiple comparisons test was performed for the comparison of Braden scores on the postoperative days. A chi-square test was performed for the comparison of categorical variables. A *P*-level of <0.05 was considered statistically significant.

Results

This is a retrospective study including 33 patients (17 males and 16 females) with T2DM who underwent SG+TB. The baseline characteristics of the patients were shown in Table 2.

The mean age was 49.2(7.54) years. The BMIs of the patients ranged between 31.3-39.7 kg/m2 with a mean of 37.4 kg/m2. The mean postoperative hospital stay was 5 days ranging from 4 to 6 days.

The mean albumin level was 43.3(2.6) g/L, and the mean total protein was 68.7(4.06) g/L. The mean Braden score was 19.2(2.77), ranging from 12 to 23 during the hospitalization period. The mean scores during the hospitalization in terms of postoperative days were given in Table 3.

The Braden scores of the patients were significantly lower on the 2nd, 3rd, 4th, and 5th postoperative days compared to postoperative day 1 (P<0.001, P<0.001, P=0.005 and P=0.004, respectively). The Braden scores of the patients were significantly lower on the 3rd, 4th, 5th, and 6th postoperative days compared to the postoperative day 2 (P<0.001 for each). Patients also showed a significant difference in the 4th, 5th, and 6th postoperative days compared to the 3rd postoperative day. There was no difference between the Braden scores on the postoperative 4 vs 5, 4 vs 6, and 5 vs 6 days. The daily trend of the Braden scores during the hospitalization period was presented in Figure 1.

Table 1: Subscales of the Braden Scale for predicting pressure sore risk [6]

Risk Factor	Score/Description			
	1	2	3	4
Sensory Perception	Completely limited	Very limited	Slightly limited	No impairment
Moisture	Constantly moist	Often moist	Occasionally moist	Rarely moist
Activity	Bedfast	Chair fast	Walks occasionally	Walks frequently
Mobility	Completely immobile	Very limited	Slightly limited	No limitations
Nutrition	Very poor	Probably inadequate	Adequate	Excellent
Friction and Shear	Problem	Potential problem	No apparent problem	

Table 2: Demographic data of the patients

Variable	Mean(SD)
Age (years)	49.2(7.54)
F/M	16/17
BMI (kg/m2)	37.4(1.86)
Albumin (g/L)	43.3(2.6)
Total protein (g/L)	68.7(4.06)
Postoperative hospital stay (days)	5(1)

Table 3: Braden scores of the patients who underwent SG+TB during the hospitalization period.

Braden score	Mean(SD)	Min	Max
Po day 1	22.1(0.92)	21	23
Po day 2	14.7(1.29)	12	16
Po day 3	18.6(1.45)	16	22
Po day 4	19.8(1.59)	18	22
Po day 5	20.2(1.05)	19	22
Po day 6	21.2(0.83)	20	22
Total score during the hospitalization	19.2(2.77)	12	23

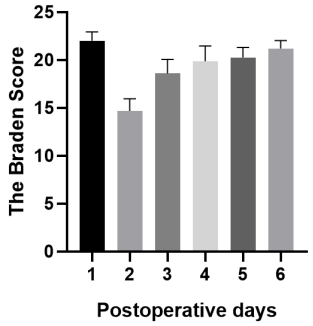


Figure 1: The postoperative daily trend of the Braden scores evaluating the pressure ulcer risk of patients who underwent metabolic surgery.

On the 1st postoperative day, all patients were in the no risk group, while, 6% of the patients were evaluated in the high risk, 8(24%) in the moderate risk group, and 19(58%) in the mild risk group on the 2nd postoperative day. On postoperative day 3, there were three patients (9%) in the moderate risk group, 16 (48%) in the mild risk group, whereas none of the patients were in the high-risk group. On postoperative day 4, the ratio of the patients was 3% in the moderate risk group, 12% in the mild risk group and 94% in the no risk group, whereas none of the patients were in the high-risk group (Table 4). None of the patients had a score of ≤9 during the follow-up period.

Table 4: Evaluation of the risk status of patients according to the Braden scores during the hospitalization period

Variables	High risk (10-12)	Moderate risk (13-14)	Mild risk (15-18)	No risk (≥19)
PO day 1 (n; %)	0	0	0	33, 100%
PO day 2 (n; %)	2, 6%	8, 24%	19, 58%	4, 12%
PO day 3 (n; %)	0	3, 9%	16, 48%	14, 43%
PO day 4 (n; %)	0	1, 3%	4, 12%	28, 85%
PO day 5 (n; %)	0	0	2, 6%	29, 94%
PO day 6 (n; %)	0	0	0	7, 100%

PO: Post-Operative

Discussion

As the number of metabolic surgery procedures increases worldwide, concerns on improved peri- and postoperative care for this specific patient group increase in order to provide a better life quality, patient safety, and decreased morbidity. The Braden Scale is a widely accepted universal tool for the determination of at-risk patients for the development of PU. In our study, we evaluated the PU risk in patients who underwent SG+TB surgery for the resolution of T2DM during their postoperative hospitalization period. According to our data, the Braden score was at its lowest on the second postoperative day, indicating a higher PU risk for the patients. The risk score started to increase initiating from the postoperative third day, and none of the patients were in the "high-risk" group starting from the postoperative day 3. The patients who underwent metabolic surgery procedures are of concern as a result of their history of chronic disease, comorbidities, and peripheral vascular disease that might interfere with the circulation of the body areas during the postoperative hospitalization period.

As the presence of T2DM, peripheral vascular diseases, and obesity are defined among the intrinsic risk factors for the development of PU, metabolic surgery patients require specific attention on the early postoperative period as a result of decreased mobility, restricted physical activity, and concomitant medical perturbances [9-12]. PU during the postoperative hospitalization period following surgery is an underestimated concern, and to our knowledge, the studies investigating the PU risk in patients who underwent metabolic procedures are limited. Surgical positioning of the patient compresses the blood vessels, increasing the tissue pressure compared to the circulation, and decreased oxygen supply to the tissues increases the risk of PU development in that phase. In addition, lymphedema and increased interstitial fluid pressure might further complicate the situation especially in patients with lower albumin and total protein levels [13-15]. Although preventive actions for the positioning of patients with table pads are related to increased costs, extra care in the immediate and early postoperative period is required for metabolic surgery patients.

Adıyeke et al. [16] defined that a higher neutrophile to lymphocyte ratio, platelet to lymphocyte ratio and mean platelet volume are independent predictors for the development of PU in intensive care patients, indicating a preexisting inflammatory state. Studies exhibited that surgery is related to the synthesis of proinflammatory cytokines, Interleukin (IL)-1, and 6, which cause decreased albumin production [17-19]. Although an albumin level lower than 35 g/L is a risk factor for PU indicating a status of malnutrition, none of our patients had an albumin level of <40 g/L [20]. However, protein supplementation starting on postoperative day 2 might have a positive effect on the

circulation and protein replacement that might lower with the synthesis of acute-phase proteins in the early postoperative period. Since proteins are essential for proper wound healing mainly through collagen synthesis and fibroblast proliferation, a positive nitrogen balance is required for the minimization of adverse events in the recovery period.

The recommended level of protein intake by The NPUAP was determined as 1.25 to 1.5 g/kg of body weight per day for patients with PU. They also concluded that the total protein leakage through the draining wounds should be of concern in order to calculate the optimum protein dose for the patient [21]. There are previous studies reporting the improving effects of the addition of high levels of protein to the daily diets of individuals with PU in terms of healing rate and decreased ulcer size [22,23]. In our study group, total protein and albumin levels were higher than those of the predetermined values for PU risk. However, the improving effect of protein supplementation on Braden scores indicates that a preoperative nutritional intervention with protein supplementation might have beneficial effects on PU in this group of patients.

Studies reported that PU can develop within hours during hospitalization, thus early identification of at-risk patients is essential in order to take certain preventive actions [24]. For the metabolic surgery patients, besides the intrinsic risk factors, the duration of the surgery and restricted mobility are among the risk factors for PU development. As most of the patients are overweight and monitored by various devices including catheters, drainage sacs, and ECG electrodes, frequent repositioning of the patient might be a burden for the medical staff, and inadequate care might be given to the patient. Thus, postoperative patient care in the early phases of hospitalization is an interdisciplinary issue, and optimum care should be given by a team of nurses and medical staff that are regularly supervised by the operating surgeon. Although the Braden scale is an effective tool for the assessment of risk status, regular inspection of the skin is crucial for the implementation of prevention and treatment strategies. Although examination of the whole body might be time-consuming and require extra effort for the caregiving team, the inspection of the skin folds is also essential especially for obese and extremely obese individuals. Previous studies reported the high-risk areas for PU development as spine, sacrum, heels, trochanter, and ischium, which are bony prominences under the pressure of skin and layers of fat and muscle [25]. Some researchers also offered the use of infrared thermometers for the detection of PU risk since increased temperature and skin moisture are among the essential risk factors for the development of PU [26,27].

Limitations

The limitations of our study include the lack of data regarding details of mobilization during the hospitalization and on other variables of nutritional status including transferrin, pre-albumin, and retinol binding protein. In addition, preexisting nutritional status of the patients had not been evaluated using proper evaluation tools by a dietitian. On the other hand, SG+TB patients are specific group of patients with their unique features, and evaluation of PU risk in this group using The Braden Score, a widely accepted universal PU evaluation tool would yield valuable data on the PU risk and life quality of metabolic surgery patients in the postoperative hospitalization period.

Conclusions

We conclude that, PU risk is increased during the postoperative period in the metabolic surgery patients, even in the early phase of hospitalization. Thus, since the patients with T2DM and obesity are among the risk group for the development of PU, certain precautions are required. The nutritional status of the patients should be evaluated prior to the surgery with proper monitoring tools, and immediate actions should be taken for at-risk individuals in order to provide a better healing process and decrease the risk of PU development. Furthermore, the PU risk should be evaluated by the caregiving team, and early protein supplementation should not be overlooked for this group of patients.

