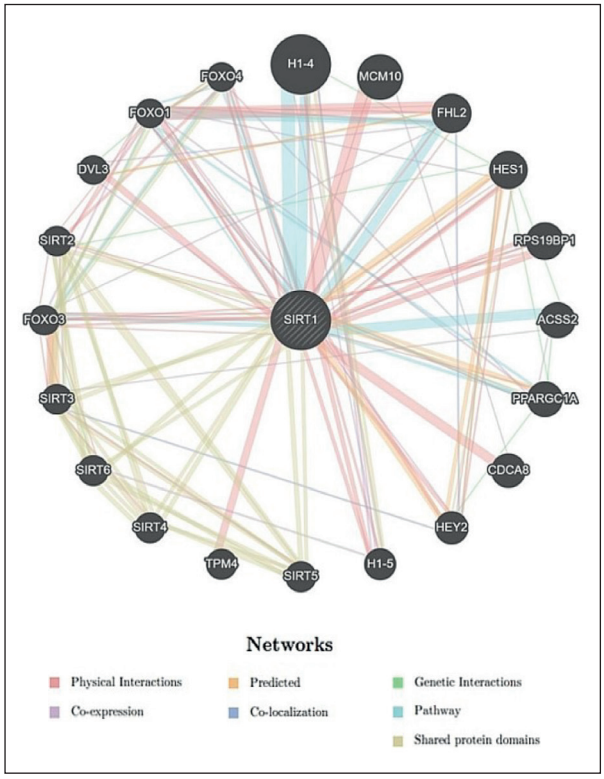
ISSN: 2822-4302
eISSN: 2587-0602

Medical Journal of Western Black Sea

Batı Karadeniz Tıp Dergisi

Cilt/Volume 7
Sayı / Number 1
Nisan / April
2023



Gene-Gene Interaction Network of SIRT1 Using a GeneMANIA Tool

https://dergipark.org.tr/tr/pub/mjwbs
https://dergipark.org.tr/en/pub/mjwbs


TIP FAKÜLTESİ

Medical Journal of Western Black Sea

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Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi Yayın Organıdır.
Official Journal of Zonguldak Bulent Ecevit University Faculty of Medicine.
Yılda üç kez yayınlanır / Published three times per year

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Yönetim Yeri / *Head Office*
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Editör / *Editor*
Prof. Dr. Taner BAYRAKTAROĞLU
baytaner@beun.edu.tr baytaner@yahoo.com baktipd@gmail.com

Yayın Türü / *Publication type*
Uluslararası süreli yayın / *International periodical*

Yılda üç kez yayınlanır (Nisan, Ağustos, Aralık)
Published three times per year (April, August, December)

Basım tarihi / *Printing date: 28.04.2023*
Asitsiz kağıda basılmıştır / *Printed on acid-free paper*

Yayın Hizmetleri / *Publishing Services*
Buluş Tasarım ve Matbaacılık Hizmetleri San. Tic.
Bahriye Üçok Caddesi 9/1 Beşevler, 06500 Ankara,
Tel: 0312 222 44 06
www.bulustasarim.com.tr

Baskı / *Printed at*
Vadi Grafik Tasarım ve Reklamcılık Ltd. Şti.
İvedik Organize San. 1420. Cadde No: 58/1, Ostim-Y. Mahalle, Ankara,
Tel: +90 (312) 395 85 71 72 Faks: 0 (312) 395 85 72
E-mail: info@stepdijital.com

Bu dergideki yazıların yayım standartlarına uygunluğu, dizimi, Türkçe ve İngilizce özlerin ve kaynakların kontrolü ile derginin yayıma hazır hâle getirilmesi, Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi sorumluluğunda gerçekleştirilmiştir. Makalelerin benzerlik oranları işleme alınmaktadır

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Batı Karadeniz Tıp Dergisi TUBİTAK ULAKBIM TR Dizini ve Türkiye Atıf Dizini tarafından dizinlenmektedir

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YAZARLAR İÇİN BİLGİLER

"Batı Karadeniz Tıp Dergisi", Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi'nin bilimsel yayım organıdır. Ulusal ve uluslararası tüm kurum ve kişilere basılı ve elektronik olarak ücretsiz ulaşmayı hedefleyen hakemli bir dergidir. Dergi yılda üç kez olmak üzere Nisan-Ağustos ve Aralık aylarında yayımlanır. Derginin yayım dili Türkçe ve İngilizcedir.

Derginin amacı Türkiye'de ve yurtdışında ilgili alanlarda yapılan nitelikli araştırma çalışmalarını ulusal ve uluslararası bilim ortamına sunarak duyurmak, paylaşmak ve sürekli bir eğitim platformu oluşturarak bilimsel ve sosyal iletişimin sağlanmasına katkıda bulunmaktır.

Dergide bu amaçlar doğrultusunda Temel, Dahili ve Cerrahi Tıp Bilimleri alanında özgün araştırmalar, olgu sunumları, derlemeler, kısa bilgi makalesi, editöre mektup, biyografi yazıları ve makale biçimine getirilen toplantı bildirileri yayımlanır. Kongre, sempozyum, elektronik ortamda sunulmuş bildiriler veya ön çalışmalar, bu durumun belirtilmesi koşuluyla yayımlanabilir.

Bu dergiye gönderilen yazılar, daha önce herhangi bir yerde yayımlanmamış ve yayımlanmak üzere başka bir dergiye gönderilmemiş olması şartı ile kabul edilir.

Tüm yazılar önce editör ve yardımcı editörler tarafından ön değerlendirmeye alınır. Daha sonra değerlendirilmesi için derginin bilimsel danışma kurulu üyelerine gönderilir. Yayımlanmak üzere dergiye iletilen tüm makalelerde hakem değerlendirmesine başvurulur. Gerekli durumlarda düzeltmeler yapılabilir. Yazarlardan bazı soruların yanıtlanması ve eksiklerin tamamlanması istenebilir. Dergide yayımlanmasına karar verilen yazılar sayfa düzenlenmesi sürecine alınır. Bu aşamada yazılar tüm bilgilerin doğruluğu için ayrıntılı kontrol ve denetimden geçirilir. Yazılar yayım öncesi son şekline getirilerek yazarların kontrolüne ve onayına sunulur.

BİLİMSEL SORUMLULUK

Yazıların tüm bilimsel sorumluluğu yazarlara aittir. Gönderilen makalede belirtilen yazarların çalışmaya belirli bir oranda katkısının olması gereklidir. Yazarların isim sıralaması ortak verilen bir karar olmalıdır. Yazarlar, yazar sıralamasını yayın hakkı devir formunda imzalı olarak belirtmek zorundadır. Yazarların tümünün ismi, yazının başlığının altındaki bölümde yer almalıdır. Yazarlık için yeterli ölçütleri karşılamayan ancak çalışmaya katkısı olan tüm bireyler "Teşekkür" kısmında sıralanabilir.

ETİK SORUMLULUK

- Etik kurallara uyulmamasından doğacak her türlü sorumluluk yazar(lar) a aittir.
- "İnsan" ögesini içeren tüm çalışmalarda Dünya Tıp Birliği Helsinki Deklerasyonu Prensipleri'ne uygunluk (http://www.wma.net/en/30 publications/10policies/b3/index.html) ilkesi kabul edilir. Dolayısıyla yayımlanmak üzere gönderilen tüm makalelerde yukarıda belirtilen kurulun etik standartlarına uyulduğu belirtilmelidir. Bu çalışmalarda yazarların, makalenin Gereç ve Yöntemler bölümünde çalışmanın yukarıdaki prensiplere uygun olarak yapıldığını, etik kuruldan onay ve çalışmaya katılmış bireylerden/ebeveynlerinden "Bilgilendirilmiş Onam" alındığını bildirmeleri gereklidir. Yerel veya uluslararası etik kurullardan alınan gerekli tüm onay belgeleri de makale ile birlikte gönderilmelidir.
- "Hayvan" ögesi ile ilgili yapılan deneysel çalışmalarda ise yazarların, makalenin Gereç ve Yöntemler bölümünde Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda hayvan haklarını koruduklarını ve çalışmanın yapıldığı kurumdaki hayvan deneyleri etik kuruldan onay aldıklarını bildirmeleri gereklidir.
- Çalışma etik kurul onayı alınmasını gerektiriyor ise, alınan onay belgesi makale ile birlikte dergi yayın kuruluna gönderilmelidir.
- Eğer makalede daha önce yayımlanmış alıntı yazı, tablo, resim vs. var ise yazarlar; yayın hakkı sahibi ve yazarlarından yazılı izin almak, ayrıca bunu makalede belirtmek zorundadır.
- Eğer makalede doğrudan ya da dolaylı ticari bağlantı veya çalışma için maddi destekte bulunan kurum varsa yazarlar; kaynak sayfasında, kullanılan ticari ürün, ilaç, ilaç firması vb. İle ticari hiçbir ilişkinin olmadığını ya da varsa nasıl bir ilişki olduğunu bildirmek zorundadır.
- Editörler ve yayımcı, reklam amacıyla dergide yayınlanan ticari ürünlerin özellikleri ve açıklamaları konusunda sorumluluk kabul etmemektedir.

Hastalar ve çalışmaya katılanların gizlilik ve mahremiyeti:

- Özellikle hastanın adı, adının kısaltılması, hasta protokol numaraları ve kayıt numarası kullanılmamalıdır.
- Hasta onayı ve/veya gözlere ilişkin özel bir bulgu olmadıkça fotoğraflarda gözler maskelenmeli ve hastanın tanınmayacağı şekle getirilmelidir.
- Tanımlayıcı bilgiler, bilimsel amaçlar açısından çok gerekli olmadıkça ve hasta (ya da anne-baba, ya da vasisi) yazılı 'Bilgilendirilmiş Onam' vermedikçe basılmazlar. 'Bilgilendirilmiş Onam' alındığı makalede belirtilmelidir.

EDİTÖRLER, YAZARLAR VE HAKEMLER İLE İLİŞKİLER

Dergiye gönderilen yazıların, dergi yazım kurallarına göre hazırlanmış ve eksiksiz olarak sayfa düzenlemesine hazır duruma getirilmiş olması gerekir. Yayım kurulu, yazım kurallarına uymayan yazıları iade etmek, düzeltilmek üzere yazara göndermek ya da şekil açısından yeniden düzeltmek yetkisine sahiptir. Yayım kurulu tarafından düzeltme istenen makalelere, yazar tarafından hakemlere verilen yanıtları içeren ayrı bir yazı eklenmelidir.

Editör ve dil editörleri, yazım dili, imla düzeltmeleri ve kaynakların yazım kurallarına uygunluğunun denetimi ve ilgili diğer konularda değişiklik ve düzeltmelerin yapılmasında tam yetkilidir.

Makalede daha önce yayımlanmış alıntı yazı, tablo, fotoğraf vb. var ise, makalenin sorumlu yazarı ilgili yayın hakkı sahibinden ve yazarlarından yazılı izin almak, ayrıca bunu makalede belirtmek zorundadır.

Dergiye gönderilen yazılar, körleme danışmanlık (peer-review) sistemine göre yazarların isimleri metinden çıkartılarak editörler kurulu tarafından hakemlere gönderilir. Yazarlara da, yazının hangi hakemlere gönderildiği ile ilgili bilgi verilmez. Editör, makalelerle ilgili bilgileri (makalenin alınması, içeriği gözden geçirme süreci, hakemlerin eleştirileri ya da varılan sonuçlar) yazarlar ya da hakemler dışında kimseyle paylaşmaz. Hakemler ve yayın kurulu üyeleri topluma açık bir şekilde makaleleri tartışamazlar. Yazarlar altı hafta içinde makalelerinin yayımlanması konusunda bilgilendirilir.

Hakemler yazıları inceledikten sonra, değerlendirmelerini editöre gönderir. Yazarın ve editörün izni olmadan hakemlerin değerlendirmeleri basılamaz ve açıklanamaz. Hakemlerin kimliğinin gizli kalmasına özen gösterilir. Bazı durumlarda editörün kararıyla, ilgili hakemlerin makaleye ait yorumları aynı makaleyi yorumlayan diğer hakemlere gönderilerek, hakemlerin bu süreçte aydınlatılması sağlanabilir.

BİLİMSEL MAKALE ÇEŞİTLERİ

Özgün Araştırma

Klinik, laboratuvar, epidemiyolojik ve her türlü deneysel çalışmalar yayımlanabillir. Özgün araştırma makaleleri aşağıdaki bölümlerden oluşmalıdır; Öz (Türkçe ve İngilizce), giriş, gereç ve yöntem, bulgular, tartışma, teşekkür, kaynaklar. Tartışma bölümünü takiben teşekkür bölümünde "çıkar çatışması" olup olmadığına dair bilgi verilmelidir.

Derleme

Temel, Dahili ve Cerrahi Tıp Bilimleri alanındaki güncel konulardan oluşan derlemeler, doğrudan veya davet edilen yazarlar tarafından yazılabilir. Derleme makaleleri aşağıdaki bölümlerden oluşmalıdır; Öz (Türkçe ve İngilizce), metin, kaynaklar.

Olgu Sunumu

Temel, Dahili ve Cerrahi Tıp Bilimleri alanında nadir görülen, tanı ve tedavisinde yenilik ve farklılıklar gösteren, tedavisi tamamlanmış ve takibi yapılmış olgulara yer verilir. Olgu sunumları aşağıdaki bölümlerden oluşmalıdır; Öz (Türkçe ve İngilizce), giriş, olgu, tartışma, kaynaklar.

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YAZARLAR İÇİN BİLGİLER

YAZIM KURALLARI

Yazılar çift aralıklı, 12 punto ve sola hizalanmış olarak, "Times New Roman" karakteri veya "Arial" yazı karakterlerinde kullanılarak yazılmalıdır. Sayfa kenarlarında 2,5 cm boşluk bırakılmalı ve sayfa numaraları her sayfanın sağ alt köşesine yerleştirilmelidir. Kapak sayfasına numara yazılmamalıdır. Makaleler "Uluslararası Tıp Dergileri Editörleri Kurulu" tarafından belirlenen: Biyomedikal Dergilere Gönderilen Makalelerin Uyması Gereken Standartlar'a (http://www.icmje.org) uygun olmalıdır. Özgün araştırma yazıları ve derlemeler çift aralıklı olarak en fazla 15 sayfa, olgu sunumları ise 5 sayfayı (öz, kaynaklar, tablo ve şekiller hariç) geçmemelidir. Yazılar "doc" veya "docx" formatında gönderilmelidir. Yazarlar düzeltme yaptıkları dosya üzerinde yapılan değişiklikleri farklı bir renk ile belirtmelidir. Yazıda aşağıdaki bölümler bulunmalıdır:

KAPAK SAYFASI

Yazının başlığını (Türkçe ve İngilizce), yazarların isimlerini ve ORCİD numaralarını, yazışmaların yapılacağı yazarın adını, çalıştıkları kurumları, açık adresini, telefon ve faks numaralarını, e-posta adresini, ayrıca 40 karakteri geçmeyen bir kısa başlığı içermelidir. Yazı daha önce bilimsel bir toplantıda sunulmuş ise toplantı adı, tarihi ve yeri belirtilerek yazılmalıdır.

ÖZ VE ANAHTAR SÖZCÜKLER

Makalelerde Türkçe ve İngilizce öz (abstract) olmalıdır. Öz, 250 sözcüğü aşmamalı, makaleyi yansıtacak nitelikte olmalı, önemli sonuçlar vermeli ve bunların çok kısa yorumu yapılmalıdır. Özde açıklanmayan kısaltmalar kullanılmamalı, kaynak gösterilmemelidir. Özgün araştırma makalelerinde Türkçe ve İngilizce özler bölümlü olmalı ve aşağıdaki gibi yapılandırılmalıdır;

Amaç, gereç ve yöntemler, bulgular, sonuç(lar).

Olgu sunumlarında ise; amaç, olgu (lar), sonuç (lar) bölümlerini içeren yapılandırılmış öz bulunmalıdır.

Türkçe ve İngilizce anahtar sözcükler

"Index Medicus: Medical Subject Headings" (http://www.nlm.nih.gov/mesh/MBrowser.html) ile uyumlu olmalı ve en az üç en fazla beş adet olmalıdır. Anahtar sözcüklerin belgeye erişimde en önemli öge olduğu göz önünde bulundurulmalıdır.

GİRİŞ

Bu bölümde, araştırmanın neden yapıldığı sorularına yanıt verilmeli, konu ile ilgili geçmiş literatür değerlendirilmelidir.

GEREÇ VE YÖNTEMLER

Çalışmada kullanılan gereç tanımlanmalı ve uygulanan yöntem ayrıntılı biçimde anlatılmalıdır. Kısaltmalar metinde, tablolarda, resim ve şekillerde ilk geçtiği yerde açıklanmalıdır. Eğer bir marka belirtiliyorsa üretici firmanın adı (şehir, ülke) verilmelidir.

BULGULAR

Elde edilen bulgular açık ve kısa bir şekilde sunulmalıdır. Bu amaçla tablo, grafik ve fotoğraflar kullanılabilir.

TARTIŞMA

Giriş bölümünün tekrarı yapılmadan, bulguların önemi belirtilmelidir. Bu bölümde çalışmanın sonuçları verilmelidir.

TEŞEKKÜR YAZISI

Makalenin sonunda ve kaynaklardan önce, varsa araştırmaya veya makalenin hazırlanmasına katkıda bulunanlara "teşekkür" yazılabilir. Bu bölümde kişisel, teknik ve gereç yardımı gibi nedenlerle yapılacak teşekkür ifadeleri yer alır.

Her türlü çıkar çatışması, finansal destek, bağış ve diğer editöryal (istatistik analiz, İngilizce/Türkçe değerlendirme) ve/veya teknik yardım var ise metnin sonunda sunulmalıdır.

KAYNAKLAR

Kaynaklar makalede geçiş sırasına göre numaralandırılmalı, numaraları metinde cümlenin sonunda parantez içinde belirtilmelidir ve metin içerisinde aldığı numaraya göre kaynak listesinde gösterilmelidir. Kaynak listesi ayrı bir sayfada olmalıdır. Kaynak listesinde "ve ark." (et al.) kısaltması kullanılmamalı, bütün yazarların isimleri belirtilmelidir. Metin içinde kaynak verirken, yazar sayısı iki veya daha az ise tüm yazarlar yazılmalı, ikiden fazla ise ilk yazar adı yazılarak "ve ark." (et al.) kısaltması kullanılmalıdır. Kaynakların doğruluğundan yazar(lar) sorumludur. Kaynak bildirme "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (http://www.icmje.org) adlı kılavuzun en son güncellenmiş şekline (Şubat 2006) uymalıdır. Dergilerin isimleri Index Medicus'a uygun olarak kısaltılmış biçimde verilir. Dergi isimlerinin kısaltmaları için Index Medicus'da dizinlenen dergiler listesine veya http://www.nlm.nih.gov/tsd/serials/lji.html adresine bakınız. Index'e girmeyen dergi isimlerinde kısaltma yapılmaz. Sadece yayımlanmış veya yayımlanmak üzere "baskıda" olan makaleler, kaynaklarda gösterilebilir.

KAYNAKLARIN YAZIMI İÇİN ÖRNEKLER

Dergiler:

Yazar ad(lar)ı, makale adı, dergi adı ("lndexMedicus" ta verilen listeye göre kısaltılmalıdır), yılı, cilt numarası, ilk ve son sayfa numarası.

Shannon KR, Nanda RS. Changes in the curve of Spee with treatment and at 2 years posttreatment. Am J Orthod Dentofacial Orthop 2004; 125: 589-596.

Çevrim-içi makaleler:

Abood S: Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [İnternet yayını]. 2002 Jun [atıf 12.08.2002];102(6). Erişim: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Kitaplar:

Bölümün yazarlarının ad(lar)ı, kitabın adı, kaçıncı baskı olduğu, yayımlandığı yer, yayınevi, yıl.

Graber TM, Rakosi T, Petrovic AG. Dentofacial orthopedics with functional appliances. 2nd ed., St. Louis, Mosby; 1997.

Kitap bölümü:

İlgili bölüm yazar ad(lar)ı, ilgili bölüm adı, editör(ler), kitabın adı, yayımlandığı yer, yayınevi, yıl, ilk ve son sayfa numarası.

Marsh PD, Nyvad B. The oral microflora and biofilms on teeth. In: Fejerskov O, Kidd E, editors. Dental caries the disease and its clinical management. 2nd ed. Blackwell Munksgaard; 2004. 29-48.

TABLOLAR

Tablolar ana metin içinde kaynaklardan sonra gelmeli, her tablo ayrı bir sayfada olacak şekilde ve çift aralıklı olarak yazılmalıdır. Makale içindeki geçiş sırasına göre numaralandırılmalı ve kısa-öz bir başlık taşımalıdır. Metin içerisinde de yerleri belirtilmelidir. Tablo başlığı tablonun üstünde, tablo açıklamaları ve kısaltmalar altta yer almalıdır. Tablolar metin içindeki bilgileri tekrarlamaktan ziyade kendini açıklayıcı nitelikte olmalıdır. Daha önce yayımlanmış olan bilgi veya tabloların kaynağı, ilgili tablonun altına iliştirilen bir dip not ile belirtilmelidir.

KISALTMALAR

Sözcüğün ilk geçtiği yerde parantez içinde verilir ve tüm metin boyunca aynı kısaltma kullanılır.

FOTOĞRAF VE ŞEKİLLER, ALTYAZILARI

Resim, şekiller, elektronik fotoğraflar, radyograflar, görüntüleri ve taranmış görüntüler ".jpeg" ya da ".tiff" formatında, piksel boyutu en az 800x600 ve 1000 dpi çözünürlükte kaydedilmeli ve çevrimiçi olarak gönderilmelidir. Histolojik kesit ve sitoloji fotoğraflarında büyütme ve boyama tekniği belirtilmelidir. Resim ve şekiller metinde geçiş sırasına göre numaralandırılmalıdır. Metin içerisinde de yerleri belirtilmelidir. Resim ve şekil alt yazıları

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makalenin sonunda ayrı bir sayfada verilmelidir. Resim ve şekil alt yazıları kısa ve açıklayıcı olmalı, metni tekrar etmemelidir. Resim veya şekillerde kullanılan sayı, sembol ve harflerin anlamı açık bir şekilde belirtilmelidir. Zorunlu olmadıkça resim üzerinde yazı yazılmasından kaçınılmalıdır.

BAŞVURU VE YAYIN HAKKI DEVİR YAZISI

Yazılar yalnızca derginin çevrimiçi makale değerlendirme sistemi üzerinden kabul edilmektedir (https://dergipark.org.tr/tr/pub/baktipd). Yazı ile birlikte, tüm yazarların imzalı onayını içeren yayın hakkı devir formu dergiye gönderilmelidir (e-posta: baktipd@gmail.com). Yazının tüm yazarlar tarafından okunduğu, onaylandığı ve orijinal bir çalışma ürünü olduğu ifade edilmeli ve yazar isimlerinin yanında imzaları bulunmalıdır. Herhangi bir yazar, kurum ya da kuruluş ile çıkar çatışması olmadığı belirtilmeli ve bunun için "International College of Medical Journal Editors Form for the Disclosure of Conflict of Interest'"e göre hazırlanmış olan "Çıkar Çatışması Formu" doldurulmalı ve Yayın Hakkı Devir Formu ile gönderilmelidir (https://dergipark.org.tr/en/pub/mjwbs/page/5815).

Kabul edilen makalenin yayın hakları **"Batı Karadeniz Tıp Dergisi"** Yayın Kuruluna devredilmelidir. Yayın hakkı makalenin basım, çoğaltım ve dağıtım haklarını içermektedir. Yazarlar, **"Batı Karadeniz Tıp Dergisi"** Yayın Kurulunun yayın hakkı sahibi olduğunu ve yayının kaynağını belirtmek koşuluyla bu makaleyi ücretsiz olarak internet ortamına açabilir. Bu durumda dergideki orjinal makaleye internet sitesinde çevrimiçi bir bağlantı yaratılmalı ve bağlantı noktasında şu ifade yer almalıdır: "Orijinal makale dergipark.gov.tr/baktipd adresinde yer almaktadır." Dergide basılan tüm makaleler yayın hakkı ile korunmaktadır. Basılmış olan hiç bir materyal **"Batı Karadeniz Tıp Dergisi"** Yayın Kurulunun yazılı izni olmadan, herhangi bir şekilde başka bir yerde yayımlanamaz. **"Batı Karadeniz Tıp Dergisi"** Yayın Kurulu bu dergide yayınlanan bilgilerden oluşabilecek yanlışlık, eksiklik ve hak iddiaları ile ilgili olarak yasal sorumluluk kabul etmez. Dergide yayımlanan makaleler için yazarlara ve hakemlere herhangi bir ücret ödenmemektedir.

YAZARLAR İÇİN SON KONTROL LİSTESİ

Makalenizi **"Batı Karadeniz Tıp Dergisi"** ne göndermeden önce lütfen bu bölümdeki maddelerle karşılaştırarak eksik olmadığından emin olunuz.

- Editöre başvuru mektubu
- Çıkar çatışması formu
- Kapak sayfası
- Makalenin metni
- Özet (Türkçe) (İngilizce)
- Kaynaklar (Ayrı sayfada)
- Tablolar ve grafikler
- Resimler ve şekiller

YAYIN POLİTİKASI ve ETİK KURALLAR

Açık Erişim Politikası

Bu dergi, araştırmayı halka ücretsiz olarak sunmanın daha büyük bir küresel bilgi alışverişini desteklediği ilkesine dayanarak içeriğine anında açık erişim sağlar.

Tüm makaleler, asıl yazar(lar)a ve kaynağa uygun atıfta bulunduğunuz sürece, herhangi bir ticari olmayan kullanım, paylaşım, uyarlama, dağıtım ve çoğaltmaya izin veren Creative Commons Alıntı-Gayri Ticari 4.0 Uluslararası Lisansı koşulları altında herhangi bir ortam veya formatta yayınlanır.

Makale İşleme Ücretleri

Zonguldak Bülent Ecevit Üniversitesi, Batı Karadeniz Tıp Dergisi'nin yayın maliyetlerini desteklediği için, makale işleme ücreti ve dergideki diğer yayın ücretleri yazarlar için ücretsizdir.

Telif hakkı uyarısı

Yazarların telif hakları vardır, ancak makalelerinde yayıncıya özel lisans hakları vardır *.

Yazarlar şu haklara sahiptir:

- Son kullanıcı lisansını ve bu dergideki kaydın sürümüne DOI bağlantısını içerdiği sürece makalelerini "Kişisel Kullanım haklarına" ** göre paylaşın.
- Fikri mülkiyet haklarını koruyun (araştırma verileri dahil).
- Yayınlanan çalışma için uygun atıf ve itibar.

* Ticari kullanım yapma ve yetkilendirme hakkını içerir.

** Kişisel kullanım hakları

Yazarlar makalelerini tamamen veya kısmen bilimsel, ticari olmayan amaçlarla kullanabilirler:

- Yazarın sınıf öğretiminde bir yazar tarafından kullanılması (kopya, kağıt veya elektronik dağıtımı dahil)
- Kopyaların (e-posta yoluyla dahil) bilinen araştırma meslektaşlarına kişisel kullanımları için dağıtılması (ancak Ticari Kullanım için değil)
- Bir tez veya teze dahil etme (ticari olarak yayınlanmaması şartıyla)
- Yazarın eserlerinin sonraki bir derlemesinde kullanın
- Makaleyi kitap uzunluğuna genişletme
- Diğer türev çalışmaların hazırlanması (ancak Ticari Kullanım için değil)
- Başka çalışmalarda bölümlerin veya alıntıların kullanılması veya yeniden kullanılması

Telif Hakkı Bildirimi

Batı Karadeniz Tıp Dergisi yazar (lar) kısıtlama olmaksızın telif hakkını verir. Dergi ayrıca yazar (lar) ın yayın haklarını kısıtlama olmaksızın korumasına izin verir.

Gizlilik Bildirimi

Bu dergi sitesine girilen isimler ve e-posta adresleri, yalnızca bu derginin belirtilen amaçları için kullanılacaktır ve başka herhangi bir amaç için veya başka bir tarafa sunulmayacaktır.

AKRAN DEĞERLENDİRMESİ POLİTİKASI

Genel bilgi

Yazarlardan ve hakemlerden makalelerini ve raporlarını Dergipark (https://dergipark.org.tr/tr/pub/baktipd) çevrimiçi sistemimiz aracılığıyla göndermelerini istiyoruz. Bu sistemin kullanımına yardımcı olacak çevrimiçi bir yardım kılavuzu ve herhangi bir teknik sorun için e-posta ile iletişime geçebilirsiniz .

MAKALE İNCELEME SÜRECİ

İLK KONTROLLER

Ön değerlendirme sürecinde makaleler yazım kurallarında ki temel kriterleri ve dosyaları içermelidir.

Tüm yazıların bir başlık sayfası, özeti, ana metni, referansları varsa tabloları, şekilleri (açıklamaları olmalıdır); revizyon aşamasına kadar uygun dosya formatları gerekli değildir.

BENZERLİK KONTROLÜ

Gönderilen makaledeki metnin orijinalliği için metin benzerliği açısından taranır. Batı Karadeniz Tıp Dergisi, birden fazla bilimsel yayın veritabanını taramak için iThenticate'i kullanır.

EDİTÖR VE DEĞERLENDİRME GÖREVİ

Bir yazı dergi için uygun bulunursa, Baş Editör ilgili uzmanlığa göre onu bir Yardımcı Editöre atayabilir. Yardımcı Editör ve/veya Alan Editörü daha sonra makaleyi derginin yayın kriterlerine göre değerlendirmek için harici hakemler atar.

Derginin kapsamının veya kalitesinin minimum gerekliliklerini karşılamayan yazılar, incelemeden önce editoryal olarak reddedilebilir. Bu tür kararlar, yazarlara başka bir dergiye makale göndermek için hızlı bir fırsat sağlamak için genellikle bir haftadan daha kısa sürede alınır.

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Baş Editör veya Editöryel Kurul Üyeleri dergisine bir makale gönderirse, makalelerinin akran değerlendirmesiyle ilgili tüm bilgilerden kör olacaktır. Yardımcı Editör makale için hakem değerlendirmesini ve karar verme sürecini denetleyecektir.

HAKEM DEĞERLENDİRMESİ

Batı Karadeniz Tıp Dergisi inceleme için gönderilen her makale için üç kurum dışı hakem önerileri alır. Hakemler makaleyi değerlendirmeyi kabul süreleri 10 gün ve değerlendirme kabulu sonrası değerlendirmeyi tamamlama süreleri 14 gündür. Editörlük hakemlere ek süre verebilir veya hakemlik davetini iptal edebilir. Hakemler davet sırasında çalışmanın başlık ve öz bilgilerini görebilir. Hakemler hem davet hem de değerlendirme sürecinde kör hakemlik yaparlar. Batı Karadeniz Tıp Dergisinde değerlendirme süreci çift-kör hakemlik sisteminde yapılır

Hakemler, hakemlik için etik kurallarda belirtilen kriterlere göre makaleyi değerlendirir ve makelenin güçlü ve zayıf taraflarını şeffaf olarak editöre yazılı olarak bildirir.

EDİTÖR KARARLARI

Makale hakkındaki karar, hakem önerileri, benzerlik raporu, yazar revizyonu doğrultusunda Baş Editör başkanlığında Editörler Kurulu tarafından aşağıdaki kararlar arasından seçilir:

- Kabul
- Minör Revizyon
- Major revizyon
- Ret

Makalelerin kabulü, bilimsel içerik ve materyalin sunumuna bağlıdır. Makale için revizyon isteği, nihai kabulü garanti etmez. Hakem eleştirileri öneri olarak sunulmaktadır nihai karar Editörler Kurulunundur.

Kabul edilen çalışmaların online ve/veya hardcopy yayınlanma süreci 180 gündür.

YAYIN SÜRECİNDE YAZAR SORUMLULUKLARI

Gözden geçirilmiş yazılar, kabul sonrası yayın aşamasında olarak görünür. Yayın süresince yazarlar aşağıdakilerden sorumludur;

- Revizyonu kabul edilmiş son versiyon dosyasının tam metni (doc veya docx dosya formatı)
- Tam metin dosyasında makalede listelenen yazar adları ve bağlı kuruluşlar, makale gönderme sistemine girilen adlar ve kuruluşlarla eşleşmelidir
- Kaynakların kontrolü
- Şekillerin, tabloların veya fotoğrafların yüksek çözünürlükte dosyalarının sisteme yüklenmesi
- Teşekkür, yazar katkı beyanı, etik olur v.s tam ve eksiksiz olarak tam metinde referanslardan önce belirtilmeli
- Dergipark üzerinde Web arayüzünde Türkçe ve İngilizce, başlık, öz, anahtar kelimeler, yazar sıralamaları (ünvansız) ve kaynaklar son versiyon dosyasıyla eşleşmelidir

ETİK KURALLAR

Zonguldak Bülent Ecevit Üniversitesi, Tıp Fakültesinin yayın organı olan "Batı Karadeniz Tıp Dergisi/ Medical Journal Of Western Black Sea" ulusal ve uluslararası tüm kurum ve kişilere ücretsiz olarak ulaşmayı hedefleyen hakemli bir dergidir.

Dergimize gönderilen bilimsel yazılarda, ICMJE (International Committee of Medical Journal Editors) tavsiyeleri ile COPE (Committee on Publication Ethics)'un Editör ve Yazarlar için Uluslararası Standartları dikkate alınmaktadır.

Yazarlarımızın etik ihlalleri ile ilgili tüm iddia ve kesinleşmiş süreçler kendi sorumluluklarında olup, kesinleşen etik ihlalleri durumunda makale otomatik iptal edilir.

Hakemler İçin Etik Kurallar

Hakemler;

- Değerlendirdiği yazıların gizliliğine saygı gösterir ve makaleyi tartışmaz veya yazı hakkında başka herhangi bir kişiyle iletişim kurmaz.
- Olası bir çıkar çatışması olduğunda editörü konu hakkında bilgilendirir.
- Önerileri için nesnel ve yapıcı bir açıklama sağlar.
- Makaleye ilişkin kararlarının konudan veya yazarlık biçiminden etkilenmesine izin vermez.
- Güçlü bir bilimsel gerekçe olmadıkça yazarın kendi makalelerini belirtmesini istemez.
- Yazarlar tarafından yayınlanmadan önce kendi çalışmalarının hiçbirinde incelenen makalenin herhangi bir bölümünü veya bilgiyi çoğaltmaz.
- Hakem değerlendirmelerini sadece uzmanlıkları dahilinde ve makul bir süre içinde kabul etmeyi kabul eder.
- Yazının yayına çıkmasını geciktirecek ertelemeler yapmaz.
- Hakaret, düşmanca veya küçük düşürücü bir dil kullanmaz.
- Gönderilen makaleleri ve ilgili tüm materyalleri inceledikten sonra imha eder.

https://publicationethics.org/files/Ethical_guidelines_for_peer_reviewers_0.pdf

Yazarlar için etik kurallar

Yazarlar ve yardımcı yazarlar;

- International Committee of Medical Journal Editors (ICMJE) tarafından belirtilen yazar kriterlerine uygunluk sağlanır;

a. Eserin tasarımına veya tasarımına önemli katkılar sağlayan verilerin elde edilmesi, analizi veya yorumlanması

b. Çalışmanın hazırlanması veya literatürün içerik için eleştirel olarak gözden geçirilmesi

c. Yayınlanacak versiyonun nihai onayı

d. Çalışmanın herhangi bir bölümünün doğruluğu veya bütünlüğü ile ilgili soruların uygun şekilde soruşturulup çözülmesini sağlamada, çalışmanın tüm yönlerinden sorumlu olacak anlaşma.