References

1. National Pressure Ulcer Advisory Panel and European Pressure Ulcer Advisory Panel. National Pressure Ulcer Advisory Panel; Washington DC: 2009. Prevention and Treatment of Pressure Ulcers: Clinical Practice Guideline.
2. Chen H, Chen X, Wu J. The incidence of pressure ulcers in surgical patients of the last 5 years. Wounds. 2012;24(9):234–41.
3. Lindgren M, Unosson M, Krantz AM, Ek AC. Pressure ulcer risk factors in patients undergoing surgery. Journal of Advanced Nursing. 2005;50(6):605–12.
4. Sala JJ, Mayampurath A, Solmos S, Vonderheid SC, Banas M, D'Souza A, et al. Predictors of pressure injury development in critically ill adults: A retrospective cohort study. Intensive Crit Care Nurs. 2020;25:102924. doi: 10.1016/j.iccn.2020.102924.
5. Aloweni F, Ang SY, Fook-Chong S, Agus N, Yong P, Goh MM, Tet al. A prediction tool for hospital-acquired pressure ulcers among surgical patients: Surgical pressure ulcer risk score. Int Wound J. 2019;16(1):164-75. doi: 10.1111/iwj.13007.
6. Bergstrom N, Braden BJ, Laguzza A, Holman V. The Braden Scale for Predicting Pressure Sore Risk. Nurs Res. 1987;36:205-10.
7. Bhandari M, Fobi MAL, Buchwald JN; Bariatric Metabolic Surgery Standardization (BMSS) Working Group. Standardization of Bariatric Metabolic Procedures: World Consensus Meeting Statement. Obes Surg. 2019;29(Suppl 4):309-345. doi: 10.1007/s11695-019-04032-x.
8. Santoro S, Castro LC, Velhote MC, Malzoni CE, Klajner S, Castro LP, et al. Sleeve gastrectomy with transit bipartition: a potent intervention for metabolic syndrome and obesity. Ann Surg. 2012;256(1):104-10. doi: 10.1097/SLA.0b013e31825370c0.
9. Hyun S, Li X, Vermillion B, Newton C, Fall M, Kaewprag P, et al. Body mass index and pressure ulcers: improved predictability of pressure ulcers in intensive care patients. Am J Crit Care. 2014 Nov;23(6):494-500; quiz 501. doi: 10.4037/ajcc2014535. PMID: 25362673; PMCID: PMC4385001.
10. Liang M, Chen Q, Zhang Y, He L, Wang J, Cai Y, Li L. Impact of diabetes on the risk of bedsore in patients undergoing surgery: an updated quantitative analysis of cohort studies. Oncotarget. 2017 Feb 28;8(9):14516-24. doi: 10.18632/oncotarget.1432
11. Kang Z, Zhai X. The Association between Pre-existing Diabetes Mellitus and Pressure Ulcers in Patients Following Surgery: A Meta-analysis. Sci Rep. 2015;5:13007. https://doi.org/10.1038/srep13007
12. Ahn H, Cowan L, Garvan C, Lyon D, Stechmiller J. Risk Factors for Pressure Ulcers Including Suspected Deep Tissue Injury in Nursing Home Facility Residents: Analysis of National Minimum Data Set 3.0. Adv Skin Wound Care. 2016;29(4):178-90; quiz E1. doi: 10.1097/01.ASW.0000481115.78879.63.
13. Montalcini T, Moraca M, Ferro Y, Romeo S, Serra S, Raso MG, et al. Nutritional parameters predicting pressure ulcers and short-term mortality in patients with minimal conscious state as a result of traumatic and non-traumatic acquired brain injury. J Transl Med. 2015;13:305.
14. Primiano M, Friend M, McClure C, Nardi S, Fix L, Schafer M, et al. Pressure ulcer prevalence and risk factors during prolonged surgical procedures. AORN J. 2011 ;94(6):555-66. doi: 10.1016/j.aorn.2011.03.014.
15. Margolis DJ, Knauss J, Bilker W, Baumgarten M. Medical conditions as risk factors for pressure ulcers in an outpatient setting. Age Ageing. 2003;32(3):259-64. doi: 10.1093/ageing/32.3.259.
16. Adıyeke E, Adıyeke L . Neutrophil to lymphocte ratio and mean platelet volume may predict the development of the pressure ulcers. J Surg Med. 2020;4(7):578-81.
17. Chamberlain CS, Leiferman EM, Frisch KE, Brickson SL, Murphy WL, Baer GS, et al. Interleukin expression after injury and the effects of interleukin-1 receptor antagonist. PLoS One. 2013;8(8):e71631. doi: 10.1371/journal.pone.0071631.
18. Jawa RS, Anillo S, Huntoon K, Baumann H, Kulaylat M. Interleukin-6 in surgery, trauma, and critical care part II: clinical implications. J Intensive Care Med. 2011;26(2):73-87. doi: 10.1177/0885066610384188.
19. MacIntosh C, Morley JE, Chapman IM. The anorexia of aging. Nutrition. 2000;16(10):983-95.
20. Bluestein D, Javaheri A. Pressure ulcers: Prevention, evaluation, and management. Am Fam Physician. 2008;78:1186–94.
21. Cox J, Rasmussen L. Enteral nutrition in the prevention and treatment of pressure ulcers in adult critical care patients. Crit Care Nurse. 2014;34:15–27.
22. Crowe T. Nutrition therapy in the prevention and treatment of pressure ulcers. Wound Practice Res. 2009;17:90–9.
23. Breslow RA, Hallfrisch J, Guy DG, Crawley B, Goldberg AP. The importance of dietary protein in healing pressure ulcers. J Am Geriatr Soc. 1993;41(4):357-62. doi: 10.1111/j.1532-5415.1993.tb06940.x.
24. Gefen A. How much time does it take to get a pressure ulcer? Integrated evidence from human, animal, and in vitro studies. Ostomy Wound Manage. 2008;54(10):26-8, 30-5. PMID: 18927481.
25. Skogestad IJ, Martinsen L, Børsting TE, Granheim TI, Ludvigsen ES, Gay CL, et al. Supplementing the Braden scale for pressure ulcer risk among medical inpatients: the contribution of self-reported symptoms and standard laboratory tests. J Clin Nurs. 2017;26(1-2):202-14. doi: 10.1111/jocn.13438. Epub 2016 Oct 20. PMID: 27322501.
26. Nakagami G, Sanada H, Iizaka S, Kadono T, Higashino T, Koyanagi H, et al. Predicting delayed pressure ulcer healing using thermography: a prospective cohort study. J Wound Care. 2010;19(11):465-6, 468, 470 passim. doi: 10.12968/jowc.2010.19.11.79695.

27. Koerner S, Adams D, Harper SL, Black JM, Langemo DK. Use of Thermal Imaging to Identify Deep-Tissue Pressure Injury on Admission Reduces Clinical and Financial Burdens of Hospital-Acquired Pressure Injuries. Adv Skin Wound Care. 2019;32(7):312-20. doi: 10.1097/01.ASW.0000559613.83195.f9.

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. 2020;4(9):835-837.
DOI: 10.28982/josam.729803

Review
Derleme

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

Tietze syndrome

Tietze sendromu

İsmail Ertuğrul Gedik [1], Timuçin Alar [1]

[1] Çanakkale Onsekiz Mart University Faculty of Medicine Department of Thoracic Surgery, Çanakkale, Turkey

ORCID ID of the author(s)
İEG: 0000-0002-1667-4793
TA: 0000-0002-4719-002X

Abstract
Tietze syndrome, first described in 1921 by Prof. Alexander TIETZE, is characterized with tender nonsuppurative swelling, pain, and tissue edema in the second or third costosternal cartilage. Differential diagnosis of Tietze syndrome includes diverse diseases, and its diagnosis relies on clinical examination, not the use of additional diagnostic techniques. The treatment of Tietze syndrome includes the use of anti-inflammatory medication and implementation of lifestyle modifications during the attacks. Surgical treatment is reserved for refractory cases and often is not necessary. Tietze syndrome can easily be diagnosed and treated in primary care medicine practice due to its benign nature.
Keywords: Tietze syndrome, Differential diagnosis, Treatment, Lifestyle modifications

Öz
Tietze sendromu ilk olarak 1921 yılında Prof. Alexander TIETZE tarafından tanımlanmıştır. Tietze sendromu ikinci veya üçüncü kostosternal kartilajda süpüratif olmayan, şişlik, hassasiyet, ağrı ve doku ödemi olarak tanımlanır. Tietze sendromunun ayırıcı tanısı birçok farklı hastalığı kapsamaktadır. Tietze sendromu tanısı esas olarak kliniktir olup genellikle ek tanı yöntemlerinin kullanılmasını zorunlu kılmaz. Tietze sendromunun tedavisi ataklar sırasında anti-inflamatuar ilaç kullanımı ve yaşam tarzı değişikliklerin uygulanması içerir. Cerrahi tedavi refrakter olgular için uygulanabilmekle birlikte genellikle gerekli değildir. Tietze sendromu iyi huylu yapısı nedeniyle birinci basamak hekimlik uygulamalarında kolayca teşhis ve tedavi edilebilir.
Anahtar kelimeler: Tietze sendromu, Ayırıcı tanı, Tedavi, Yaşam tarzı değişiklikleri

Corresponding author / Sorumlu yazar:
İsmail Ertuğrul Gedik
Address / Adres: Çanakkale On sekiz Mart Üniversitesi Tıp Fakültesi, Göğüs Cerrahisi Anabilim Dalı, Çanakkale, Türkiye
E-mail: ertugrulgedik@gmail.com

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

How to cite/Atıf için: Gedik İE, Alar T. Tietze syndrome. J Surg Med. 2020;4(9):835-837.

Introduction

Tietze syndrome (TS), first described in 1921 by Prof. Alexander TIETZE [1], is characterized with tender nonsuppurative swelling, tenderness, pain, and tissue edema in the second or third costosternal cartilage (Figure 1). TS is one of the musculoskeletal causes of chest wall pain. In primary care, about 35% of all patients who are admitted with chest pain are diagnosed with musculoskeletal pain [2].

Etiology and epidemiology

The exact epidemiology of the TS is obscure. It is a rare cause of chest wall pain and is known to affect people under the age 40, mainly during the second and third decades [3]. Male to female ratio is thought to be equal but the exact incidence and prevalence of this entity remains unknown. TS occurs equally on right and left sides of thorax [4]. TS's exact etiology is unknown. Tuberculosis is blamed as an etiological factor but has never been proven [1,3].