- Gönderilen makaleler yazar(lar)ın özgün çalışması olmalıdır ve eşzamanlı olarak farklı yayıncılara gönderilmemelidir
- Yazar(lar) araştırma önerisinde, icrasında ya da araştırma sonuçlarını raporlarken araştırma suiistimali olarak tanımlanan uydurma, tahrifat ya da intihalden sorumludur.
- Gönderilen makalelerde çıkar çatışması varsa editöre bilgi verilmelidir
- Gönderilen makalelerde ön kontrol, değerlendirme süreci ya da yayınlanmış olan sürümünde yazar veya yardımcı yazarlar tarafından hata fark edilirse bilgi vermek, düzeltmek ya da geri çekmek için editörü bilgilendirmelidir.
- Makale gönderildikten sonra yazar sıralamaları ve yazar ekleme-çıkartmaları önerilmemelidir
- Yazar(lar), etik kurul kararı gerektiren araştırmalar için etik kurul onayı aldığını; etik kurul adı, karar tarihi ve sayısı aday makalenin ilk-son sayfasında ve yöntem bölümünde belirtmeli, etik kurul kararını gösteren belgeyi makalenin başvurusuyla birlikte sisteme yüklemelidir.
- Yazarlar olgu sunumlarında olur/onam formunun alındığına ilişkin bilgiye makalede yer vermelidir.
- Kullanılan fikir ve sanat eserleri için telif hakları düzenlemelerine riayet edilmesi gerekmektedir.
- Makale sonunda; Araştırmacıların Katkı Oranı beyanı, varsa Destek ve Teşekkür Beyanı, Çatışma Beyanı verilmelidir.

http://www.icmje.org/icmje-recommendations.pdf

https://www.ease.org.uk/wp-content/uploads/2018/11/doi.10.20316.ESE_.2018.44.e1.tr_.pdf

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Editörler İçin Etik

Editörler:

- Okuyucular, araştırmayı veya diğer bilimsel çalışmaları kimin finanse ettiği ve fon verenlerin araştırmada ve yayınlanmasında herhangi bir rolü olup olmadığı ve eğer öyleyse bunun ne olduğu konusunda bilgilendirilmelidir.
- Editörlerin yayın için bir makaleyi kabul etme veya reddetme kararları, makalenin önemi, özgünlüğü ve netliği ile çalışmanın geçerliliği ve derginin görev alanına uygunluğuna dayanmalıdır.
- Editörler, gönderimle ilgili ciddi sorunlar tespit edilmedikçe, gönderimleri kabul etme kararlarını tersine çevirmemelidir.
- Yeni editörler, bir önceki editör tarafından yapılan başvuruları yayınlama kararlarını bozmamalıdır ciddi sorunlar tespit edilmedikçe.
- Hakem değerlendirmesi süreçlerinin bir açıklaması yayınlanmalı ve editörler açıklanan süreçlerden önemli sapmaları ortaya çıkarır.
- Yazarların editoryal kararlara itiraz edebilmeleri için beyan edilmiş bir mekanizmaya sahiptir.
- Editörler, kendilerinden beklenen her şey hakkında yazarlara rehberlik etmelidir. Bu rehberlik düzenli olarak güncellenmeli ve bu koda atıfta bulunmalı veya bu koda bağlantı vermelidir.
- Editörler International Committee of Medical Journal Editors (ICMJE) önerdiği yazarlık kriterlerini belirtmeli
- Editörler, hakemlere, kendilerinden beklenen her şey hakkında rehberlik sağlamalıdır. gönderilen materyalin güvenle ele alınması ihtiyacı. Bu rehber düzenli olarak güncellenmelidir ve bu koda başvurmalı veya bu kodu bağlamalıdır
- Editörler, kabul etmeden önce gözden geçirenlerin rekabet edebilecek potansiyel çıkarları ifşa etmelerini istemelidir bir sunumu gözden geçirin.
- Editörler, hakemlerin kimliklerinin korunmasını sağlayacak sistemlere sahip olmalıdır yazarlara ve hakemlere bildirilen açık bir inceleme sistemi kullanır.
- Editörler, yeni yayın kurulu üyelerine kendilerinden beklenen her şey hakkında kılavuzlar sunmalı ve mevcut üyeleri yeni politikalar ve gelişmeler hakkında güncel tutmalıdır.
- Editörler, derginin kalitesine ve uygunluğuna göre ve dergi sahibinin / yayıncının müdahalesi olmadan hangi makalelerin yayınlanacağına karar vermelidir.
- Editörlerin derginin sahibi ve / veya yayıncı ile ilişkilerini belirleyen yazılı bir sözleşmesi olmalıdır. Bu sözleşmenin şartları Dergi Editörleri için COPE Davranış Kuralları ile uyumlu olmalıdır.
- Editörler dergilerindeki hakem değerlendirmelerinin adil, tarafsız ve zamanında yapılmasını sağlamak için çaba göstermelidir.
- Editörler, dergilerine gönderilen materyallerin incelenirken gizli kalmasını sağlayacak sistemlere sahip olmalıdır.
- Editörler, dergilerdeki bölümlerin farklı amaç ve standartlara sahip olacağını kabul ederek, yayınladıkları materyalin kalitesini sağlamak için tüm makul adımları atmalıdır.

https://publicationethics.org/files/Code%20of%20Conduct.pdf

Yazarlar ve yardımcı yazarların tanımları;

- Yazarlığın ICMJE'deki dört kriterine uyar:

1- Eserin tasarımına veya tasarımına önemli katkılar sağlayan verilerin elde edilmesi, analizi veya yorumlanması

2- Çalışmanın hazırlanması veya literatürün içerik için eleştirel olarak gözden geçirilmesi

3- Yayınlanacak versiyonun nihai onayı

4- Çalışmanın herhangi bir bölümünün doğruluğu veya bütünlüğü ile ilgili soruların uygun şekilde soruşturulup çözülmesini sağlamada, çalışmanın tüm yönlerinden sorumlu olacak anlaşma.

- Bir yazar, yaptığı çalışmanın bölümlerinden sorumlu olmanın yanı sıra, çalışmanın diğer belirli bölümlerinden hangi ortak yazarların sorumlu olduğunu belirleyebilmelidir. Ayrıca yazarlar, ortak yazarlarının katkılarının bütünlüğüne güvenmelidir.
- Yazar olarak atananların tümü yazarlık için dört kriteri de karşılamalı ve dört kriteri karşılayanlar yazar olarak tanımlanmalıdır.
- Yazar olarak adlandırılan tüm insanların dört kriteri de karşıladığını belirlemek, çalışmanın gönderildiği derginin değil yazarların kolektif sorumluluğudur; yazarlık için kimlerin hak kazanabileceğini veya hak kazanamayacağını belirlemek veya yazar çatışmaları için hakemlik yapmak derginin editörlerinin rolü değildir.
- Kimin yazarlık hakkı kazanacağı konusunda anlaşmaya varılamazsa, dergi editörü değil, çalışmanın yapıldığı kurum (lar) dan araştırılması istenmelidir.
- Yazarların satırda listelenme sırasını belirlemek için kullanılan kriterler değişebilir ve editörler tarafından değil, yazar grubu tarafından toplu olarak kararlaştırılmalıdır.
- Yazarlar makalenin gönderilmesi veya yayınlanmasından sonra yazarın kaldırılmasını veya eklenmesini talep ederse, dergi editörleri, listelenen tüm yazarlardan ve kaldırılacak veya eklenecek yazardan istenen değişiklik için bir açıklama ve imzalanmış bir sözleşme beyanı aramalıdır.
- İlgili yazar, makalenin teslimi, akran değerlendirmesi ve yayın sürecinde dergi ile iletişim için birincil sorumluluğu üstlenen kişidir.
- İlgili yazar genellikle derginin tüm idari gereksinimlerinin, yazarlık detayları, etik komite onayı, klinik araştırma kayıt belgeleri ilgili yazar sorumluluğundadır.
- İlgili yazar, editoryal sorguları zamanında yanıtlamak için gönderim ve hakem inceleme süreci boyunca hazır bulunmalıdır ve yayından sonra çalışmanın eleştirilerine cevap vermek ve dergiden herhangi bir veri talebiyle işbirliği yapmak için hazır bulundurulmalıdır.
- Çok yazarlı büyük bir grup çalışmayı yürüttüğünde, grup ideal olarak çalışma başlamadan önce kimin yazar olacağına karar vermeli ve makaleyi yayına göndermeden önce kimin yazar olduğunu doğrulamalıdır.

Yardımcı Yazarlık İçin;

- Yukarıdaki yazarlık kriterlerinin 4'ünden daha azını karşılayan katılımcılar yazar olarak listelenmemeli, ancak beyan edilmelidir.
- Tek başına (başka katkılar olmadan) yazarlık için katkıda bulunan bir kişiyi hak etmeyen faaliyetler (Örneğin finansman sağlanması; bir araştırma grubunun genel denetimi veya genel idari destek; Yazma yardımı, teknik düzenleme, dil düzenleme ve düzeltme)
- Katkıları yazarlığı haklı göstermeyenler, bireysel olarak veya tek bir başlık altında bir grup olarak kabul edilebilir (örneğin, "Klinik Araştırmacılar" veya "Katılımcı Araştırmacılar"), ve katkıları belirtilmelidir (örneğin, "bilimsel danışman olarak hizmet", "çalışma önerisini eleştirel olarak gözden geçirir," "toplanan veriler", "çalışma hastaları için sağlanır ve bakım yapılır", "makalenin yazılı veya teknik düzenlemesine katılır")

İLETİŞİM BİLGİLERİ

Taner BAYRAKTAROĞLU

Zonguldak Bülent Ecevit Üniversitesi,

Tıp Fakültesi, Dahili Tıp Bilimler Bölümü, İç Hastalıkları Anabilim Dalı,

Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı

67100, Zonguldak, Türkiye

Tel: +90(372) 291 24 44

E-posta: baytaner@beun.edu.tr

baytaner@yahoo.com

baktipd@gmail.com

Web adresi: https://dergipark.org.tr/tr/pub/baktipd

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INSTRUCTIONS FOR AUTHORS

Medical Journal of Western Black Sea is a scientific publication of Zonguldak Bulent Ecevit University Faculty of Medicine. This is a refereed journal, which aims at achieving free knowledge to the national and international organizations and individuals related to medical sciences in published and electronic forms. This journal is published three annually in April, August and December. The publication language of the journal is Turkish and English.

The aim of the journal is to announce quality researches in medicine and respective subjects to the national and international scientific environment, sharing and creating a continuous training platform to contribute to the provision of scientific and social communication in Turkey and abroad.

In pursuit of these objectives in the journal original research, case reports, reviews, letters to the editor, biography, writings and conference proceedings brought to articles format are published. The papers presented at the symposium, congress, electronic media or preliminary studies can be published provided that this is stated.

The manuscripts will be reviewed for possible publication with the understanding that they are being submitted to one journal at a time and have not been published, simultaneously submitted or already accepted for publication elsewhere.

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All manuscripts' scientific responsibility belongs to the authors. Authors specified in the article must be at a certain rate of contribution. The order of authorship should be a joint decision. Authors must indicate in the form of a signed transfer copyright of the author rankings. All of the author's name should be placed in the paper section at the bottom of the title. Contributions that need acknowledging but do not justify authorship can be listed in the section 'Acknowledgements'.

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- Especially patient's name, the shortening of the name, patient protocol number and registration number should not be used.
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Manuscripts submitted to the journal, must be prepared according to journal writing rules and brought to ready to complete the page edition. Extension board has the authority to ask the author revise the article and has also the authority to return writings which do not obey the spelling rules. An article containing answers to the referees should be added by the author with the desired corrections.

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Articles submitted to the journal will be sent to the referee by the editorial board according to blinding consultation system (peer-review) by removing author names from the text. Also, the authors do not be provided information about the referees. Editor does not share any information regarding articles (article receipt, review the contents of the review process, criticism of the referees or final results) with anyone except from the authors and referees. The referees and editorial board members cannot discuss articles publicly. The authors of the article are about to be released within six weeks.

After reviewing the article, referees send evaluation to editor. Referee's evaluation cannot be printed or disclosed without author and editor's permission. Attention is paid to the anonymity of the referees. In some cases, the decision of the editor's interpretation of the relevant article is informed to other referees to review the referee sent the same article for clarifying the process.

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Clinical, laboratory, epidemiological and all kinds of experimental studies can be published. Original research articles should consist of the following chapters; Abstract (Turkish and English), introduction, materials and methods, findings, discussion, thanks, resources. After the discussion section, information should be given about "conflict of interest.

Review

Compilations of current topics in Basic, Internal and Surgical Medical Sciences can be written directly or by invited authors. Review articles should consist of the following sections;Review articles should consist of the following sections; Abstract (Turkish and English), Text, References.

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Patients who are rarely seen in the field of Basic, Internal and Surgical Medical Sciences, who have innovations and differences in their diagnosis and treatment, have been treated and followed up, are included. Case reports

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should consist of the following sections; Abstract (Turkish and English), Introduction, Case, Discussion, References.

WRITING RULES

Articles should be written in double-spaced, 12-point and aligned right-left, "Times New Roman" or "Arial ' as font. 2.5 cm space should be left in the margins and page numbers should be placed in the lower right corner of each page. Number should not be written on the cover page. Articles should be appropriate to "International Committee of Medical Journal Editors," defined by: Uniform Standards Required for Manuscripts Submitted to Biomedical Journals (from http://www.icmje.org). The original research papers and review articles should not exceed 15 pages with double-spaced, and case reports up to 5 pages (extract resources, excluding tables and figures). Writings should be sent in "doc" or "docx" format. Authors must indicate the changes made on the file they edited in a different color. The article should contain the following sections:

TITLE PAGE

Title of the paper (Turkish-English), authors' names, institutions they work, correspondence author's name, full address, telephone and fax numbers, e-mail address should also include a short title not exceeding 40 characters. If the article was presented at a scientific meeting name, date and place specified to be written.

ABSTRACT AND KEYWORDS

Each article should have abstracts both in Turkish and in English. The abstract should not exceed 250 words, should be capable of reflecting the article, it should give significant results and author's interpretation should be made very short. Undisclosed abbreviations should not be used in the abstract, the references should not be shown.

Original research articles should have Turkish and English abstracts segment and configured as follows:

Objective, materials and methods, results, conclusion(s).

In a case report; objective case (s), result(s) must be configured containing partitions that essence.

Turkish and English keywords should be compatible with "Index Medicus: Medical Subject Headings" (http://www.nlm.nih.gov/mesh/mbrowser.html) and should be at least three to ten. The key words should be considered as the most important element in accessingto documents.

INTRODUCTION

This section should answer the question why the research performed and it should be considered as the historical literature on the subject.

MATERIALS AND METHODS

Means must be defined and applied methods used in the study should be discussed in detail. Abbreviations in the text, tables, images and figures should be disclosed in its first occurrence. If a brand name is cited in the manufacturer's name and address (city, country) should be given.

RESULTS

The findings should be presented in a clear and concise manner. For this purpose, tables, graphs and photos could be used.

DISCUSSION

Without repetition of introduction, the importance of the findings should be noted.

RESULT(S)

In this section, the results of the study should be given.

ACKNOWLEDGEMENTS

Before the end of the article and references, contributing to the preparation of research or article appreciation can be written. In this section, personal, technical and acknowledgments will be included for some reasons such as aid supplies.

REFERENCES

References should be numbered consecutively in an order.The article number should be mentioned in parentheses at the end of the sentence within the text.The reference list should be based on numbers that appear paranthetical documentation. Reference list must be on a separate page. Do not use "et al" in the references. List all the authors of the reference. While sources in the text, number of authors, all authors should be written in less than two or more than two first author's name is written "et al." abbreviations should be used. Authors are responsible for the accuracy of the references. Reference inform must comply the updated form of "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (http://www.icmje.org) (February 2006). The names of journals abbreviated in the form according to Index Medicus is given. To see the names or abbreviations of journal list see. http://www.nlm.nih.gov/tsd/serials/lji.html journals indexed in Index Medicus. No abbreviations are made if the journal names are not in the index. Only published or to be published "in press" articles, in references.

EXAMPLES FOR THE WRITING OF REFERENCES

Journals:
Author names, article title, journal name (shortened according to the "Indexmedicus" list) year, volume number, first and last page number.

Giugliano D, Ceriollo A, Paolisso G. Oxidative stress and diabetic vascular complications. Diabetes Care. 1996;19:257–267.

On-Line Articles:
El-Hage J. Peroxisome proliferator-activated receptor (PPAR) agonists: preclinical and clinical cardiac safety considerations. Rockville, MD: Center for Drug Evaluation and Research, 2006. (Accessed May 18, 2007, at http://www.fda.gov/cder/present/DIA2006/El-Hage_CardiacSafety.ppt.)

Books:
Authors' name of the parts, the book's name, the numberof the edition, place of publication, publisher, year. Larsen PR, Kronenberg HM, Melmed S, Polonsky KS. Williams Textbook of Endocrinology, 10th Edition, Philadelphia, Elsevier Science, 2003.

Book section:
Related section, the author name (s), section names, editor (s), book title, place of publication, publisher, year, first and last page number.

Klein S, Romijn JA. Obesity. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS. Williams Textbook of Endocrinology, 10th Edition, Philadelphia, Elsevier Science, 2003, p.1642-1706.

TABLES

Tables should come after the references in the main text, each table should be typed double-spaced and will be on a separate page. According to the order mentioned in the article should be numbered with Roman numerals and short extracts should carry a title. It should be noted also within the text. Table header should be on the table; included descriptions and abbreviations should be below the table. Tables should have a selfexplanatory nature rather than repeating the information in the text. References of the information or statements that are published recently should be indicated in a footnote attached to the corresponding table below.

ABBREVIATIONS

Word'sabbreviation is given in parenthesis where it first time passes and used the same abbreviation allthrough the text.

PHOTO AND FIGURES, SUBTITLES

Images, shapes, electronic photographs, radiographs, CT scans, and scanned images in .jpeg or .tiff format, 500 × 400 pixel size and 300 dpi resolution should be recorded and submitted online. In histological sections enlargement of the photo and staining technique should be stated. The figures should be numbered according to their sequence in the text. It should also be noted in the text areas. The pictures and illustrations' subtitles should be given on a separate sheet at the end of the article. Pictures and captions

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should be short and should be in descriptive manner, the text must not have repetition. Pictures or numbers used in the figures, the meaning of symbols and letters should be stated clearly. Writing text on the drawing should be avoided unless it is necessary.

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- Application Letter to the Editor
- Conflict of interest form
- Cover page
- Article text
- Abstract (Turkish) (English)
- References (Separate page).
- Tables and graphs
- Pictures and figures

EDITORIAL POLICY and ETHICAL RULES

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ARTICLE REVIEW PROCESS

FIRST CHECKS

In the pre-evaluation process, the articles should include the basic criteria and files in the writing rules.

All articles must have a title page, summary, main text, tables if references, figures (explanations); proper file formats are not required until the revision stage.

SIMILARITY CHECK

For originality of the text in the submitted article, it is scanned for text similarity. Western Black Sea Medical Journal uses iThenticate to search multiple scientific publication databases.

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If an article is found suitable for the journal, the Editor-in-Chief may appoint it to an Associate Editor based on the relevant specialization. The Associate Editor and/or Field Editor then appoints external reviewers to evaluate the article against the journal's publication criteria.

Manuscripts that do not meet the minimum requirements for the scope or quality of the journal may be editorially rejected prior to review. Such deci-

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sions are often made in less than a week to provide authors with a quick opportunity to submit articles to another journal.

If the Editor-in-Chief or Members of the Editorial Board submits an article to the journal, they will be blinded from all information regarding the peer review of their article. The Associate Editor will oversee the peer-review and decision-making process for the article.

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The Western Black Sea Journal of Medicine receives three external referee recommendations for each article submitted for review. The time for the referees to accept the evaluation of the article is 10 days, and the period for completing the evaluation after acceptance is 14 days. The editorship may give additional time to the referees or cancel the invitation to referee. Referees can see the title and abstract information of the study during the invitation. Referees act as blind referees during both the invitation and evaluation process. In the Western Black Sea Journal of Medicine, the evaluation process is done in a double-blind peer-review system.

The referees evaluate the article according to the criteria specified in the ethical rules for refereeing and report the strong and weak sides of the article to the editor in writing in a transparent manner.

EDITORIAL DECISIONS

The decision about the article is chosen by the Editorial Board under the chairmanship of the Editor-in-Chief in line with the referee suggestions, similarity report and author revision among the following decisions:

- Acceptance - Minor Revision
- Major Revision - Reject

Acceptance of articles depends on the presentation of scientific content and material. Requesting revisions for the article does not guarantee final acceptance. Referee criticisms are presented as suggestions, the final decision rests with the Editorial Board.

The online and/or hardcopy publication period of accepted works is 180 days.

AUTHOR RESPONSIBILITIES IN THE PUBLICATION PROCESS

Revised manuscripts appear as publications after acceptance. During the publication, the authors are responsible for the following;

The full text of the last version file whose revision has been accepted (doc or docx file format)

Author names and affiliates listed in the article in the full text file must match the names and organizations entered in the article submission system

References check

Uploading high resolution files of figures, tables or photographs to the system

Acknowledgments, author's statement of contribution, ethical consent, etc. should be stated completely and completely in the full text before the references

In the web interface on Dergipark, the title, abstract, keywords, author rankings (without title) and references must match the latest version file.

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https://publicationethics.org/files/Ethical_guidelines_for_peer_reviewers_0.pdf

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Authors and co-authors,

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a. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;

b. Drafting the work or revising it critically for important intellectual content;

c. Final approval of the version to be published;

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http://www.icmje.org/icmje-recommendations.pdf

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- Editors should not reverse decisions to accept submissions unless serious problems are identified with the submission.
- New editors should not overturn decisions to publish submissions made by the previous editor unless serious problems are identified.
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- Editors should state the authorship criteria suggested by International Committee of Medical Journal Editors (ICMJE).
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- Drafting the work or revising it critically for important intellectual content;
- Final approval of the version to be published;
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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- Examples of activities that alone (without other contributions) do not qualify a contributor for authorship are acquisition of funding; general supervision of a research group or general administrative support; and writing assistance, technical editing, language editing, and proofreading.
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CONTACT INFORMATION

Taner BAYRAKTAROĞLU
Zonguldak Bulent Ecevit University,
Faculty of Medicine, Internal Sciences, Department of Internal Medicine,
Division of Endocrinology and Metabolism
67100, Zonguldak, Turkey
Phone: +90(372) 291 24 44
E-mail: baytaner@beun.edu.tr baytaner@yahoo.com baktipd@gmail.com
Web address: https://dergipark.org.tr/en/pub/baktipd

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi
Cilt / Volume 7 Sayı / Number 1 Nisan / April 2023

EDİTÖRDEN

Değerli Okuyucular,

Zonguldak Bülent Ecevit Üniversitesi, Tıp Fakültesi tarafından yayımlanan Batı Karadeniz Tıp Dergisi (Medical Journal of Western Black Sea-Med J West Black Sea) 2023 yılı Nisan sayısını sizlere sunuyoruz.

Ülkemizde pandeminin etkileri ortadan kalktıktan sonra 6 Şubat 2023 tarihli Kahramanmaraş Merkezli ardışık iki deprem 11 ilimizde büyük yıkıma neden olmuştur. Bu depremler Cumhuriyet döneminde yaşadığımız en büyük deprem felaketi olarak kayıtlara geçmiştir. Kaybedilen yaşamların ardından yaralar ve acıların sarılması için toplumun her katmanı bir mücadeleye başladığı bir dönemden geçmekteyiz.

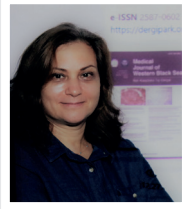
2017 yılında yayına başlayıp 2019 yılından itibaren TrDizin tarafından indekslenen dergimiz toplamda 18 sayı ve 216 makale ile literatüre katkı sağlamıştır. Dergimizin ulusal ve uluslararası görünebilirliği arttıkça değerli bilim insanlarının dergimize göndermiş olduğu yayın akışıyla birlikte yoğun bir çalışma sürecini sürdürüyoruz.

Batı Karadeniz Tıp Dergisi (Med J West Black Sea) olarak ondokuzuncu sayımızda (Cilt:7 Sayı:1) siz değerli okurlara oniki araştırma makalesi ve üç olgu sunumunu paylaşıyoruz.

- SIRT1 Gen Polimorfizmleri ve Vitiligo Riski İlişkisi: Moleküler ve "in Siliko" Yaklaşım
- Akut Pankreatitte Yeni Bir İnflamatuar Belirteç Olarak Ortalama Trombosit Hacmi ve C-Reaktif Protein ile Başvuru Anındaki Ranson Skoru ile İlişkisi
- Subakut Tiroiditte Prognoz Öngörülebilir mi?
- Kronik Obstrüktif Akciğer Hastalığı (KOAH) Olanlarda Dispnenin Bilişsel Duruma Etkisi
- Servikal Disk Hernisi Olan Hastalarda Depresyon, Anksiyete ve Uyku Kalitesi Skorlarının Değerlendirilmesi: Türkiye'de Yapılan Bir Araştırma
- Yetmiş Beş Yaş Üstü Metastatik Mide Kanserli Hastalarda Hemoglobin, Albümin, Lenfosit, Platelet (HALP) Skoru ile Geriatrik Nütrisyonel İndeks (GNRI) ve Prognoz Arasındaki İlişki
- Helicobacter pylori ile Enfekte Çocukların Yanak Epiteli Döküntü Hücrelerinde Mikronükleer ve Binükleer Hücre Sıklığının Değerlendirilmesi
- Tıp Fakültesi Öğrencilerinde COVID-19 Korkusu ve Sigara Kullanımını Etkileyen Faktörlerin Değerlendirilmesi
- Kırmızı Kantaron (Hypericum capitatum) Bitkisi: Fenolik içeriklerinin, Antioksidan Aktivitesinin Belirlenmesi ve Klinik İzolatlar Üzerinde Antimikrobiyal Etkinliğinin Araştırılması
- Pilates Egzersizlerinin Doğum Sonu Dönemde Depresyon ve Uyku Kalitesine Etkisi: Randomize Kontrollü Bir Çalışma
- Konservatif Olarak Tedavi Edilen Distal Radius Kırıklarında El Bilek Çevresinin Rolü (Bölgesel Obeziteye Karşı Lokal Şişlik): Tek Merkez Deneyimi
- Türk K Kuşağı Ergenlerinde Ergenlik Sorunları ile Bilgisayar (Bilgisayar, İnternet, Oyun) Bağımlılığı Arasındaki İlişkinin Kanonik Korelasyon Analizi ile İncelenmesi: Ordu İl Merkez (Altınordu) Örneği
- Ani Kardiyak Ölüm İçin Önemli Bir Risk Faktörü: Tip 2 Brugada Sendromu
- Üst Ekstremite Yerleşimli Pilomatrikoma: Olgu Sunumu
- Nadir Görülen Bir Vaka: Dyke-Davidoff-Masson Sendromu

Dergimizin yayınlanmasında; Rektör Prof. Dr. İsmail Hakkı ÖZÖLÇER'e, yazarlara, yazıları titizlikle değerlendiren hakemlerimize, Danışma Kurulumuza, Türkçe ve İngilizce Dil Redaksiyon Kurulumuza, Alan Editörlerine ve Editör yardımcılarına, teknik görevlilerimize, Biyoistatistik Editörlerimize, Yayın Kurulumuza ve yayınevimize teşekkür ederim.

Dergimizin gittikçe artan kalite standartları doğrultusunda önümüzdeki sayılarımızda da literatüre katkı sağlayan makaleler yayınlamaya devam etmeyi umuyoruz.



Prof. Dr. Hale Sayan ÖZAÇMAK
2023 Nisan Sayı Editörü

Prof. Dr. Taner BAYRAKTAROĞLU
Baş Editör
Nisan 2023

Medical Journal of Western Black Sea
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Cilt / Volume 7 Sayı / Number 1 Nisan / April 2023

EDITORIAL

Dear Readers,

We present to you the April 2023 issue of the Medical Journal of Western Black Sea-Med J West Black Sea (Batı Karadeniz Tıp Dergisi), published by Zonguldak Bülent Ecevit University, Faculty of Medicine.

After the effects of the pandemic disappeared in our country, two consecutive earthquakes in Kahramanmaraş on February 6, 2023 caused great destruction in 11 provinces. These earthquakes were recorded as the biggest earthquake disaster we experienced in the Republican period. We are going through a period where every layer of society starts a struggle to heal the wounds and pain after the lost lives.

Our journal, which started publication in 2017 and has been indexed by TrIndex since 2019, has contributed to the literature with a total of 18 issues and 216 articles. As the national and international visibility of our journal increases, we continue an intensive work process with the publication flow of valuable scientists to our journal.

As the Western Black Sea Journal of Medicine (Med J West Black Sea), we share twelve research articles and three case reports with you, dear readers, in our nineteenth issue (Volume: 7 Issue: 1).

- SIRT1 Gene Polymorphisms and the Risk of Vitiligo: Molecular Association and in Silico Approach
- Mean Platelet Volume as a New Inflammatory Marker in Acute Pancreatitis and Its Relation to C-Reactive Protein and Ranson's Score on Admission
- Can the Prognosis be Predicted in Subacute Thyroiditis?
- The Effect of Dyspnea on the Cognitive Status in Patients with Chronic Obstructive Pulmonary Disease (COPD)
- Evaluation of Depression, Anxiety and Sleep Quality Scores in Patients with Cervical Disc Herniation: A Study Conducted in Turkey
- Relationship Between Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score and Geriatric Nutritional Risk Index (GNRI) and Prognosis in Patients Over 75 Years of Age with Metastatic Gastric Cancer
- Evaluation of Micronucleer and Binucleer Cells Frequencies in Buccal Epithelial Cells of Children Infected with Helicobacter pylori
- Evaluation of the Factors Affecting the Smoking Habit and Fear of COVID-19 Among Faculty of Medicine Students
- Red Centaury (Hypericum capitatum): Determination of Phenolic Content, Antioxidant Activity and Investigation of Antimicrobial Efficacy on Clinical Isolates
- Effects of Pilates Exercises to Depression and Sleep Quality on the Postpartum Period: A Randomized Controlled Study
- The Role of Wrist Circumference (Regional Obesity Versus Local Swelling) in Conservatively Treated Distal Radius Fractures: A Single Center Experience
- Examining the Relationship between Adolescence Problems and Computer (Computer, Internet, Game) Addiction with Canonic Correlation Analysis in Turkish Generation K Adolescents: Ordu Province Center (Altinordu) Example
- An Important Risk Factor for Sudden Cardiac Death: Type 2 Brugada Syndrome
- Pilomatricoma of the Upper Extremities: A Case Report
- A Rarely Seen Case Report: Dyke-Davidoff-Masson Syndrome

In the publication of our journal; I would like to thank to Rector, Prof. İsmail Hakkı ÖZÖLÇER, the authors, our referees who carefully evaluated the articles, our Advisory Board, our Turkish and English Language Editorial Board, Field Editors and Assistant Editors, our technical staff, our Biostatistics Editors, our Editorial Board and our publishing house.

In line with the increasing quality standards of our journal, we hope to continue to publish articles that contribute to the literature in our upcoming issues.

Özaçmak, Hale Sayan, Prof., MD.
The Editor of 2023 April's Issue

Bayraktaroglu, Taner, Prof., MD.
Chief Editor
April 2023

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Editör, Alan Editörü, Yardımcı Editör, Sekreterya

YAYIN POLİTİKASI

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi
eISSN: 2587-0602
dergipark.org.tr/baktipd

Değerlendirme süreci

HAKEM A/B/C..

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ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2023;7(1): 1-8
DOI: 10.29058/mjwbs.1223300

SIRT1 Gene Polymorphisms and the Risk of Vitiligo: Molecular Association and in Silico Approach

SIRT1 Gen Polimorfizmleri ve Vitiligo Riski İlişkisi: Moleküler ve "in Siliko" Yaklaşım

Oktay KURU[1], Nilgün SOLAK[2], Ümmühani ÖZEL TÜRKCÜ[3], Sevim KARAKAŞ ÇELİK[4], Tuba EDGÜNLÜ[5]

[1]Muğla Sıtkı Koçman University, Faculty of Health Sciences, Department of Physical Therapy and Rehabilitation, Muğla, Turkey
[2]Memorial Ankara Hospital, Department of Dermatology, Ankara, Turkey
[3]Muğla Sıtkı Koçman University, Faculty of Medicine, Department of Medical Biochemistry, Muğla, Turkey
[4]Zonguldak Bülent Ecevit University, Faculty of Medicine, Department of Medical Genetics, Zonguldak, Turkey
[5]Muğla Sıtkı Koçman University, Faculty of Medicine, Department of Medical Biology, Muğla, Turkey

ORCID ID: Oktay Kuru 0000-0002-8947-0505, Nilgün Solak 0000-0002-6572-9615, Ümmühani Özel Türkcü 0000-0003-2244-7965, Sevim Karakaş Çelik 0000-0003-0505-7850, Tuba Edgünlü 0000-0002-9300-9324

Cite this article as: Kuru O et al. SIRT1 gene polymorphisms and the risk of vitiligo: Molecular association and in silico approach. Med J West Black Sea. 2023;7(1):1-8.

Corresponding Author
Oktay Kuru

E-mail
oktayk@mu.edu.tr

Received
23.12.2022

Revision
28.02.2023

Accepted
11.03.2023

ABSTRACT

Aim: The aim of our study is to analyze the SIRT1 gene rs2273773, rs7895833 and rs7069102 polymorphisms and the association of SIRT1 gene and interacting genes with vitiligo disease by molecular and in silico methods.

Material and Methods: The study group consisted of 78 vitiligo patients and 85 unrelated healthy controls. SIRT1 polymorphisms were determined using the Polymerase chain reaction confronting two-pair primers (PCR-CTPP) method. In addition, other genes with which the SIRT1 gene interacts and gene ontology (GO) were determined using the GeneMANIA and GeneCodis 4 tools, respectively.

Results: We have determined a significant difference in genotypes of rs7895833 in SIRT1 gene. Especially, the AG genotype was observed more in the group with vitiligo. It was determined that the rs7895833 G allele had a protective effect in terms of vitiligo (p=0.001). Intergene interaction analysis was also performed by in silico method, and it was shown that SIRT 1 is co-expressed with 16 genes and shares an area with only 12 genes physically interacting with 19 genes. We showed gene ontology and pathway analyzed with all relevant genes. It was determined that especially apoptosis and systemic sclerosis were associated with these genes.

Conclusion: The SIRT1 rs7895833 SNP genotype and allele frequencies of vitiligo patients are significantly different from healthy controls. Our study shows that the rs7895833 polymorphism of the SIRT1 gene may be associated with vitiligo susceptibility. Considering the role of sirtuin and related genes, especially in the apoptotic pathway, its effect on vitiligo can be further investigated to elucidate the molecular aspect of the disease.

Keywords: Gene polymorphism, In silico, SIRT1, Vitiligo

ÖZ

Amaç: Çalışmamızın amacı, SIRT1 geni rs2273773, rs7895833 ve rs7069102 polimorfizmlerinin ve SIRT1 geni ile etkileşimli genlerin vitiligo hastalığı ile ilişkilisinin moleküler ve in silico yöntemler ile analizini yapmaktır.

Gereç ve Yöntemler: Çalışma grubu 78 vitiligo hastası ve 85 sağlıklı kontrol katılımcısını kapsamaktadır. SIRT1 polimorfizmleri, iki çift primer (PCR-CTPP) yöntemiyle karşılıklı Polimeraz zincir reaksiyonu kullanılarak belirlendi. Ayrıca SIRT1 geninin etkileştiği diğer genler ve gen ontolojisi (GO) sırasıyla GeneMANIA ve GeneCodis 4 araçları kullanılarak belirlendi.

Bulgular: SIRT1 geninde rs7895833 genotipinin analiz edilen gruplar arasında anlamlı bir farklılık gösterdiğini belirledik. Özellikle AG genotipi vitiligolu grupta daha fazla gözlendi. rs7895833 G allelin vitiligo açısından koruyucu bir etki gösterdiği tespit edilmiştir (p=0.001). In silico yöntemle genler arası etkileşim analizi de yapılarak SIRT 1'in 16 gen ile birlikte eksprese edildiğini ve 19 gen ile sadece 12 gen fiziksel etkileşimi olan bir alanı paylaştığı gösterildi. İlgili tüm genlerle analiz edilen gen ontolojisini ve yolunu gösterdik. Özellikle apoptoz ve sistemik sklerozun bu genlerle ilişkili olduğunu belirlendi.

Sonuç: Vitiligo hastalarının SIRT1 rs7895833 SNP genotipi ve allel frekansları, sağlıklı kontrollerden önemli ölçüde farklıdır. Çalışmamız, SIRT1 geninin rs7895833 polimorfizmiyle vitiligo duyarlılığının ilişkili olabileceğini göstermektedir. Sirtuin ve ilgili genlerin özellikle apoptotik yolaktaki görevleri göz önüne alındığında vitiligoya etkisi, hastalığın moleküler yönünü aydınlatmak için daha fazla araştırılabilir.

Anahtar Sözcükler: Gen polimorfizmi, In silico, SIRT1, Vitiligo

INTRODUCTION

Vitiligo is an acquired dermatological disease with hard medical treatment, even though various healing interventions are applied. Milky white patches seen on the skin are areas with hypopigmentation or depigmentation, based on local loss of epidermal melanocytes (1). Worldwide occurrence frequency ranges between 0.1% and 2% (2). Several suggestions for the pathophysiological changes leading to vitiligo have been proposed and these diverse theories include genetic predisposition and other neural or autoimmune factors linked with apoptosis and oxidative stress (3, 4). However, the assumption for melanocyte damage is induced by autoimmune reasons prevails among neural and self-destruction hypotheses (5).

Sirtuins represent a deacetylase enzyme family, which is functionally NAD (nicotinamide adenine dinucleotide) dependent (6). They are involved in regulation of the metabolic processes in the cells by acting like sensors for the energy level (7). Human Sirtuins are represented in 7 types of enzymes (Silent Information Regulator T1-7, SIRT) with NAD^+- dependent activity (8). SIRT 1-3, and 5 were indicated to have powerful deacetylase effect toward histone proteins while remaining types have no such catalytic activity on the same substrates (9).

SIRT transcription status during oxidative stress and with their regulating role in chromatin dynamics, SIRT enzymes could be associated with cellular life span, glucose homeostasis, inflammation, apoptosis, autophagy and even cancer (10-14). Similarly, impaired normal cellular function beside those counted above, only a few studies investigated the relation of the SIRT 1 gene / enzyme with skin diseases (15). Its role and possible implication in dermatological diseases were also not studied in detail.

SIRT1 enzyme is mainly present in the nucleus and is partly localized in the cytoplasm as well (16). Different cellular compartments contain these enzymes which take on different deacetylation reactions like those of histones and several transcription factors in the nucleus and specific proteins in mitochondria (17-19).

The aim of our present study is to investigate the rs2273773, rs7895833 and rs7069102 polymorphisms of SIRT 1 gene in clinically diagnosed vitiligo patients, by focusing on evaluation of the frequency of the polymorphisms and a possible relation to the tendency for vitiligo occurrence. We also aimed to determine the possible interactions of SIRT 1 and related proteins by a web-based ontological analysis with *in silico* approach.

MATERIAL and METHODS

Study population

The whole procedure was carried out in accordance with the Declaration of Helsinki. Approval for the study was issued by the Committee for Clinical Research in Zonguldak Bülent Ecevit University - Faculty of Medicine, where the whole blood samples were obtained from. The participants in the present study group were recruited from the Department of Dermatology at Bülent Ecevit University Hospital and all declared their written informed consent. Questionnaire based data about clinical status and demographic information were obtained from all the subjects who were then evaluated for further analyses under two different groups as control (n=85) and vitiligo patients (n=78). Healthy control individuals were with no clinical evidence for family history of vitiligo or any other autoimmune disease or systemic disorders. Genomic DNA extraction was performed by using of separated venous blood samples, stored at -20 °C prior to extraction procedure. DNA extraction was performed by the spin column kit method in the Medical Biology laboratory (Invitrogen™ PureLink™ Genomic DNA Mini Kit, Catalog number: K182002).

DNA Extraction and Genotyping

Amplification procedure of the SIRT1 gene and the proper sequence site for the gene polymorphisms (rs7895833, rs7069102 and rs2273773) was performed by Polymerase

Chain Reaction (PCR) method with Confronting Two-pair Primers (CTPP). The PCR process was accomplished in a volume of 20μl distilled water containing 100ng DNA, 2mM dNTPs, 5 pmol of primers (for each F and R), 1.0 mM $MgCl_2$ and 0.5U Taq polymerase. Primers used for identification of rs7895833, rs2273773 and rs7069102 polymorphisms and band length specifications are presented in Table 1. Electrophoretic separation of PCR-CTTP products was performed on a 3% agarose gel and samples were visualized by using UV light.

Prediction of Gene-Gene Interactions and gene ontology with in silico analysis

SIRT 1 gene investigation of its association with other genes in order to predict the effect of SNPs on other related genes was used, GeneMANIA (https://genemania.org/) (accessed on 25 September 2022). The prediction of gene-gene interaction by GeneMANIA is that interaction is based on the basis of pathways, co-localization, co-expression protein domain similarity, and genetic and protein interaction (20). The ontological analysis for the list of the SIRT1-interacted genes was done by using the online GeneCodis 4 software (https://genecodis.genyo.es/). This tool is a web-based method for the ontological analysis of lists of proteins, genes and regulatory elements like miRNAs, transcription factors, and CpGs (21).

Statistical analysis

The analysis for all data obtained was completed by Statistical Package for the Social Sciences (SPSS) 20 program. Shapiro-Wilk test was applied for evaluation of conformity of quantitative data to the normal distribution. Two independent groups were compared by using the independent samples t-test. Categorical data comparison analysis was performed by Pearson's $\chi 2$ (exact) test. Results are presented as median (min-max) for non-continuous data. The categorical values are presented as number (n) and percentage (%). The confidence level chosen was 95% and the p value below 0.05 was accepted as significant. The association between the SIRT1 genotypes and the patients with vitiligo was estimated by computing the odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression analyses. Beside the above mentioned analyses, the effect of the genetic correlation between two polymorphic regions was determined by using a haplotype analysis.

RESULTS

Demographical information for vitiligo patients and control individuals is presented in Table 2. The mean age in the vitiligo group was 35.5 years and similarly, 34 years in the control group, with no statistical difference between 78 patients and 85 controls who participated in the study (p>0.05).

The SIRT1 gene allele distributions and genotypes of the vitiligo patients and the control group are shown in Tables 3 and 4. The distribution of the SIRT1 gene for the persons in the vitiligo and control groups was in Hardy-Weinberg equilibrium.

While TT, TC and CC genotype frequencies of rs2273773 were 29%, 21% and 28% respectively for the group with vitiligo, these were 29%, 36% and 20% for the control group (p = 0.083). While the frequencies of T and C alleles of the vitiligo group were 79% and 77%, these were 94% and 76% for the control subjects (p=0.558). While GG, AG and AA genotype frequencies of rs7895833 were 14%, 44% and 20% respectively for the vitiligo patients, these were 38%, 35% and 12% for the control group (p = 0.001). The frequencies of G and A alleles of the vitiligo group were 46% and 54% respectively, these results are significantly different from the control group allele frequency (p = 0.001. While CC,

Table 1: Primer sequences and annealing temperature values applied for detection of rs2273773, rs7895833 and rs7069102 polymorphisms of SIRT1 gene.

Polymorphism (SIRT1 gene)	Primers Sequence 5' - 3'	Annealing temperature (°C)	Fragment size (bp)
rs2273773	P1-P4	63	**CC:** 314, 228 **CT:** 314, 228, 135 **TT:** 314, 135
rs7895833	P5-P8	64	**AA:** 320, 241 **AG:** 320, 241,136 **GG:** 320, 136
rs7069102	P9-P12	64	**CC:** 391, 277 **CG:** 391, 277, 167 **GG:** 391, 167

P1:5'GTGTGTCGCATCCATCTAGATAC 3'; P2:5'CTCTCTGTCACAAATTCATAGCCT 3'
P3:5'GTAGTTTTCCTTCCTTATCTGACAG 3'; P4:5'CTGAAGTTTACTAACCATGACACTG 3'
P5:5'CCCAGGGTTCAACAAATCTATGTTG 3'; P6: 5'GGTGGTAAAAGGCCTACAGGAAA 3'
P7:5'GCTTCCTAATCTCCATTACGTTGAC 3'; P8: 5'CCTCCCAGTCAACGACTTTATC 3'
P9:5'GTAGCAGGAACTACAGGCCTG 3'; P10:5'GAGAAGAAAGAAAGGCATAATCTCTGC 3'
P11:5'CTATCTGCAGAAATAATGGCTTTTCTC 3'; P12:5' GATCGAGACCATCCTGGCTAAG 3'

CG and GG genotype frequencies of rs7069102 were 18%, 26% and 34% respectively for the vitiligo patients group, these were 17%, 39% and 29% for the control subjects group (p = 0.255). While the frequencies of C and G alleles of the vitiligo group were 62 % and 94%, these were 73% and 97% for the control group (p = 0.558) (Tables 3 and 4). GG, AG and AA genotypes of rs7895833 were found to be significantly different in between; especially the GG genotype of vitiligo group revealed a significant difference. Significantly lower percentages in the AG and AA genotypes were calculated by analysis. No significant difference was revealed in both groups for CC, CG and GG genotypes of

Table 2: Demographic characteristics of patients and controls

Clinical Characteristics		Vitiligo (n=78) Median (Min.-Max.)	Control (n=85) Median (Min.-Max.)	p-value
Age		35.50 (8-82)	34 (17-80)	0.950
Gender, n (%)	**Female**	36 (46)	46 (54)	
	Male	42 (54)	39 (46)	
Family history	**Yes**	60 (0.77)	–	
	No	18 (0.23)	–	
Vitiligo Types	**Generalized**	38 (0.49)		
	Segmental	2 (0.02)		
	Localized	22 (0.28)	–	
	Acrofacial	11 (0.15)	–	
	Vulgaris	2 (0.02)		
	Focal	3 (0.04)		
Stability	**Stable**	16 (0.21)	–	
	Active	62 (0.79)	–	

Table 3: Distribution of genotypes of patients and controls

SNP	Genotypes	Vitiligo, n (%)	Control, n (%)	p value*	OR (95% CI)	p value**
rs2273773	TT	29 (37)	29 (34)	0.083	**1 (Reference)**	
	TC	21 (27)	36 (42)		0.58 (0.27-1.22)	0.156
	CC	28 (36)	20 (24)		1.40 (0.64-3.02)	0.392
rs7895833	GG	14 (18)	38 (45)	**0.001**	**1 (Reference)**	
	AG	44 (56)	35 (41)		3.41 (1.60-7.27)	0.001
	AA	20 (26)	12 (14)		4.52 (1.76-11.60)	0.002
rs7069102	CC	18 (23)	17 (20)	0.255	**1 (Reference)**	
	CG	26 (33)	39 (46)		0.63 (0.27-1.44)	0.273
	GG	34 (44)	29 (34)		1.10 (0.48-2.53)	0.809

Results are given as n (%). **OR:** Odds ratio, **CI:** Confidence interval. The ORs were calculated with references to the risk genotype and allele. * χ^2 analysis p-value, p< 0.05; ** Logistic regression analysis, p< 0.05

Table 4: Allele frequencies for vitiligo patients and control subjects

SNP	Allele frequency	Vitiligo, n (%)	Control, n (%)	p value*	OR (95% CI)	p value**
rs2273773	T	79 (51)	94 (55)	0.400	1 (Reference)	0.401
	C	77 (49)	76 (45)		1.20 (0.78-1.86)	
rs7895833	G	72 (46)	111 (65)	0.001	1 (Reference)	0.001
	A	84 (54)	59 (35)		2.19 (1.40-3.42)	
rs7069102	C	62 (40)	73 (43)	0.558	1 (Reference)	0.558
	G	94 (60)	97 (57)		1.14 (0.73-1.77)	

Results are given as n (%). **OR:** Odds ratio, **CI:** Confidence interval. The ORs were calculated with references to the risk genotype and allele. * χ^2 analysis p-value, p< 0.05; ** Logistic regression analysis, p< 0.05

rs7069102 and TT, TC and CC genotypes of rs2273773. It shows that these polymorphisms of the SIRT1 gene could be associated with the vitiligo.

There was a significant difference between the two groups with regards to G and A alleles of rs7895833. While the percentage of the G allele, which was dominant in the control group, was decreasing in the group with vitiligo, the A allele, which was seen less often in the control group, was determined as more dominant in the group with vitiligo. While no difference was found in both groups with regards to G and C alleles of rs7069102, a high rate of G allele was determined in both groups. A difference was not found in both groups with regards to T and C alleles of rs2273773. A dominant rate of C allele was also found in this group.

Haplotype analysis of the rs2273773, rs7895833, and rs7069102 SIRT1 polymorphisms revealed that the AGT haplotype frequency was 23% in vitiligo patients and 12% in the controls, and the difference was significant (OR=2.99; 95% CI, 1.26–7.06) (Table 5). A further haplotype analysis among all three above mentioned polymorphisms has shown that the AGT haplotype could be a risk factor in etiology of vitiligo (p=0.013).

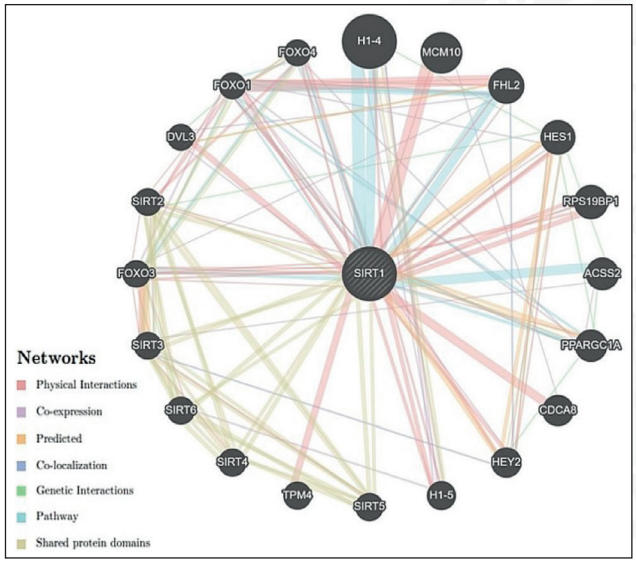

Figure 1: Gene-gene interaction network of SIRT1 using a GeneMANIA tool.

Prediction of Gene-Gene Interactions and gene ontology with in silico analysis

Our findings revealed that SIRT 1 is co-expressed with 16 genes (H1-4, MCM10, FHL2, HES1, ACSS2, PPAR6C1A, CDCA8, HEY2, H1-5, SIRT6 SIRT3, FOXO3, SIRT2, DVL3, FOXO1, FOXO4), shared a domain with only 12 genes (H1-4, HES1, HEY2, H1-5, SIRT5, SIRT4, SIRT3, FOXO3, SIRT2, FOXO1, FOXO4), physical interaction with 19 genes (all shown in figure 1 excepted ACSS2 gene) (Figure 1).

20 identified genes were found to be related to apoptosis, autoimmunity and oxidative stress genes and molecular events as revealed via a regulatory and functional analysis by GeneCodis 4 (Figure 2). The figures represent the visualizations generated for 10 top terms of associations with Gene Ontology (GO) and GO Annotations Biological Process (Figure 2A), GO Cellular Component (Figure 2B), GO Molecular Function (Figure 2C), annotation of Reactome Pathway Database (Figure 2D).

DISCUSSION

The present study investigated the possible interrelation between the SIRT1 gene and vitiligo disease, the first among other genetic research studies. Consequently, a significant linkage was detected for rs7895833 polymorphism of the SIRT1 gene which is known to be involved in the apoptotic process and histone modification. As demonstrated from the perspectives of biological process and molecular function (Figure 2A,C, respectively), the genes analyzed are responsible for cellular roles such as histone modifications, control of transcription, and chromatin-DNA interaction. The cellular activities determined as a result of

Table 5: Association between haplotypes of SIRT1 gene polymorphisms and risk of vitiligo

Haplotypes	Vitiligo, n (%)	Control, n (%)	OR (95% CI)	p-value
GCT	25 (16)	39 (23)	Reference	-
GGT	22 (14)	31 (18)	1.10 (0.52-2.32)	0.788
GGC	14 (9)	27 (16)	0.80 (0.35-1.83)	0.611
GCC	12 (7)	14 (8)	1.33 (0.53-3.35)	0.536
AGT	**23 (14)**	**12 (7)**	**2.99 (1.26-7.06)**	**0.013**
ACT	12 (7)	12 (7)	1.56 (0.60-4.01)	0.356
ACC	38 (24)	24 (16)	2.19 (1.08-4.43)	0.290
AGC	14 (9)	8 (5)	2.73 (1.00-7.44)	0.050

Results are given as n (%). **OR:** Odds ratio, **CI:** Confidence interval. The ORs were calculated with references to the risk haplotype. * Logistic regression analysis, p< 0.05

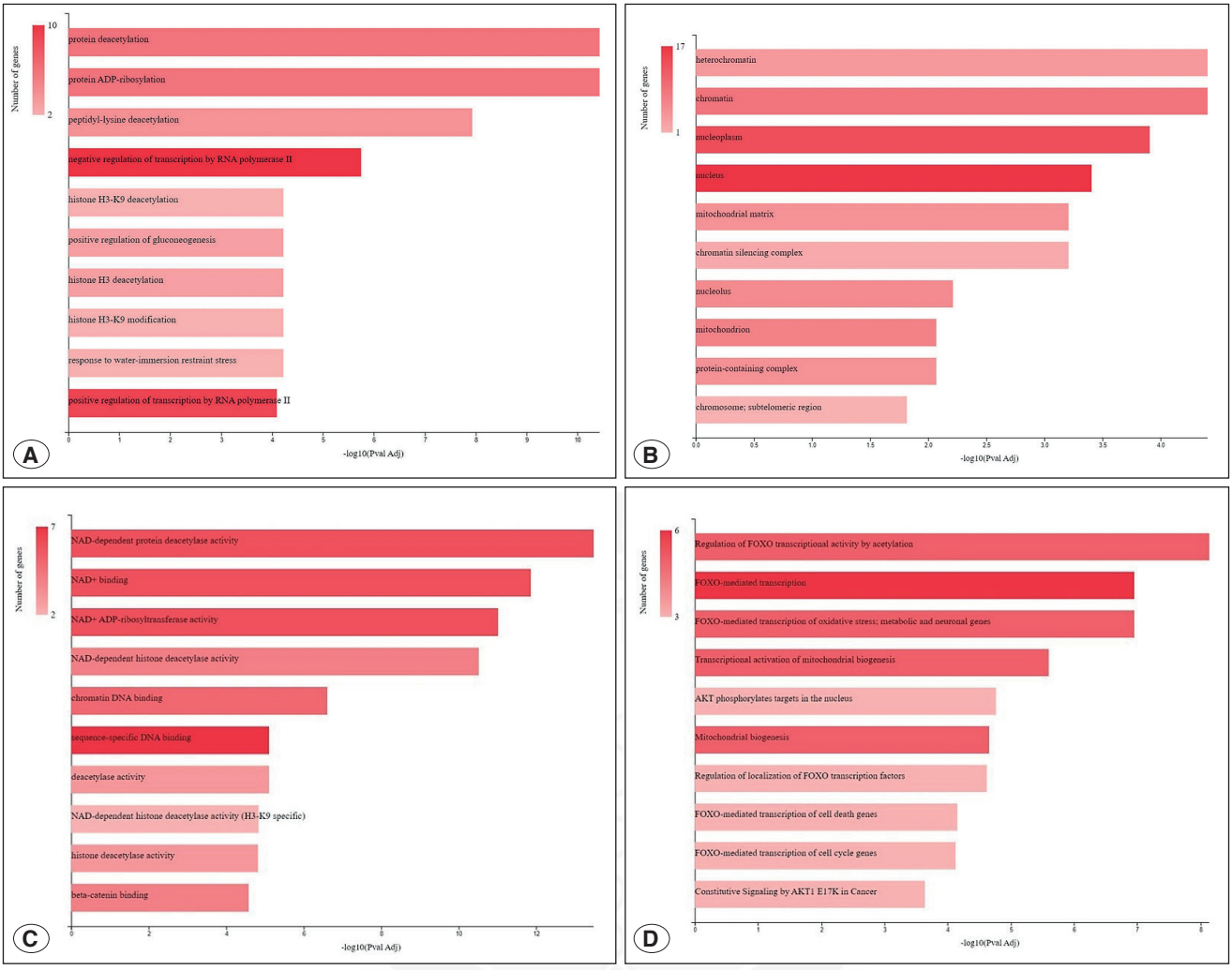

Figure 2: GeneCodis Ontological analysis. Visualizations generated for 10 top terms of related categories with our identified gene list are presented here for GO Biological Process **(A)**, GO Cellular Component **(B)**, GO Molecular Function **(C)**, Annotation of Reactome database **(D)**.

the analyzes control the genetic and epigenetic processes in the regulation of gene expression.

All seven sirtuins have been expressed in human epidermal and dermal cells (22). Sirtuins are involved in cellular pathways related to many skin diseases, including photoaging, inflammation, and cancer (23). SIRT1 expression was decreased in cultured skin keratinocytes damaged by UV and H_2O_2 (24). Upregulation of SIRT1, 3 and 7 are potential therapeutic targets for improving skin ageing and appearance (23).

It has been reported that the SIRT1 pathway is protective against skin damage as a result of H_2O_2-induced keratinocyte death (25). Becatti et al. showed decreased SIRT1 expression and activity in lesioned psoriatic fibroblasts (26).

Another study emphasized that SIRT1 has a critical role in maintaining the skin barrier and preventing atopic dermatitis (27). The rs7069102 polymorphism of the SIRT1 gene has been shown to be associated with early-onset psoriasis (28). SIRT1-related interaction and its possible contribution and involvement in dermatological diseases are not investigated enough as far.

Further investigation on cellular mRNA and the protein levels of SIRT1 and other genes involved in the apoptotic pathways may provide detailed data for their implication in vitiligo pathogenesis. Genes, cellular process and pathways that may be important in the pathogenesis of vitiligo have been demonstrated with in silico approaches. By in silico approaches, genes with which the SIRT1 gene interacts are determined, and target genes (FOXO3, SIRT2, DVL3, MCM10, etc.) that may be associated with apoptosis, oxidative stress and autoimmunity, which are the basis of vitiligo pathogenesis revealed. FOXO-mediated transcription, oxidative stress, mitochondrial biogenesis, and AKT signaling

pathway draw attention in the Reactome pathway analysis. Studies have revealed the relationship between FOXO genes, oxidative stress and apoptosis processes and vitiligo (23, 29-32). In a recent study, the AKT/MAPK pathway has been associated with apoptosis and oxidative stress of keratinocytes in vitiligo (23, 32). In this context, the importance of these pathways and related genes in the pathogenesis of vitiligo has been reported in some studies (33-36).

There is a limited number of studies investigating the linkage between the SIRT1 enzyme/gene and dermal fibroblasts or microvascular endothelial cells. SIRT1 related interaction and its possible contribution and involvement in dermatological diseases are not investigated enough as far.

Acknowledgment

We thank to Çilem Özdemir for the support in performing the in silico analysis of previously unpublished results, interpretation of digital data for risk relation and for the contribution in structural design of the present manuscript.

Author Contributions

Concept: **Oktay Kuru, Tuba Edgünlü, Ümmühani Özel Türkcü, Nilgün Solak,** Design: **Tuba Edgünlü, Nilgün Solak, Oktay Kuru, Sevim Karakaş Çelik,** Data Collection or Processing: **Nilgün Solak, Sevim Karakaş Çelik, Tuba Edgünlü, Oktay Kuru,** Analysis or Interpretation: **Ümmühani Özel Türkcü, Oktay Kuru, Tuba Edgünlü,** Literature search: **Oktay Kuru, Tuba Edgünlü, Writing: Oktay Kuru, Tuba Edgünlü,** Approval: **Sevim Karakaş Çelik, Oktay Kuru.**

Conflicts of Interest

No conflict of interest is reported by authors.

Financial Support

This study was supported by a grant from the Muğla Sıtkı Koçman University Research Projects Coordination Office (Project Grant Number 13/114).

Ethical Approval

Ethical approval for the current study was issued by the Institutional Review Board upon request (13-05-22/01-04). All procedures were performed in compliance with Declaration of Helsinki. Participants gave their written consent after being informed for contribution to study.

Review Process

Extremely peer-reviewed and accepted.

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ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2023;7(1): 9-13
DOI: 10.29058/mjwbs.1228491

Mean Platelet Volume as a New Inflammatory Marker in Acute Pancreatitis and Its Relation to C-Reactive Protein and Ranson's Score on Admission

Akut Pankreatitte Yeni Bir İnflamatuar Belirteç Olarak Ortalama Trombosit Hacmi ve C-Reaktif Protein ile Başvuru Anındaki Ranson Skoru ile İlişkisi

Barış KARAGÜN[1], **Tayyibe SALER**[2]

[1]Tarsus State Hospital, Department of Endocrinology and Metabolic Diseases, Mersin, Turkey
[2]Adana City Training and Research Hospital, Department of Internal Medicine, Adana, Turkey

ORCID ID: Barış Karagün 0000-0002-4011-4622, Tayyibe Saler 0000-0001-5588-5609

Cite this article as: Karagün B and Saler T. Mean platelet volume as a new inflammatory marker in acute pancreatitis and its relation to c-reactive protein and Ranson's score on admission. Med J West Black Sea. 2023;7(1):9-13.

Corresponding Author
Barış Karagün

E-mail
bariskaragunn@gmail.com

Received
02.01.2023

Revision
15.02.2023

Accepted
26.03.2023

ABSTRACT

Aim: The study's aim is to evaluate mean platelet volume (MPV) as a marker of inflammation in patients with acute pancreatitis (AP) and to analyse the relationships among MPV, CRP (C-reactive protein) and Ranson's score.

Material and Methods: In this study, 119 patients with AP (mean age 53.8 ± 18.0 years) and 88 healthy control group (mean age 53.1 ± 6.8 years) were enrolled. Among the patients with AP, 75 were classified as having biliary AP, and 44 were classified as having nonbiliary AP. All patients' demographic data, clinical and laboratory findings and Ranson's scores were examined from the hospital's database.

Results: MPV was significantly lower among patients with AP than among the control group (p = 0.001). CRP was significantly higher among patients with AP than among the control group (p< 0.001). The difference in MPV between the biliary and nonbiliary AP group was statistically not significant. When we compared MPV based on patients' lengths of hospital stay, there was no significant difference. In correlation analysis, there was no correlation among CRP, Ranson's score and serum MPV levels.

Conclusion: We observed that MPV levels in the AP group were lower than healthy controls. Thus, like other inflammation markers, MPV might be a useful marker for AP diagnosis.

Keywords: Acute pancreatitis, Mean platelet volume, Inflammation

ÖZ

Amaç: Bu çalışmada akut pankreatitli (AP) hastalarda inflamasyon belirteci olarak ortalama trombosit hacmini (MPV) değerlendirmek ve MPV, CRP (C-reactive protein) ile Ranson skoru arasındaki ilişkiyi inceleme amaçlandı.

Gereç ve Yöntemler: Bu çalışmaya AP'li 119 hasta (ortalama yaş 53.8 ± 18.0 yıl) ve 88 sağlıklı kontrol grubu (ortalama yaş 53.1 ± 6.8 yıl) alındı. AP'li hastalardan 75'i biliyer AP, 44'ü biliyer olmayan AP olarak sınıflandırıldı. Tüm hastaların demografik verileri, klinik ve laboratuvar bulguları ve Ranson skorları hastanenin veri tabanından incelendi.

Bulgular: MPV, AP'li hastalarda kontrol grubuna göre anlamlı olarak daha düşüktü (p = 0.001). AP'li hastalarda CRP, kontrol grubuna göre anlamlı olarak daha yüksekti (p < 0.001). Biliyer ve biliyer olmayan AP grup arasındaki MPV farkı istatistiksel olarak anlamlı bulunmadı. Hastaların hastanede kalış sürelerine göre MPV değerlerini karşılaştırdığımızda anlamlı bir fark yoktu. Korelasyon analizinde CRP, Ranson skoru ve serum MPV seviyeleri arasında korelasyon yoktu.

Sonuç: AP grubunda MPV düzeylerinin sağlıklı kontrollere göre daha düşük olduğunu gözlemledik. Bu nedenle, diğer inflamasyon belirteçleri gibi MPV de AP tanısı için yararlı bir belirteç olabilir.

Anahtar Sözcükler: Akut pankreatit, Ortalama trombosit hacmi, İnflamasyon

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disease of the pancreas and it's characterized by abdominal pain and elevated levels of pancreatic enzymes (1,2). Abdominal pain in concur with elevation of plasma levels of pancreatic enzymes, which is known as amylase and lipase, that secreted by pancreatic acinar cells are the cornerstone of diagnosis (3). The pathogenesis of acute pancreatitis is not fully understood. However, there are known to be certain conditions that trigger this disorder. The most common risk factors for AP are gallstones and alcohol; and the incidence this disease has been increasing globally (4).

Of all AP patients, 15 to 25% will develop moderately severe AP or severe AP. According to epidemiologic studies, acute pancreatitis mortality fell from 14% to 2% between 1988 and 2003(5). The importance of severity prediction is well established and an early assessment of severity would diminish the financial burden of AP (6). Acute pancreatitis severity has been predicted using a variety of scoring methods. Ranson score is a frequently used scoring system that evaluates the severity of AP. APACHE II (Acute Physiology And Chronic Health Examination), Systemic Inflammatory Response Syndrome (SIRS), BISAP (Bedside Index Of Severity In Acute Pancreatitis) and CT Severity Index [CTSI] scoring systems are other scoring systems used to predict the severity of acute pancreatitis (7).

Mean platelet volume (MPV) is a sign of platelet activation and aggregation. MPV has been found in many studies to be related to inflammation resulting from disorders. Chronic inflammatory diseases with high-grade inflammation (i.e. inflammatory bowel disease, rheumatoid arthritis and familial Mediterranean fever) are characterised by changes in platelet size during active or remissive periods (8). However, MPV's role as an inflammation indicator in the pathophysiology of acute pancreatitis (AP) has not yet been clearly elucidated. Our study is aimed at evaluating MPV as a marker of inflammation in patients with AP and analysing the relationships among MPV, CRP and Ranson's score.

MATERIAL and METHODS

In this study, data from 119 AP patients admitted to our hospital from July 2015 to March 2016 were retrospectively analysed. As the control group, 88 healthy people were retrospectively enrolled. These controls were healthy adults with no history of acute or chronic inflammatory disease or drug use. In the study group, 75 patients were diagnosed with biliary AP, and 44 patients were diagnosed with nonbiliary AP. To diagnose acute pancreatitis, we evaluated the patients' physical examinations and laboratory and radiological findings. Patients who presented at least two of the following findings were diagnosed with AP: (i) characteristic abdominal pain (i.e. acute onset of persistent and severe epigastric pain that often radiates to the back); (ii) elevated levels of pancreatic enzymes – namely, serum amylase and/or lipase – higher than three times the upper normal limit; (iii) characteristic findings of AP in imaging studies, including abdominal ultrasonography or computed tomography (9).

Platelet numbers and MPV values from the first complete blood count (CBC) were recorded at the time of admission. The mean platelet volume (MPV), which is estimated by hematological analyzers based on volume distribution during a regular blood morphology test, is an accurate measurement of their dimension. MPV ranges from 7.5 to 10.5 fl (10). The patients' characteristics and biochemical parameters were also obtained from our database.

Ranson admission score of the all patients were calculated. Ranson's criteria were created in 1974 and it is a clinical estimation method used to estimate the severity of acute pancreatitis (11). The Ranson criteria include 11 parameters, with five parameters evaluated at admission and the other 6 after 48 hours of follow-up. Age over 55, WBC (white blood cell) count over 16,000 cells/cmm, blood glucose over 200 mg/dL (11 mmol/L), serum AST over 250 IU/L, and serum LDH over 350 IU/L are the five criteria for admission. For each parameter, one point is given. If the score is below three, mortality is below 3%. If the score is above six, mortality is predicted to be more than 40% (12). The study population was determined minimum as 74 using the G power program by taking impact size 0.863(based on similar study result), a=0.05, power (1-b)= 0.95 at a confidence level of 95% (version 3.1.9.6; Axel Buchner, Universität Düsseldorf).