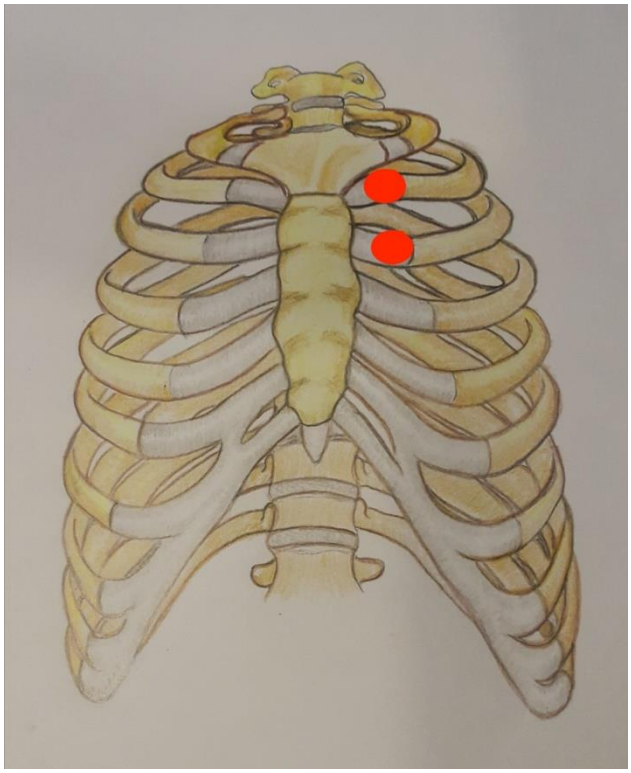


Figure 1: Demonstration of common sites of Tietze syndrome

Differential diagnosis

Differential diagnosis of TS includes costochondritis, other musculoskeletal pain syndromes, cartilage tumors (chondroma, chondrosarcoma), primary spontaneous pneumothorax and acute myocardial infarction. The comparison between TS and these diseases are described in Table 1 [3,5-10]. Other diseases in the differential diagnosis of TS are fibromyalgia (FM), gastro-esophageal reflux disease (GERD), chest wall infections and abscesses. Fibromyalgia (FM) is a common chronic musculoskeletal pain syndrome, characterized by diffuse musculoskeletal pain with a widespread soft tissue tenderness on physical examination, fatigue and sleep disturbance [11]. It is the most common disease in the differential diagnosis of TS. 2-8% of the general population is considered to have FM [12,13]. It is a benign condition which can cause anterior chest pain, and lead to misdiagnosis [13]. Pain caused by GERD is dull and aching-type, with acid reflux to mouth which cannot be aggravated with palpation and movement [14]. Chest wall infections and abscesses can also cause chest pain with swelling on the affected site, a superficial infection with erythema, or a draining sinus [15,16].

Table 1: Comparison of the major characteristics of the Tietze Syndrome, Costochondritis, Cartilage Tumors, Primary Spontaneous Pneumothorax and Acute Myocardial Infraction

	Tietze Syndrome	Costochondritis	Cartilage Tumors	Primary Spontaneous Pneumothorax	Acute Myocardial Infarction
Age of onset	Common under 40	All ages	Common over 40	Common in second and third decades	Common over 40
Prevalence	Uncommon	Common	Uncommon	Relatively Common	Common
Pain nature	Aching, dull or sharp. Sometimes pleuritic. Aggravated with palpation and movement	Sharp aching	Sharp	Sharp and pleuritic	Aching, dull. Cannot be aggravated with palpation and movement
Pain onset	Recent onset with physical activity	Pain onset with repetitive physical activity	Usually chronic	Sudden	Recent onset or sudden
Symptoms	Painful swelling on the chest, sometimes erythema	Chest pain without swelling on the chest	Chest pain, usually swelling on the affected site	Sharp chest pain, dyspnea	Aching dull chest pain (angina pectoris), palpitation
Signs	Tenderness and edema of the 2nd or 3rd costosternal cartilage	Tenderness on palpation without edema on 4th, 5th and 6th costosternal cartilages	Tenderness on palpation, MRI findings specific to cartilage tumors	Sharp pleuritic pain with sudden onset, diminished lung auscultation sounds, tachypnea and dyspnea are usually present	Angina pectoris, Q wave presence, inverted T wave presence, bundle branch block on ECG, myocardial movement abnormalities in echocardiography
Diagnosis	Physical examination is usually enough, thoracic CT if infection is suspected	Physical examination, USG, MRI, bone scintigraphy	Physical examination, PA chest x-ray, CT, USG, MRI, bone scintigraphy, PET/CT	Physical examination, chest x-ray is usually enough, USG and thoracic CT are seldom necessary	Physical examination, ECG, Echocardiography, PTCA
Treatment	Analgesic treatment with NSAID, local corticosteroid injections in relapsing cases	Analgesic treatment with NSAID, local lidocaine and corticosteroid injections in relapsing cases	Resection	Chest tube thoracostomy, oxygen inhalation and analgesic treatment with NSAID	Antiaggregants, PTCA, CABG

PA: posterior-anterior, CT: computer tomography, USG: Ultrasonography, MRI: magnetic resonance imaging, NSAID: non-steroid anti-inflammatory drugs, PTCA: Percutaneous transluminal coronary angioplasty, CABG: Coronary artery bypass graft, PET/CT: positron emission tomography/computer tomography, ECG: electrocardiography

Diagnosis

For the diagnosis of TS, an accurate medical history-taking and physical examination is usually enough. Patients express a painful swelling on the anterior chest wall on one side, but some cases of TS are bilateral. The pain is usually dull and aching in character but can also be expressed as a pleuritic pain. Movements involving chest wall such as sneezing, coughing, deep breathing and physical activity may exacerbate the pain [17].

Signs of the TS include erythematous swelling of the second or third costosternal cartilage on inspection, and tenderness on palpation. The reproduction of pain with palpation is useful to rule out acute myocardial infraction [18]. Lung auscultation must be performed to rule out spontaneous pneumothorax and should be normal in TS.

Laboratory tests usually show elevated inflammatory parameters on blood chemistry such as leukocytosis, elevated erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels, thus they are nonspecific and usually inconclusive. Imaging studies which may be performed include posterior-anterior (PA) chest x-ray, ultrasonography, magnetic resonance imaging (MRI), and nuclear imaging studies such as bone scintigraphy with technetium-99 [19]. PA chest x-rays can rule out spontaneous pneumothorax and cartilage tumors.

Ultrasonography and MRI may reveal edema and non-specific inflammation in the costochondral cartilage. MRI can also rule out cartilage tumors of the chest wall with good accuracy. Bone scintigraphy with technetium-99 may be used to rule out neoplasms of the cartilage tissue. Electrocardiography should be performed in cases in which AMI is suspected. The presence of ST segment changes, new-onset left bundle branch block, presence of Q waves, and new-onset T wave inversion increase the likelihood of acute coronary syndrome or acute myocardial infarction [7].

Treatment

Management of TS is conservative in nature. Limiting the movement of involved costochondral cartilage by activity restriction and oral non-steroid anti-inflammatory drugs (NSAID) with or without topical agents are usually adequate for the treatment of TS. Local cold application over the affected site may relieve tissue swelling. This is based upon clinical experience and widespread practice, but this approach has not been established in randomized trials [20]. The choices of NSAID include naproxen sodium (220 mg tablet, 2x1 or 2x2 tablets daily), ibuprofen (200 mg tablet, 3-4x2-3 tablets daily) and flurbiprofen (100 mg tablet, 2x1 tablets daily). There is no consensus for the duration of NSAID treatment; while we prefer to treat patients diagnosed with TS for 3 weeks. Patient education should include suggestions regarding abstaining from lifting heavy objects, exercise and sports including chest wall movements (such as swimming, weightlifting, martial arts), pushing heavy objects, carrying bags on the shoulder of the involved side and applying massage on the affected costochondral cartilage during the TS episode. In our clinics we suggest patients with TS to implement these lifestyle modifications for a duration of 3 weeks. Patients should also be notified that TS is a chronic disorder and recurrences are common. It should be explained that the swelling may improve slightly with treatment and lifestyle modifications but may not recover completely. Patient education should also address a common concern in these patients: The chest pain is of non-cardiac origin. The pain can be reproduced with certain physical activities during the outpatient clinics examination, which may be helpful in reassuring the patient. Scheduling a follow-up appointment four to six weeks after the initial examination to reassure the patient, assess the effectiveness of initial therapy, the need for additional therapy or further diagnostic workup is suggested [20].

In refractory cases who are unresponsive to oral NSAIDs and patients who report and increase in the swelling of the chest wall should be referred to a thoracic surgeon for further diagnosis and treatment. Local injection of corticosteroids can be performed to these refractory or severe cases of TS to relieve the symptoms [10]. Increase in the swelling of the chest wall may be secondary to a growing cartilage tumor, thus further diagnostic work-up in a thoracic surgery clinic is necessary [4]. Surgical treatment is only performed in a rare selection of patients who are refractory to medical treatment and have low qualities of life because of TS [21]. Costochondral cartilage resection sites usually tend to develop a hypertrophic scar, which is an important cosmetic cause of patient dissatisfaction and thus, decrease in the quality of life [22].

Conclusion

TS is a benign and rare cause of erythematous swelling and chest wall pain which is usually unilateral, in the second or third costochondral cartilage. It can easily be diagnosed and treated in primary care medicine practice due to its benign nature. Careful history taking and physical examination is usually enough for the diagnosis of TS, but physicians should be careful in ruling out potentially dangerous entities in the differential diagnosis of TS because of their morbidity and mortality. It should also be kept in mind that TS is a chronic cause of decrease in the quality of life and preventive medicine practices such as lifestyle modification is important in its treatment.

References

1. Tietze A. Über eine eigenartige Häufung von Fällenmit Dystrophieder Rippenknorpel. Berliner Klinische Wochenschrift. 1921;58:829-31.
2. Hoorweg BB, Willemsen RT, Cleef LE, Boogaerts T, Buntinx F, Glatz JF, et al. Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses. Heart. 2017;103:1727-32. doi: 10.1136/heartjnl-2016-310905.
3. Rokicki W, Rokicki M, Rydel M. What do we know about Tietze's syndrome? Kardiochirurgia i Torakochirurgia Polska. 2018;15:180-2.
4. Kaplan T, Gunal N, Gulbahar G, Kocer B, Han S, Eryazgan MA, et al. Painful Chest Wall Swellings: Tietze Syndrome or Chest Wall Tumor? Thorac Cardiovasc Surg. 2016;64:239-44. doi: 10.1055/s-0035-1545261.
5. Ayloo A, Cvengros T, Marella S. Evaluation and treatment of musculoskeletal chest pain. Prim Care. 2013;40:863-87, viii. doi: 10.1016/j.pop.2013.08.007.
6. Shah AA, D'Amico TA. Primary chest wall tumors. J Am Coll Surg. 2010;210:360-6. doi: 10.1016/j.jamcollsurg.2009.11.012.
7. McConaghy JR, Oza RS. Outpatient diagnosis of acute chest pain in adults. Am Fam Physician. 2013;87:177-82.
8. Rascoe PA, Reznik SI, Smythe WR. Chondrosarcoma of the thorax. Sarcoma. 2011;2011:342879. doi: 10.1155/2011/342879.
9. Dhua A, Chaudhuri AD, Kundu S, Tapadar SR, Bhuniya S, Ghosh B, et al. Assessment of spontaneous pneumothorax in adults in a tertiary care hospital. Lung India. 2015;32:132-6. doi: 10.4103/0970-2113.152622.
10. Cho JY, Park D. Ultrasound-Guided Corticosteroid Injection in a Patient With Tietze Syndrome Combined With Costochondral Joint Swelling. Am J Phys Med Rehabil. 2019;98:e71-3. doi: 10.1097/PHM.0000000000001072.
11. Wise CM. Major causes of musculoskeletal chest pain in adults. 2019. https://www.uptodate.com/contents/major-causes-of-musculoskeletal-chest-pain-in-adults.
12. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014;311:1547-55. doi: 10.1001/jama.2014.3266.
13. Almansa C, Wang B, Achem SR. Noncardiac chest pain and fibromyalgia. Med Clin North Am. 2010;94:275-89. doi: 10.1016/j.mcna.2010.01.002.
14. Clarrett DM, Hachem C. Gastroesophageal Reflux Disease (GERD). Mo Med. 2018;115:214-8.
15. Bergeron EJ, Meguid RA, Mitchell JD. Chronic Infections of the Chest Wall. Thorac Surg Clin. 2017;27:87-97. doi: 10.1016/j.thorsurg.2017.01.002.
16. Schipper P, Tieu BH. Acute Chest Wall Infections: Surgical Site Infections, Necrotizing Soft Tissue Infections, and Sternoclavicular Joint Infection. Thorac Surg Clin. 2017;27:73–86. doi: 10.1016/j.thorsurg.2017.01.001.
17. Karabudak O, Nalnant S, Ulusoy RE, Dogan B, Harmanmyeri Y. Generalized nonspecific postular lesions in Tietze's syndrome. J Clin Rheumatol 2007;13:300-30.
18. Gräni C, Senn O, Bischof M, Cippà PE, Hauffe T, Zimmerli L, et al. Diagnostic performance of reproducible chest wall tenderness to rule out acute coronary syndrome in acute chest pain: a prospective diagnostic study. BMJ Open. 2015;5(1):e007442. doi: 10.1136/bmjopen-2014-007442.
19. Sawada K, Ihoriya H, Yamada T, Yumoto T, Tsukahara K, Osako T, et al. A patient presenting painful chest wall swelling: Tietze syndrome. World J Emerg Med. 2019;10:122-4. doi: 10.5847/wjem.j.1920-8642.2019.02.011.
20. Phillips K, Schur PH. Management of isolated musculoskeletal chest pain. 2020. https://www.uptodate.com/contents/management-of-isolated-musculoskeletal-chest-pain.
21. Gologorsky R, Hornik B, Velotta J. Surgical Management of Medically Refractory Tietze Syndrome. Ann Thorac Surg. 2017;104:e443-e445. doi: 10.1016/j.athoracsur.2017.07.035.
22. Wee JH, Park MH, Oh S, Jin HR. Complications associated with autologous rib cartilage use in rhinoplasty: a meta-analysis. JAMA Facial Plast Surg. 2015;17:49-55. doi: 10.1001/jamafacial.2014.914.