Statistical Analysis

Data were analyzed by using a commercially available statistics software package MedCalc 16.8.4 (MedCalc Belgium). Kolmogorov-Smirnov and D'Agostino-Pearson tests were used to evaluate continuous variables in terms of normality. Normally distributed data were presented as mean ± standard deviation. Non-normally distributed data were presented as median and range. Comparison of percentages between different patient groups was made using the chi-square test. Mann-Whitney U-test was performed for normally distributed data for independent subgroups. P values below 0.05 were considered as statistically significant.

RESULTS

Of the 119 patients with AP, 34 (28.6%) were men and 85 (71.4%) were women. Of the 88 healthy control subjects, 30 (34.1%) were men and 58 (65.9%) were women. The mean ages of the patient and control groups were 53.8 ± 18 years and 53.1 ± 6.8 years, respectively. The groups were similar in terms of sex and age.

The distribution of patients according to the Ranson score was assessed at admission. The Ranson score was calcu-

lated as 0 in 30 (25.2%) patients, 1 in 43 (36.1%) patients, 2 in 29 (24.4%) patients, 3 in 15 (12.6%) patients, and 4 in 2 (1.7%) patients.

MPV levels were significantly lower in the AP patient group than in the control group (p = 0.001; Table 1, Figure 1).

In the correlation analysis, there was no correlation between MPV serum levels and CRP (p = 0.661) or Ranson's score assessed upon admission (p = 0.485). We also compared MPV values between biliary and nonbiliary AP patients. There were no significant differences between the two groups (p = 0.566).

Moreover, there was no relationship between MPV values and Ranson's admission scores. There were no significant associations between MPV and WBC count (p = 0,083), age (p = 0,814), glucose (p = 0,916), aspartate aminotransferase (AST) (p = 0.540), or lactate dehydrogenase (LDH) (p = 0.120; Table 2).

There was no statistically significant difference between the patients' MPV values based on their hospital stay durations (5.6±2.4, days) (p = 0.968).

DISCUSSION

Acute pancreatitis is a disease characterized by pancreatic inflammation that clinically appears with signs of specific abdominal pain and raised levels of pancreatic enzymes (1,2) (e.g. amylase and lipase). It is one of the most common diseases of the gastrointestinal tract, and it can cause mortality and morbidity, resulting in tremendous emotional, physical and financial burdens (13,14). MPV's role in pancreatitis-related inflammation is not fully understood, but many studies have pointed out that MPV may indicate inflammatory burden (15,16). In our study, we investigated MPV's role in AP's diagnosis and prognosis and found that MPV served as an inflammatory marker in patients with AP. When we compared the AP patient group and the healthy control group, the MPV values in patients with AP were markedly lower than those in the healthy control group.

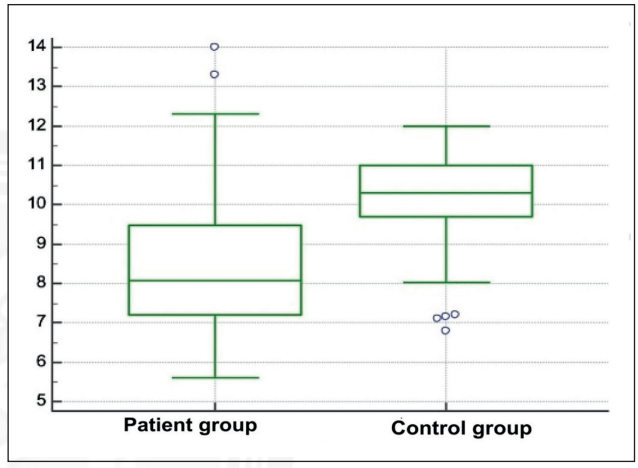

Figure 1: MPV levels between AP patients and control group

Table 1: Demographic characteristics and laboratory values.

	Patient Group (n=119)	Control Group (n=88)	p value
Age(year)	53.8 ±18.0	53.1±6.8	NS
Gender(F/M)	85 (71.4%) / 34(28.6%)	58 (65.9%) / 30(34.1%)	NS
WBC (/mm^{3}x10^3)	12.8±4.6	7.7±1.5	<0.001
Platelets (/mm^3)	261.1±78.8	301.9±76.4	0.003
MPV (fL)	8.4±1.7	10.1±1.06	0.001
CRP (mg/dl)	4.3±7.2	0.3±0.16	0,001
Amylase (µ/l)	1162±835	69.9±24.3	<0.001
AST (µ/l)	167.9±171.9	20.0±6.6	<0.001
Glucose(mg/dl)	149.2±66.1	85.6±8.1	<0.001
LDH (µ/l)	403.3±234.4	138.1±40.5	<0.001

NS: Not significant

Table 2: Coreletion MPV and Ranson admission score criterias

	Ranson Score	WBC (/mm^{3}x10^3)	Age (year)	Glucose (mg/dl)	AST (µ/l)	LDH (µ/l)	Duration of hospital stay (5.6±2.4, days)
MPV (fL)	r:0,06 p:0,485	r:0.159 p:0.083	r: -0.021 p:0.814	r:0.009 p:0.916	r:0.05 p:0.540	r:0.143 p:0.120	r:0.003 p:0.968
Ranson Score		r:0.191 p:0.037	r:0.393 p<0.001	r:0.221 p:0.016	r:0.459 p<0.001	r:0.566 p<0.001	r:0.162 p:0.078

There was no significant difference between the MPV values of the patients with biliary AP and those of the nonbiliary AP patients. The relationship between acute pancreatitis and MPV has been examined in many studies and shown to decrease (17,18). A meta-analysis investigating ten studies showed that MPV was lower at AP's onset than during the disease's remission, regardless of disease severity (19). Lei et al. reported that MPV had higher sensitivity than WBC, LDH and CRP in predicting AP with persistent organ failure on Day 1 after admission (20).

Ranson's scoring in acute pancreatitis provides information about the disease's prognosis (21). In our study, there was no significant correlation between MPV and Ranson's score on admission. Although in our study we could not find a significant correlation with MPV and Ranson criteria, which is an important prognosis predictor, there are studies showing a significant correlation relationship between its and other important prognostic predictor scoring systems such as APACHE II and mGPS (Modified Glasgow Prognostic Score) (17,22). In addition, MPV has been studied even in pancreatic cancers and has been shown to be a predictor of poor prognosis (23).

CRP, is a protein produced by the hepatocytes, is an acute phase reactant and is usually elevated in inflammatory conditions (24). Although we could not find a significant relationship between CRP and MPV in this study, there are studies in the literature showing that they are correlated in inflammatory diseases (25,26).

We compared the MPV value with the duration of hospital stay in patients with acute pancreatitis in order to determine the association of MPV with the duration of hospital stay, but no significant difference was found. This study was the first to investigate the relationship between MPV value and length of hospital stay.

There are some limitations of the present study. First of all, our study is a retrospective study with a limited number of patients. Secondly our data included in the study consisted of one-time measurements. We think that our findings might offer new evidence for additional research using larger sample sizes. Further prospective studies are needed on the role of MPV as a marker of inflammation in patients with AP.

In conclusion, MPV was detected lower in patients with acute pancreatitis than healthy group. MPV is a cheap and easily detectable marker that can be used as other inflammatory markers in the diagnosis of acute pancreatitis It may be useful as a new marker of inflammation in acute pancreatitis.

Acknowledgment

None.

Author Contributions

The idea of presenting the study to the literature and collecting the data of the study:Barış Karagün, Tayyibe Saler. Analysis of patient's data, writing of article: Barış Karagün

Conflicts of Interest

The author of this article declare no conflicts of interest.

Financial Support

No financial support was used for this study.

Ethical Approval

Prior to the study, approval was obtained from the Adana Numune Training and Research Hospital Clinical Research Ethics Committee (Date: 26.04.2016, Decision No: 71) and the study was conducted in accordance with the "Helsinki Declaration".

Review Process

Extremely peer-reviewed and accepted.

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ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2023;7(1): 14-20
DOI: 10.29058/mjwbs.1221562

Can the Prognosis be Predicted in Subacute Thyroiditis?

Subakut Tiroiditte Prognoz Öngörülebilir mi?

Ali SAKLAMAZ, Özcan ÇİFTÇİ

Izmir University of Economics, Faculty of Medicine, Private Medicalpoint Hospital, Clinic of Endocrinology, İzmir, Turkey

ORCID ID: Ali Saklamaz 0000-0001-9190-2242, Özcan Çiftçi 0000-0002-2841-5588

Cite this article as: Saklamaz A and Çiftçi Ö. Can the prognosis be predicted in subacute thyroiditis?. Med J West Black Sea. 2023;7(1):14-20.

Corresponding Author
Ali Saklamaz

E-mail
asaklamaz@hotmail.com

Received
19.12.2022

Revision
13.04.2023

Accepted
14.04.2023

ABSTRACT

Aim: Subacute thyroiditis (SAT) is a thyroid disease that seriously affects the quality of life for patients caused by acute inflammation of the thyroid gland. Apart from classical acute phase reactants, the values and rates obtained from peripheral blood count (mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR)) values are also accepted as practical indicators of systemic inflammation. Our aim in this study is to compare the effects of systemic inflammation markers and the treatments given in the laboratory tests of our patients with a diagnosis of SAT, on the hypothyroid state one year later.

Material and Methods: In this study, which was carried out with a retrospective method, 133 patients were included in the study. The medical data of these patients at the time of SAT diagnosis and one year later were analyzed. 37 patients were in the steroid group and 97 patients were in the nonsteroidal anti-inflammatory drug (NSAID) group.

Results: The male/female ratio was similar in both groups. Female dominance was observed in both groups in patients diagnosed with SAT. The thyroid tests of the groups, which were hyperthyroid at the beginning and euthyroid one year later, were similar between the groups ($p>0.05$). Both groups had an increase in acute phase reactants at baseline (erythrocyte sedimentation rate [ESR] and C-reactive protein (CRP) levels) and normalized after treatment. Neutrophil ($p<0.05$), lymphocyte ($p>0.05$) and platelet ($p<0.05$) counts decreased with the reduction of inflammation. Monocyte count decreased in both groups, but it was significant in the steroid group, but not in the NSAID group. The development of permanent hypothyroidism was 8/37 (21.6%), 24/97 (24.74%) in steroid and NSAID groups respectively ($p>0.05$). There was no statistical difference in inflammation markers (CRP etc.) and follow-up parameters before and after treatment in both groups (steroid vs. NSAID) with and without a diagnosis of permanent hypothyroidism ($p>0.05$).

Conclusion: Inflammation markers and treatments applied in SAT patients did not have a significant effect on the prognosis.

Keywords: Subacute thyroiditis, Glucocorticoid, NSAID, Hypothyroidism

ÖZ

Amaç: Subakut tiroidit (SAT), tiroid bezinin akut inflamasyonu nedeniyle oluşan hastalar için yaşam kalitesini ciddi oranda etkileyen bir tiroid hastalığıdır. Klasik akut faz reaktanları dışında periferik kan sayımından elde edilen değerler ve oranları da sistemik inflamasyonun pratik göstergesi olarak kabul edilmektedir. Bu çalışmada amacımız, SAT tanısı olan hastalarımızın laboratuvar tetkiklerinde sistemik inflamasyon markerlarının ve verilen tedavilerin, bir yıl sonraki hipotiroidik duruma etkisini karşılaştırmaktır.

Gereç ve Yöntemler: Bu retrospektif çalışmada 133 hasta çalışmaya dahil edildi. Bu hastaların SAT tanı anında ve 1 yıl sonraki tıbbi verileri incelendi. 37 hasta steroid grubunda, 97 hasta nonsteroid antiinflamatuar ilaç (NSAİİ) grubunda yer aldı.

Bulgular: Her iki grupta erkek/kadın oranı benzerdi. SAT tanısı alan hastalarda kadın hakimiyeti her iki grupta da görüldü. Grupların başlangıçta hipertiroidi ve bir yıl sonra ötiroid olan tiroid testleri gruplar

arası benzerdi (p>0.05). Her iki grupta da başlangıçta akut faz reaktanlarından artış (eritrosit sedimantasyon hızı [ESR] ve C-reaktif protein (CRP) seviyeleri) ve tedavi sonrası normale gelmiştir. İnflamasyonun azalması ile nötrofil (p<0.05), lenfosit (p>0.05) ve trombosit (p<0.05) sayıları azaldı. Monosit sayısı her iki grupta da azaldı, ancak steroid grubunda anlamlıydı, ancak NSAID grubunda değildi. Steroid ve NSAİİ gruplarında kalıcı hipotiroidi gelişimi sırasıyla 8/37 (%21,6), 24/97 (%24,74) idi (p>0,05). Tedavi öncesi ve sonrasında, her iki grupta da (steroid vs. NSAID) kalıcı hipotiroidizm tanısı alan/almayan arasında inflamasyon belirteçleri (CRP etc.) ve izlem parametrelerinde istatistiksel olarak fark bulunmamıştır (p>0.05).

Sonuç: SAT hastalarında uygulanan inflamasyon belirteçleri ve tedavilerin prognoz üzerine anlamlı bir etkisi olmamıştır.

Anahtar Sözcükler: Subakut tiroidit, Glukokortikoid, NSAİİ, Hipotiroidizm

INTRODUCTION

Subacute thyroiditis (SAT) is a thyroid disease that seriously affects the quality of life for patients caused by acute inflammation of the thyroid gland (1). Most of the time, patients are examined in various branches before the definitive diagnosis is made. Because of the neck pain that hits the ear, antibiotics are first prescribed with pre-diagnoses of throat infection or otitis. For some patients, after the diagnosis is made, the treatment process can be a bit difficult. Patients can be diagnosed easily with pain in the thyroid gland area and increased acute phase responses in blood tests. In most patients, a viral upper respiratory tract infection is detected in the anamnesis before the onset of symptoms. On thyroid ultrasound, areas of inflammation are seen as hypoechoic areas with irregular edges. Sometimes, the image on ultrasound is thought to be malignant, and fine needle aspiration biopsy is mistakenly performed on painful thyroid tissue.

Inflammation markers are high in SAT. Along with classical markers, parameters such as mean platelet volume (MPV), neutrophil / lymphocyte ratio, thrombocyte / lymphocyte ratio, monocyte / lymphocyte ratio obtained from complete blood count are also important markers of inflammation (2-4). These new inflammation markers were also examined in patients with SAT (5-9). These markers were correlated with the inflammation, but there was no correlation with the recurrence of the SAT attack or causing permanent hypothyroidism (7).

When prescribing NSAIDs or glucocorticoids, the patient's clinical condition and the practice of the doctor are important. The degree of inflammation in the thyroid, the level of acute phase reactants in blood tests and the differences in drug selection were investigated (7,10-14). To date, there has been no clear indication of disease recurrence or persistent hypothyroidism.

In this study, we wanted to compare the new inflammation markers of our SAT patients and investigate their effects on the development of permanent hypothyroidism with treatment options.

MATERIAL and METHODS

The records of patients who applied to the endocrinology outpatient clinic between 2018 and 2022 were reviewed. 172 Patients diagnosed with subacute thyroiditis were identified retrospectively. The diagnosis of SAT was made with painful thyroid gland, increased acute phase reactants, thyroiditis area on thyroid ultrasound, and low uptake on thyroid scintigraphy if performed. Of the 172 patients, only those who took steroids and NSAIDs were included in the study. Users of both drugs during their treatment were excluded. For this reason, 37 patients in the steroid group and 96 patients in the NSAID group were enrolled in the study. Patients with acute exacerbation of chronic thyroiditis, bleeding into the thyroid cyst, acute suppurative thyroiditis, and those who used levothyroxine before diagnosis were excluded from the study.

This study was conducted in accordance with the Declaration of Helsinki with the approval of the Izmir University of Economics Faculty of Medicine Ethics Committee.

Laboratory Methods

Thyroid stimulating hormone (TSH) (15), free thyroxine (FT4), free trio-iodothyronine (FT3), anti-thyroglobulin antibodies (Anti-Tg) and anti-thyroid peroxidase antibodies (Anti-TPO) concentrations were measured using chemiluminescent microparticle enzyme immunoassay (CMIA) method. Thyroglobulin (Tg) was measured using an electrochemiluminescence immunoassay (ECLIA); CRP was measured by particle association turbidimetric assay (Cobas Integra 400 plus; Roche Diagnostics, Indianapolis, USA).

Hematological parameters were obtained from standard CBC. The NLR was calculated as the ratio between NEU count and LYM count. The PLR was calculated as the ratio between platelet (PLT) count and LYM count. The MLR was calculated as the ratio between MONO count and LYM count.

Statistical Analysis

Statistical analyzes were performed using Rstudio software (version 0.98.501, Wirtschaftsuniversität Wien Welthandel-

splatz 1 1020 Vienna, Austria). Continuous variables were reported as mean±standard deviation, categorical variables as numbers and percentages. Normality conditions were determined for continuous variables in the groups with the Shapiro Wilk test. The homogeneity of the variances was evaluated with the Levine test. Continuous and categorical variables were compared between groups using one-way ANOVA and Pearson's chi-square test. Paired post-hoc tests were performed on the data, where overall significance was observed in the ANOVA using the LSD test. For homogeneous data, the paired sample t-test was used to compare the pre- and post-treatment data of the groups with the baseline data and the data obtained 1 year later. The independent t-test was used to compare the permanent hypothyroidism (yes vs. no) groups. A p value of <0.05 was considered statistically significant.

Power analysis was calculated using G-Power ver. 3.1.9.7 (Heinrich Heine Universitat Düsseldorf, Germany) software. In the calculation made with the sample numbers in the groups, the effect size value was determined as (d) 0.9 for the steroid group and (d) 0.4 for the NSAID group, and the actual power was calculated as 82.53% and 80.44% for both groups separately. According to Cohen, a scientific study should have at least 80% power and according to this criterion, the study was completed with an appropriate power.

RESULTS

Demographic Data

133 patients were classified in 2 groups. The steroid or NSAIDs given groups had 37 and 96 patients respectively. There was no statistically difference in the mean ages of the groups (p>0.05). The male/female ratios were 10/27 in steroid group and 25/71 in NSAID group (p>0.05). Male/female ratio was similar and female domination was demonstrated in all groups.

Laboratory Data

Thyroid function tests were consistent with hyperthyroidism in the steroid and NSAID groups at the time of admission (Table 1). A significant difference was observed between the thyroid function tests (TSH, FT4, FT3) of the two groups before and 1 year after treatment (p<0.05). There was no significant difference in the values of Anti-Tg and Anti-TPO in both groups, measured at 1-year intervals (p>0.05). While there was no significant difference in thyroglobulin value in the steroid group (p>0.05), a statistical difference was found in the thyroglobulin value in the NSAID group (p<0.05). In

Table 1: Demographic and laboratory parameters of patients (before and one year later)

	STEROID (n=37)			NSAID (n=96)		P
Age (years)	43.5±11.8			43.0±10.1		0.808
Male/Female	10/27			25/71		0.909
	Pretreatment	**1 Year Later**	**p**	**Pretreatment**	**1 Year Later**	**p**
TSH (0.5-4.4 uIU/mL)	0.44±1.02	3.33±3.61	0.018	0.37±0.75	4.18±9.67	<0.001
FT3 (2-4.4 ng/dL)	6.72±3.19	2.86±0.63	<0.001	5.28±3.07	2.73±0.48	<0.001
FT4 (0.93-1.7 ng/dL)	2.77±1.44	1.15±0.35	<0.001	2.02±1.10	1.02±0.30	<0.001
Anti-Tg (<115 uIU/mL)	251.14±343.69	162.82±236.82	0.07	123.84±212.58	87.167±168.59	0.336
Anti-TPO (<34 uIU/mL)	8.01±5.15	7.20±3.98	0.054	31.43±97.63	24.63±77.97	0.112
Thyroglobulin (ng/dL)	461.69±902.45	126.16±244.41	0.052	257.82±233.93	35.131±33.62	0.024
ESR (<20 mm/h)	47.74±19.10	12.27±7.77	<0.001	49.06±25.96	16.05±17.22	<0.001
CRP (<0.5 mg/l)	7.47±6.38	1.12±2.8	0.007	13.64±32.66	0.86±1.75	0.001
NEUTROPHIL	6.10±1.67	4.04±1.55	0.011	5.94±2.13	4.00±1.32	<0.001
LYMPHOCYTE	2.20±0.78	2.04±0.77	0.520	2.32±0.716	2.24±0.52	0.402
MONO	0.651±0.26	0.537±0.15	0.027	0.77±0.24	0.76±0.17	0.653
PLATELETS	349.36±104.16	269.44±58.03	<0.001	309.20±77.40	271.70±67.93	<0.001
NLR (NEU/LYM)	2.91±1.63	1.85±0.76	<0.001	2.776±1.45	1.84±0.77	<0.001
PLR (PLT/LYM)	169.73±82.28	133.39±45.63	0.018	140.67±53.14	124.92±40.79	0.005
MLR (MONO/LYM)	0.32±0.18	0.27±0.12	0.145	0.32±0.16	0.22±0.09	<0.001
MPV	9.30±0.95	9.67±0.70	0.050	9.42±1.27	9.66±1.22	0.271

TSH: Thyrotropin, **FT3:** Free triiodothyronine, **FT4:** Free thyroxine, **Anti-TPO:** Antithyroid peroxidase antibodies, **Anti-Tg:** Anti-thyroglobulin antibodies, **NLR:** Neutrophil-to-lymphocyte ratio, **PLR:** Platelet-to-lymphocyte ratio, **MLR:** Monocyte-to-lymphocyte ratio, **MPV:** Mean platelet volume, **ESR:** Erythrocyte sedimentation rate, **CRP:** C-reactive protein (Data are shown as mean±standart deviation).

two groups the ESR and CRP levels were increased in the pretreatment period and decreased with the treatment (p<0.05). The pretreatment ESR level of the steroid group was lower than the other group (p<0.05). One year after the treatment the ESR level of the steroid group was significantly lower than the NSAID group (p<0.05). In the beginning the CRP levels of the two groups were increased and one year later the levels were decreased. There was no statistically difference between the groups (p>0.05).

There was a significant difference in neutrophil counts in both groups before and after treatment, respectively (p<0.05). There was no significant difference in lymphocyte counts before and after treatment in both groups (p>0.05). While there was a statistical difference in monocyte counts during the acute attack and 1 year later in the steroid group (p<0.05), no difference was found in the NSAID group (p>0.05). Platelet counts were found to be significantly higher in both groups during the attack (p<0.05). While NLR and PLR values were high during the attack in both groups, a significant decrease was observed in the values 1 year later (p<0.05). While the decrease in MLR was not significant in the steroid group after the treatment (p>0.05), the decrease in the value was significant in the NSAID group (p<0.05). No significant difference was observed in MPV values before and after the treatment in both groups (p>0.05).

Permanent Hypothyroidism

Permanent hypothyroidism observed in steroid and NSAID groups were 8/37 (21.6%), 5/97 (24.74%) in steroid and NSAID groups respectively (p>0.05).

Before treatment, there was no statistically significant difference between the CRP measurement levels (Yes=11.3±9.3 vs. No=6.2±4.2) between those with and without a diagnosis of permanent hypothyroidism in the steroid group (p=0.143). Similarly, no statistically significant difference was found between the CRP measurement levels (Yes=9.4±9.7 vs. No=15.2±10.3) in the NSAID group between those with and without a diagnosis of permanent hypothyroidism (p=0.230). After treatment, there was no statistically significant difference between the CRP measurement levels (Yes=1.3±3.2 vs No=0.5±0.3) in the steroid group between those with and without a diagnosis of permanent hypothyroidism (p=0.494). Similarly, no statistically significant difference was found between the CRP measurement levels (Yes=1.9±2.6 vs No=0.68±1.5) in the NSAID group between those with and without a diagnosis of permanent hypothyroidism (p=0.148).

Also, there was no statistical difference in other inflammation markers (CRP etc.) before and after treatment in both groups (steroid vs. NSAID) with and without a diagnosis of permanent hypothyroidism (p>0.05) (Table 2 and Table 3)

DISCUSSION

Subacute thyroiditis is a disease that usually develops after a viral infection and is characterized by inflammation in the thyroid gland.

The age of our patients was between 30-50 years old and female dominant. This situation was consistent with the publications in the literature (5,16).

Table 2: Comparison of pre-treatment inflammation markers in steroid and NSAID groups of patients with and without persistent hypothyroidism.

Variables	STEROID (n=37)		p	NSAID (n=96)		p
	Permanent hypothyroidism			Permanent hypothyroidism		
	No (n=29)	Yes (n=8)		No (n=72)	Yes (n=24)	
ESR (<20 mm/h)	47.0±18.6	52.5±24.3	0.504	49.01±25.6	65.8±41.5	0.271
CRP (<0.5 mg/l)	6.2±4.2	11.3±9.3	0.143	15.2±35.2	9.4±9.7	0.230
NEUTROPHIL	6.6±2.4	5.7±1.8	0.284	6.0±2.3	5.9±2.0	0.821
LYMPHOCYTE	2.2±0.8	2.4±0.7	0.485	2.4±0.83	2.4±0.36	0.905
MONO	0.69±0.21	0.64±0.17	0.556	0.70±0.26	0.76±0.39	0.447
PLATELETS	319.8±100.5	312.4±67.8	0.831	311.6±74.4	297.1±90.64	0.495
NLR (NEU/LYM)	3.6±3.0	2.6±1.2	0.323	2.8±1.6	2.5±0.84	0.436
PLR (PLT/LYM)	167.3±86.7	139.5±48.4	0.354	142.7±53.3	130.6±52.9	0.408
MLR (MONO/LYM)	0.34±0.11	0.29±0.12	0.272	0.32±0.16	0.32±0.17	0.935
MPV	9.2±1.3	8.6±1.5	0.277	8.9±1.5	9.3±1.21	0.304

TSH: Thyrotropin, **FT3:** Free triiodothyronine, **FT4:** Free thyroxine, **Anti-TPO:** Antithyroid peroxidase antibodies, **Anti-Tg:** Anti-thyroglobulin antibodies, **NLR:** Neutrophil-to-lymphocyte ratio, **PLR:** Platelet-to-lymphocyte ratio, **MLR:** Monocyte-to-lymphocyte ratio, **MPV:** Mean platelet volume, **ESR:** Erythrocyte sedimentation rate, **CRP:** C-reactive protein (Data are shown as mean±standart deviation).

Table 3: Comparison of post-treatment inflammation markers in steroid and NSAID groups of patients with and without persistent hypothyroidism.

Variables	STEROID (n=37)		p	NSAID (n=96)		p
	Permanent hypothyroidism			Permanent hypothyroidism		
	No (n=29)	Yes (n=8)		No (n=72)	Yes (n=24)	
ESR (<20 mm/h)	11.9±7.8	13.6±8.1	0.621	14.8±14.1	21.9±30.9	0.286
CRP (<0.5 mg/l)	1.3±3.2	0.5±0.3	0.494	0.68±1.5	1.9±2.6	0.148
NEUTROPHIL	4.2±1.4	3.9±1.5	0.637	3.9±1.3	4.0±1.1	0.738
LYMPHOCYTE	2.1±0.6	2.4±1.2	0.242	2.3±0.5	2.3±0.4	0.518
MONO	0.57±0.17	0.49±0.14	0.174	0.50±0.16	0.56±0.17	0.188
PLATELETS	281.5±81.1	269.1±60.9	0.664	268.7±69.9	283.1±56.9	0.442
NLR (NEU/LYM)	2.1±1.0	2.1±1.8	0.907	1.8±0.8	1.8±0.6	0.748
PLR (PLT/LYM)	143.9±59.2	137.0±80.5	0.777	124.9±42.2	125.1±33.8	0.981
MLR (MONO/LYM)	0.29±0.11	0.24±0.14	0.239	0.23±0.09	0.25±0.10	0.446
MPV	8.8±1.5	9.1±1.4	0.627	9.2±1.5	9.6±0.96	0.360

TSH: Thyrotropin, **FT3:** Free triiodothyronine, **FT4:** Free thyroxine, **Anti-TPO:** Antithyroid peroxidase antibodies, **Anti-Tg:** Anti-thyroglobulin antibodies, **NLR:** Neutrophil-to-lymphocyte ratio, **PLR:** Platelet-to-lymphocyte ratio, **MLR:** Monocyte-to-lymphocyte ratio, **MPV:** Mean platelet volume, **ESR:** Erythrocyte sedimentation rate, **CRP:** C-reactive protein (Data are shown as mean±standart deviation).

ESR and CRP are found to be high in SAT patients when evaluated together with clinical findings at the time of diagnosis. While these two parameters are found to be high in the active period of the disease, they decrease to normal levels with the decrease of inflammation. In the literature, ESR and CRP were found to be higher in SAT patients compared to control groups (5,7,13). There was no difference between the steroid group and the NSAID group during the illness and after 1 year. Since ESR and CRP are nonspecific parameters, it should be evaluated together with clinical findings for diagnosis in patients with SAT.

In inflammation, there are changes in cell distribution in the hemogram due to cytokines. While leukocytosis and neutrophil dominance occur in bacterial infections, leukopenia and lymphocytosis are observed in viral infections. While lymphocytosis is expected to be observed as a viral factor that is generally responsible for the etiology of SAT, neutrophil dominance was found in SAT patients in the study by Ergün and Tuzcu (5). The NLR ratio is a parameter that indicates systemic inflammation (17). In the study of Calapkulu et al., It was shown that NLR was higher in SAT patients compared to the control group and correlated with classical acute phase responses (ESR, CRP) (7). In our study, NLR was found to be significantly higher at the time of first diagnosis compared to the situation after 1 year, in parallel with inflammation. No significant difference was found between steroid users and NSAIDs. In the literature, MLR, PLR and MPV have been shown to be increased in cardiovascular, malignant and inflammatory diseases as markers of inflammation (17). In one study, NLR, PLR, and MLR also reported a significant increase in SAT patients. They found no difference in MPV compared to the control group (6). In another study, PLR and NLR also reported significantly higher values in SAT patients and significantly lower values in MPV (7). In the study of Ergün and Tuzcu, NLR was found to be higher in the SAT group compared to the control group, while MPV values were reported to be significantly lower in the SAT group (5). In our study, PLR values at the time of diagnosis of SAT were found to be significantly higher in both groups compared to the values 1 year later. There was no significant difference between the groups. In both groups, it was observed that MLR values were high during the period of high inflammation, and the values decreased after 1 year. This decrease was significant ($p<0.05$) in the steroid group, but not in the NSAID group ($p>0.05$). In our study, a non-significant increase was observed in MPV values in both groups.

In patients with SAT, thyroid hormone levels increase temporarily in blood tests due to damage to thyroid follicles and TSH levels also decrease. During this period, it is not necessary to give a drug that will suppress thyroid hormone synthesis. Symptomatic treatment is sufficient. The height of FT4 and FT3 has been reported in the literature, and the high ratio of FT4 / FT3 is also highlighted (5-7). Similar results were found in our study.

Thyroid autoantibodies can be detected mildly positive in patients with SAT. In general, Anti Tg was found to be higher positive. In the study of Ergün and Tuzcu, AntiTg was reported to be significantly different from Anti TPO compared to the control group (5). In the study of Taşkaldıran et al., autoantibodies were not found to be significantly higher (6). In our study, Anti Tg levels were found to be higher than Anti TPO and higher in the steroid group than in the NSAID group.

There are a limited number of studies in the literature on the treatment modality in SAT and the development of permanent hypothyroidism (10-12). Theoretically, it has been suggested that the severity of attacks in SAT may be an important factor affecting persistent hypothyroidism. However, the levels of inflammation markers indicating the severity of the attack or the width of the thyroiditis areas on ultrasound were evaluated, but no significant correlation was found. Similarly, no significant effect of the drugs used in the treatment was found on permanent hypothyroidism (11,16,18,19). In our study, in accordance with the clinical situation, inflammation markers were correlated with the parameters showing classical acute phase reaction at the time of diagnosis, but it was observed that they had no effect on determining the prognosis. Also in our patients, treatment drug option did not affect the permanent hypothyroidism one year after the first examination ($p>0.05$). In 2017, a similar publication was published by me as a letter to the editor in Acta Endocrinologica (Buc), using more limited data on inflammation markers and a smaller number of patients (20). 81 patients were examined in 3 groups (steroids, NSAIDs, steroids+NSAIDs) and no correlation was found between the drug and persistent hypothyroidism in that publication (20).

The limitation of our study is that the treatment drugs and doses are not homogeneous for all patients. So these should be taken into consideration because this is a retrospective study.

We think that the level of inflammatory markers and treatment options at the time of first diagnosis of the disease have no effect on the development of permanent hypothyroidism. However, prospective studies in more homogeneous groups are needed.

Acknowledgment

None.

Author Contributions

Concept: **Ali Saklamaz,** Design: **Ali Saklamaz,** Data collection or processing: **Ali Saklamaz, Özcan Çiftçi,** Analysis or Interpretation: **Ali Saklamaz,** Literature search: **Özcan Çiftçi,** Writing: **Ali Saklamaz,** Approval: **Özcan Çiftçi.**

Conflicts of Interest

The authors declare no conflict of interest.

Financial Support

None to declare.

Ethical Approval

The present study was approved by the Ethics Commitee of Izmir University of Economics, Faculty of Medicine Since the study was retrospective, informed consent was not obtained from the patients.

Review Process

Extremely peer-reviewed and accepted.

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ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2023;7(1): 21-30
DOI: 10.29058/mjwbs.1174031

The Effect of Dyspnea on the Cognitive Status in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Kronik Obstrüktif Akciğer Hastalığı (KOAH) Olanlarda Dispnenin Bilişsel Duruma Etkisi

Döndü ŞANLITÜRK[1], Nurgül KAPLAN[2]

[1]Tokat Gaziosmanpaşa University, Erbaa Faculty of Health Sciences, Tokat, Türkiye,
[2]Tokat Gaziosmanpaşa University, Erbaa Vocational School of Health Services, Tokat, Turkey

ORCID ID: Döndü Şanlıtürk 0000-0002-2055-759X, Nurgül Kaplan 0000-0001-9200-3302

Cite this article as: Şanlıtürk D and Kaplan N. The effect of dyspnea on the cognitive status in patients with chronic obstructive pulmonary disease (COPD). Med J West Black Sea. 2023;7(1):21-30.

Corresponding Author
Nurgül Kaplan

E-mail
nurgul.kaplan@gop.edu.tr

Received
12.09.2022

Revision
10.01.2023

Accepted
30.03.2023

ABSTRACT

Aim: The aim of this study is to examine the effect of the dyspnea on cognitive status in patients with chronic obstructive pulmonary diseases (COPD).

Material and Methods: The universe of this descriptive study consist of 315 COPD patients. Data were collected with a Questionare, Medical Research Council Scale (MRCS) and Standardize Mini Mental State Examination (SMMT-E). In the analyses of the data, descriptive statistics, independent t-test, one-way analysis of variance and regression and Tamhane T2 analysis were employed.