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. 2020;4(9):838-841.
DOI: 10.28982/josam.716164

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

Pigmented villonodular synovitis of the knee confused with juvenile rheumatoid arthritis in a 3-year-old child: A case report

3 yaşındaki bir çocukta juvenil romatoid artrit olarak karışan dizde pigmente villonodüler sinovit: Olgu sunumu

Ertuğrul Şahin [1], Hasan Tatari [1]

[1] Dokuz Eylul University Hospital, Department of Orthopedics and Traumatology, Izmir, Turkey

ORCID ID of the author(s)
EŞ: 0000-0002-8509-3570
HT: 0000-0002-7661-9606

Abstract
Pigmented villonodular synovitis (PVNS) is rare and characterized by diffuse synovial cell proliferation with the development of villi, or round/ovoid lobulated nodules of varied sizes. It usually presents in adults between the ages of 30 and 40 years and is uncommon in the pediatric population. We herein report a 3-year-old female patient with PVNS causing a femoral subchondral lesion in the right knee. Her symptoms started at the age of one and she had gotten treatment for juvenile rheumatoid arthritis for 2 years. The patient was operated, and the tumor was excised. Arthrotomy was performed for diffuse PVNS and diagnosis was made histopathologically. She was followed-up for 18 months with clinical examinations and MRI, as necessary. She had no pain or limitation in range of motion. She is currently fully functional and ambulatory.
Keywords: PVNS, Pediatric, Knee, Juvenile rheumatoid arthritis

Öz
Pigmente villonodüler sinovit (PVNS), farklı boyutlardaki yuvarlak veya oval loblu nodüllerin oluşturduğu sinovyal hücrelerdeki diffüz proliferasyona bağlı nadir görülen bir patolojidir. Genellikle 30-40 yaş arasındaki erişkinlerde görülür ve pediatrik popülasyonda nadirdir. Bu çalışmada, sağ diz femoral kondillerin subkondrol lezyonuna neden olan PVNS tanılı 3 yaşında bir kız sunuldu. Bir yaşında semptomları başlayan hasta 2 yıl boyunca juvenil romatoid artrit tedavisi aldı. Şikayetleri geçmemesi üzerine hasta opere edildi. Kitle, tanı ve tedavi için eksize edildi. Diffüz PVNS olan hasta için artrotomi yapıldı ve histopatolojik olarak incelemeyle tanısı kesinleştirildi. Klinik ve MRG ile 18 ay takip edildi. 18. ayındaki kontrollerinde hastanın sağ dizinde hareket kısıtlılığı veya ağrı mevcut değildi. Tüm semptomları geçen hasta tam olarak fonksiyonel olarak mobilize olmaktadır.
Anahtar kelimeler: PVNS, Pediatri, Diz, Juvenil romatoid artrit

Corresponding author / Sorumlu yazar:
Ertuğrul Şahin
Address / Adres: Dokuz Eylül Üniversitesi Hastanesi, Ortopedi ve Travmatoloji Bölümü, İzmir, Türkiye
E-mail: ertugrulsahinn@hotmail.com

Informed Consent: The authors stated that the written consent was obtained from the parents of the patients presented with images in the study.
Hasta Onamı: Yazarlar çalışmada görüntüleri ile sunulan hastanın ebeveynlerinden yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/27/2020
Yayın Tarihi: 27.09.2020

Introduction

Pigmented villonodular synovitis (PVNS), a rare pathology, was first described by Jaffe [1] in 1941. It is characterized by diffuse synovial cell proliferation and concomitant development of villi, or round/ovoid lobulated nodules in varied sizes. It generally occurs in adults between 30-40 years of age [2]. As PVNS is uncommon in children, diagnosis is often delayed, insidious, unclear, and difficult to figure out from the initial radiographic findings. Differential diagnosis is also challenging: Careful distinction should be made between PVNS and rheumatoid arthritis, arthropathies related to coagulopathies, tuberculosis, other inflammatory and synovial processes [3]. There are reports in the literature stating that initial age of knee involvement in the pediatric population varies from 12 months to 15 years of age [3-5].

PVNS occurs in two forms: Localized or diffuse. Hemosiderin, macrophages, and giant cells are located in synovium. The joint, tendon sheath or bursa are the affected areas. When a single mass is present in the synovium, affecting a smaller portion, it is called localized PVNS, but mostly, the entire synovium is affected, which indicates diffuse form [2].

It is very uncommon to see PVNS and related bone erosion in children. We herein report these two uncommon conditions in one patient with diffuse PVNS, who was followed up for 18 months with clinical examinations and MRIs.

How to cite / Atıf için: Şahin E, Tatari H. Pigmented villonodular synovitis of the knee confused with juvenile rheumatoid arthritis in a 3-year-old child: A case report. J Surg Med. 2020;4(9):838-841.

Case presentation

A 3-year-old girl presented with swelling and pain in her right knee for the last 2,5 years. Her family reported that the swelling and pain began after a rotational trauma. Joint fluid aspiration was studied, yielding a normal result. The patient was followed up with cast and anti-inflammatory drugs. The symptoms did not improve in 5 months, after which ultrasonographic examination showed fluid collection in the knee, which was evaluated as synovitis. MRI showed a diffuse lesion of high T2 signal intensity at the suprapatellar bursa (Figure 1).

The patient was referred to the Pediatric Rheumatology Clinic with the diagnosis of mono-articular juvenile idiopathic arthritis. The treatment was held at the Pediatric Rheumatology Department with subcutaneous Methotrexate 10 mg/kg and Ibuprofen for 2 years, nevertheless, knee swelling, and pain did not regress. Rheumatological markers, tuberculosis and brucellosis tests were all normal. Repeat MRI was comparatively examined with the one obtained 2 years ago, which showed an increase in the size and signal intensity of the mass in the knee (Figure 2).

The last MRI showed that there was a vascular malformation, and a large hemangioma was suspected. The patient was then referred to our clinic for further evaluation. Physical examination revealed a diffuse swelling over the knee with a palpable smooth mass all around the knee without any distinct borders (Figure 3).

There was no sign of inflammation. The range of motion (ROM) was normal with little limitation in extension, approximately 10 degrees. No fluid was found inside the knee. Muscle strength was normal and gait was a little antalgic. Plain radiography of the knee showed no abnormality (Figure 4). The laboratory examinations and rheumatologic tests were normal.

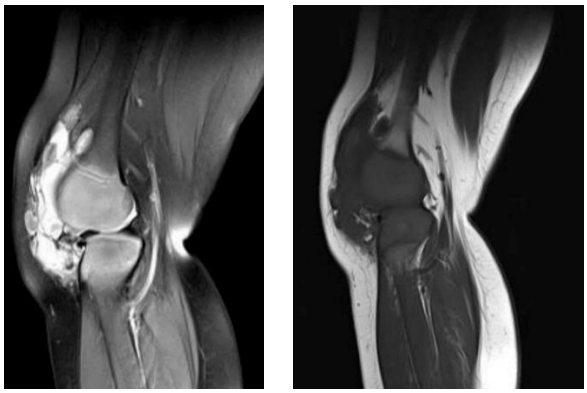


Figure 1: (A) MRI T2-weighted sequences (a) and T1-weighted sequences (B) showing high intensity mass in retropatellar and suprapatellar regions

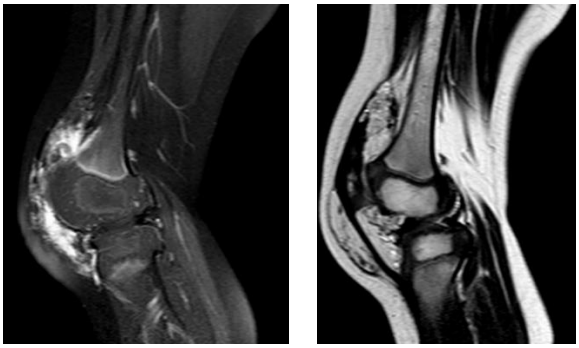


Figure 2: (A) T2 MRI and (B) T1 MRI images of the PVNS. Images delineate the extent of the PVNS anterior to the patella and subcutaneous area.