Results: The mean age of the patients patricipating the study was 54.06 (11.41) years. 38% of the patients were determined to experienced moderate dyspnea (2.20±0.95). The patients' cognitive status mean scores were found low (21.38±5.74) and 58.7% had cognitive impairment. It was determined in multiple regression analysis that severe dyspnea level, inadequacy in dyspnea management, associating dyspnea with breathlessness, feeling of low mood and fear of death, use of oxygen tube and bipod at home were associated with cognitive status. Moreover, it was found that 31% of the variance in the cognitive level of the patients was explained by the independent variables related to dyspnea (R2 = 0.581; adjusted R2= 0.311). It was found that there was a strong positive correlation between dyspnea and cognition status (r=-0.705, p=0.000).

Conclusion: It was determined that dyspnea effects to SMMT-E and therefore it could be advised to taking measures to reduce dyspnea COPD patients.

Keywords: Cognitive status, Dyspnea, COPD

ÖZ

Amaç: Bu çalışmada KOAH hastalarında dispnenin bilişsel duruma etkisini incelemek amaçlanmıştır.

Gereç ve Yöntemler: Tanımlayıcı tipte tasarlanan çalışmanın örneklemini 315 KOAH hastası oluşturmuştur. Verilerin toplanmasında Kişisel Bilgi Formu, Medical Research Council Scale (MRCS) ve Standardize Mini Mental değerlendirme testi (SMMT-E) kullanılmıştır. Verilerin değerlendirilmesinde; yüzdelik, student t testi, tek yönlü varyans analizi, Pearson korelasyon testi, çoklu regresyon analizi ve Tamhane T2 post-hoc testi kullanılmıştır.

Bulgular: Çalışmaya katılan hastaların yaş ortalaması 54.06 (11.41) yıldır. Hastaların %38'inin orta düzeyde dispne (2.20±0.95) yaşadığı belirlenmiştir. Hastaların bilişsel durum puan ortalamalarının düşük düzeyde (21.38±5.74) olduğu ve %58.7'sinde bilişsel durumda bozulma olduğu saptanmıştır. Çoklu regresyon analizinde şiddetli dispne düzeyi, dispne yönetimindeki yetersizlik, dispneyi nefessizlik, moral bozukluğu ve ölüm korkusu hissi ile ilişkilendirme, evde oksijen tüpü ve bibap kullanımının bilişsel durumla ilişkili olduğu saptanmıştır. Hastaların bilişsel düzeyindeki varyansın %31'inin dispne ilişkili bağımsız değişkenler tarafından açıklandığı saptanmıştır (R2 = 0.581; adjusted R2= 0. 311). Dispne düzeyi ile bilişsel durum arasında negatif yönde, güçlü düzeyde ilişki olduğu saptanmıştır (r=-0.705, p=0.000).

Sonuç: KOAH hastalarında dispne düzeyinin bilişsel durumu etkilediği ve bu nedenle hastalara dispnenin azaltılmasına yönelik önlemlerin alınması önerilmektedir.

Anahtar Sözcükler: Bilişsel durum, Dispne, KOAH

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterized by progressive airflow obstruction and is a crucial respiratory tract illness causing significant mortality and morbidity all across the world (1). COPD is one of the top three diseases causing death throughout the world (2). COPD is an inflammatory process that develops in association with harmful gases and particles, especially cigarette smoke, is not fully reversible, and is a progressive disease (3,4). The above-mentioned inflammation affects the lungs and is preventable, and there are treatment options that alleviate its symptoms. In flare-up periods, the severity and negative effects of COPD increase, and the accompanying comorbidities affect its prognosis (5).

COPD requires hospitalization and professional healthcare during flare-up periods (4-9). Patients have intense anxiety, hopelessness, and stress due to being in need of healthcare for a long period along with constant drug use and sudden flare-ups as well as COPD-related physiological problems (8,9). Dyspnea is known as the most common symptom that causes stress in COPD patients (10). Individuals having dyspnea have no idea about how long the dyspnea will last, and they experience the fear of the unknown (11-13).

Dyspnea is defined as an unpleasant or uncomfortable breathing feeling and a personal experience of respiratory distress produced by sensations that vary in intensity (14,15). Dyspnea emerges in association with disorders occurring in several systems, not solely as a consequence of a single pathophysiological mechanism (16). Dyspnea and stress cause COPD patients primarily to have cognitive impairment. Besides, dyspnea paves the way for hypoxemia in COPD patients. Cognitive impairment in COPD patients is a multi-factorial process associated with a decrease in physical activity and cerebral blood flow, tissue hypoxia, systemic inflammation, and oxidative stress (17). In previous studies, it was stated that cognitive functions were adversely affected especially in COPD patients who gravely suffered from hypoxemia. In the study performed by Hung et al. to compare the control group with groups of patients with severe and non-severe COPD, it was found that COPD patients obtained lower cognitive scores (18).

In this context, this study aims to analyze the relationship of cognitive level with dyspnea, which is a negative experience for COPD patients.

MATERIAL and METHODS

This study was conducted as descriptive, cross-sectional, and correlational research to analyze the effect of dyspnea on the cognitive state of COPD patients. Before the study, permission was received from the Health Department of the province where the research was carried out, and also, ethical endorsement for the research was obtained from the Clinical Trials Ethics Committee of Tokat Gaziosmanpaşa University (No: 2021/22). After patients consented that they voluntarily participated in the study upon being informed about the research, the research data were collected.

Research Design and Participants

This research was carried out from 20 January 2022 to 20 March 2022 at pulmonology clinics of the two public hospitals in the Black Sea Region of Turkey. The research population was the COPD patients who applied to these hospitals on the above dates. As per the power analysis, the sample size was calculated as 112 (n=112). The GOLD system categorizes airflow limitation into stages. In patients with FEV1/FVC <0.70: GOLD 1 - mild: FEV1 ≥80% predicted, GOLD 2 - moderate: 50% ≤ FEV1 <80% predicted, GOLD 3 - severe: 30% ≤ FEV1 <50% predicted and GOLD 4 - very severe: FEV1 <30% predicted. COPD patients in all stages (stages I, II, III, IV according to the GOLD 2022 guideline) were included in the study to determine the effect of various severity of dyspnea on cognitive status. It was not taken into account whether the patients were stable or in the exacerbation. The study was finalized with 315 patients who were selected for the sample with the purposive sampling method, satisfied the inclusion criteria designated for the research, and agreed to participate in the study.

The researcher collected the research data by using the face-to-face interview method in the patient rooms. The researcher read aloud the data collection form to each patient and filled the data collection form with answers given by the patient.

Initially, a total of 323 COPD patients took part in the study. However, afterward, eight patients were excluded from the research as six patients did not want to participate in the research, one patient had a visual problem, and one patient failed to fully answer the questions in the data collection form. Therefore, the data collected from 315 patients were included in the analysis conducted in the context of the research.

Inclusion Criteria

1. Being diagnosed with COPD according to the GOLD 2022 guideline (2)
2. Being aged 18 years or above
3. Having no communication barrier
4. Being hospitalized at a pulmonology clinic of the aforementioned hospitals
5. Agreeing to participate in the research

Exclusion Criteria

1. Being aged below 18 years
2. Having an audiovisual communication barrier

3. Not being hospitalized at a pulmonology clinic of the aforementioned hospitals
4. Refusing to participate in the research

Data Collection Tools

The Personal Information Form that was created in light of expert opinions, the Standardized Mini-Mental State Examination, and the Medical Research Council Scale were used as data collection tools in the research. Information about measurement tools used in the research were presented below:

The Medical Research Council Scale (MRCS)

The MRCS is a scale measuring the effects of dyspnea on daily life activities and the perceived shortness of breath. It was developed by Fletcher (1952) (17). The MRCS was created on the basis of a variety of physical activities producing the feeling of dyspnea. The MRCS has five items. Upon reading choices for each MRCS item, patients are supposed to select the choice that best describes the degree of respiratory distress experienced by them. MRCS items are scored from 0 to 4 points. The MRCS was previously used in numerous studies to evaluate the dyspnea perception (9,19,20).

The Standardized Mini-Mental State Examination (SMMSE)

Developed by Folstein et al., this measurement tool is a test that is easy to administer and presents information about the degree of cognitive impairment (21). It has parts that assess functions such as orientation, registration, attention & calculation, spontaneous recall, language, and visual construction. The validity and reliability study for the SMMSE designed for the educated was performed in Turkish by Güngen et al. whilst the validity and reliability study for the SMMSE for the uneducated (SMMSE-U) that was designed for individuals with education below five years was conducted in Turkish by Babacan Yıldız et al. (21,22). In the current study, the SMMSE-U was used. The maximum score to be obtained from this measurement tool is 30 points. Even if different cut-off points serve as a reference for the evaluation of scores, a score of 23 points or below is in general accepted as an indicator of the presence of cognitive impairment in the respondent. In the evaluation of scores, a score of 21-23 points refers to mild cognitive impairment while a score of 20 points or below points to a moderate or advanced cognitive impairment. It is put forward that, in the case of mild cognitive impairment, a person can continue to live without any external assistance even if the person has problems with work and social environment in the clinical sense, however, in the case of moderate or advanced cognitive impairment, the person may need assistance to continue to live (21,22).

Statistical Analysis

After the research data were coded by researchers, they were analyzed with the Statistical Package for Social Science 25.0. In the context of the evaluation of research data, descriptive characteristics were expressed as numbers and percentages, the student's t-test was used in the comparison of two independent groups whilst the one-way analysis of variance (ANOVA) was utilized in the comparison of more than two independent groups, and additionally, in the framework of comparing more than two independent groups, the Tamhane's T2 test as a post hoc analysis method was employed to identify which group had a statistically significant difference from other groups. Moreover, the relationship between variables was identified with Pearson's correlation test. The multiple regression analysis was used in the identification of predictor variables affecting the predicted variable. Obtained results were evaluated at a 5% statistical significance level ($p<0.05$) and a 95% confidence interval.

RESULTS

In this study that evaluated the effect of the dyspnea level on the cognitive state in COPD patients, a total of 315 patients took part. In this regard, it was discerned that the mean age of the participant patients was 54.06±11.41 years, and of all participant patients, 56% were male, 37% were primary school graduates, 91% were married, 57% were not working, 48% had an income equaling their expenses, and 38% did not smoke (Table 1).

Additionally, upon the review of participant patients' COPD-related and treatment-related characteristics, it was identified that, of all patients, 43% were diagnosed with COPD for 11-20 years, 65% had comorbidities accompanying COPD, 62% visited a doctor for health controls on a regular basis, 54% were hospitalized once or twice in the last year, 68% had a caregiver, 45% had their spouses as the caregiver, 90% had people around to share their sad and happy memories (38% of these patients received support from their spouses at such moments), 63% regularly used their drugs, 57% received COPD-related training (66% of these patients received training from the doctor), 75% had no history of having a psychiatric disease, 62% did not receive any psychiatric therapy, and 39% had no willingness to receive psychological assistance (Table 2).

Besides, Table 1 and Table 2 displayed the comparison of patients' mean SMMSE-U scores as per their certain characteristics. In this regard, there were statistically significant differences in patients' mean SMMSE-U scores as per gender, marital status, employment status, the status of having comorbidities accompanying COPD, the status of having a history of having a psychiatric disease, the status of receiving psychiatric therapy, the status of regularly using drugs,

Table 1: The analysis of patients' cognitive levels as per certain variables

Sociodemographic characteristics		SMMSE-U
	n (%)	Mean±SD
Age (Year±SD)	(<24 points) 185 (58.7)	21.38±5.74 (11.00-29.00)
Gender n(%)		
Female	140 (44.5)	22.10±5.79
Male	175 (55.6)	20.80±5.65
p		0.045
Education level n(%)		
Illiterate	20 (6.3)	20.75±3.35
Literate	35 (11.1)	21.57±5.71
Primary school	115 (36.5)	20.13±6.08
High school	95 (30.2)	21.05±4.76
University	50 (15.9)	25.00±6.09
p		**<0.001**
Post Hoc (University)		**<0.001***
Marital status n(%)		
Married	285 (90.5)	21.16±5.68
Single	30 (9.5)	23.40±5.98
p		**0.043**
Employment status n(%)		
Working	135 (42.9)	22.33±5.44
Not working	180 (57.1)	20.66±5.87
p		**0.011**
Perceived income level n(%)		
Income below expenses	135 (42.9)	22.18±4.50
Income equaling expenses	150 (47.6)	20.00±6.11
Income above expenses	30 (9.5)	24.66±60.88
p		**<0.001**
Post Hoc (Income above expenses)		**<0.001***
Status of cigarette smoking n(%)		
Yes, smoking	91 (28.9)	24.65±4.28
No, never smoked	118 (37.5)	21.30±5.29
Smoked but quit smoking	106 (33.7)	18.65±5.90
p		**<0.001**
Post Hoc (Yes, smoking)		**<0.001**

and the health professional giving the COPD-related training ($p<0.05$). On the other hand, there was no statistically significant difference in patients' mean SMMSE-U sores as per the status of having social support and the status of receiving COPD-related training ($p>0.05$).

Also, it was found that patients who were university graduates, had income above expenses, were smoking, were diagnosed with COPD for 1-10 years, would like to receive psychological assistance, and visited a doctor for health controls partially on a regular basis obtained higher mean SMMSE-U scores than other corresponding groups of patients, and also, patients who were hospitalized three times or more in the last year, and had a caregiver obtained lower mean SMMSE-U scores than other corresponding groups of patients, and these differences between groups of patients in terms of mean SMMSE-U scores were statistically significant ($p<0.05$) (Table 1, Table 2).

Furthermore, Table 3 presented patients' views about dyspnea. When patients were asked the question, "What does dyspnea make you feel?", 85% of them stated that they would be short of breath/their breath would be insufficient, 82% of them said that they had the feeling of suffocation, and 77% of them told that they had the fear of death (Table 3).

Moreover, Table 4 indicated the analysis of participant patients' mean SMMSE-U scores as per their dyspnea-related characteristics. It was discerned that, of all patients, 52% defined breathing as "existence, living, life, water", 38% experienced moderate dyspnea according to MRCS scores, 56% felt incompetent in the management of dyspnea, and 57% used inhaler at home (Table 4).

Next, upon the examination of patients' mean SMMSE-U scores as per their dyspnea-related characteristics, it was identified that patients who had highly severe dyspnea according to MRCS scores, felt incompetent in the management of dyspnea, and used an oxygen tube and bipod at home obtained lower mean SMMSE-U scores than other corresponding groups of patients, and these differences between groups of patients in terms of mean SMMSE-U scores were statistically significant ($p<0.05$) (Table 4).

A multiple regression analysis was conducted to identify the effects of patients' dyspnea-related characteristics on their cognitive levels. It was found that the multiple regression model with 12 predictor variables was statistically significant ($F (12-302) = 12.830$. $p<.001$), and these variables explained 31% of the total variance in the predicted variable of cognitive state ($R^2 = 0.581$; adjusted $R^2= 0.311$) (Table 5). It was discerned that the dyspnea level, the competence in the management of dyspnea, the feeling of being short of breath, the feeling of disappointment, and the fear of death were significant factors affecting the cognitive state. Average decreases in the mean of SMMSE-U scores were successively 1.62 units ($p<.001$, % 95 CI=2,091-1,154), 1.62 units ($p=.016$, % 95 CI=2,943-0,302), 3.18 units ($p<.001$, % 95 CI=4,875-1,480), 2.44 units ($p=.005$, % 95 CI=4,151-0.730), and 2.21 units ($p=.003$, %95 CI=772-3,642) for each increase of one unit in the dyspnea level, the competence in

Table 2: The analysis of cognitive status and disease-related parameters

Disease-related variables	SMMSE-U* (n=315)	p
Duration of being diagnosed with COPD		
1-10 years [131 (%41.6)]	23.61±5.48	
11-20 years [135 (%42.9)	20.20±5.58	**<0.001**
21 years or above [49 (%15.9)]	18.65±4.68	
Post Hoc (1-10 years)		**<0.001****
Status of having comorbidities accompanying COPD		
Yes [206 (65.4)]	19.48±5.59	
No [109 (34.6)]	24.96±4.07	**<0.001**
Status of having a history of having a psychiatric disease		
Yes [80 (25.4)]	19.56±5.15	
No [235 (74.6)]	22.00±5.81	**0.001**
Status of receiving psychiatric therapy		
Yes [120 (38.1)]	19.70±5.62	
No [195 (61.9)]	22.41±5.58	**<0.001**
Status of having the willingness to receive psychological assistance		
Yes, I did [47 (14.9)]	20.97±4.02	
I had willingness but I did not receive psychological assistance [78 (24.8)]	19.41±5.50	
No, I did not [124 (39.4)]	21.68±6.55	**<0.001**
I would like to receive psychological assistance [66 (21.0)]	23.42±4.64	**<0.001***
Post Hoc (I would like to receive psychological assistance)		
Status of visiting a doctor for health controls on a regular basis		
Yes [194 (61.6)]	21.11±5.91	
No [26 (8.3)]	19.38±5.12	**0.030**
Partially [95 (30.2)]	22.47±5.38	**0.030**
Post Hoc (Partially)		
Status of being hospitalized in the last year		
Never [61 (19.4)]	26.40±2.43	
Once or twice [169 (53.0)]	22.02±5.13	**<0.001**
Three times or more [85 (27.0)]	16.49±4.79	**<0.001**
Post Hoc (Three times or more)		
Status of having a caregiver		
Yes [214 (67.9)]	19.78±5.84	
I need a caregiver but there is no one to provide me with care [32 (10.2)]	24.25±2.85	
I do not need a caregiver [69 (21.9)]	25.01±4.03	**<0.001**
Post Hoc (Yes)		**<0.001**
Status of having social support		
Yes [284 (90.2)]	21.31±5.77	
No [31 (9.8)]	22.00±5.50	0.528
Status of regularly using drugs		
Yes [197 (62.5)]	20.90±6.17	
No [17 (5.4)]	24.88±5.31	
Partially [101 (32.1)]	21.71±4.66	**0.018**
Post Hoc (Yes)		0.025
Status of receiving COPD-related training		
Yes [178 (56.5)]	21.59±5.93	
No [137 (43.5)]	21.10±5.50	0.451
Health professionals giving the COPD-related training		
Doctor [118 (66.3)]	22.72±5.63	
Nurse [60 (33.7)]	19.38±5.91	**<0.001**

*Mean±SD: Mean ± Standard Deviation, **: Tamhane's T2 test

the management of dyspnea, the feeling of of being short of breath, the feeling of disappointment, and the fear of death. It was identified that variables of the feeling of suffocation, the feeling of hopelessness, experiencing depression, the feeling of having a squeezing tape around the chest, the feeling of guilt/regret, crying from time to time, and the burning sensation in the chest affected the cognitive level, however, these effects were not statistically significant (p>0.05) (Table 5) (Figure 1).

Lastly, exhibited the analysis of the correlation between patients' cognitive and dyspnea levels. In this regard, there was a statistically significant strong negative correlation between cognitive state and dyspnea level (r=-0.705, p=0.000).

Table 3: COPD patients' views on dyspnea

What dyspnea makes the patient feel * [a]	**Findings (n=315)**
Feeling that the breath will be insufficient/Feeling of being short of breath	268 (85.1)
Feeling of suffocation	258 (81.9)
Feeling of hopelessness	143 (45.4)
Feeling of having a squeezing tape around the chest	134 (42.5)
Feeling of disappointment	47 (14.9)
Feeling of guilt/regret	76 (24.1)
Crying from time to time	65 (20.6)
Burning sensation in the chest	74 (23.5)
Fear of death	244 (77.5)
Experiencing depression	152 (48.3)

***Data are presented as n(%).** [a]: More than one choice was selected. Selected choices were expressed as numbers and percentages.

Table 4: The analysis of COPD patients' cognitive levels as per their dyspnea-related characteristics

		SMMSE-U	
		(Mean±SD)	**p**
Dyspnea levels as per MRCS scores *			
Mild	84 (26.7)	27.02±2.71	
Moderate	119 (37.8)	21.56±4.75	**<0.001**
Severe	77 (24.4)	17.84±3.75	
Highly severe	35 (11.1)	15.00±5.24	
Breathing means *			
Existence, living, life, water	164 (52.1)	21.70±5.73	
Blessing, gift, great chance, treasure	54 (17.1)	21.61±5.94	0.071
Struggle, impossibility, challenging endeavor, fatigue	61 (19.4)	21.70±5.19	
Insatiable taste, flavor, comfort	36 (11.4)	19.00±6.04	
Status of having competence in the management of dyspnea*			
Yes	20 (6.3)	23.00±5.28	
No	176 (55.9)	19.86±5.88	**<0.001**
Partially	119 (37.8)	23.34±4.91	
Type of device used at home [b] *			
Oxygen tube	145 (46.0)	19.82±5.69	**<0.001**
Nebulizer	135 (42.9)	21.51±5.70	0.713
Oxygen concentrator	55 (17.5)	21.49±5.91	0.876
Bipod	50 (15.9)	18.50±6.84	**<0.001**
Inhaler	180 (57.1)	21.01±5.63	0.187

***Data are presented as n(%).** [a]: Tamhane's T2 test, [b]: More than one choice was selected. Selected choices were expressed as numbers and percentages.

Table 5: The effects of dyspnea-related characteristics on the cognitive level

Predictor variables	B	SE	Beta	95% CI	
				Lower	Upper
Constant p	24.444	1.140	- .000	22.201	26.687
Dyspnea level [a] p	-1.622	.238	-.356 **.000**	-2.091	-1.154
Status of having competence in the management of dyspnea [b] p	-1.623	.671	-.141 **.016**	-2.943	-.302
Feeling that the breath will be insufficient/Feeling of being short of breath p	-3.178	.863	-.194 **.000**	-4.875	-1.480
Feeling of suffocation p	-.015	.784	-.001 .984	-1.559	1.528
Feeling of hopelessness p	-1.029	.586	-.089 .080	-2.183	.125
Feeling of having a squeezing tape around the chest p	.730	.632	.063 .249	-.514	1.974
Feeling of disappointment p	-2.441	.869	-.149 **.005**	-4.151	-.730
Feeling of guilt/regret p	1.143	.687	.085 .097	-.208	2.494
Crying from time to time p	.024	.725	.002 .974	-1.403	1.451
Burning sensation in the chest p	1.512	.771	.112 .051	-.004	3.028
Fear of death p	2.207	.729	.160 **.003**	.772	3.642
Experiencing depression p	-1.141	.629	-.099 .071	-2.380	.098

[a]: Patients who had highly severe dyspnea were included in the analysis, [b]: Patients who felt incompetent in the management of dyspnea were included in the analysis.

The cognitive state was designated as the predicted variable in the multiple regression analysis. β: Standardized Beta coefficient; SE: Standard error. R^2 =0.581; adjusted R^2= 0. 311.

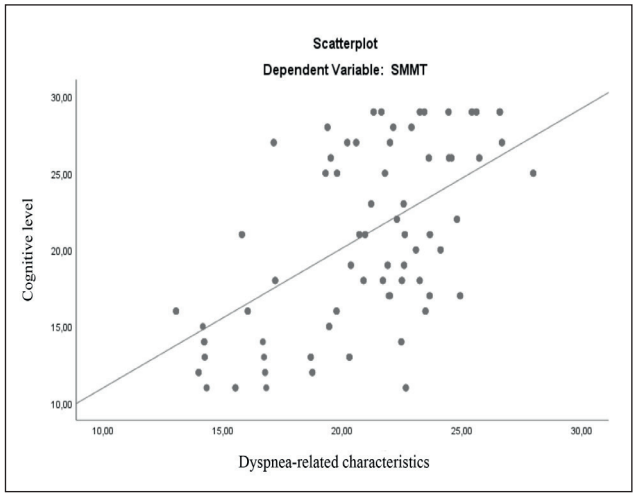

Figure 1: The multiple regression analysis on the effects of dyspnea-related characteristics on the cognitive level

DISCUSSION

This study analyzed COPD patients' dyspnea and cognitive levels and the relationship between these two variables. According to results obtained in the study, 38% of the patients were found to have moderate dyspnea. Besides, it was identified that patients obtained a low mean cognitive state score from the SMMSE-U (21.38±5.74 points) and 58.7% of them had cognitive impairment. The cognitive state in COPD patients is affected by socio-demographic variables such as gender, marital status, employment status, education level, and the perceived income level. Moreover, COPD-related and treatment-related characteristics such as the status of having comorbidities accompanying COPD, the status of having a history of having a psychiatric disease, the status of receiving psychiatric therapy, the status of having the willingness to receive psychological

assistance, the health professional giving the COPD-related training, the status of cigarette smoking, the duration of being diagnosed with COPD, the status of visiting a doctor for health controls on a regular basis, the status of being hospitalized in the last year, the status of having a caregiver, and the status of regularly using drugs affected the cognitive state.

Upon the review of the relevant literature, it was discerned that 22.6-39.4% of the COPD patients had cognitive impairment (23-26). In the study by Ozyemisci-Taskiran et al., it was reported that 22.6% of the COPD patients having acute flare-ups had cognitive impairment (<24 points) (24). In the study by O'Conor et al, it was put forward that 37.7% of the COPD patients had cognitive impairment (<24 points) (23). In the study by Antonelli-Incalzi et al., it was found that 35.5% of the patients with stable COPD had cognitive impairment (26). In the study by Roncero et al., it was stated that 39.4% of the COPD patients had cognitive impairment (<27 points) (25). In our study, 58.7% of the patients had cognitive impairment. Differences between the above-cited studies in terms of the percentages of patients having cognitive impairment can be explained by the fact that these studies were performed in different countries in different periods under different circumstances. Also, it is considered that the high percentage of patients having cognitive impairment in our study may have been connected with the collection of data from hospitalized patients and the conduct of data collection during the COVID-19 pandemic.

Cognitive impairment can reduce COPD patients' abilities to adhere to drug regimens, adjust their drugs as a response to respiratory symptoms, and self-manage the disease (27). A large financial burden can be imposed on healthcare services due to problems likely to develop along with cognitive impairment. The cognitive impairment was identified with adverse consequences such as the increase in morbidity and mortality rates in COPD patients. Therefore, to avoid the development of negative health outcomes for COPD patients, the early diagnosis of cognitive impairment is important (25). If the factors affecting the cognition are realized, the cognitive impairment can be diagnosed earlier and COPD patients who are at higher risk can be identified. In our study, it was found that socio-demographic variables such as gender, marital status, employment status, the education level, the perceived income level, besides COPD-related and treatment-related characteristics such as, the status of having comorbidities accompanying COPD, the status of having a history of having a psychiatric disease, the status of receiving psychiatric therapy, and the health professional giving the COPD-related training the status of cigarette smoking, the duration of being diagnosed with COPD, the status of having the willingness to receive psychological assistance, the status of visiting a doctor for health controls on a regular basis, the status of being hospitalized in the last year, the status of having a caregiver, and the status of regularly using drugs affected the cognitive state. In a similar vein to the findings of our study, the study by Roncero et al. reported that factors such as age, education level, the status of having a caregiver, the duration of being diagnosed with COPD, the status of being hospitalized in the last year, the status of using an oxygen tube at home, dyspnea level, depression, and social support affected the cognitive state in COPD patients (25). In the study by Ozyemisci-Taskiran, it was asserted that age, education level, and depression were factors affecting the cognitive state (24). In the study by Thakur et al., it was stated that the education level and the status of cigarette smoking were the factors affecting the cognitive state (27).

As per the examination of the relevant literature, it was discerned that COPD patients' mean MRCS scores ranged from 2.2 to 2.8 for dyspnea (28,29). In the study by Cleutjens et al., the mean dyspnea score was found as 2.2±1.0 points (28). In the study by Dal Negro et al., the mean dyspnea score was reported as 2.8±0.7 points (29). In this respect, the mean MRCS score of 2.20±0.95 points in our study was in a similar vein to the findings in the relevant literature.

Hypoxia is known to have led to cognitive impairment by affecting the memory. Also, it was identified that the perception, attention, and short-term memory were significantly impaired in hypoxemic COPD patients, and the cause of this cognitive impairment was associated with neurophysiological events such as the sustained presence of a reduced prefrontal cortex circulation (29). Knowing the dyspnea-related factors that affect the cognitive state will be of use to the follow-up and the management of the cognitive state. In our study, it was found that highly severe dyspnea, incompetence in the management of dyspnea, identification of dyspnea with the feeling of being short of breath, the feeling of disappointment, and the fear of death, and the use of an oxygen tube or bipod at home were the dyspnea-related factors that affected the cognitive state. In a similar vein to the findings of our study, the study by Roncero et al. stated that there was a statistically significant difference in the cognitive level as per the dyspnea level, which was measured with the MRCS, and the dyspnea level affected the cognitive state (25). In the study by Thakur et al., the hypoxemia was reported as the most significant risk factor for cognitive impairment in COPD patients (27).

In the correlation analysis conducted in this study, a statistically significant strong negative relationship between dyspnea level and cognitive state was identified (r=-0.705, p=0.000). In our study, the cognitive impairment identified even in COPD patients with moderate dyspnea and the aggravation of cognitive state along with the increase in dyspnea level indicate that the dyspnea affects the cogni-

tive state. In a systematic review and meta-analysis, it was reported that there was a negative relationship between hypoxia and cognitive state (30). Thus, dyspnea negatively affects the cognitive state.

In conclusion, it is discerned that the cognitive state got worsened as the dyspnea level increased. The use of an oxygen tube and bipod at home, the incompetence in the management of dyspnea, the feeling of being short of breath, and the fear of death were dyspnea-related factors that affected the cognitive state. It was found that there was a statistically significant strong negative relationship between the dyspnea level and cognitive state.

The findings obtained in this study will help clinicians better understand the dyspnea-related factors that contribute to the cognitive impairment in COPD patients. When there is an impairment in a COPD patient's cognitive state, clinicians can think that dyspnea is likely to be linked to this problem. It can be necessary to put in place a mechanism to closely follow up on the cognitive state of COPD patients who have highly severe dyspnea, feel incompetent in the management of dyspnea, and identify dyspnea with the feeling of being short of breath, the feeling of disappointment, and the fear of death.

Secondly, this study provided data that would offer a better understanding of socio-demographic characteristics and COPD-related and treatment-related factors that were associated with cognitive impairment. In this context, it was found that patients who used an oxygen tube or bipod at home, had relatively low-level education, were married, were not working, quit smoking, were diagnosed with COPD for 21 years or longer, had a history of having a psychiatric disease, received psychiatric therapy, had the willingness to receive psychological assistance, did not visit a doctor for health controls on a regular basis, were hospitalized three times or more in the last year, had a caregiver, had social support, regularly used their drugs, and received COPD-related training from a nurse had lower cognitive levels than other respective groups of patients. Identifying the factors associated with cognitive impairment in COPD patients can help to provide information about how to apply cognitive rehabilitation.

Thirdly, the findings of this study demonstrated that there was a negative relationship between dyspnea and cognitive state in COPD patients. This finding stresses the importance of paying attention to dyspnea and cognitive functions in the treatment of COPD patients. Along with the use of cognitive therapies, there will be an enhancement in COPD patients' cognitive levels, and this situation will be accompanied by an improvement in COPD patients' dyspnea levels.

It is recommended that findings obtained in this study be verified and researched in prospective studies to be performed with larger populations. Also, it is considered that interventional studies aimed at the management of dyspnea and the improvement of cognitive state should be conducted.

The design of the study as cross-sectional research is accepted as a limitation. Also, not addressing the partial pressure of oxygen (PaO_2) that is closely associated with dyspnea and cognitive level in COPD patients is another limitation of this research.

Acknowledgment

None.

Author Contributions

Concept: **Döndü Şanlıtürk, Nurgül Kaplan,** Design: **Döndü Şanlıtürk, Nurgül Kaplan,** Supervision: **Döndü Şanlıtürk,** Resource - **Döndü Şanlıtürk,** Materials: **Döndü Şanlıtürk, Nurgül Kaplan,** Data Collection and/or Processing: **Döndü Şanlıtürk, Nurgül Kaplan,** Analysis and/or Interpretation: **Döndü Şanlıtürk, Nurgül Kaplan,** Literature Search: **Döndü Şanlıtürk, Nurgül Kaplan,** Writing: **Döndü Şanlıtürk, Nurgül Kaplan,** Critical Reviews: **Döndü Şanlıtürk, Nurgül Kaplan.**

Conflicts of Interest

There is no conflict of interest in our study.

Financial Support

There is no financial support.

Ethical Approval

Ethics committee approval was received for this study from Clinical Trials Ethics Committee of Tokat Gaziosmanpaşa University (No: 2021/22)

Review Process

Extremely peer-reviewed and accepted.

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ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2023;7(1): 31-37
DOI: 10.29058/mjwbs.1220876

Evaluation of Depression, Anxiety and Sleep Quality Scores in Patients with Cervical Disc Herniation: A Study Conducted in Turkey

Servikal Disk Hernisi Olan Hastalarda Depresyon, Anksiyete ve Uyku Kalitesi Skorlarının Değerlendirilmesi: Türkiye'de Yapılan Bir Araştırma

Alper UYSAL[1], **Murat GUNTEL**[2]

[1]Hatay Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Hatay, Turkey
[2]Hatay Mustafa Kemal University, Medicine Faculty, Department of Neurology, Hatay, Turkey

ORCID ID: Alper Uysal 0000-0002-4114-1649, Murat Guntel 0000-0002-5885-7571

Cite this article as: Uysal A and Guntel M. Evaluation of depression, anxiety and sleep quality scores in patients with cervical disc herniation: A study conducted in Turkey. Med J West Black Sea. 2023;7(1):31-37.

Corresponding Author
Alper Uysal

E-mail
alperuysal82@gmail.com

Received
19.12.2022

Revision
01.03.2023

Accepted
15.03.2023

ABSTRACT

Aim: Neck pain is one of the most prevalent medical complaints. Chronic pain conditions can lead to depression, anxiety and sleep problems in individuals. Thus, both the pain itself and the psychiatric problems it causes impair the quality of life of the patient. Depression and anxiety can also cause changes in the perception of pain. In this study, we aimed to investigate the effects of cervical disc herniation (CDH), which causes chronic neck pain, on the level of neck disability, sleep quality, anxiety and depression.

Material and Methods: Patients' pain intensity, neck disability indexes, depression and anxiety status, and sleep quality were evaluated using a visual analog scale (VAS), the neck disability index (NDI), Beck Depression Inventory (BDI), beck anxiety inventory (BAI) and the Pittsburgh Sleep Quality Index (PSQI), respectively.

Results: We found a statistically significant relationship between CDH and anxiety, depression and sleep quality. In addition, we found higher levels of pain, anxiety and depression in the group with poor sleep quality.

Conclusion: For optimal treatment approaches of patients with chronic neck pain, accompanying sleep disorder, depression and anxiety should also be evaluated.

Keywords: Neck pain, Cervical disc herniation, Depression, Anxiety, Sleep disorder

ÖZ

Amaç: Boyun ağrısı en sık görülen tıbbi şikayetlerden biridir. Kronik ağrı durumları bireylerde depresyon, anksiyete ve uyku sorunlarına yol açabilir. Böylece hem ağrının kendisi hem de yol açtığı psikiyatrik sorunlar hastanın yaşam kalitesini bozmaktadır. Depresyon ve anksiyete de ağrı algısında değişikliklere neden olabilir. Bu çalışmada kronik boyun ağrısına neden olan servikal disk hernisinin (SDH) boyun özürlülük düzeyi, uyku kalitesi, depresyon ve anksiyete üzerine etkilerini araştırmayı amaçladık.