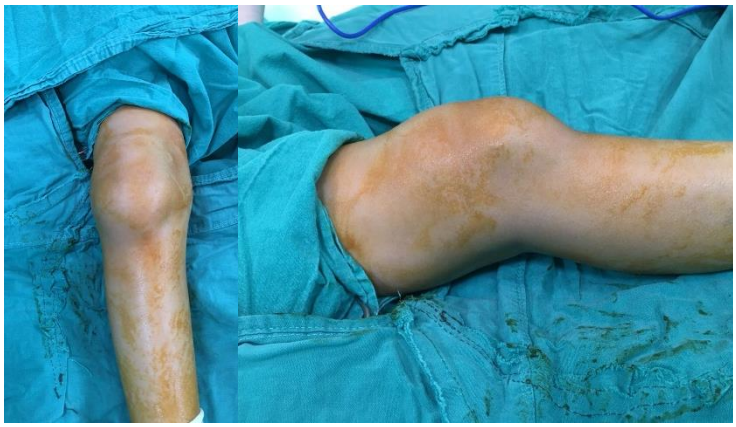


Figure 3: Preoperative photographs demonstrating diffuse swelling of right knee joint

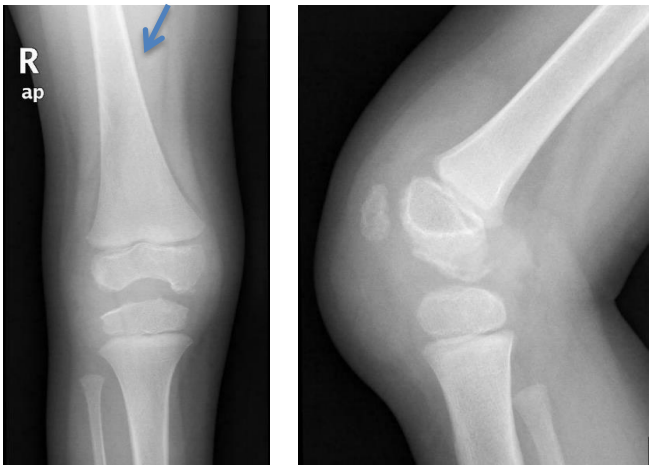


Figure 4: (A) Anteroposterior and (B) lateral radiographic views of the right knee with soft tissue swelling

Almost complete excision of the lesion was performed through arthrotomy with medial parapatellar approach with the tourniquet inflated under general anesthesia. Macroscopically, the knee joint was covered by hypertrophic villous synovium, which was diffuse, dense, and reddish-brown pigmented (Figure 5). Bone erosions were seen in both femoral condyles, especially medially (Figure 6). Total synovectomy was performed and almost all brown pigment on the cartilage was debrided (46 x 27 x 13 mm) (Figure 7). The final histopathologic diagnosis was PVNS with brown pigment accumulation on synovial epithelium (Figure 8).

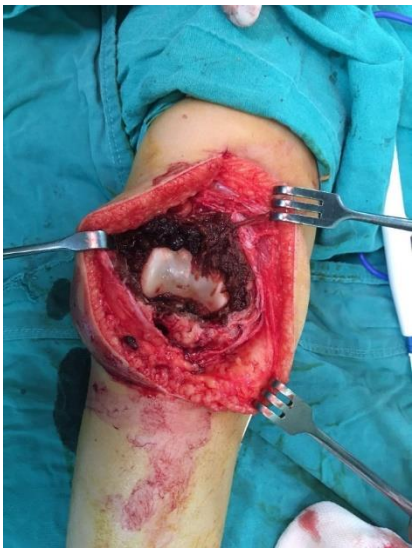


Figure 5: Macroscopic view of PVNS covering the suprapatellar area and intercondylar notch in the right knee joint

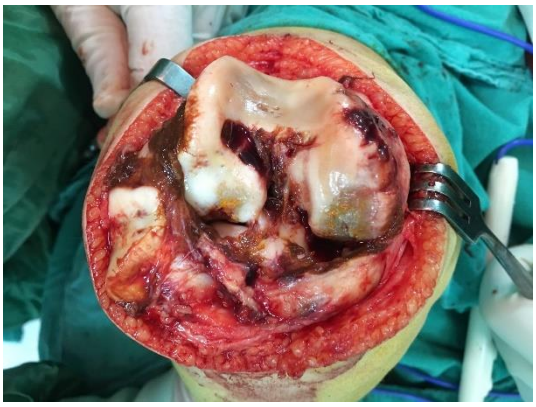


Figure 6: Bone erosion and subchondral bone damage on the femoral condyles

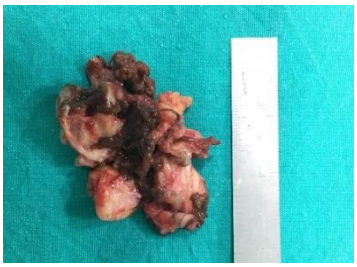


Figure 7: Total synovectomy and resected Brown tumor mass (46x27x13 mm)

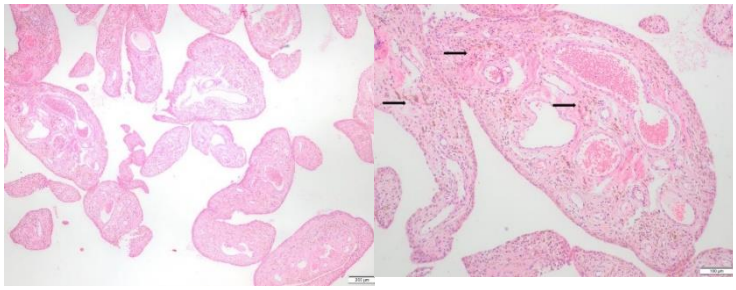


Figure 8: (A) Histologic appearance of the villlonodular synovial lesion. H&E, x4 original magnification (B) Overlying synovial epithelium, prominent vascularity, chronic inflammatory cell infiltration and brown pigment (arrows). H&E x100 original magnification.

After skin closure, elastic dressing was applied and immediate postoperative rehabilitation was started with weight-bearing and early knee range of motion.

At eighteen months of follow-up, the patient is asymptomatic with no signs of recurrence. Control MRI showed a dramatic decrease in effusion and regression of almost all hemosiderin-containing pigments (Figure 9). Inspection of the knee showed no swelling or palpable mass (Figure 10). There was no pain and the right knee had full range of motion.

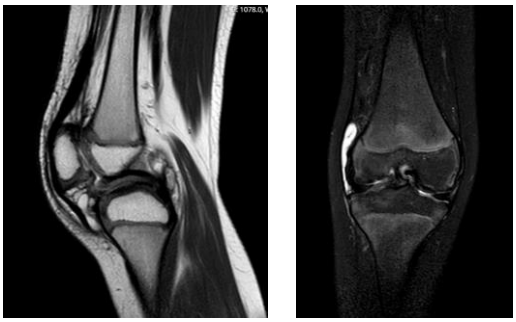


Figure 9: (A) Postoperative MRI T1-weighted sagittal sequences (B) T2-weighted coronal sequences with 18 months followed-up: decrease in area of lesion and contrasting of synovium

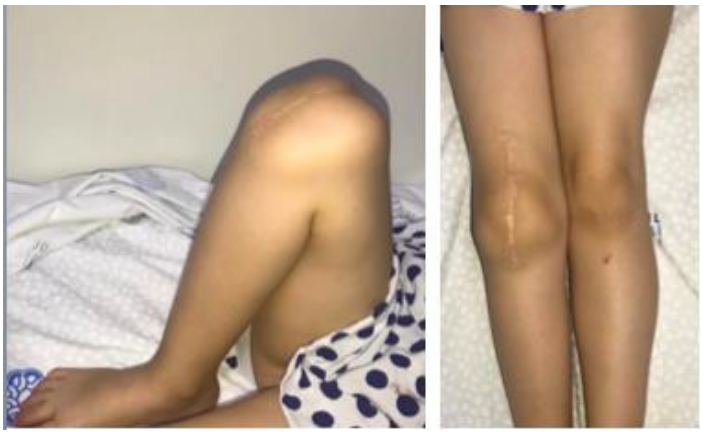


Figure 10: Patient has full range of motion with no limitations

Discussion

Pigmented villonodular synovitis (PVNS) is a benign but locally aggressive proliferative lesion of the synovial membrane. The etiology of PVNS is not certain, but genetic factors, chronic inflammation, some pathologic conditions with chromosomal abnormalities that induce hemorrhagic disorders, are thought to be potential causes [3]. There is also a relationship with traumatic events. The most frequent representation is monoarticular involvement of the knee and mostly affects young adults [3]. This pathology is rare in children [5], therefore the diagnosis is often late. Presentation is mostly unspecific like swelling and effusion with or without pain. Differential diagnosis is also challenging: Careful distinction should be made between PVNS and rheumatoid arthritis, arthropathies related to coagulopathies, tuberculosis, other inflammatory and synovial processes [3].

The patient in this report had only one affected joint and her symptoms were similar to those of arthritis. She got treatment for JRA for 2.5 years. Baroni et al. [3] reported that there was an interval between the onset of the symptoms (pain, swelling, change of posture and decreasing of the range of motion) and diagnosis, it can take from 3 to 48 months (mean: 18 months). In their study, most cases were first diagnosed with pathologies other than PVNS, JRA being the most common. Like the presented case, they were followed for at least two years. Eventually, each patient was examined by histopathologic tissue sampling, which confirmed PVNS [4]. In adults, the interval between the onset of clinical symptoms to definitive diagnosis was 18 months. In this case, symptoms had started at 12 months of age. The delay in diagnosis is close to the average duration reported in the literature.

MRI is useful for diagnosing PVNS, as X- ray findings are negative in most of cases. X-ray yields positive findings in only 33 % of pediatric PVNS [3] patients. Our patient also had no significant radiographic signs other than soft tissue swelling sign at the anterior aspect of the knee (Figure 2). On MRI, the pathognomonic finding of PVNS is low to intermediate intensity signal in both T1 and T2 sequences, which is compatible with hemosiderin-laden tissue. In this case, MRI demonstrated increased signal intensity at the suprapatellar area in T2 images, which was evaluated as effusion and synovitis. There was no sign associated with hemosiderin deposits. The last MRI demonstrated a mass under skin over patella and the patients was recommended for evaluation in terms of hemangioma. It was

expected, because there were three cases in the literature, in which vascular proliferation in the synovial membrane mimicked PVNS [6].

PVNS can induce synovial hyperplasia, invade the joint capsule and synovium. It erodes the cartilage and bones [7]. In this case, diffuse synovial hyperplasia caused bone erosions, and defects on the femoral condyles were demonstrated. Bone erosion is not a common entity in the pediatric population.

Surgical treatment aims to resect all abnormal tissue in the knee joint to reduce the degree of bone erosion, relieve pain and prevent recurrences. There are a lot of therapeutic options described but the best option has not yet been defined. For diffuse forms, the most popular and accepted treatment is subtotal open or arthroscopic synovectomy [8]. It is still controversial which technique is better for lowering recurrence and morbidity. In a literature review, Nakahara et al. [9] found a 23.2 % recurrence rate with open synovectomy and a 39 % recurrence rate with all-arthroscopic synovectomy. Colman et al. [10] reported that the overall recurrence rate of the combined open and arthroscopic techniques was lower compared with all-arthroscopic or open groups (9 vs. 62 vs. 64%, respectively). Combined open and arthroscopic synovectomy is a comprehensive approach associated with low recurrence and postoperative complication rates. In this case, the patient underwent open resection via medial parapatellar approach, because the lesion was diffuse and total resection was possible with open approach only. For the presented case, we thought that arthroscopic technique had some disadvantages, such as possibility of inadequate resection of the mass, which would increase the risk of recurrence.