Gereç ve Yöntemler: Hastaların ağrı şiddeti, boyun özürlülük indeksleri, depresyon ve anksiyete durumları ve uyku kaliteleri sırasıyla görsel analog skala (GAS), boyun özürlülük indeksi (BÖİ), Beck Depresyon Envanteri (BDE), Beck anksiyete envanteri (BAE) ve Pittsburgh Uyku Kalitesi İndeksi (PUKİ) kullanılarak değerlendirildi.

Bulgular: SDH ile anksiyete, depresyon ve uyku kalitesi arasında istatistiksel olarak anlamlı bir ilişki bulduk. Ayrıca uyku kalitesi düşük olan grupta daha yüksek düzeyde ağrı, anksiyete ve depresyon bulduk.

Sonuç: Kronik boyun ağrısı olan hastalarda optimal tedavi yaklaşımları için eşlik eden uyku bozukluğu, depresyon ve anksiyete de değerlendirilmelidir.

Anahtar Sözcükler: Boyun ağrısı, Servikal disk hernisi, Depresyon, Anksiyete, Uyku bozukluğu

INTRODUCTION

About half of the people experience neck pain at least one time in their lifespan (1). Neck pain, the incidence of which is increasing, is observed more frequently in some specific professions. If this pain becomes chronic, it can negatively affect the quality of life, mood and sleep quality of the patient (2).

One of the considerably important causes of chronic neck pain is cervical disc herniation (CDH). CDH is caused by expulsion of nucleus pulposus of the intervertebral disc in the cervical spine. This can lead to compression of the nerve roots. Although there are broad classifications to define the terminology, we can divide disc herniations into the following subcategories: bulging, protrusion, extrusion and sequestration (3). The prevalence of CDH increases with age and is most commonly observed in the 4th and 5th decades of life. Women account for about 60% of cases (4). CDH may present with pain in the neck or radiating from the neck to the arm and fingers. The pain may be sharp or dull in character. Complaints such as numbness and loss of sensation, may accompany the pain or may be a primary complaint. Flexion of the head may reveal or exacerbate these complaints (5).

Depression and anxiety are very common health problems all over the world. In cases of chronic pain, the frequency of major depression, anxiety and sleep problems may increase (6). While these psychiatric comorbidities may complicate CDH and pain management, they may also create negative differences in pain perception. In this study, we aimed to reveal the relationship between CDH and chronic neck pain and psychiatric pathologies such as depression, anxiety and sleep disorders. Thus, clinicians will look at patients presenting with CDH and chronic neck pain from a wider range and plan their treatment accordingly. The difference of the present study from other studies with similar subjects and content in the literature is that it evaluates the patients' neck pain and disability, depression and anxiety levels according to whether their sleep quality is good or bad.

MATERIAL and METHODS

The study consisted of 46 patients (8 men, 38 women) who met the inclusion criteria. A control group was formed from 50 participants who were similar to the patient group in terms of characteristics such as gender and age. After the approval of the ethics committee, patients were started to be included in the study between 15 June 2021 and 15 December 2021. A written informed consent form was obtained from all participants.

Participants

The study included 46 patients who applied to Hatay Training and Research Hospital Physical Medicine and Rehabilitation outpatient clinic with the complaint of neck pain and were diagnosed with cervical disc herniation. The patients were diagnosed with CDH after anamnesis, detailed physical and neurological examination, cervical X-Ray graphy and cervical MRI examinations. Complete blood count, erythrocyte sedimentation rate and serum C-reactive protein (CRP) levels were evaluated to exclude rheumatic diseases. The control group consisted of healthy hospital personel and their relatives.

The following were accepted as exclusion criteria in the study; serious psychiatric illness and receiving medical treatment for it, extruded and/or sequestrated cercical disc herniation, having undergone cervical disc surgery, kyphosis or scoliosis, neurologic deficit, inflammatory rheumatologic disease, cardiovascular problems, pregnancy, malignancy or infection, physical therapy in the last 3 months and a history of endocrine disease (thyroid, parathyroid or diabetes). The present study was approved by the Clinical Study Ethics Committee of Hatay Mustafa Kemal University (approval no. 06, dated May 06, 2021).

Evaluations

Demographic data, height and weight values of the participants were questioned and recorded. Body mass indexes (BMI) were determined by dividing their weight by the square of their height.

Pain intensity was evaluated by visual analog scale VAS (7). Anxiety levels of the participants were assessed with Beck Anxiety Inventory (BAI), depression levels were assessed via Beck Depression Inventory (BDI), and sleep quality was assessed via Pittsburgh Sleep Quality Index (PSQI). Disability status due to CDH was also evaluated with the Neck Disability Index (NDI).

BDI includes 21 items: items between 1 and 13 assess depressive mood, while items between 14 and 21 evaluate physical symptoms. Total score varies between 0 and 63. 1-10 points are considered normal. 11-16 points,17-20 points 21-30 points, 31-40 points and over 40 points reveal mild mood disturbance, borderline depression, moderate depression, severe depression and extreme depression, respectively (8, 9).

With BAI, common symptoms of anxiety are questioned. The total score is calculated by summing the scores from 21 items. 0 to 21 points assess low anxiety. 22 to 35 points assess moderate anxiety and >36 points assess worrying anxiety levels (10).

According to PUKI, the total score ranges from 0 to 21, and scores equal to or greater than 6 indicate poor sleep quality (11).

The Neck Disability Index (NDI) is done to evaluate the impact of neck pain on the patient's daily life. NDI consists of

10 items and each item is scored between 0-5 points. Total score varies between 0-50. As a result of the evaluation, the level of the disability is classified as no disability (0 to 4 points), mild (5 to 14 points), moderate (15 to 24 points), severe (25 to 34 points) and complete (>34 points) (12).

Statistical Analyses

Descriptive statistics were presented as arithmetic mean ± standard deviations and median (minimum-maximum) for continuous variables, and as the frequency and percentage for categorical variables. Conformity of continuous variables with normal distribution was checked by the Shapiro Wilk test. If the data conformed to the normal distribution, the Independent Samples t-Test (Student's t-Test) was used to compare the mean of the patient and control groups in terms of continuous variables, and if not, the Mann Whitney-U Test was used. The Pearson Chi-Square Test and Fisher's Exact Test were used to compare patient and control group percentages in terms of categorical variables. The direction and strength of the relationship between continuous variables were determined by the Pearson correlation coefficient (r) if the data were normally distributed, and by the Spearman correlation coefficient (Rs) if they were not normally distributed. Mukaka's guide was used to specify the size of the correlation coefficient and was shown in Table 6 (13). The statistical significance limit was accepted as $p<0.05$. SPSS 21 statistical package program was used for all statistical analyses.

RESULTS

The study consisted of 46 patients (8 men, 38 women) who met the inclusion criteria. A control group was formed from 50 participants (8 male, 42 female). Of the patient group, 39 (84.8%) were married, 5 (10.9%) were single, and 2 (4.3%) were divorced. In the control group, the rate of married people was 84% (42 participants). While the mean age of the patient group was 40.20±9.21, it was 42.46±12.28 in the control group. While the mean BMI was 26.23±3.09 in the patient group, it was 26.11±3.15 in the control group. It was observed that the gender, marital status, age and BMI distributions of the patient and control groups were statistically similar (Table 1).

NDI, BDI, BAI and PSQI mean scores were statistically significantly higher in the patient group than in the control group. While the mean NDI was 23.01±7.69 in the patient group, it was 3.38±1.87 in the control group. While the mean BDI was 11.02±7.42 in the patient group, it was 6.16±3.14 in the control group. While the mean BAI was 14.35±9.22 in the patient group, it was 5.04±3.02 in the control group. When we evaluated it in terms of PSQI, it was 9.39±4.47 in the patient group, while it was 3.56±2.33 in the control group (Table 2).

While the mean duration of pain experienced in the patient group was 56.43±55.61 months, the duration of diagnosis was 23.02±21.31 months. The mean VAS was 7.15±1.26 (Table 3).

Table 1: Demographic Data

Demographic Characteristics		Patients (n=46)	Control (n=50)	p
Gender, n(%)	Male	8 (17.4)	8 (16.0)	0.855*
	Female	38 (82.6)	42 (84.0)	
Marital Status n(%)	Married	39 (84.8)	42 (84.0)	0.916*
	Single or Divorced	7 (15.2)	8 (16.0)	
Age (year±SD)		40.20 ± 9.21	42.46 ± 12.28	0.307**
BMI (kg/m^2±SD)		26.23 ± 3.09	26.11 ± 3.15	0.846**

BMI: Body Mass Index, * Pearson Chi-Square Test, ** Student's t-Test

Table 2: Results of NDI, BDI, BAI and PSQI of patient and control groups

Indices	Patients (n=46)	Control (n=50)	p
NDI (score±SD)	23.01 ± 7.69	3.38 ± 1.87	<0.001*
BDI (score±SD)	11.02 ± 7.42	6.16 ± 3.14	0.001*
BAI (score±SD)	14.35 ± 9.22	5.04 ± 3.02	<0.001*
PSQI (score±SD)	9.39 ± 4.47	3.56 ± 2.33	<0.001*

NDI: Neck Disability Index, **BDI:** Beck Depression Inventory, **BAI:** Beck Anxiety Inventory, **PSQI:** Pittsburgh Sleep Quality Index, * Mann Whitney U-Test

Table 3: Pain duration, Diagnosis time and VAS of the patients

Pain's Characteristics	Findings
Pain duration	
(months±SD)	56.43 ± 55.61
Median (Min-Max)	48 (3-240)
Diagnosis time	
(months±SD)	23.02 ± 21.31
Median (Min-Max)	15 (3-84)
VAS	
(Scale±SD)	7.15 ± 1.26
Median (Min-Max)	7 (5-9)

VAS: Visual Analog Scale, **X:** Mean, **SD:** Standard Deviation

According to PSQI, 11 patients had good sleep quality and 35 patients had poor sleep quality. It was observed that the gender, marital status, age and BMI distributions of the groups with good and bad sleep quality were statistically similar (p=0.374, p=0.171, p=0.231, p=0.379, respectively) (Table 4).

While the mean duration of pain was 92.18±84.52 months in the good sleep quality group, it was 45.20±38.06 months in the poor sleep quality group. While the mean time to diagnosis was 33.27±14.79 months in the good sleep quality group, it was 19.80±22.18 months in the poor sleep quality group. The mean VAS, NDI, BDI and BAI values in the good sleep quality group were 6.18±1.08, 15.82±2.75, 5.36±2.77, 7.64±2.38, respectively. In the poor sleep quality group, mean VAS, NDI, BDI and BAI values were 7.46±1.17, 25.27±7.34, 12.80±7.55, 16.46±9.58, respectively (Table 5).

The mean values of VAS, NDI, BDI and BAI were statistically significantly higher in the poor sleep quality group than in the good sleep quality group (p=0.004, p<0.001, p=0.001, p=0.001, respectively). The diagnosis time was found to be statistically significantly lower in the poor sleep quality group than in the good sleep quality group (p=0.015). There was no statistically significant difference between the two groups in terms of pain duration (p=0.075).

There is a high level of positive correlation between VAS and NDI (rs=0.741, p=0.001) and between NDI and PSQI (rs=0.740, p<0.001). There is a moderate positive correlation between VAS and PSQI (rs=0.530, p<0.001), BDI and PSQI (rs=0.599, p<0.001), and BAI and PSQI (rs=0.574, p<0.001). There is a low positive correlation between VAS and BDI (rs=0.374, p=0.010), VAS and BAI (rs=0.317, p=0.032), NDI and BDI (rs=0.441, p=0.002), NDI and BAI (rs=0.353, p=0.016), and BDI and BAI (rs=0.418, p=0.004) (Table 6).

DISCUSSION

Cervical disc herniation is one of the most common causes of neck pain. Chronic pain conditions can lead to psychological problems, deterioration in sleep quality and limitations in activities of daily living. Many studies have shown the relationship between chronic pain, neck or low back pain and psychiatric conditions. However, there are very few studies examining the relationship between CDH, psychiatric diseases and sleep quality.

This study was designed to determine the relationship between pain intensity, neck disability index, depression, anxiety and quality of sleep in patients with CDH. We found that the anxiety and depression scores were higher in the patient group, and their sleep quality was worse. This shows that chronic pain conditions such as CDH and deteri-

Table 4: Demographic data, Age and BMI of patients with good and poor sleep quality

		Group Quality of Sleep		p
		Good (0-5)	Poor (6-21)	
Gender, n (%)	Male	3 (27.3)	5 (14.3)	0.374*
	Female	8 (72.7)	30 (85.7)	
Marital Status, n (%)	Married	11 (100.0)	28 (80.0)	0.171*
	Single or Divorced	0 (0.0)	7 (20.0)	
Age (year±SD)		42.36±5.28	39.51 ± 10.10	0.231**
BMI (kg/m^2±SD)		26.96±2.83	26.00 ± 3.17	0.379**

BMI: Body Mass Index, * Fisher's Exact Test, ** Student's t-Test

Table 5: Pain duration, Diagnosis time, VAS, NDI, BDI, BAI of groups with good and poor sleep quality

Parameters	Group Quality of Sleep		p*
	Good (0-5)	Poor (6-21)	
Pain duration (months±SD)	92.18 ± 84.52	45.20 ± 38.06	0.075
Diagnosis time (months±SD)	33.27 ± 14.79	19.80 ± 22.18	0.015
VAS (score±SD)	6.18 ± 1.08	7.46 ± 1.17	0.004
NDI (score±SD)	15.82 ± 2.75	25.27 ± 7.34	<0.001
BDI (score±SD)	5.36 ± 2.77	12.80 ± 7.55	0.001
BAI (score±SD)	7.64 ± 2.38	16.46 ± 9.58	0.001

VAS: Visual Analog Scale, **NDI:** Neck Disability Index, **BDI:** Beck Depression Inventory, **BAI:** Beck Anxiety Inventory, * Mann Whitney U-Test

Table 6: Correlation size between VAS, NDI, BDI, BAI and PSQI

		VAS	NDI	BDI	BAI	PSQI
VAS	Correlation coefficient (rs)	1,000	0.741	0.374	0.317	0.530
	p	-	**<0.001**	**.010**	**.032**	**<0.001**
NDI	Correlation coefficient (rs)		1.000	0.441	0.353	0.740
	p		-	**0.002**	**0.016**	**<0.001**
BDI	Correlation coefficient (rs)			1.000	0.418	0.599
	p			-	**0.004**	**<0.001**
BAI	Correlation coefficient (rs)				1.000	0.574
	p				-	**<0.001**
PSQI	Correlation coefficient (rs)					1.000
	p					-

0.90 to 1.00 (-0.90 to -1.00): Very high positive/negative correlation
0.70 to 0.90 (-0.70 to -0.90): High positive/negative correlation
0.50 to 0.70 (-0.50 to -0.70): Moderate positive/negative correlation
0.30 to 0.50 (-0.30 to -0.50): Low positive/negative correlation
0.00 to 0.30 (-0.00 to -0.30): Insignificant correlation

VAS: Visual Analog Scale, **NDI:** Neck Disability Index, **BDI:** Beck Depression Inventory, **BAI:** Beck Anxiety Inventory, **PSQI:** Pittsburgh Sleep Quality Index, **rs:** Rank Correlation Coefficient, **p:** Spearman Correlation Analysis

oration in sleep quality may pave the way for mood changes such as depression and anxiety in patients. As expected, we found the mean NDI to be higher in the CDH group. Accordingly, these results, we found positive high-moderate and low-level relationships between VAS, NDI, PSQI, BDI and BAI.

Parikh and Amarnath found a positive correlation between neck pain and anxiety in a study of 154 computer workers (6). Lerman et al. found that more than half of the participants suffered from depression and anxiety in their study which included 428 patients with chronic pain (14). Elbinoune et al. investigated the prevalence of anxiety and depression in 80 patients with chronic neck pain. They found the depression rate 55.7% and the anxiety rate 68.4%. They evaluated these rates as high (15).

Liu et al. reviewed 13 studies involving 2339 patients and 3290 healthy people to evaluate the possible relationship between neuropathic pain and mood disorders. As a result, it was determined that chronic pain conditions may adversely affect the mental health of patients and may also predispose them to depression and anxiety, so the quality of life of the person deteriorates (16). Dimitriadis et al. found a relationship between pain severity and anxiety level in a study that included 45 patients with chronic neck pain (17). Supporting the study of Dimitriadis et al., a low positive correlation was found between pain and depression or anxiety in our study. Also, Batcik and Özdemir found a positive correlation between pain severity and anxiety and depression levels in a study that included patients with acute low back pain (18). Talvari et al., in their study, which included 200 elderly participants with neck pain over the age of 60, found that older individuals with neck pain were more prone to symptoms of anxiety and depression (19).

Blozik et al. suggested that depression and anxiety are important triggers of neck pain (20). Moreover, Gerrits et al. suggested that compared to other anatomical localizations, neck pain may reveal anxiety and depression more (21).

Psychiatric disorders can cause or exacerbate chronic nonspecific pain. A bidirectional relationship has been reported between pain and psychiatric disorders. It is emphasized that psychiatric disorders can change pain sensitivity, especially anxiety reduces tolerance (22, 23). It is thought that dysfunction in the autonomic nervous system and hypothalamic-pituitary-adrenal axis of patients with anxiety and depression may be related to the change in pain perception. In addition, when neurotransmitters such as norepinephrine (NE) and 5 hydroxytryptamine (5-HT) decrease, loss of mechanisms to eliminate pain and development in psychiatric diseases such as anxiety and depression can be observed. High levels of systemic inflammatory markers in the blood of patients with chronic pain and mood disorders may indicate that common pathogenetic mechanisms may be responsible (16).

Similar to our work, Sayilir found in his study that the perceived stress levels in patients with chronic neck pain were significantly higher than in healthy controls. Also, he found that physical medicine & rehabilitation (PMR) applications provide an improvement in these perceived stress levels. At the end of PMR applications, NDI scores were also improved (24).

In chronic pain conditions, the frequency of sleep disturbances and daytime sleepiness is increased. These sleep-related conditions can also cause many serious conditions that should be taken into account, such as falls in elderly individuals (24). We found that 35 (76%) participants in the patient group had poor sleep quality. Mean VAS values were also higher in patients with poor sleep quality. While this may indicate that patients cannot sleep well due to pain, it may also suggest that patients with bad sleep quality may have a change in their perception of pain. Also, patients with poor sleep quality had higher mean anxiety and depression scores. This may show that poor sleep quality, anxiety and depression are in mutual interaction.

Similar to our study, Muñoz-Muñoz et al. researched pain and disability levels and sleep quality in individuals with neck pain, and found that sleep quality was poorer in patients than in healthy people (25). Artner et al. evaluated 1016 patients with chronic low or upper back pain, retrospectively. Similar to our study, they showed a significant association between pain intensity and sleep disorder (26). Auvinen et al. declared that poor sleep quality was a risk factor for low back or neck pain, and they also discussed that an improvement in sleep quality may be beneficial for the treatment of these pains (27). Valenza et al., in their study examining the change in sleep quality of 59 neck pain patients, emphasized that the cycle of pain and sleep disturbance should be taken into account in the treatment of these patients (28).

De Heer et al. showed that the presence of depression and anxiety increased the severity of existing pain and pain-related disability (29). Seçer et al. found a low to moderate negative correlation between pain score and sleep quality in chronic neck pain patients, and a low positive correlation between pain score and anxiety score (2).

According to Yalçınkaya et al., there was a positive correlation between PSQI and NDI, BAI and BDI. They also stated that impaired sleep quality may have a function in the pathogenesis of chronic pain (30). In our study, we found a relationship between sleep disorder severity and depression, anxiety and disability levels. Moreover, we found that patients with worse sleep quality had higher scores for pain, disability, depression and anxiety compared to those with better sleep quality.

We found that in patients with poor sleep quality, the mean duration of pain was shorter. In addition, the time to diagnosis of CDH was shorter in patients with poor sleep quality. This may suggest that the accompanying sleep quality deterioration leads to earlier treatment seeking in patients with chronic pain.

Adequate number of patients were included in the study in terms of statistical significance, but the number of patients could have been higher to minimize errors. Other psychological factors such as insomnia that may be associated with CDH could also be investigated. The effect of treatment approaches for anxiety, depression and sleep problems on pain could be investigated. Conditions such as work related factors that could affect psychological factors and sleep quality could also be evaluated in the study. Therefore, studies that will involve more participants, evaluate the efficacy of treatment and with longer follow-up periods will contribute more to the literature in terms of investigating the relationship between CDH and anxiety, depression and sleep quality.

We found a statistically significant relationship between CDH and anxiety, depression and sleep quality. In addition, we found higher levels of pain, anxiety and depression in the group with poor sleep quality due to CDH. As a result, we found positive high-moderate and low-level relationships between VAS, NDI, PSQI, BDI and BAI. Thus, clinicians should approach patients presenting with CDH and neck pain from a broader perspective and evaluate them in terms of anxiety, depression, and sleep quality. Because with a two-way interaction, depression and anxiety can lower the pain threshold or the severity of pain can reveal the psychiatric problems of the patients. It will be possible to get better clinical results with the detection and treatment of these accompanying conditions.

Acknowledgment

My dear friend Murat Güntel, it is very difficult to accept your death. Thank you for the beauty and values you add to my life.

Author Contributions

Concept: **Alper Uysal, Murat Guntel,** Design: **Alper Uysal, Murat Guntel,** Data Collection or Processing: **Alper Uysal,** Analysis or Interpretation: **Alper Uysal, Murat Guntel,** Literature Search: **Alper Uysal, Murat Guntel,** Writing: **Alper Uysal, Murat Guntel.**

Conflicts of Interest

Authors declare that there is no conflict of interest. The second author of the study died in Hatay on February 6, 2023 due to the 7.7 magnitude earthquake.

Financial Support

None.

Ethical Approval

The present study was approved by the Clinical Study Ethics Committee of Hatay Mustafa Kemal University (approval no. 06, dated May 06, 2021). The guidelines of the Declaration of Helsinki were followed during the conduct of this study. A written informed consent form was obtained from all participants.

Review Process

Extremely peer-reviewed and accepted.

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ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2023;7(1): 38-44
DOI: 10.29058/mjwbs.1198056

Relationship Between Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score and Geriatric Nutritional Risk Index (GNRI) and Prognosis in Patients Over 75 Years of Age with Metastatic Gastric Cancer

Yetmiş Beş Yaş Üstü Metastatik Mide Kanserli Hastalarda Hemoglobin, Albümin, Lenfosit, Platelet (HALP) Skoru ile Geriatrik Nütrisyonel İndeks (GNRI) ve Prognoz Arasındaki İlişki

Serkan MENEKŞE, Engin KUT

Manisa State Hospital, Medical Oncology Clinic, Manisa, Turkey

ORCID ID: Serkan Menekşe 0000-0002-2134-2128, Engin Kut 0000-0002-5328-5607

Cite this article as: Menekşe S and Kut E. Relationship between hemoglobin, albumin, lymphocyte and platelet (HALP) score and geriatric nutritional risk index (GNRI) and prognosis in patients over 75 years of age with metastatic gastric cancer. Med J West Black Sea. 2023;7(1):38-44.

Corresponding Author
Engin Kut

E-mail
drenginkut@gmail.com

Received
01.11.2022

Revision
14.04.2023

Accepted
19.04.2023

ABSTRACT

Aim: Gastric cancer (GC) is a common cancer with high mortality. Stage is the most important predictor of prognosis. But the clinical course of patients who are at the same stage may be different. Therefore, other prognostic markers other than stage are needed. Hemoglobin, albumin, lymphocyte and platelet (HALP) score and geriatric nutritional risk index (GNRI) related with prognosis in many malignancies, but their relationship to prognosis in patients with GC with advanced age is unknown. For this reason, we retrospectively analyzed patients older than 75 years, receiving chemotherapy, and metastatic GC.

Material and Methods: We retrospectively analyzed 145 patients with metastatic gastric cancer, older than 75 years, receiving chemotherapy in secondary level state hospital between 2009 and 2022. Patients' gender, age, Eastern Cooperative Oncology Group (ECOG) performance score, diagnosis dates, follow-up visits, albumin, hemoglobin, lactate dehydrogenase (LDH) levels, white blood cell, neutrophil, lymphocyte and platelet count, weight (kg), height (cm) values were examined. Using these values, HALP score, GNRI, and overall survival (OS) were calculated. Then, the relationship of these parameters with OS was analyzed retrospectively.

Results: The median overall survival (OS) was 8.1 (95% Confidence interval (CI), 7.07 – 9.13) months. In multivariate analysis, GNRI (0.035) and HALP (p<0.001) were associated with survival time. Median OS was 4.5 (95% C,3.77-5.24) months in the low HALP group, and 10.2 (95% CI, 9.04- 11.36) months in the high HALP group (p<0.001). Median OS was 6.2 (95% CI, 4.25-8.14) months in the low GNRI group and 8.6 (95% CI, 7.92-9.27) months in the high GNRI group.

Conclusion: GNRI and HALP score are associated with survival in metastatic GC patients older than 75 years. GNRI and HALP score can be used as an easy, cheap and practical method for follow-up, treatment and prognosis in elderly patients with metastatic GC.

Keywords: Elderly gastric cancer, HALP score, GNRI, Geriatric nutritional risk index, Prognosis

ÖZ

Amaç: Mide kanseri (MK) sık görülen ve mortalitesi yüksek bir kanserdir. Evre, prognozun en önemli belirleyicisidir. Ancak aynı evrede olan hastaların klinik seyri farklı olabilir. Bu nedenle evre dışında başka prognostik belirteçlere ihtiyaç vardır. Hemoglobin, albümin, lenfosit ve trombosit (HALP) skoru ve

geriatrik nütrisyonel risk indeksi (GNRI) birçok malignitede prognoz ile ilişkilidir, ancak ileri yaştaki mide kanserli hastalarda prognozla ilişkisi bilinmemektedir. Bu nedenle metastatik, 75 yaş üstü, kemoterapi alan mide kanserli hastaları retrospektif olarak inceledik.

Gereç ve Yöntemler: İkinci basamak bir devlet hastanesinde 2009-2022 yılları arasında kemoterapi alan, 75 yaş üstü metastatik mide kanserli 145 hasta retrospektif olarak incelendi. Hastaların cinsiyeti, yaşı, Eastern Cooperative Oncology Group (ECOG) performans skoru, tanı tarihleri, kontrole geliş tarihleri, albümin seviyeleri, hemoglobin, laktat dehidrogenaz (LDH), beyaz küre sayısı, nötrofil, lenfosit ve trombosit sayısı, ağırlık (kg), boy (cm) değerleri incelendi. Bu değerler kullanarak HALP skoru, GNRI, genel sağkalım (OS) hesaplandı. ardından bu parametrelerin OS ile ilişkisi retrospektif olarak analiz edildi.

Bulgular: Medyan genel sağkalım (OS) 8.1 (%95 Güven aralığı (GA), 7.07 – 9.13) aydı. Çok değişkenli analizde, GNRI (0.035) ve HALP skoru (p<0.001) sağkalım süresi ile ilişkiliydi. Medyan OS, düşük HALP grubunda 4,5 (%95 C,3.77-5.24) ay ve yüksek HALP grubunda 10.2 (%95 CI, 9.04- 11.36) ay saptandı (p<0.001). Medyan OS, düşük GNRI grubunda 6.2 (%95 GA, 4.25-8.14) ay ve yüksek GNRI grubunda 8.6 (%95 GA, 7.92-9.27) ay saptandı.

Sonuç: GNRI ve HALP skoru, 75 yaş üstü metastatik, mide kanserli hastalarda sağkalım süresi ile ilişkilidir. Metastatik mide kanserli yaşlı hastalarda takip stratejisi geliştirmek, tedavi planlamak ve prognoz belirlemek için kolay, ucuz ve pratik bir yöntem olarak kullanılabilir.

Anahtar Sözcükler: Yaşlı mide kanseri, HALP skoru, GNRI, Geriatrik nutrisyonel risk indeksi, Prognoz

INTRODUCTION

Gastric cancer (GC) is the sixth most common and third deadliest cancer according to GLOBOCAN' 2020 data (1). Although the incidence and mortality of GC vary considerably according to the region, it is generally seen in advanced ages. According to the 2017 data of cancer statistics in Turkey, it is seen at a rate of 14.3% in men and 6.4% in women, and 27.3% of them are metastatic at the time of diagnosis (2).

The most important standard marker in prognosis is stage. However, in daily practice, the clinical course of patients with the same stage and metastasis site may be different. Therefore, other prognostic factors are needed besides the stage. Age is one of these prognostic factors. However, physiologic changes that occur in patients with age and related changes in immune escape lead to decreased renal clearance, decreased organ reserves, and changes in drug clearance and metabolism. As a result of all these, drug tolerance in patients may decrease and accordingly, there may be differences in the clinical course of patients. Age-related cancer types and behaviors may also differ. For example, while GC screening programs in advanced ages tend to decrease in incidence and mortality in the last 1-2 decades due to easier access to endoscopy and advances in treatment, studies have reported an increase in incidence and mortality in non-cardiac tumors under the age of 50 (3).

Studies have reported an intertwined relationship between nutrition, immun system, inflamatuar system and cancer. There are many studies showing that nutrition, inflammation and immune system may be associated with cancer formation, progression and prognosis (4-6).

In recent years, a number of scores and indices have been developed that show inflammation, immune and nutritional status. A relationship has been reported between these scores, which provide information about the immune inflammation and nutritional status of the patients, and many cancers. Therefore, besides the stage of the disease, these scores can be used to determine the prognosis of the disease.

The HALP score and GNRI score show the inflammatory immune and nutritional status of patients and have been previously related with many cancers. However, its relationship with prognosis in advanced age GC patients is unknown. For this reason, we retrospectively analyzed patients older than 75 years with metastatic GC who were followed up in our center and received chemotherapy.

MATERIAL and METHODS

Patients aged 75 years and older, who have been diagnosed with metastatic GC in in the Medical Oncology division of Manisa State Hospital between 2009 and 2022, were examined retrospectively. The study was conducted by the principles of the Declaration of Helsinki (as revised in 2013) and reviewed and approved by the Health Sciences Ethics Committee of Manisa Celal Bayar University (Decision no: 20.478.486/1115, Date 28.12.2021).

Patients older than 18 years of age with GC, with metastasis at the time of diagnosis, with adenocarcinoma histology, who received at least one step of chemotherapy and who had a blood test at least one week before chemotherapy in our hospital were accepted in the study. Patients under the age of 18, who had never received chemotherapy, who did not have adenocarcinoma histology, and who did not have a blood test in our hospital before chemotherapy were considered as exclusion criteria.

Patients sex, age, Eastern Cooperative Oncology Group (ECOG) performance score, albumin levels (g/dL), hemoglobin (g/dL), lactate dehydrogenase (LDH) (U/L), white blood cell counts (10^3/μL), neutrophil (10^3/μL), lymphocyte (10^3/μL) and platelet counts (10^3/μL), weight (kg), height

(cm), tumor location, HALP score , GNRI , and overall survival (OS) and the relationschip between OS and these parameters was analyzed retrospectively. These values were examined from the blood samples taken 24-48 hours after the pathological diagnosis of the patients. The main evaluation criterion was overall survival and the secondary evaluation criterion was factors affecting overall survival. Overall survival time is the time between diagnosis and death of the patient. HALP score was calculated as hemoglobin (g/dL) x albumin (g/dL) x lymphocytes ($10^3/\mu L$) / platelets ($10^3/\mu L$). Albumin-to-globulin ratio (AGR) calculated with the albumin / (total protein - albumin). GNRI is calculated as 14.87 x serum albumin concentration (g/dL) + 41.7 x weight/ideal weight (kg) (ideal body weight calculated as: 22 × height squared (m)).

The median HALP score of the patients was 2.71, the median value of the GNRI score was 98, and the median albumin to globulin ratio was 1.1. Patients were grouped according to HALP score (>2.71 or 2.71), GNRI (>98 or ≤98), ECOG performance score (3> or 3≤), age (≤80 or >80), AGR (>1.10 or ≤1.10).

Statistical Analyses

Descriptive statistics were reported as median (minimum, maximum), mean (± standart deviation) values for numeric variables and numbers and percentages for categoric variables. Survival analyses and curves were conducted using the Kaplan-Meier method. Determinants were analyzed by Cox regression analysis. In all statistical analyzes, p< 0.05 was considered significant.

RESULTS

One hundred and forty-five patients, 60 (41.4 %) females and 85 (58.6%) males were examined retrospectively. Median patient age was 80 (75-88) years (Table 1 and Table 2).

The median OS time of the patients was 8.1 (95% CI, 7.07 - 9.13) months. The median OS time was 4.5 (95% C,3.77-5.24) months in the low HALP group, 10.2 (95% CI, 9.04-11.36) months in the high HALP group (p<0.001), (Table 3, Figure 1). The median OS time was 6.2 (95% CI, 4.25-8.14) months in the low GNRI group, 8.6 (95% CI, 7.92-9.27) months in the high GNRI group (Table 3, Figure 1).

Age (p=0.039), ECOG performance score (p=0.043), BMI (p=0.023), albumin (p=0.001), hemoglobin (p=0.001), platelet (p=0.036), lymphocyte (p=0.036) in univariance analysis 0.045), neutrophil (p=0.044), liver metastasis (p=0.037) bone metastasis (p=0.028), lung metastasis (p=0.045), pleura (p=0.042), peritoneum (p=0.034) LVI (p= 0.026), AGR (p=0.026), GNRI (p=0.013) HALP (p<0.001) were associated with OS. In multivariate analysis, GNRI (0.035) and HALP (p<0.001) were associated with overall survival (Table 3).