Due to the high rate of recurrence reported in this type of PVNS, radiotherapy was suggested as an adjuvant treatment method. However, the use of radiotherapy in children is controversial due to epiphyseal growth plate damage and occurrence of post-radiation sarcomas [4]. Because of these reasons, we did not use radiotherapy. The patient had good functional motion and no recurrence at the end of 18 months.

Conclusion

If such a pediatric patient with long term joint swelling is non-responsive to treatment, PVNS must be considered. This suspicion must be confirmed with MRI and joint tissue sample examination. Our case is the second earliest reported knee joint PVNS after Jawadi et al. [5], who reported a 12-month-female with PVNS of knee.

References

1. Jaffe HL. Pigmented villonodular synovitis, bursitis, and tenosynovitis. Arch Pathol. 1941;31:731-65.
2. Duncan N, Rajan R. Case report of pigmented villonodular synovitis arising from the calcaneocuboid joint in a 12 year old male. Foot(Edinb). 2015;25(1):59-61.
3. Baroni E, Russo BD, Masquijo JJ, Bassini O, Miscione H. Pigmented villonodular synovitis of the knee in skeletally immature patients. J Child Orthop. 2010;4(2):123-7.
4. Bruns J, Schubert TH, Eggers-Stroeder G. Pigmented villonodular synovitis in children. Arch Orthop Trauma Surg. 1993;112(3):148-51.
5. Jawadi AH. Pigmented villonodular synovitis of the knee in a 12-month-old girl. J Taibah Univ Med Sci. 2014;9(4):335-7.
6. Burnett RA. A cause of erroneous diagnosis of pigmented villonodular synovitis. J Clin Pathol. 1976;29(1):17-21.
7. Saulsbury FT. Pigmented villonodular synovitis of the knee in a 9-year-old child. South Med J. 2004;97(1):80-2.
8. De Ponti A, Sansone V, Malcherè M. Result of arthroscopic treatment of pigmented villonodular synovitis of the knee. Arthroscopy. 2003;19(6):602-7.
9. Nakahara H, Matsuda S, Harimaya K, Sakamoto A, Matsumoto Y, Okazaki K, et al. Clinical results of open synovectomy for treatment of diffuse pigmented villonodular synovitis of the knee: case series and review of literature. Knee. 2012;19(5): 684-7.
10. Colman MW, Ye J, Weiss KR, Goodman MA, McGough RL 3rd. Does combined open and arthroscopic synovectomy for diffuse PVNS of the knee improve recurrence rates? Clin Orthop Relat Res. 2013;471(3):883-90.

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

J Surg Med. 2020;4(9):842-844.
DOI: 10.28982/josam.710826

Case report
Olgu sunumu

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

Early lipogranuloma formation after foreign material injection to the face

Yüze yabancı madde enjeksiyonu sonrası erken lipogranüloma oluşumu

Perçin Karakol [1], Melihcan Sezgiç [1]

[1] Health Science University, Bağcılar Education and Training Hospital, Department of Plastic, Reconstructive and Aesthetic Surgery, Istanbul, Turkey

ORCID ID of the author(s)

PK: 0000-0003-0068-2139
MS: 0000-0002-8213-8526

Abstract

Aging is a physiological process that progresses both physically and mentally. In today's conditions, there are medical devices and cosmetic procedures that support the external appearance and make the person feel good socially in order to age well. Over the years, thanks to the advancing technology, different solutions have been developed to compensate the loss of facial volume due to aging. Although the use of dermal fillers increases with each passing year, their excessive costs, and the need for periodic repetition force people to seek different and unhealthy solutions. In this study, we present a 32-year-old female patient who was injected with egg white in both nasolabial folds and presented with widespread redness and tenderness on the face. Surgical excision was performed after systemic corticosteroid therapy. The patient's granulomas excised from the mouth were reported as lipogranuloma by the pathology department. The frequency of foreign substance injections for cosmetic purposes has increased in recent years. Early diagnosis and follow-up is critical in the treatment of these cases.

Keywords: Lipogranuloma, Foreign body reaction, Facial volume loss

Öz

Yaşlanma hem fiziksel hem de ruhsal olarak ilerleyen, fizyolojik bir süreçtir. Günümüz şartlarında güzel bir şekilde yaşlanmak için, dış görünümü destekleyen ve kişinin kendini sosyal olarak iyi hissetmesini sağlayan medikal cihazlar ve kozmetik prosedürler mevcuttur. Gelişen teknoloji sayesinde yıllar içinde, yaşlanma nedeni ile olan yüzdeki volüm kaybını kompanse etmek için farklı çözümler türemiştir. Dermal dolguların kullanım sıklığı her geçen yıl artsa da, yüksek maliyetleri ve belli aralıklarla tekrarlanma gereksinimleri insanları farklı ve sağlıksız çözümler aramaya itmektedir. Bu çalışmada her iki nazolabial katlantıya yumurta akı enjekte edilen, yüzde yaygın kızarıklık ve hassasiyet ile başvuran, 32 yaşında bir kadın hastayı sunduk. Hastaya sistemik kortikosteroid tedavisinin ardından cerrahi eksizyon yapıldı. Hastanın ağız içinden eksize edilen granülomları patoloji sonucuna göre lipogranülom olarak belirlendi. Yüze kozmetik amaçlı yapılan yabancı madde enjeksiyonların sıklığı son yıllarda artış göstermektedir. Bu olguların tedavisinde erken tanı ve takip kritik önem taşımaktadır.

Anahtar kelimeler: Lipogranülom, Yabancı cisim reaksiyonu, Yüzde volüm kaybı

Introduction

Aging is a process that takes place both physically, spiritually, and physiologically. Facial aging is multifactorial, not just about one component. As people get older, their skin becomes drier, thinner, less elastic, and their resistance to external forces weakens. This leads to breakage of the skin, the percentage of fat compartments to change, decrease in facial volume and prominence in the facial lines [1,2]. Treatment methods for facial volume reduction are the applications in which the lost volume is replaced either by using the person's own fat tissue or with dermal fillers.

Dermal filler applications on the face have gained popularity in recent years, especially due to their ease of application, rapid effects, and lack of donor site morbidity. Today, the perception of beauty and the high financial burden of these treatment methods cause people with low socioeconomic status in developing countries to try non-professional treatment methods and non-sterile foreign substance injections [1,3,4]. In this study, a 32-year-old patient who was injected with egg whites to her facial lines and wrinkles due to volume loss is presented.

Corresponding author / Sorumlu yazar:
Perçin Karakol
Address / Adres: Sağlık Bilimleri Üniversitesi, Bağcılar Eğitim ve Araştırma Hastanesi, Plastik, Rekonstrüktif ve Estetik Cerrahi Kliniği, İstanbul, Türkiye
E-mail: ppercin@gmail.com

Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazarlar çalışmada görüntüleri ile sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

How to cite / Atıf için: Karakol P, Sezgiç M. Early lipogranuloma formation after foreign material injection to the face. J Surg Med. 2020;4(9):842-844.

Case presentation

A 32-year-old female patient without any additional disease was admitted to the clinic with the complaint of swelling, pain and palpable nodules in her both nasolabial sulci (Figure 1). It was learned that 10 days ago, her neighbor had injected egg whites into her both nasolabial sulci for cosmetic purposes. The patient stated that she visited the infectious diseases department due to the swelling, tenderness and redness that occurred 3 days after this application. When the patient visited our clinic, she had been prescribed 40 mg corticosteroid daily and oral antibiotics for 2 weeks. The patient, who was still on antibiotic and corticosteroids, was not considered for an intervention on the same day and was called for control again after the medication was finished. At the control examination 1 month after the injection, multiple granulomas were palpated in the bilateral nasolabial folds (Figure 2). No cervical lymphadenopathy was detected on physical examination. For the erythematous nodules, an incisional biopsy was performed by accessing through the oral mucosa under local anesthesia. Tissue culture was obtained. Blood tests revealed elevated white blood cell count (1.2×10^{10}/L), neutrophilia (68.3.5%), and lymphocytosis 14.3%, with normal ESR and CRP.

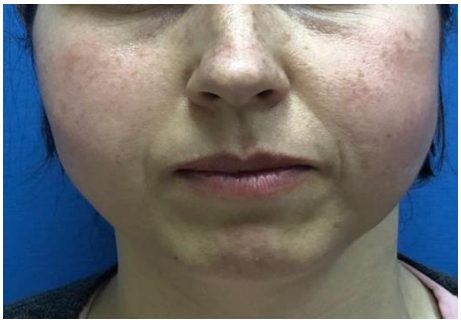


Figure 1: 10^{th} day after application

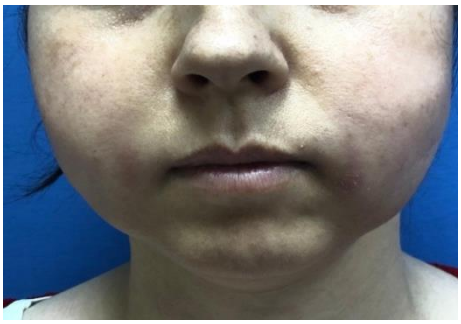


Figure 2: Nodule formation in the 1st month

In histopathological examination of tissue, subcutaneous adipose tissue was compatible with hyaline necrosis in septa, while oral mucosa pathogens were detected in wound culture (Figure 3). Because the patient was in the postpartum period, she was started on suitable antibiotherapy. The nodules were reported as lipogranuloma by the pathology department. Because the nodules responded well to steroid treatment, the treatment was continued for 2 weeks. Afterwards, treatment was ceased after the symptoms subsided. In addition, psychiatric support was provided to the patient who said that she had this procedure due to her postpartum depressive state (feeling old and ugly).

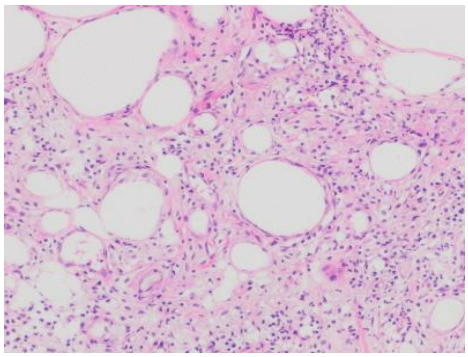


Figure 3: Microscopical slide of the biopsy (Stained with Hematoxylin and eosin)

Discussion

The use of dermal fillers is rapidly increasing every year. Numerous soft tissue fillers without enough experimental and clinical data is introduced each year. The increasing costs of developing a safe and effective dermal filler are driving people to cheap and unhealthy solutions for beauty. Unfortunately, the frequency of these unhealthy methods is increasing day by day. These inappropriate and non-sterile methods cause permanent effects on the person by creating granulomas, foreign tissue reaction and skin necrosis in the area where they are applied [5].