Table 1: Demographic and clinicopathological characteristics of the patients

Parameters*		Findings (n= 145)	
Age	<80 years	67	(46.2)
	≥80 years	78	(53.8)
Sex	Female	60	(41.4)
	Male	85	(58.6)
ECOG performance score	3≤	106	(71.2)
	3>	39	(38.8)
Metastasis site	Liver	77	(53.1)
	Bone	34	(23.4)
	Lung	28	(19.3)
	Ovary	2	(1.4)
	LN	71	(49.0)
	Peritoneum	51	(25.2)
Comorbidities	Diabetes mellitus	46	(31.7)
	Hypertension	48	(33.1)
	CAD	30	(20.7)
	CRF	3	(2.1)
	COPD	8	(5.5)
	CVD	3	(2.1)
Grade	Grade 1	21	(14.5)
	Grade 2	106	(73.1)
	Grade 3	18	(12.4)
PNI	Positive	118	(81.4)
LVI	Positive	102	(70.3)
Localisation	Corpus	48	(33.1)
	Antrum	45	(31)
	Cardia	31	(21.4)
	Pylorus	5	(3.4)
Gastrectomy	Yes	42	(29.0)
AGR	(>1.10)	61	(42.2)
	(≤1.10)	84	(57.8)
GNRI	(>98)	67	(46.2)
	(≤98)	78	(52.8)
HALP score	(>2.71)	73	(50.3)
	(≤2.71)	72	(49.7)

***Data are presented as n(%). ECOG:** Eastern Cooperative Oncology Group, **CAD:** Coronary artery disease, **CRF:** Chronic renal failure, **COPD:** Chronic obstrictive pulmonary disease, **CVD:** Cerebrovascular disease, **LVI:** Lymphovascular invasion, **PNI:** Perineural invasion, **GNRI:** Geriatric Nutritional Risk Index, **AGR:** Albumin-to-globulin ratio, **HALP:** Hemoglobin, albumin, lymphocyte ve platelet score

DISCUSSION

The purpose of this study was to examine the relation between HALP scores, GNRI scores and prognosis in patients older than 75 years with metastatic GC receiving chemoetherapy at diagnosis. In our study, we found that patients with low HALP scores and low GNRI values at the time of diagnosis had worse prognosis and shorter median survival times.

Immune, inflammatory, and nutritional status of patients are intertwined in many cancers, and studies have reported that immune,inflammation, and nutrition status are associated with carcinogenesis and post-carcinogenesis stages (4-7). For example, in patients with GC, lack of oral intake, malnutrition as a result of weight loss causes chronic inflammation, cytokine release, and ultimately cachexia. Cytokines and proinflammatory mediators released in this process cause changes in the immune system and inflammatory system, and a decrease in albumin, which is a negative acute phase reactant. These proinflammatory cytokines are also involved in malignant transformation, neoangiogenesis, and cancer progression. Lack of oral intake and malnutrition can lead to treatment toxicities, prolonged hospital stays, nosocomial infections and reduced quality of life in patients (8).

Table 2: Laboratory values of the patients

Parameters	Values (n=145)
Age (Year) (Median [min-max])	80 (65-88)
Hemoglobin (g/dL) (Median [min-max])	12.37 (11-15.5)
Albumin (g/dL) (Mean± SD)	3.66 ± 0.04
Platelet (10^3/µL) (Median [min-max])	265 (112-644)
Lymphocyt (10^3/µL) (Median [min-max])	1.7 (0.8-3.4)
Neutrophil (103/µL) (Median [min-max])	5.6 (1.5-14.6)
WBC (10^3/µL) (Median [min-max])	8.5 (4.00-18.6)
GNRI (Median [min-max])	98 (70-121)
AGR (Median [min-max])	1.1 (0.6-1.9)
HALP (Median [min-max])	2.71 (0.41-12.41)

Min: Minimum, **Max:** Maximum, **SD:** Standard deviation, **WBC:** Whole blood cell, **GNRI:** Geriatric Nutritional Risk Index, **AGR:** Albumin-to-globulin ratio, **HALP:** Hemoglobin, albumin, lymphocyte ve platelet score

In daily clinical practice, there is a need for prognostic indicators other than stage because the clinical course and survival time of patients with the same stage may be different. Peripheral blood-derived cells and biochemical parameters can provide simple and inexpensive practical information about prognosis by showing inflammation, immune status and malnutrition (9). Albumin is synthesized in the liver. Its production is arranged by proinflammatory cytokines like tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), interleukin-1 (IL-1) (10).

Platelets plays a role in hemostasis, thrombosis and inflammation by releasing pro-inflammatory cytokines such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Platelets cause the movement of inflammatory cells into the inflammatory zone. As a result of these, the microenvironment of the tumor is formed. Tumor cells escape and evade the immune system and angiogenesis and progression occur, which are essential for the development of cancer and metastasis (11).

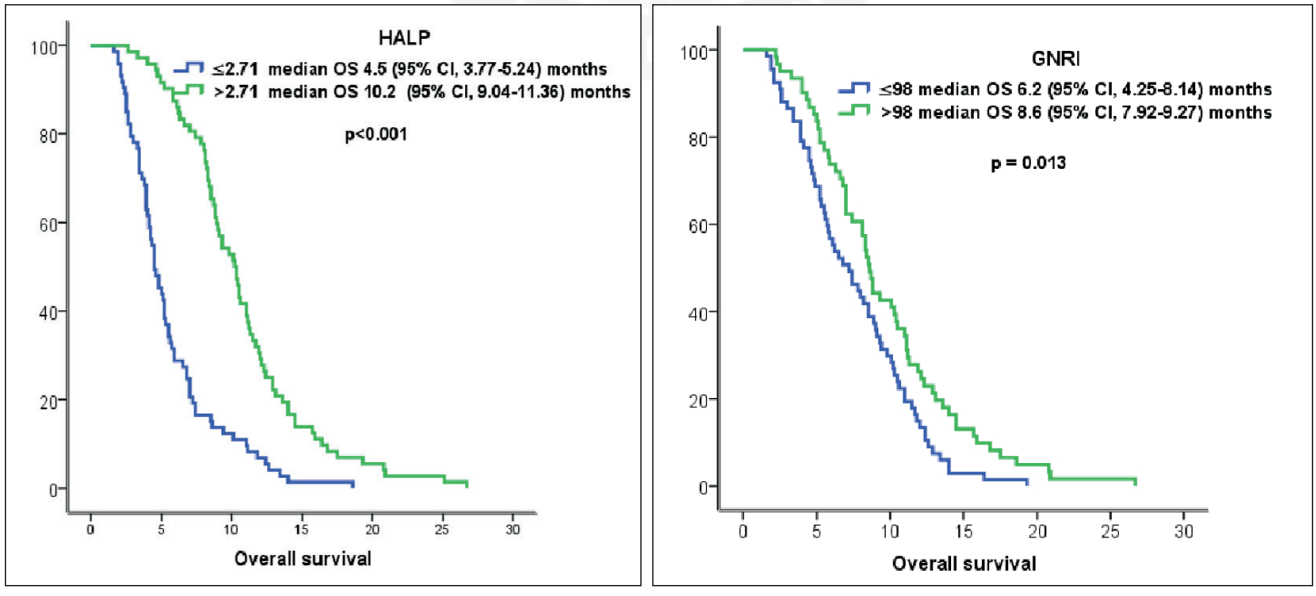

Figure 1: Kaplan-Meier curves of hemoglobin, albumin, lymphocyte and platelet (HALP) score and geriatric nutritionel risk index (GNRI), for overall survival.

Table 3: Univariate and multivariate analyses of overall survival

	Univariate analysis (HR, 95% CI)	p	Multivariate analysis (HR, 95% CI)	p
Age (80< vs 80≥)	1.76 (1.25-2.46)	0.039	0.68 (0.45-1.04)	0.761
Sex	1.20 (0.86-1.68)	0.281		
ECOG (<3 vs 3≤)	3.92 (2.19-7.05)	0.043	-0.96 (0.28-3.38)	0.962
BMI(kg/m^2)	-0.909 (0.87-.95)	0.023	-0.95 (0.89-1.02)	0.140
Diabetes Mellitus	1.05 (0.74-1.49)	0.760		
Hypertension	0.99 (.70-1.40)	0.973		
CAD	1.32 (0.88-1.97)	0.192		
CRF	1.78 (0.56-5.60)	0.384		
COPD	2.58 (0.54-30.40)	0.170		
CVD	-.0408 (0.28-0.95)	0.050	1.18 (0.80-16)	0.513
Albumin(g/dL)	-0.34 (0.25-0.49)	<0.001	-0.55 (0.29-1.04)	0.642
Hemoglobin(g/dL)	-0.78 (0.71-0.86)	<0.001	1.15 (0.97-1.37)	0.121
Platelet(10^3/µL)	1.02 (1.00-1.03)	0.036	1.15 (0.62-2.10)	0.664
Lymphocyte(10^3/µL)	-0.99 (0.99-0.99)	0.045	-0.89 (0.54-1.45)	0.652
Neutrophil(10^3/µL)	1.00 (1.00-1.01)	0.014	1.26 (0.82-1.96)	0.290
WBC(10^3/µL)	1.00 (1.00-1.01)	0.760		
Liver metastasis	1.89 (1.35-2.64)	0.037	1.41 (0.92-2.18)	0.121
Bone metastasis	-0.42 (0.28-0.62)	0.028	1.28 (.073-2.729	0.392
Lung metastasis	1.98 (1.36-2.90)	0.045	1.23 (0.74-2.07)	0.413
Pleura metastasis	-0.65 (0.43-0.98)	0.042	-0.62 (0.33-1.19)	0.151
Peritoneal metastasis	1.72 (1.20-2.44)	0.034	0.92 (0.57-1.49)	0.750
LN	1.12 (0.80-15)	0.504		
AGR	1.59 (1.15-2.25)	0.026	1.10 (0.83-1.45)	0.055
GNRI	1.57 (1.10-2.25)	0.013	1.22 (1.03-1.78)	0.035
HALP	3.121 (2.20-4.42)	<0.001	2.07 (1.40-3.05)	<0.001
LVI	-0.66 (0.46-0.95)	0.026	-0.82 (0.51-1.299	0.381
PNI	-0.76 (0.66-1.075)	0.132		
Grade	-0.77 (0.55-1.09)	0.153		

HR: Hazard ratio, **CI:** Confidence interval, **ECOG:** Eastern Cooperative Oncology Group, **BMI:** Bady mass index, **CAD:** Coronary artery disease, **CRF:** Chronic renal failure, **COPD:** Chronic obstrictive pulmonary disease, **CVD:** Cerebrovascular disease, **LN:** Lymphadenopathy, **WBC:** Whole blood cell, **AGR:** Albumin-to-globulin ratio, **GNI:** Geriatric Nutritional Risk Index, **HALP:** Hemoglobin, albumin, lymphocyte ve platelet score **LVI:** Lymphovascular invasion, **PNI:** Perineural invasion.

Lymphocytes are immune system elements that play an important role in host defense. They inhibit proliferation and metastasis of tumor cells. In their deficiency, tumor cells escape immune elimination. Lymphocyte levels have been associated with many cancers (12). Anemia reduces the oxygen capacity of the blood, that caues hypoxia. Chronic hypoxia can lead to an increase in VEGF secretion, neovascularization and prognosis in cancer (13). In addition to malnutrition, changes in the microbiota, increase in adipose tissue, increase in inflammatory mediators and free oxygen radicals, chronic inflammatory condition and DNA damage may be associated with carcinogenesis and subsequent stages in obesity-related carcinogenesis (14).

The HALP score consists of hemoglobin, albumin, lymphocyte and platelet values of patients and is an indicator of nutritional and systemic inflammation and can be used as a prognostic marker (15-17). Studies have found that it is associated with prognosis with many cancers such as colorectal cancers, bladder cancers, kidney cancers, pancreatic cancers, esophageal cancers, and small cell lung cancers (18-23). However, its relationship with prognosis in patients older than 75 years with metastatic GC is unknown. In our study, we found that patients with low HALP values in this group had a shorter median life expectancy and this value was statistically significant (p< 0.001).

GNRI shows the nutritional status . The GNRI consists of two parameters: serum albumin level and comparison of current body weight with ideal body weight (24). It has also been found to be associated with prognosis in previous studies in the literature (12). However, its relationship with prognosis in patients older than 75 years with metastatic GC was unknown. In our study, we found that the survival time of patients with low GNRI in this group of patients was low as in other cancers and this value was statistically significant.

Although the retrospective, single-center and small number of patients constitute the weaknesses of the study, our study is important because it is the first study to show the relationship between GNRI, HALP and prognosis in patients older than 75 of age with metastatic GC.

In metastatic gastric cancer patients older than 75 years, GNRI and HALP scores are associated with survival time. In addition, GNRI and HALP scores can be used as an easy and inexpensive practical method in daily practice for follow-up treatment and prognostic determination as well as the stage in elderly metastatic GC patients.

Acknowledgment

None.

Author Contributions

Concept: **Serkan Menekşe,** Design: **Engin Kut,** Data collection or processing: **Serkan Menekşe,** Analysis or Interpretation: **Engin Kut,** Literature search: **Engin Kut, Serkan Menekşe,** Writing: **Serkan Menekşe,** Approval: **Serkan Menekşe.**

Conflicts of Interest

There is no conflict of interest in our study.

Financial Support

There is no financial support.

Ethical Approval

The study was conducted by the principles of the Declaration of Helsinki (as revised in 2013) and reviewed and approved by the Health Sciences Ethics Committee of Manisa Celal Bayar University (Decision no: 20.478.486/1115, Date 28.12.2021).

Review Process

Extremely peer-reviewed and accepted.

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ÖZGÜN ARAŞTIRMA

Batı Karadeniz Tıp Dergisi
Medical Journal of Western Black Sea

Med J West Black Sea 2023;7(1): 45-50
DOI: 10.29058/mjwbs.1205737

Helicobacter pylori ile Enfekte Çocukların Yanak Epiteli Döküntü Hücrelerinde Mikronükleer ve Binükleer Hücre Sıklığının Değerlendirilmesi

Evaluation of Micronucleer and Binucleer Cells Frequencies in Buccal Epithelial Cells of Children Infected with *Helicobacter pylori*

Zehra SAFİ ÖZ[1], Gonca Handan ÜSTÜNDAĞ[2], Halime TOPUZ[2], Nilüfer ONAK KANDEMİR[3]

[1]Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi, Tıbbi Biyoloji Anabilim Dalı, Zonguldak, Türkiye
[2]Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Zonguldak, Türkiye
[3]T.C. Sağlık Bakanlığı Ankara Şehir Hastanesi, Tıbbi Patoloji Bölümü, Ankara, Türkiye

ORCID ID: Zehra Safi Öz 0000-0003-1359-5026, Gonca Handan Üstündağ 0000-0003-3027-833X, Halime Topuz 0000-0002-0696-8173, Nilüfer Onak Kandemir 0000-0001-9035-4475

Bu makaleye yapılacak atıf: Safi Öz Z ve ark. *Helicobacter pylori* ile enfekte çocukların yanak epiteli döküntü hücrelerinde mikronükleer ve binükleer hücre sıklığının değerlendirilmesi. Med J West Black Sea. 2023;7(1):45-50.

Sorumlu Yazar
Zehra Safi Öz

E-posta
safizehra@yahoo.com

Geliş Tarihi
18.11.2022

Revizyon Tarihi
04.01.2023

Kabul Tarihi
20.01.2023

ÖZ

Amaç: *Helicobacter pylori (H. pylori)* gastroduodenal inflamasyon, ülser ve atrofik gastrite yol açan bakteriyel bir patojendir. Mikronüklus (MN)' lar hücrenin mitoz bölünmesi sırasında ortaya çıkan esas çekirdeğe dahil olmayan oluşumlardır. Bu çalışmada, *H. pylori* ile mikronükleer ve binükleer hücre arasındaki ilişkinin eksfolyatif sitoloji yöntemi ile değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmada Zonguldak Bülent Ecevit Üniversitesi Uygulama ve Araştırma Hastanesi Çocuk Gastroenteroloji polikliniğine yaşam kalitesini etkileyecek tarzda ciddi dispeptik yakınmalarla başvuran ve endoskopik biyopsi yapılan hastalar yer aldı. Biyopsi örnekleri formalinde fikse edildi ve parafin bloklardan hazırlanan kesitler Hematoksilen & Eozin (H&E) ile boyandı. *H. pylori* varlığı açısından ışık mikroskobik olarak değerlendirildi. Biyopsi sonucu sadece *H. pylori* pozitif örnekler çalışma grubu (n=30) hiçbir enfeksiyon etkeni saptanmayanlar ise kontrol grubu (n=30) olarak alındı. Tüm bireylerden alınan yanak epitel hücreleri lamlara yayıldı, % 95'lik etil alkolde fikse edildi ve Papanicolaou boyama yöntemine göre boyandı. Mikronükleer ve binükleer hücreler iyi boyanmış 1000 epitel hücrede sayıldı. İstatistiksel değerlendirme SPSS 18.0 (SPSS Inc., Chicago, IL, USA) programı kullanıldı ve $p<0.05$ anlamlı olarak kabul edildi.

Bulgular: Çalışmamızda yer alan çocuklar 7 ile 15 yaşları arasında olup çalışma grubunun yaş ortalaması 11,87± 2,92, kontrol grubunun ise 11,63± 2.73'tür. *H. pylori* pozitif çocuklarda mikronükleer ve binükleer hücreler kontrol grubuna göre anlamlı derecede yüksek bulundu ($p<0.001$).

Sonuç: Mikronükleer ve binükleer hücreler, *H.pylori* patogenezinde genotoksik hasarın ve düzensiz sitoplazma bölünmesinin önemli olduğunu vurgulamıştır. Kullanılan yöntemin *H. pylori* ön tanısında kolay uygulanabilen, az maliyetli invaziv olmayan tanı yöntemi olma yönünde aday olabileceği düşünülmekle birlikte bu sonucun daha geniş örneklemle teyit edilmesine ihtiyaç bulunmaktadır.

Anahtar Sözcükler: Binükleer hücre, DNA hasarı, *Helicobacter pylori,* mikronükleus, PAP boyama

ABSTRACT

Aim: *Helicobacter pylori (H. pylori)* is a bacterial pathogen that causes gastroduodenal inflammation, ulcer and atrophic gastritis. Micronuclei (MNs) are formations that are not included in the main nucleus that emerge during the mitosis of the cell. In this study, it was aimed to evaluate the relationship between *H. pylori* and micronuclear and binuclear cells using exfoliative cytology method.

Material and Methods: In this study, patients who applied to the Pediatric Gastroenterology outpatient clinic of Zonguldak Bülent Ecevit University Practice and Research Hospital with severe dyspeptic complaints that would affect their quality of life and underwent endoscopic biopsy were included. Biopsy samples were fixed in formalin and sections prepared from paraffin blocks were stained with Hematoxylin & Eosin (H&E). It was evaluated light microscopically for the presence of *H. pylori.* Only *H. pylori* positive specimens as a result of biopsy were taken as the study group (n=30), and those with no infectious agents were taken as the control group (n=30). Buccal epithelial cells from all patients were spread on slides, fixed in 95% ethanol and stained according to the Papanicolaou technique. Micronuclear and binuclear cells were counted in 1000 well-stained epithelial cells. Statistical evaluation SPSS 18.0 (SPSS Inc., Chicago, IL, USA) program was used and $p<0.05$ was considered significant.

Results: The children in our study were between the ages of 7 and 15, and the mean age of the study group was 11.87±2.92, and the control group was 11.63±2.73. Micronuclear and binuclear cells were found to be significantly higher in *H. pylori* positive children compared to the control group ($p<0.001$).

Conclusion: Micronuclear and binuclear cells emphasized that genotoxic damage and irregular cytoplasm division are important in the pathogenesis of *H.pylori*. Although it is thought that the method used may be a candidate to be an easy-to-apply, low-cost non-invasive diagnostic method in the preliminary diagnosis of *H. pylori*, this result needs to be confirmed with a larger sample.

Keywords: Binuclear cell, DNA damage, *Helicobacter pylori,* mikronucleus, PAP technique

GİRİŞ

Helicobacter pylori (H. pylori), ilk defa 1983 yılında Marshall ve Warren tarafından tanımlanan gram negatif, spiral şekilli, hareketli, mikroaerofilik ve kamçılı bakteriyel bir patojendir (1). Organizma, düşük oksijen seviyesi, öğünler arasında uzun aralıklar, sıcaklık, pH değişiklikleri ve antibiyotik tedavisi gibi olumsuz çevre koşullarında bile hayatta kalabilmektedir. *H. pylori,* genellikle spiral şeklinde olmasına rağmen çubuk şeklinde de görülebilir. Ayrıca, uzun süreli in vitro kültür ve hatta antibiyotik tedavisi sırasında kokoid şekillerde de olabilir. Spiralden kokoid forma geçme yeteneği, aynı zamanda bu bakterinin konakçının gastrointestinal sisteminde hayatta kalmak için kullandığı önemli mekanizmalardan biri olup enfeksiyonun tedavisinde büyük zorluklara neden olabilmektedir (2). *H. pylorinin* neden olduğu enfeksiyon, dünyada en sık görülen enfeksiyonlardan biri olup dünya nüfusunun yarısından fazlasını etkilemektedir (3-5). Türkiye'den bildirilen çalışmalarda yetişkinlerin %70-80 inin çocukların ise % 30–56 sının bu bakteri ile enfekte olduğu bildirilmektedir (6). Patojen, çocukluk çağında alınmakla birlikte ağır klinik tablo genellikle yetişkinlik döneminde görülmektedir (7). *H. pylori* gastrik ve duodenal ülsere ve atrofik gastrite yol açmasının yanısıra uzun dönemde lenfoma ve adenokarsinoma da neden olmaktadır (3-5).

Helicobacter pylori tanısında kullanılan invaziv testler arasında endoskopik biyopsi ile alınan parçanın histopatolojik olarak incelenmesi, hızlı üreaz testi, kültürde üretilmesi, PCR uygulaması varken invaziv olmayan testler arasında ise üre nefes testi, gaitada antijen tayini ve serolojik ve moleküler testler yer almaktadır (8). *H. pylori,* gastrik epitelial hücre proliferasyonu ve DNA hasarında artış, inflamasyon, oksidatif stres, özellikle çift zincir kırıkları ve genomik kararsızlığa neden olmaktadır (9-13). Organizma bu hasarlara karşın DNA tamir mekanizmalarını devreye sokmaya çalışırken bu kez patojen bu tamir mekanizmasını da engellemeye çalışmaktadır. DNA hasarı neticesinde hücre çekirdeğinde önemli değişiklikler oluşmaktadır. Bu değişikliklerden biri de mikronükleusların (MN) oluşumudur. MN'lar, hücrenin mitoz bölünmesi sırasında serbest kalan kromozom fragmentinin ya da kromozomların bir zarla çevrilmesi ile oluşan ve ana nükleusun yanında yer alan yapılardır. MN'ler pek çok farklı yöntem ile gösterilebilmektedir (14-16). DNA hasarı pekçok moleküler yöntemle gösterilmekte ancak bu yöntemler oldukça pahalı ekipmanları gerektirmektedir (17). MN'lerin ışık mikroskobik olarak değerlendirildiği yöntemlerden biri de eksfolyatif sitoloji yöntemidir. Eksfolyatif sitoloji dökülen hücrelerin alınarak lamlar üzerine yayılması ve özel boyalarla boyanıp mikroskopik olarak incelenmesi esasına dayanmakta olup yanak ve dil epitel hücrelerine de uygulanabilmektedir (14-18).

Bu çalışmada, *H. pylori* ile DNA hasarının, sayısal ve yapısal kromozom düzensizliklerinin indirekt göstergesi olarak kabul edilen mikronükleer ve binükleer hücre sıklığının yanak epiteli hücrelerinde değerlendirilmesi amaçlanmıştır.

GEREÇ ve YÖNTEMLER

Bu çalışmada *H. pylori* ile hücrenin mitoz bölünmesi sırasında serbest kalan kromozom fragmentinin ya da kromozomların bir zarla çevrilmesi ile oluşan, ana nükleusun yanında yer alan ve DNA hasarının indirekt göstergelerinden biri olan mikronükleer hücreler arasındaki ilişki araştırıldı. Bu amaçla Zonguldak Bülent Ecevit Üniversitesi Uygulama ve Araştırma Hastanesi Çocuk Gastroenteroloji Polikliniğine yaşam kalitesini etkileyecek tarzda ciddi dispeptik yakınmalarla başvuran ve endoskopik biyopsi sonucu *H. pylori* pozitif ve negatif bulunan kişiler çalışma kapsamına alındı. Çalışmanın örneklem büyüklüğü Cohen'nin* tanımladığı "large effect size" a göre yapıldı (19). Hastaların yaşı, cinsiyeti ve başvuru yakınmaları kaydedildi, kronik enfeksiyonu olan ve sürekli ilaç kullandığı belirlenen hastalar çalışmaya alınmadı.

Bu çalışmanın etik kurul izni Helsinki Deklarasyonu çerçevesinde, Zonguldak Bülent Ecevit Üniversitesi Klinik Araştır-

malar Etik kurulundan 03.06.2010 tarih ve 2010/03-11 karar no ile alındı.

Histopatolojik değerlendirme

Üst GİS endoskopisi yapılarak alınan biyopsi örnekleri formalinde fikse edildi. Doku takibinde parafin bloklardan hazırlanan kesitler Hematoksilen & Eozin (H&E) ile boyandı. *H. pylori* varlığı açısından ışık mikroskobik olarak değerlendirildi (Olympus BX 51). *H. pylori* yoğunluğu ise Sydney sınıflamasına göre yok (0), hafif (+1), orta (+2), şiddetli (+3) olarak gruplandı. Biyopsi değerlendirilmesinde ve yanak epitel hücre yaymasında *H. pylori* ile birlikte farklı bir enfeksiyon etkeni saptanan bireyler de çalışma kapsamına alınmadı.

Sitolojik Değerlendirme

Çalışma kapsamında yer alan tüm bireylerden sitolojik değerlendirme için ise yanak epiteli döküntü hücreleri alınıp, lamlara yayıldı ve %95'lik etil alkolde fikse edildi. Hazırlanan yaymalar Papanicolaou (PAP) boyama yöntemine göre boyanıp ışık mikroskobik (Olympus BX 51) olarak nükleer değişiklikler açısından değerlendirildi. İyi boyanmış 1000 epitel hücrede mikronükleer hücreler yine aynı mikroskopta sayıldı. MN tanımlamasında; MN çapı ana nükleusun 1/3'ü kadar ya da daha küçük olmalı, ana nükleus ile aynı yoğunluğa ve boyanma kalitesine sahip olmalı, ana nükleusun yakınında ya da aralarındaki sınır belirli olmak kaydı ile teğet olmalı kriterleri kullanıldı (20). Aynı yaymalar İyi boyanmış 1000 epitel hücrede binükleer hücre varlığı açısından da değerlendirildi.

İstatistiksel Analiz

İstatistiksel değerlendirme SPSS 18.0 (SPSS Inc., Chicago, IL, USA) programı kullanılarak yapıldı. Sayısal değişkenlerin normal dağılıma uygunlukları Shapiro-Wilks testi ile incelendi. Sayısal değişkenler için tanımlayıcı istatistikler ortalama±standart sapma ve ortanca (minimum-maksimum) olarak ifade edildi. Sayısal değişkenler bakımından iki grubun karşılaştırılmasında Mann-Whitney U testi kullanıldı. Sonuçlar % 95 güven aralığında değerlendirildi ve $p<0.05$ değeri anlamlı kabul edildi.

BULGULAR

Çalışma kapsamındaki hastaların yaşları 7-15 arasındadır. *H. pylori* pozitif (Ort. ± SS = 11,87 ± 2,92) ve negatif (Ort.± SS=11,63± 2.73) hastalarda kız, erkek oranı aynıdır (16 kız, 14 erkek). H. pylori pozitif hastalarda karın ağrısı şikayeti %93,3 oranı ile ön plandadır. Hastaların %60'unun (n=18) bulantı, %40'unun (n=12) kusma, %36,6'ünün (n=11) pyrosis ve %43,3'ünün (n=13) regurjitasyon yakınmaları ile kliniğe başvurmuştur.

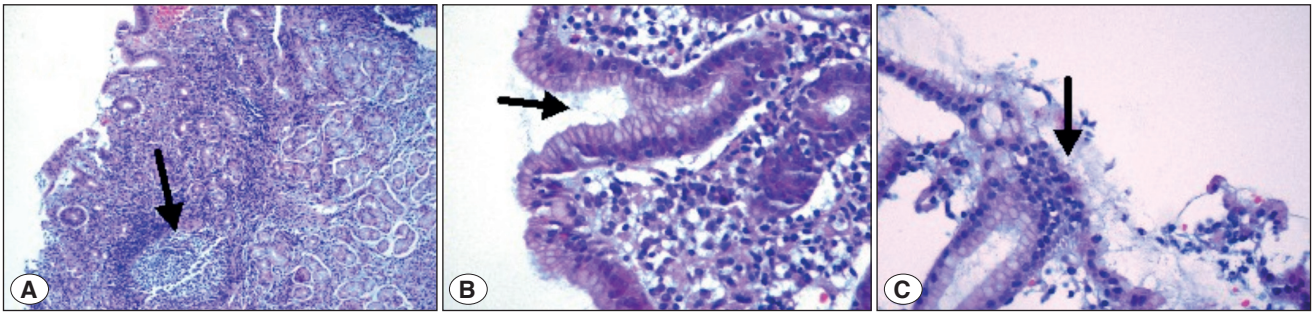
Endoskopik biyopsi örneklerinde *H. pylori* varlığı ve yoğunluğu Sydney sınıflamasına göre yapılmış olup preparatların değerlendirilmesi ışık mikroskobik olarak yapılmıştır. Şekil 1' de kriptlerde ve yüzeyel mukus içerisinde yoğun basil morfolojisinde *H. pylori* ile uyumlu mikroorganizmalar ve yoğun miks tipli iltihabi hücre infiltrasyonu izlenmektedir. Yer yer bazı alanlarda müsin kaybı görülmektedir (Şekil 1).

Şekil 2 de *H. pylori* pozitif hastalardan alınan yanak epiteli örneklerinde normal epitel hücreler, binükleer hücreler ve Tolbert kriterlerine göre değerlendirilmiş mikronükleer hücreler sunulmuştur. Bazı yaymalarda epitel hücrelerinde tek mikronükleus görülürken bazı yaymalarda ise üç adet mikronükleus görülmüştür.

İstatistiksel değerlendirme sonucunda *H. pylori* ile enfekte çocuklarda mikronükleer ve binükleer hücrelerin ortalaması (median, min-max) kontrol grubuna göre anlamlı derecede yüksek bulundu ($p<0.001$) (Şekil 3,4).

TARTIŞMA

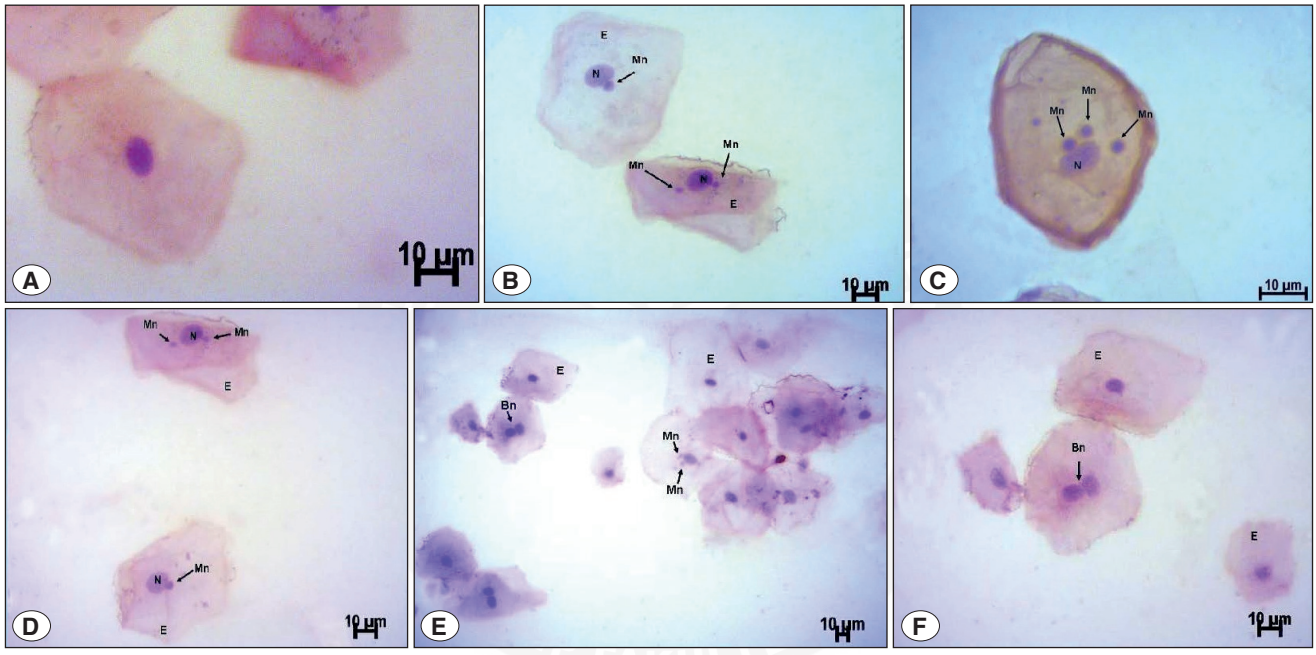
Helicobacter pylori, karsinojen olduğu saptanan ilk bakteri olup dünya nüfusunun yarıdan fazlasında bulunmaktadır. Epidemiyolojik olarak, gelişmekte olan ülke popülasyonunun %85-95'inde, gelişmiş ülkelerin ise yaklaşık %30-50'sinde



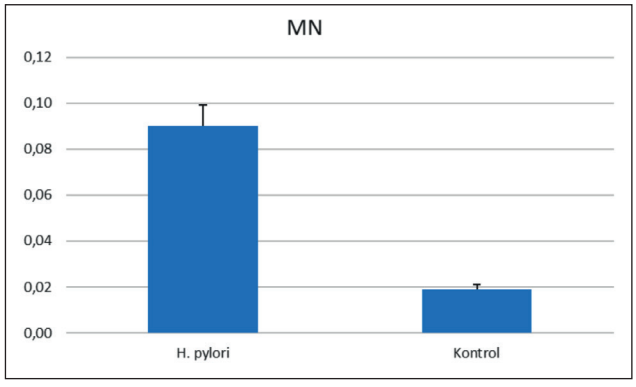
Şekil 1: A) Gastrik biyopsi örneğinde lamina propriada lenfoid agregat oluşturan yoğun miks tipli iltihabi hücre infiltrasyonu (→) izlenmektedir (Hemotoksilen-Eosin, x 200) **B)** Kriptlerde yüzeyel mukus içerisinde *H. pylori* ile uyumlu mikroorganizmalar (→) dikkati çekmektedir. Lamina propriada lenfositler, plazma hücreleri eosinofil ve nötrofil lökositlerden oluşan kronik aktif inflamasyon görülmektedir (Hemotoksilen-Eosin, x 400) **C)** Yüzeyel mukus içerisinde yoğun basil morfolojisinde *H. pylori* uyumlu mikroorganizmalar (→) ve yüzey epitelinde müsin kaybı izlenmektedir (Hemotoksilen-Eosin, x 630).