Granuloma is a chronic inflammatory reaction of various etiologies, and macrophages are the main cells that form granulomas [6]. Dermal filler-related foreign body granulomas are non-allergic reactions consisting of multi-core giant cells and occur 6-24 months after filling injections [6,7]. There are different opinions about granulomas associated with filling. Bentkover [8] stated that dermal filler particles that cannot be phagocytosed by macrophages may form granulomas. Lemperle et al. [4] explained that particle surface and impurity are the factors that associated with foreign body granulomas.

In this case, egg white was thought to be suitable for providing the facial tissue volume due to its gel form. Although hypersensitivity is regarded as the cause of lipogranuloma in some sources, the general belief is that foreign body granulomas do not cause an allergic reaction [9,10]. While granulomas generally occur as a chronic inflammatory reaction with various etiologies, this case was an early type lipogranuloma [11]. Traumatization of endogenous lipids in subcutaneous tissue injections can cause lipogranuloma formation as well [12].

There are different options in the treatment of foreign body granulomas such as intralesional injections, systemic therapy and surgical treatment. Intralesional corticosteroid therapy is usually one of the first options in limited cases due to its easy application. It is known that local corticosteroid injection has an effect on the activities of fibroblasts, macrophages, giant cells and collagen synthesis [13]. 30-60mg of oral prednisolone per day is effective for recurrent granulomas [4]. Surgical treatment is the only option in patients whose symptoms do not improve with local and systemic treatment [14]. In this case, since the foreign material was injected under medically unsuitable (non-sterile) conditions and widespread redness and tenderness occurred after the injection, the patient was prescribed oral prednisolone. Since the patient responded well to systemic therapy, the treatment continued until the granulomas were reduced in size after which they were surgically excised.

Conclusion

Injection of contaminated substances such as industrial silicone, mineral oil, petroleum jelly, vitamin E, paraffin, egg white into any region of the face or body may cause foreign body reaction, local abscess formation, and recurrent infections, thus reducing self-confidence. In fact, it can also cause serious life-threatening complications in some cases. As dermal filler applications are difficult to afford in developing countries, foreign material injections that can cause such effects are common. In this respect, rapid diagnosis and treatment with a detailed and correct approach is important. Since the lesions have the potential to persist and recur and it is not possible to clean foreign body reaction materials, long-term follow-up of the patients is critical in managing this process.

References

1. Kim MW, Park HS, Yoon HS, Cho S. Late-Onset Complication of Fillers: Paraffinoma of the Lower Eyelids Clinically Mimicking Xanthelasma. Ann Dermatol. 2016;28:753-6.
2. Whitney F, Louis M. Foreign Body Reaction to Facial Dermal Fillers:Case Report. J Oral Maxillofac Surg. 70:2012;2352-5.
3. Anderson JM, Rodriguez A, Chang DT. Foreign body reac¬tion to biomaterials. Semin Immunol. 2008;20:86-100.
4. Lemperle G, Gauthier-Hazan N, Wolters M, et al. Foreign body granulomas after all injectable dermal fillers: part 1. Possible causes. Plast Reconstr Surg. 2009;123:1842-63.
5. Wang LL, Thomas WW, Friedman O. Granuloma formation secondary to silicone injection for soft-tissue augmentation in facial cosmetics: Mechanisms and literature review. Ear Nose Throat J. 2018;97(1-2):E46-E51. doi:10.1177/0145561318097001-211
6. Williams GT, Williams WJ. Granulomatous inflammation: a review. J Clin Pathol. 1983;36:723-33.
7. Lemperle G, Gauthier-Hazan N, Wolters M, et al. Foreign body granulomas after all injectable dermal fillers: part 1. Possible causes. Plast Reconstr Surg. 2009;123:1842-63.
8. Bentkover SH. The biology of facial fillers. Facial Plast Surg. 2009;25:73-85.
9. Park TH, Seo SW, Kim JK, et al. Clinical experience with polymethylmethacrylate microsphere filler complications. Aesthetic Plast Surg. 2012;36:421-6.
10. Tanna N, Zalkind D, Glade RS, Bielamowicz SA. Foreign body reaction to calcium hydroxylapatite vocal fold augmentation. Arch Otolaryngol Head Neck Surg. 2006;132:1379-82.
11. Graivier MH, Bass LS, Busso M, Jasin ME, Narins RS, Tzikas TL. Calcium hydroxylapatite (Radiesse) for correction of the mid- and lower face: consensus recommendations. Plast Reconstr Surg. 2007;120:55S-66S.
12. Yang JH, Lee SM, Won CH, et al. Foreign body granuloma caused by hyaluronic acid/dextranomer microsphere filler injection. Int J Dermatol. 2012;51:1517-8.
13. Conejo-Mir JS, Sanz Guirado S, Angel Munoz M. Adverse granulomatous reaction to Artecoll treated by intralesional 5-fluorouracil and triamcinolone injections. Dermatol Surg. 2006;32:1079-81.
14. Lee JM, Kim YJ. Foreign body granulomas after the use of dermal fillers: pathophysiology, clinical appearance, histologic features, and treatment. Arch Plast Surg. 2015;42(2):232-9. doi:10.5999/aps.2015.42.2.232.

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. 2020;4(9):845-847.
DOI: 10.28982/josam.792258

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

Torticollis due to aneurysmal bone cyst located in the thoracic vertebrae: A case report

Torasik vertebrada bulunan anevrizmal kemik kistine bağlı tortikollis: Olgu sunumu

Ali Şahin [1], Ayşe Kaçar Bayram [2], Abdulfettah Tümtürk [3], Hüseyin Per [4], Ali Kurtsoy [3]

[1] Department of Neurosurgery, Kayseri City Education and Research Hospital, Kayseri, Turkey
[2] Department of Pediatrics, Division of Pediatric Neurology, Kayseri City Education and Research Hospital, Kayseri, Turkey
[3] Department of Neurosurgery, Erciyes University, Faculty of Medicine, Kayseri, Turkey
[4] Department of Pediatrics, Division of Pediatric Neurology, Erciyes University, Faculty of Medicine, Kayseri, Turkey

ORCID ID of the author(s)
AŞ: 0000-0001-7231-2394
AKB: 0000-0003-0261-9336
AT: 0000-0001-5883-9819
HP: 0000-0001-9904-6479
AK: 0000-0002-5777-8871

Corresponding author / Sorumlu yazar:
Ali Şahin
Address / Adres: Kayseri Şehir Eğitim ve Araştırma Hastanesi Nöroşirürji Kliniği, Kayseri, Türkiye
E-mail: dralishn@gmail.com

Informed Consent: The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.
Hasta Onamı: Yazarlar çalışmada görüntüleri ile sunulan hastanın ebeveynlerinden yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/30/2020
Yayın Tarihi: 30.09.2020

Abstract
Aneurysmal bone cyst is a benign, tumor-like, highly vascular, locally aggressive and relatively rare osteolytic lesion of unknown etiology. Aneurysmal bone cysts of the spine account for 12%–30% of all aneurysmal bone cyst cases. They mostly occur in the lumbar vertebrae, followed by the thoracic, cervical, and sacral vertebrae. Torticollis, a condition characterized by an abnormal tilted position, rotation, and flexion of the head and neck is considered a sign rather than a specific diagnosis. To our knowledge, the presentation of torticollis in children with aneurysmal bone cysts in the thoracic vertebrae has not been reported in the literature. We should keep in mind that acquired torticollis can be a sign of underlying life-threatening conditions. Here we present the case of a 9-year-old boy with muscle spasm, progressively increasing pain, and right torticollis (lasting for 45 days) who presented to the emergency department with paraplegia.
Keywords: Aneurysmal bone cyst, Torticollis, Acute paraplegia, Children

Öz
Anevrizmal kemik kisti, etiyolojisi bilinmeyen, iyi huylu, tümör benzeri, oldukça vasküler, lokal olarak agresif ve nispeten nadir osteolitik bir lezyondur. Omurganın anevrizmal kemik kistleri, tüm anevrizmal kemik kisti vakalarının% 12 ila 30'unu oluşturur. Çoğunlukla lomber vertebralarda, ardından torasik, servikal ve sakral vertebralarda görülürler. Doğal olmayan bir baş ve boyun eğik pozisyonu, rotasyonu ve fleksiyonu olan tortikolis, spesifik bir tanıdan çok bir işaret olarak kabul edilir. Bildiğimiz kadarıyla, literatürde, çocuklarda torasik vertebrada oluşan anevrizmal kemik kistleri tortikollis ile birlikte bildirilmemiştir. Edinilmiş tortikollisin altta yatan yaşamı tehdit eden koşulların bir işareti olabileceğini aklımızda tutmalıyız. Bu rapor, acil servise parapleji ile başvuran; kas spazmı, giderek artan ağrı ve 45 gündür süren sağ tortikolisi olan 9 yaşında bir erkek çocuğu tanımlamaktadır.
Anahtar kelimeler: Anevrizmal kemik kisti, Tortikollis, Akut parapleji, Çocuklar

Introduction

Aneurysmal bone cysts (ABCs) are rare benign bone tumors that were first described by Jaffe and Lichtenstein in 1942 [1]. ABC is the third most common benign bone tumor after osteoid osteoma and osteoblastoma; however, ABCs are relatively uncommon with annual incidences ranging from1.4 to 3.2 cases per million people [2].

ABCs of the spine account for approximately 10%–30% of all ABC cases and approximately 10%–20% of all spinal tumors [3]. ABC occurs as a primary lesion in 70% of cases, whereas it is associated with other bone diseases (chondroblastoma, giant cell tumor, telangiectatic osteosarcoma, osteoblastoma) in 30% of cases [4]. Despite being benign, ABCs can be locally expansive and destructive and can lead to pathological fractures of the vertebrae and neurological complications [3,4].

The most common complaint associated with ABCs is pain; it occurs especially at night and is localized to the site of the lesion. Neurological symptoms are present if the lesion encroaches on the nerve roots or spinal cord. Neurological involvement is uncommon but can manifest as paraplegia, cord compression and cauda equina syndrome. Thus, to prevent disabling neurological sequelae, early recognition and treatment of ABCs is necessary [5-7].

Direct radiographs, computed tomography (CT) and magnetic resonance imaging (MRI) are helpful in diagnosis. An expansile osteolytic cavity on direct radiographs as well as fluid levels seen on both CT and MRI are pathognomonic [6,7].

How to cite / Atıf için: Şahin A, Bayram AK, Tümtürk A, Per H, Kurtsoy A. Torticollis due to aneurysmal bone cyst located in the thoracic vertebrae: A case report. J Surg Med. 2020;4(9):845-847.

Torticollis, a condition characterized by an abnormal tilted position, rotation, and flexion of the head and neck, is considered a sign rather than a specific diagnosis. Torticollis can be congenital or acquired in childhood. The underlying causes of torticollis in children can vary from relatively benign to life-threatening conditions [8-10]. Torticollis due to ABCs is rare [11,12] and mostly occurs in cases of ABCs located in the cervical vertebrae. However, to our knowledge, the presentation of torticollis in children with ABCs in the thoracic vertebrae has not been reported in the literature.

Here we describe the case of a 9-year-old boy with muscle spasm, progressively increasing pain, and right torticollis (lasting for 45 days) who presented to the emergency department with paraplegia.

Case presentation

A 9-year-old boy presented to our hospital with acute weakness in the bilateral lower limbs and painful torticollis. He had no history of trauma and systemic illness. He had been treated with physical therapy including hot pack therapy and home stretching exercises for 45 days. He developed abnormal head posture and started experiencing neck pain 45 days prior to admission. The pain was severe enough to disturb his sleep; furthermore, the patient had painful torticollis unresponsive to conservative therapy, which included naproxen medication. He was admitted with the complaints of bilateral lower limb weakness, inability to walk and painful torticollis lasting for 2 days.

On physical examination, while the patient's head turned to the left, his jaw turned to the right (Figure 1). The patient had back pain and scoliosis with torticollis. Muscle strength was 2/5 in the bilateral lower extremities. Deep tendon reflexes were exaggerated, with positive bilateral Babinski sign.

Spinal MRI showed a large cystic lesion arising from the posterior parts of the vertebrae, with fluid levels causing prominent mass effect on the spinal cord at T4-5 level (Figure 2a, 2b). Histopathological examination revealed an aneurysmal bone cyst. The patient underwent emergency surgery; total tumor resection was performed, and no postoperative complications were observed. After the surgery, the patient immediately recovered from the neck pain. In the first 24 h, the patient started walking using a crutch and his torticollis improved. On the 15th postoperative day, the patient started walking without support and his focal neurological deficit improved. No signs or symptoms of neurological dysfunction were observed in the 1-year postoperative follow-up visit.

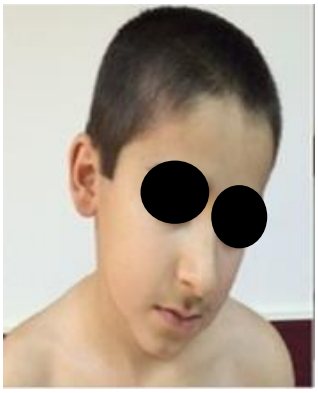


Figure 1: Torticollis view of the patient before surgery

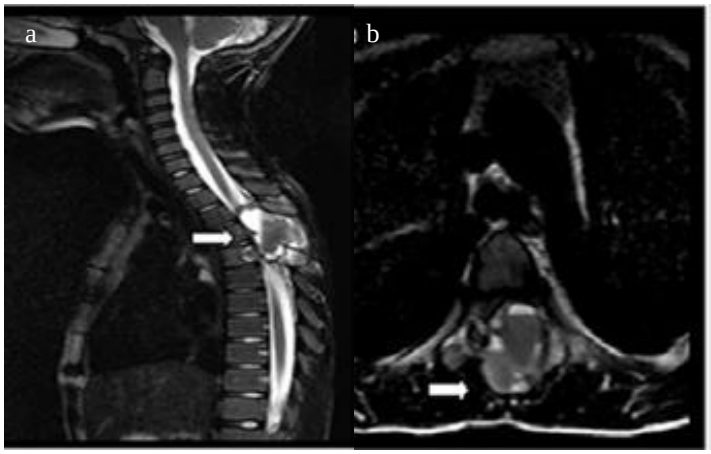


Figure 2: Sagittal (a) and axial (b) spinal MRI show a large cystic lesion arising from posterior parts of vertebrae with fluid levels causing prominent mass effect to the spinal cord at T4-5 level.

Discussion

ABC is a benign, tumor-like, highly vascular, locally aggressive, and relatively rare osteolytic lesion of a completely unknown etiology. The following causes have been suggested for ABC development: Vascular disturbances of the bone, hemorrhage into a preexisting lesion and improper repair of a traumatic subperiosteal hemorrhage [3]. Most patients are aged <20 years, and slight female predominance has been observed [2]. In our patient, the tumor had appeared in the first decade.

Primary ABCs represent 1.4% of all primary bone tumors. The lesions are usually present in the long bones, particularly the humerus, femur, tibia and fibula and the vertebral column. In the vertebral column, the lesions mostly occur in the lumbar vertebrae, followed by the thoracic, cervical, and sacral vertebrae [13]. The posterior elements of the vertebrae (lamina, pedicle, facet joints) are more frequently affected, and the lesions may also spread to the nearby vertebrae and costa through the facet joints and intervertebral disc [4], like in our patient, in which a similar tumor was detected in the T4–T6 segment.

Despite being benign, ABCs can result in pathological fractures of the vertebrae and neurological complications and can be locally expansive and destructive. Neurologic symptoms are observed when the lesion encroaches on the nerve roots or spinal cord. A palpable mass may be present in the posterior elements, and tenderness may be elicited. The most common complaint of patients with ABC is back pain and a palpable mass [6,14]. Our patient presented to the hospital with complaints of acute weakness in the bilateral lower limbs and painful torticollis. Two days before the presentation, he had developed acute paraplegia due to spinal cord compression. Thus, delay in the diagnosis and treatment of patients with ABC may result in the development of acute paraplegia.

More than 80 different causes of torticollis have been described; it is observed in childhood with an estimated incidence of 1.3% [15]. The differential diagnosis of torticollis in children is wide, extensive and includes all systems. The differential diagnosis in children with acquired torticollis is common because of the wide range of underlying trauma, infection, ligamentous inflammatory, vascular, muscular, drug reactions, osseous, ocular, psychiatric, and neurologic disorders [8-10]. The underlying central nervous system pathologies can originate from three main regions: Brain, spinal cord, and spinal

nerve root/peripheral nerve. Delay in the diagnosis in case of pathologies arising from these regions may lead to progressive neurological deterioration and an increase in the tumor size. However, early diagnosis of these disorders helps reduce mortality and morbidity. In our patient, the diagnosis of ABC in the thoracic region was delayed. If torticollis had been detected earlier and spinal imagining performed, the patient would not have come to hospital in a severe condition. Pediatric clinicians and neurosurgery practitioners must be aware of the exaggeration of this warning sign.

The treatment of ABC is controversial; treatment options include curettage with or without bone grafting, complete excision, arterial embolization, intralesional drug injections, chemotherapy, and radiation [6,7]. Surgical treatment is the first choice in cases with pathological fractures or spinal instability or symptomatic cord compression [6,7]. Early diagnosis and appropriate surgical treatment of ABCs in the spine remain the key factors to successful management [7]. Our patient underwent emergency surgery with total tumor resection. No postoperative complications were observed. The patient immediately recovered from neck pain, torticollis, and inability to walk after the surgery. No signs or symptoms of neurological dysfunction were observed in the postoperative 1-year follow-up.

Conclusion

In this report, we presented a case of torticollis caused by an ABC in the thoracic vertebrae. It is noteworthy that acquired torticollis can be a sign of underlying life-threatening conditions and requires an extensive multidisciplinary approach.

References

1. Jaffe HL, Lichtenstein L. Solitary unicameral bone cyst. Arch Surg. 1942;44:1004–25.
2. Leithner A, Windhager R, Lang S, Haas OA, Kainberger F, Kotz R. Aneurysmal bone cyst. A population based epidemiologic study and literature review. Clin Orthop Relat Res. 1999;363:176–9.
3. Boriani S, De Iure F, Campanacci L, Gasbarrini A, Bandiera S, Biagini R, et al. Aneurysmal bone cyst of the mobile spine: report on 41 cases. Spine (Phila Pa 1976). 2001;26:27–35. doi: 10.1097/00007632-200101010-00007
4. Barbanti-Brodano G, Girolami M, Ghermandi R, Terzi S, Gasbarrini A, Bandiera S, et al. Aneurysmal bone cyst of the spine treated by concentrated bone marrow: clinical cases and review of the literature. Eur Spine J. 2017;26(1):158-66. doi: 10.1007/s00586-017-4978-x
5. Mesfin A, McCarthy EF, Kebaish KM. Surgical treatment of aneurysmal bone cysts of the spine. Iowa Orthop J. 2012;32:40-5.
6. Zhao Y, He S, Sun H, Cai X, Gao X, Wang P, et al. Symptomatic aneurysmal bone cysts of the spine: clinical features, surgical outcomes, and prognostic factors. Eur Spine J. 2019;28(6):1537-45. doi: 10.1007/s00586-019-05920-7
7. Zileli M, Isik HS, Ogut FE, Is M, Cagli S, Calli C. Aneurysmal bone cysts of the spine. Eur Spine J. 2013;22(3):593-601. doi: 10.1007/s00586-012-2510-x
8. Tumturk A, Kaya Ozcora G, Kacar Bayram A, Kabaklioglu M, Doganay S, Canpolat M, et al. Torticollis in children: an alert symptom not to be turned away. Childs Nerv Syst. 2015;31(9):1461-70. doi: 10.1007/s00381-015-2764-9
9. Per H, Canpolat M, Tümtürk A, Gumuş H, Gokoglu A, Yikilmaz A, et al. Different etiologies of acquired torticollis in childhood. Childs Nerv Syst. 2014;30(3):431-40. doi: 10.1007/s00381-013-2302-6
10. Tomczak KK, Rosman NP. Torticollis. J Child Neurol. 2013;28(3):365-78. doi: 10.1177/0883073812469294
11. Mishra A, Pruthi N, Nandeesh BN, Shukla D. Cervical Spine Osteoblastoma with an Aneurysmal Bone Cyst in a 2-Year-Old Child: A Case Report. Pediatric Neurosurgery. 2019;54(1):46-50. doi: 10.1159/000495065
12. Karampalis C, Lenthall R, Boszczyk B. Solid variant of aneurysmal bone cyst on the cervical spine of a child: case report, differential diagnosis and treatment rationale. Eur Spine J. 2013;22(3):523-31. doi: 10.1007/s00586-012-2548-9
13. Hay MC, Paterson D, Taylor TK. Aneurysmal bone cysts of the spine. J Bone Joint Surg Br. 1978;60:406–11.
14. Benayada B, Allali N, Sefiani S, Arkha Y, Dafiri R. Aneurysmal bone cyst: A rare cause of medullary compression and painful scoliosis in children. Presse Med. 2010;39(7-8):837-40. doi: 10.1016/j.lpm.2010.01.008
15. Cheng JCY, Au AWY. Infantile torticollis: a review of 624 cases. J Pediatr Orthop. 1994;14:802–8.

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.