H. pylori enfeksiyonu vardır (2). Esas olarak midede yerleşmesine rağmen ağız boşluğu da bu bakteri için iyi bir rezervuardır (21). *H. pylori*, midenin epitel hücrelerine doğru hareket etmek ve mukus astarına nüfuz etmek için kamçısını kullanır. Konak epitel hücrelerine bağlanması adezinler vasıtası ile olur (2). Kronik gastrit, peptik ülsere neden olan *H. pylori*'nin fekal-oral ve oral-oral yolla bulaştığı gösterilmiştir (11,22). Kötü hijyen, beslenme ve coğrafi belirleyicilerdeki farklılıklar enfeksiyonda rol oynayan faktörlerdendir (2). Gastrik kanserler dünya genelinde kanser nedenli ölümler içerisinde ikinci sırada yer almaktadır. Ülkemizde kadınlarda görülen en sık 4. kanser tipi, erkeklerde ise en sık 5. kanser tipi olarak bildirilmiştir (11).

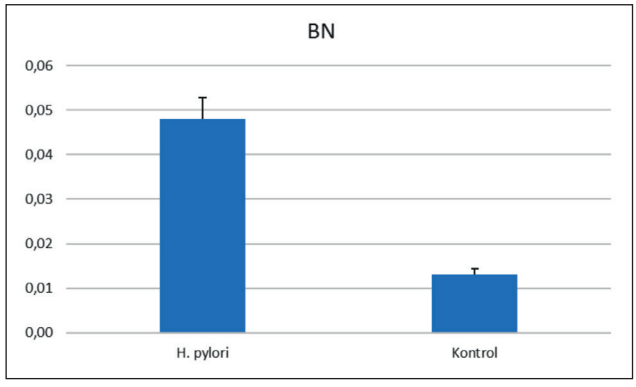
Konakçı genetik faktörleri ve genetik geçmiş, bakterinin enfeksiyondan gastrik kanser oluşumuna kadar olan süreci ni önemli ölçüde etkilemektedir. Özellikle bakterinin konakçı tarafından alınımında etkili olan reseptör genler üzerindeki tek nükleotid gen polimorfizmleri enfeksiyon ve karsinogenez arasındaki ince çizgide rol oynamaktadır. Bu genler aynı zamanda inflamatuar sinyale, oluşuma ve otofajiye yol açan hücresel yolakları da etkilemektedir (12,23). *H. pylori*'nin neden olduğu karsinojenezde bakteriyel virülans faktörleri, kronik inflamasyonun yol açtığı oksijen radikalleri ve oksidatif stres, konakçıya bağlı intrinsik ve ekstrinsik faktörlerin bir bütün olarak tetiklediği epigenetik ve genetik mekanizmalar rol oynamaktadır (9-13). DNA hasarı, MN



Şekil 2: Helicobacter pylori pozitif hastalardan alınan bukkal örneklerde **A)** normal epitel hücreler **B)** nükleus (N) ve mikronükleus (Mn, (→) içeren yanak epitel hücreleri (E) **C)** nükleus (N) ve üç adet mikronükleus (MN, →) içeren yanak epitel hücresi (E) **D)** mikronükleus (Mn) içeren epitel hücreleri (E) **E)** mikronükleus (MN, →) ve binükleus (BN, →) içeren epitel hücreleri F. binükleus içeren epitel hücresi (BN, →) (PAP x 40).



Şekil 3: *Helicobacter pylori* pozitif ve negatif grupta mikronükleer hücre oranı.



Şekil 4: *Helicobacter pylori* pozitif ve negatif grupta Binükleer hücre oranı.

oluşumunun temelini oluşturur. MN'ler periferal kan lenfositlerinde incelenebildiği gibi yanak epitel hücrelerinde de incelenebilmektedir (24,25). Bu yöntemde memeli hücreleri mikroskopik olarak değerlendirilmekte, ana nükleusa yakın ancak daha küçük olan nükleer yapılar incelenmektedir. MN testi, sigara, pestisid, radyasyon, parazitik enfeksiyonlar ile çevresel ve mesleki etkileri değerlendirebilmek için de kullanılmaktadır (24-26). Çeşitli hastalıklarda MN oluşumu ve sıklığı son dönemde önemle üzerinde durulan konular arasında yer almaktadır. Suárez ve ark.nın *H. pylori* ile enfekte hastaların periferal kan lenfositlerinde yaptıkları çalışmada mikronükleus sıklığı artış göstermiştir. Bulgularımız Suárez ve ark.nın bulguları ile uyum içindedir (24). Çalışmamızda, örnek alımı esnasında çocuklarda herhangi bir rahatsızlık ve acıya neden olmayan, maliyeti oldukça düşük ve non-invaziv bir yöntem olan eksfolyatif sitoloji yöntemi kullanılmış ve mikronükleus sıklığı yanak epitel hücrelerinde değerlendirilmiştir. *H. pylori* pozitif hastaların yanak epitel hücrelerinde gördüğümüz ve istatistiksel olarak da anlamlı bulunan bir diğer değişiklik ise binükleer hücrelerdir. Binükleer hücreler, birbirinin hemen hemen aynı büyüklükte ve yoğunlukta iki ana nükleus içerir. Bu hücrelerin oluşum mekanizması tam olarak aydınlatılmamakla birlikte, hücre bölünmesi esnasında nükleus bölünmesini takiben sitoplazma bölünmesinin gerçekleşmemesinden kaynaklandığı düşünülmektedir. Sitoplazma bölünmesinin olmamasının ve kontraktil halka oluşmamasının, hücre iskeleti elemanlarından aktin filamentlerdeki hasardan kaynaklandığı düşünülmekte olup *H. pylori* ve hücre iskeleti hasarına ilişkin hücresel düzeyde çalışmalara ihtiyaç bulunmaktadır (26). Sonuç olarak, *Helicobacter pylori,* yanak epitel hücrelerinde mikronükleus insidansını artırmıştır. Bu patojen tarafından oluşturulan DNA hasarı, sayısal ve yapısal kromozom düzensizliklerinin indirekt göstergesi olarak kabul edilen mikronükleus testi ile incelenebilir. Eksfolyatif sitoloji, bu bakteri tarafından oluşturulan nükleer değişikliklerin yanak epitel hücrelerinde incelenmesine olanak verir. Kolay uygulanabilen ve invaziv olmayan bu değerlendirmede, mikronükleer ve binükleer hücrelerin varlığı, *H. pylori* patogenezinde genotoksik hasarın ve düzensiz sitoplazma bölünmesinin önemli önemli olduğunu vurgulamıştır. Bu konunun açıklığa kavuşmasının *H. pylori* ve gastrik karsinogenez arasındaki ilişkinin açıklanmasına da önemli katkılar sağlayacağı düşünülmektedir.

Teşekkür

Yok.

Yazar Katkı Beyanı

Makalenin planlanması, literatür taraması yanak içi epitel hücrelerinin preparasyonu ve ışık mikroskobik değerlendirilmesi, makalenin yazımı ve son gözden geçirme: **Zehra Safi Öz,** Hastaların klinik muayenesi, endoskobik değerlendirme ve biyopsi materyalinin alımı, makalenin yazımı: **Gonca Handan Üstündağ,** Hastaların klinik muayenesi ve bilgilerin toplanması: **Halime Topuz,** Biyopsi örneklerinin değerlendirimesi: **Nilüfer Onak Kandemir.**

Çıkar Çatışması

Yazarlar aralarında herhangi bir çıkar çatışması bulunmamaktadır.

Finansal Destek

Çalışma sırasında herhangi bir kurumdan finansal destek alınmamıştır.

Etik Kurul Onayı

Zonguldak Bülent Ecevit Üniversitesi Klinik Araştırmalar Etik kurulundan etik onay alınmıştır (03.06.2010 tarih, 2010/03-11 Karar No).

Hakemlik Süreci

Kör hakemlik süreci sonrası yayınlanmaya uygun bulunmuş ve kabul edilmiştir.

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ÖZGÜN ARAŞTIRMA

Batı Karadeniz Tıp Dergisi
Medical Journal of Western Black Sea

Med J West Black Sea 2023;7(1): 51-56
DOI: 10.29058/mjwbs.1143866

Tıp Fakültesi Öğrencilerinde COVID-19 Korkusu ve Sigara Kullanımını Etkileyen Faktörlerin Değerlendirilmesi

Evaluation of the Factors Affecting the Smoking Habit and Fear of COVID-19 Among Faculty of Medicine Students

Ayşegül Tomruk ERDEM[1], Farice Beyza DEMİREL[2], Semih EROL[2], Enes KARATAŞ[2], Sinem EDİNÇ[2], Zeynep AŞIK[2], İlayda BAŞOĞLU[2], Zeynep KURU[2], Veli Mert BÜYÜKDUMLU[2], Ece TUNA[2], Kadriye TABAK[2], Ayşe Beril ALAY[2], Ahmet Hazar BÜYÜKAKPINAR[2], Kübra ÖZAYDIN[2]

[1]Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Zonguldak, Türkiye
[2]Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi, 2020-2021 Eğitim Yılı Dönem 3 Öğrencileri, Zonguldak, Türkiye

ORCID ID: Ayşegül Tomruk Erdem 0000-0002-5346-9107, Farice Beyza Demirel 0000-0001-6572-7372, Semih Erol 0000-0002-1091-9681, Enes Karataş 0000-0001-5426-1677, Sinem Edinç 0000-0003-1152-7118, Zeynep Aşık 0000-0001-6102-8953, İlayda Başoğlu 0000-0002-0981-8736, Zeynep Kuru 0000-0001-6646-1545, Veli Mert Büyükdumlu 0000-0002-4114-1083, Ece Tuna 0000-0001-5921-1767, Kadriye Tabak 0000-0003-4137-0019, Ayşe Beril Alay 0000-0001-6523-0964, Ahmet Hazar Büyükakpınar 0000-0003-4743-0852, Kübra Özaydın 0000-0002-3078-274X

Bu makaleye yapılacak atıf: Tomruk Erdem A ve ark. Tıp fakültesi öğrencilerinde COVID-19 korkusu ve sigara kullanımını etkileyen faktörlerin değerlendirilmesi. Med J West Black Sea. 2023;7(1):51-56.

Sorumlu Yazar
Ayşegül Tomruk Erdem

E-posta
aysegultomruk@yahoo.com

Geliş Tarihi
18.07.2022

Revizyon Tarihi
01.02.2023

Kabul Tarihi
15.02.2023

ÖZ

Amaç: Çalışmada amacımız COVID-19 pandemisi sırasında tıp fakültesinde öğrenim gören öğrencilerde sigara tüketimini etkileyen faktörleri ve bunun COVID-19 korkusu ile ilişkisini belirlemektir.

Gereç ve Yöntemler: Çalışma kesitsel ve tanımlayıcı tipte dizayn edilmiş olup, çalışmaya Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesinde öğrenim gören 293 öğrenci katıldı. Öğrencilere hazırlanan anketler elektronik ortamda iletildi, çalışmaya gönüllü olanlar katıldı. Anket formunda öğrencilerin sosyodemografik özellikleri, sigara alışkanlıkları sorgulandı, Fagerström nikotin bağımlılık testi ve COVID-19 Korku Ölçeği kullanıldı.

Bulgular: Çalışmaya dahil olan öğrencilerin %70.6'sı kadın idi. Yaş ortalaması 21.38±04 saptandı. Halen sigara içen katılımcı oranı %17.7 (n=52) idi. Daha önce hiç sigara içmemiş katılımcıların %7.1'inin (n=15) pandemi sırasında sigaraya başlamayı düşündüğü öğrenildi. Sigarayı bırakmış katılımcıların %64.5'i (n=20) pandemi sırasında bu kararı almıştı. Sigarayı bırakanların %54.5'i (n=12) mevcut sağlık sorunları ve hastalanma kaygısı nedeniyle sigara içmeyi bırakmış ve %74.2'si (n=23) tekrar sigara içmeyi düşünmemekteydi. Sigara içmeye devam eden ve düşük bağımlılık düzeyine sahip katılımcı oranı %69.2 (n=36) idi. Pandemi sırasında sigara içen katılımcıların %38.4'ünde (n=20) tüketim miktarında değişiklik olmazken, %34.6'sında (n=18) tüketimde azalma, %27'sinde (n=14) ise tüketimde artış olduğu görüldü. Sigara tüketiminin değişmesinde haberlerin, kamu spotlarının, sigara yasağının rol almadığı belirlendi. Sigara içen ve COVID-19 hastalığı geçirenlerin de sigara ile ilgili fikirlerinde değişiklik olmadığı belirlendi. Katılımcıların COVID-19 korku puanı ortalaması 18.71± 4.91 olup, korku düzeyi orta seviyede olarak belirlendi. COVID-19 korku düzeyi kadın katılımcılarda erkek katılımcılara göre istatistiksel olarak anlamlı düzeyde yüksekti (p=0.001). COVID-19 korku düzeyinin sigara kullanım özellikleri ve diğer sosyodemografik özellikler ile arasında istatistiksel anlamlı fark bulunmadı (p>0.05).

Sonuç: Katılımcılarda COVID-19 korku düzeyi orta seviyede saptanmış olup, kadın katılımcılarda daha yüksekti. Sigarayı bırakmış olan öğrencilerin çoğunluğu pandemi sırasında bu kararı vermişti. Haberlerin, kamu spotlarının, sigara yasağının, COVID-19 geçirmenin sigara içen katılımcılarda tüketimde değişikliğe yol açmadığı belirlendi.

Anahtar Sözcükler: COVID-19, Korku, Sigara kullanımı, Öğrenci

ABSTRACT

Aim: Our aim in the study is to determine the factors affecting cigarette consumption in medical school students during the COVID-19 pandemic and its relationship with the fear of COVID-19.

Material and Methods: The study was designed as cross-sectional and descriptive, and 293 students studying at Zonguldak Bülent Ecevit University Faculty of Medicine participated in the study. Questionnaires prepared for the students were delivered electronically, and those who volunteered participated in the study. In the questionnaire, students' sociodemographic characteristics, smoking habits were questioned, Fagerström nicotine addiction test and COVID-19 Fear Scale were used.

Results: 70.6% of the students included in the study were women. The mean age was 21.38±04 years. The rate of current smokers was 17.7% (n=52). It was learned that 7.1% (n=15) of the participants who had never smoked before thought to start smoking during the pandemic. 64.5% (n=20) of the participants who had quit smoking made this decision during the pandemic. Of those who quit smoking, 54.5% (n=12) quit smoking due to existing health problems and anxiety about getting sick, and 74.2% (n=23) were not considering smoking again. The rate of participants who continued to smoke and had low addiction level was 69.2% (n=36). While there was no change in the amount of consumption in 38.4% (n=20) of the participants who smoked during the pandemic, it was observed that there was a decrease in consumption in 34.6% (n=18) and an increase in consumption in 27% (n=14). It was determined that the news, public service announcements and smoking ban did not play a role in the change in cigarette consumption. It was determined that smokers and those who had COVID-19 disease did not change their ideas about smoking. The mean COVID-19 fear score of the participants was 18.71±4.91 and the fear level was determined as moderate. The level of fear of COVID-19 was statistically significantly higher in female participants than in male participants (p=0.001). There was no statistically significant difference between the COVID-19 fear level and smoking characteristics and other sociodemographic characteristics (p>0.05).

Conclusion: The level of fear of COVID-19 was found to be moderate in the participants, and it was higher in female participants. The majority of students who had quit smoking made this decision during the pandemic. It has been determined that news, public service announcements, smoking ban, and having COVID-19 do not cause any change in consumption among smokers.

Keywords: COVID-19, Fear, Student, Smoking

GİRİŞ

Dünya Sağlık Örgütü (DSÖ) 30 Ocak 2020'de koronovirüs hastalığı (COVID-19) salgınını uluslararası boyutta halk sağlığı acil durumu olarak ilan etti. 11 Mart 2020'de DSÖ Genel Direktörü, COVID-19'u bir pandemi olarak nitelendirdi (1). Ülkemizde ilk COVID-19 vakası görülmesi sonrasında alınan kararlarla üniversitelerde eğitime ara verilmesi ve daha sonra uzaktan eğitime geçilmesi ile birlikte öğrenciler için yeni bir süreç başladı.

COVID-19'a özgü endişelerin, sosyal ortamlardan izolasyonun, etkileşim ve duygusal destek eksikliğinin ve fiziksel izolasyonun öğrenciler arasında olumsuz ruh sağlığı ile ilişkili olduğu bildirildi (2).

COVID-19 salgını sırasındaki erken bulgular, ergenlerde daha yüksek depresyon, anksiyete ve stres seviyeleri ile ilişkili olarak sigara ve alkol alımında negatif değişiklikler olduğunu göstermektedir (3).

Tıp fakültesi öğrencileri öz bakımlarını, hastaların katılımını, öz yönetim yeteneklerini güçlendirmek için kapsamlı kapasitelere ihtiyaç duyan geleceğin sağlık hizmeti sağlayıcılarıdır (4, 5). Dünyada tıp fakültesi öğrencilerinin ruh sağlığı sorunları pandemi öncesinde de mevcutken (6) , COVID-19 salgını ile klinik uygulama dersleri alan öğrenciler enfeksiyon riski ile de karşı karşıya kaldı.

COVID-19 korkusu, intihara neden olabilecek boyutta görülebilir (7). COVID-19 yayılımını hafifletmek ve olumsuz ruh sağlığı sonuçlarını azaltmak için olumsuz psikolojik sorunlar (örneğin korku) tespit edilmesi esastır ve uygun müdahaleleri erken bir aşamada uygulamak gereklidir (8, 9).

Bu çalışmada, tıp fakültesi öğrencilerinde sigara içme alışkanlığını sorgulamak, COVID-19 korkusunu belirlemek ve COVID-19 pandemisi süresince sigara içme konusunda tutum ve davranışlarını değerlendirmek, pandeminin ve bu süreçte meydana gelen sosyal yaşam değişikliklerinin sigara içme alışkanlığına etkisi olup olmadığını araştırmak amaçlandı.

GEREÇ ve YÖNTEMLER

Tanımlayıcı ve kesitsel tipteki bu çalışmanın evrenini halen eğitimine devam etmekte olan Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi öğrencileri oluşturdu. Tüm öğrencilere, 15 Mart 2021 – 15 Nisan 2021 tarihleri arasında katılabilecekleri anketin linki elektronik ortamda ulaştırıldı. Katılımcıların anket öncesi bilgilendirilmiş sözlü onamları alınarak anketi yanıtlamayı kabul eden öğrenciler çalışmaya alındı. Çalışmaya 293 öğrenci katıldı Zonguldak Bülent Ecevit Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurul Başkanlığı'ndan10/03/2021 Tarih ve 2021/05 sayılı toplantı ile etik onay alındı.

Anketin ilk bölümünde yaş, cinsiyet, medeni durum, gelir durumu, çalışma durumu, anne babanın eğitim durumu, evde yaşadığı kişi sayısı gibi sosyodemografik özelliklerin ve devam ettiği sınıf, kronik hastalığı olup olmadığı, sigara içme durumu ile ilgili sorular yer aldı. Katılımcılar sigara içme durumuna göre ayrılarak, sigara içmeyenler, içmeyi bırakanlar ve halen sigara içenler olarak ayrı bölümler-

de sorular yöneltildi. Diğer bir bölümde ise kendilerinin ya da ailelerinden bir kişinin COVID-19 geçirip geçirmediği, COVID-19 ve sigara kullanımı ile ilgili görüşlerinin yer aldığı sorular yer aldı.

Sigara içen katılımcıların Fagerström Nikotin Bağımlılık Testi (FNBT) ile nikotin bağımlılık düzeyi ölçüldü ve diğer faktörlerle ilişkisi araştırıldı. Fagerström ve ark. tarafından geliştirilen bu testte 6 soru yer almakta ve cevaplara göre puanlanmaktadır. FNBT'nin Türkçe geçerlilik ve güvenilirlik çalışması Uysal ve ark. tarafından "Fagerstrom nikotin bağımlılık testinin Türkçe versiyonunun güvenirliği ve faktör analizi" adı ile yayınlanmıştır. Minimum ve maksimum skoru sırasıyla 0 ve 10'dur. Yüksek skor yüksek bağımlılık ile ilişkilidir. Bağımlılık düzeyi çok düşük (0-2), düşük (3-4) , orta (5-6), yüksek (7-8) çok yüksek (9-10) olarak sınıflanmaktadır (10).

COVID-19 korkusu ölçeği ile katılımcıların korku düzeyi ölçülerek diğer faktörlerle ilişkisi araştırılmıştır. Bireylerin COVID-19 kaynaklı korku düzeylerinin ölçülmesi için Ahorsu ve ark. (2020) tarafından geliştirilmiştir. Ölçek tek faktörlü yapıdadır ve beşli Likert tipinde (1 = Kesinlikle katılmıyorum; 5 = Kesinlikle katılıyorum) yedi maddeden oluşmaktadır. COVID-19 Korkusu Ölçeği'nin Türkçe Güvenirlik Ve Geçerlik Çalışması Ladikli ve ark. tarafından yapılmıştır (11).

Araştırmada elde edilen verilerin istatistiksel analizi için SPSS programı (IBM Corp. Released 2011. IBM SPSS Statics for Windows Version 20.0. Armonk, NY: IBM Corp) kullanılmıştır. Verilerin normal dağılıma uygunluğu Kolmogorov Smirnov Testi ile analiz edildi. Normal dağılıma uyduğu için, tanımlayıcı istatistikler için sayı, ortalama ve yüzdelik, nicel verilerin analizi için T testi ve One way ANOVA testleri kullanıldı. Güven aralığı %95, $p < 0.05$ anlamlı kabul edilmiştir.

BULGULAR

Çalışmaya 293 tıp fakültesi öğrencisi katıldı. İnternet üzerinden ulaşılan anket sonuçlarına göre katılımcıların temel özellikleri Tablo 1'de verilmiştir.

Hiç sigara içmemiş katılımcılara pandemi döneminde sigaraya başlama düşüncesi olup olmadığı sorulduğunda sadece 15 (% 7.1) katılımcıdan evet cevabı alındı.

Sadece 5 öğrencinin pandemi döneminde sigara içmeye başladığı öğrenildi.

Sigarayı bırakmış olan 31 katılımcının 20'sinin (%64.5) sigarayı son 1 yıl içinde bıraktığı öğrenildi. Bu kişilerin 12'si (%54.5) sigarayı hastalanma kaygısı ve mevcut hastalıkları nedeni ile bıraktığını ve sigarayı bırakan kişilerin %74.2'si pandemi bitince sigaraya tekrar başlamak istemediklerini belirttiği görüldü.

Halen sigara içen katılımcıların sigara içme durumları ve özellikleri Tablo 2'de belirtilmiştir.

Öğrencilerin %15,7 'si (n=46) COVID-19 enfeksiyonu geçirdiğini belirtti. Ailesinde COVID-19 enfeksiyonu geçiren kişilerin oranı ise %65.6 (n=192) saptandı. 12 katılımcının ailesinde COVID-19 kaynaklı ölüm gerçekleştiği öğrenildi. Öğrencilerin %84.3'ü (n=247) sigaranın COVID-19 hastalığını ağır geçirmeye ve ölüme sebep olabileceğini düşündüğünü belirtti.

COVID-19 geçiren 46 katılımcıdan 15'i sigara içmekteydi.15 katılımcının 1'i sigarayı bırakmış, 1'i bırakmayı düşünüyor, 1'i miktarını artırmış, 12'sinde ise içilen sigara miktarında değişiklik olmadığı öğrenildi.

Öğrencilerin sosyodemografik ve bazı özelliklere göre COVID-19 Korku Ölçeği Puan Ortalamalarının Dağılı-

Tablo 1: Katılımcıların Temel Özellikleri

Katılımcıların Temel Özellikleri	n (%)
Yaş , mean , yıl	21,38 (17-31)
Cinsiyet	
Kadın	207 (70,6)
Erkek	86 (29,4)
Medeni durum	
Bekâr	291 (99,3)
Evli	2 (0,7)
Gelir durumu	
Gelir giderden az	48 (16,4)
Gelir gidere eşit	136 (46,4)
Gelir giderden fazla	109 (37,2)
Beraber yaşadığı kişi sayısı	
1	25 (8,5)
2	9 (3,0)
3 ve üstü	259 (88,3)
Çalışma durumu	
Çalışmıyor	284 (96,9)
Çalışıyor	9 (3,1)
Devam ettiği sınıf	
1	47 (16,0)
2	75 (25,6)
3	88 (30,0)
4	41 (14,1)
5	30 (10,2)
6	12 (4,1)
Kronik hastalık durumu	
Var	31 (10,6)
Yok	262 (89,4)
Sigara içme durumu	
Hiç içmemiş	210 (71,7)
Halen içen	52 (17,7)
Bırakmış	31 (10,6)
COVID-19 geçirdi mi?	
Evet	46 (15,7)
Hayır	247 (84,3)
COVID-19 Korku Ölçeği puanı ort.	18,71± 4,91

mı Tablo 3'te verilmiştir. COVID-19 Korku Ölçeği Puanı açısından cinsiyetler arasında anlamlı fark bulunmuştur (p=0.000). Kız öğrencilerin puanı istatistiksel olarak erkek öğrencilerden anlamlı derece yüksektir (Şekil 1). Maddi durum, çalışma durumu, kronik hastalık varlığı, sigara içme durumu, COVID-19 geçirme durumu ve yaş açısından ise COVID-19 Korku Ölçeği Puanları arasında anlamlı bir fark saptanmamıştır (p>0.05).

TARTIŞMA

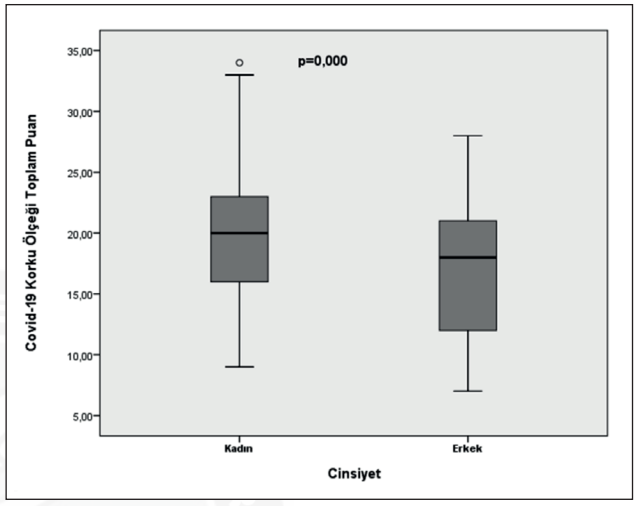
COVID-19 pandemisi sigara içme üzerinde çeşitli şekilde etki gösterdi. Bazı insanlar sokağa çıkma yasağını sigarayı bırakmak için bir fırsat olarak görürken, diğerleri stres ve duygularla başa çıkmak için sigaraya güvendi (12).

İngiltere'de yapılan bir araştırma, COVID-19 pandemisi sırasında sigara içme veya tekrarlayan sigara içme yoğunluğunda yaklaşık %9'luk bir artış olduğunu ortaya koydu. Bununla birlikte, bu, psikolojik bozuklukların artan semptomları, uyku bozukluğu, aşırı kilo ve uzun süreli karantinanın neden olduğu düşük yaşam kalitesi ile ilişkiliydi. (13, 14)

Yapılan bazı çalışmalarda genel popülasyonda COVID-19 pandemisi sırasında sigara içimi artarken (15, 16), öğrenci-

Tablo 2: Halen Sigara İçen Katılımcıların Sigara İçme Durumları ve Özellikleri

Sigara içen katılımcıların özellikleri	Sayı (%)
Fagerstörm Nikotin Bağımlılık Düzeyi	
Düşük	36 (69,2)
Orta /yüksek	16 (30,8)
Sigara bırakma girişimi oldu mu? (Pandemi Döneminde)	
Evet	18 (34,6)
Hayır	34 (65,4)
Sigara miktarında değişiklik oldu mu? (Pandemi Döneminde)	
Olmadı	20 (38,4)
Azaldı	18 (34,6)
Arttı	14 (27,0)
Koronavirüs önlemleri kapsamında getirilen sigara içme yasağı sigara tüketiminizin azalmasına katkıda bulundu mu?	
Evet	5 (9,6)
Değişiklik olmadı	47 (90,4)
Pandemi döneminde evde çok sık vakit geçirmek sigara tüketiminizi nasıl etkiledi?	
Artmasına neden oldu	17 (32,6)
Herhangi bir etkisi olmadı	15 (28,8)
Azalmasına neden oldu	20 (38,4)
Sigara tüketimi ve koronavirüs hastalığı arasındaki bağlantıyı anlatan kamu spotları, haberler sigara tüketiminizde olumlu değişikler oluşturdu mu?	
Evet	8 (15,4)
Hayır, hiçbir değişiklik olmadı.	44 (84,6)
COVID-19 enfeksiyonu geçirdi iseniz bu sizin sigara ile ilgili görüşlerinizi nasıl etkiledi?	
Sigarayı bırakmayı düşünüyorum	1 (10,0)
İçtiğim sigara miktarı arttı	1 (10,0)
Değişiklik olmadı	8 (80,0)



Şekil 1: Cinsiyete göre COVID-19 Korku Ölçeği Puan Ortalamalarının Dağılımı

Tablo 3: Sosyodemografik ve Bazı Özelliklere Göre Covid 19 Korku Ölçeği Puan Ortalamalarının Dağılımı

Sosyodemografik Özellikler	Covid-19 Korku Ölçeği Puan Ortalaması	p
Cinsiyet		
Kadın	19,56 ± 4,60	**0,000***
Erkek	16,61± 5,05	
Maddi durum		
Gelir giderden az	18,65 ± 3,45	0,83
Gelir gidere eşit	18,20 ± 1,72	
Gelir giderden fazla	18,05 ± 4,96	
Çalışma durumu		
Çalışmıyor	17,75 ± 4,81	0,57
Çalışıyor	17,06±3,66	
Kronik hastalık durumu		
Var	18,01 ± 4,81	0,72
Yok	18,23±,2,10	
Sigara içme durumu		
Hiç içmemiş	17,62 ± 3,05	0,66
Halen içen	17,83±4,55	
Bırakmış	17,71±3,25	
COVID-19 geçirdi mi?		
Evet	18,74 ± 6,81	0,48
Hayır	18,29±4,97	
Yaş	r:0,014	0,54

*p:0.001

lerde azaldığı belirtilmiştir (15). Alman öğrenciler arasında COVID-19 döneminde sağlıksız davranışlar (sigara içimi, alkol kullanımı) önemli ölçüde azaldı (17).

Bizim çalışmamızda sigarayı bırakan öğrencilerin %64.5 inin pandemi döneminde sigarayı bıraktığı tespit edildi. Sigaraya pandemi döneminde başlayan kişi sayısı ise sadece 5 idi. Sigara içen katılımcıların içtiği sigara miktarı %34.6 oranında azaldı. İçilen sigara miktarının azalmasında evde vakit geçirmenin daha büyük oranda etkisi olduğunu düşünmekteyiz. Öğrencilerin daha çok arkadaş etkisi ve bulunduğu sosyal ortamlarda sigara içimini artırdığı bilinmektedir. Nitekim çalışmamızda sigara ile ilgili yapılan kamu spotları, haberlerin, ya da sigara yasaklarının sigara içen katılımcılarda içilen sigara miktarına etkisi olmadığı görüldü. Bunun yanında COVID-19 enfeksiyonu geçiren ve sigara içen katılımcıların %80'inin sigara ile görüşlerinde değişiklik olmadığı belirlendi.

Katılımcılarda orta düzeyde korku saptandı. Çalışmamızda üniversite öğrencileri ile yapılan diğer bir çalışmada (18) olduğu gibi kadın öğrencilerde COVID-19 korku düzeyi erkek öğrencilere göre daha yüksek bulundu.

Kadınlar genellikle erkeklere göre daha stresli yaşam olaylarından yakınmaktadırlar (19,20) ve ayrıca pandemi döneminde kadınların ev işlerindeki rolü ve aile içindeki rolünün daha fazla olmasından kaynaklanabileceğini düşündürmektedir (21).

Yapılan çalışmada (18) COVID-19 korkusu yüksek olanlarda sigara içme oranı yüksek saptanmışken bizim çalışmamızda istatistiksel anlamlı bir sonuç bulunamadı.

Nguyen ve ark. (18) sigara kullanımı ve alkol içimi gibi sağlıksız davranışları olan öğrencilerin COVID-19 korku düzeylerinin daha yüksek olduğunu saptamasına rağmen bizim çalışmamızda anlamlı bir sonuç alamadık.

Sonuç olarak katılımcılarda COVID-19 korku düzeyi orta seviyede saptanmış olup, kadın katılımcılarda daha yüksekti. Sigarayı bırakmış olan öğrencilerin çoğunluğu pandemi sırasında bu kararı vermişti. Haberlerin, kamu spotlarının, sigara yasağının, COVID-19 enfeksiyonu geçirmenin sigara tüketiminde değişikliğe yol açmadığı belirlendi.

Çalışmamızın yapıldığı tarihlerde pandemi önlemleri kapsamında uzaktan eğitim görüldüğünden, öğrencilere toplu halde ulaşmak mümkün olmamıştır. Çalışma elektronik ortamda duyurularak katılmaya gönüllü öğrencilerle yapılabilmiştir. Bu durum çalışmamızın en önemli kısıtlılığıdır.

Küreselleşen dünyada geçmişte olduğu gibi salgınlar görülmeye devam edecektir. Geleceğin sağlık hizmet sunucularının salgınlar konusunda bilgili olması ve ruhsal olarak hazırlıklı olmaları gerektiği bir gerçektir. Bu nedenle tıp fakültesi öğrencilerinin ruhsal bozukluklarla başa çıkma, kaygılarını kontrol edebilme, sağlıksız davranışlardan uzak durmaları konusunda eğitimlere de yer verilmeli ve gerektiğinde danışmanlık almalarına olanak sağlanmalıdır.

Teşekkür

Yok.

Yazar Katkı Beyanı

Fikir, Tasarım: **Ayşegül Tomruk Erdem, Senem İmam, Yusuf Uludağ, Yaren Türkömer, Çağrı Demirci, Revşan Pelit, Hayru Nisa Eger, Deniz Yiğit Öztürk, Ali Eren Ersin, Hazal Uysal, Eda Çakar, Zehra Nur Bağışlayıcı, Burak Dincel, Dilara Uçar, Senanur Demiray, Tuncay Celal Şimşek,** Veri Toplama: **Senem İmam, Yusuf Uludağ, Yaren Türkömer, Çağrı Demirci, Revşan Pelit, Hayru Nisa Eger, Deniz Yiğit Öztürk, Ali Eren Ersin, Hazal Uysal, Eda Çakar, Zehra Nur Bağışlayıcı, Burak Dincel, Dilara Uçar, Senanur Demiray, Tuncay Celal Şimşek,** Analiz veya Yorumlama, Literatür taraması, Yazım: **Ayşegül Tomruk Erdem.**

Çıkar Çatışması

Çalışmamızda herhangi bir çıkar çatışması bulunmamaktadır.

Finansal Destek

Finansal destek alınmamıştır.

Etik Kurul Onayı

Çalışma için Zonguldak Bülent Ecevit Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurul Başkanlığı'ndan10/03/2021 Tarih ve 2021/05 sayılı toplantı ile etik onay alındı.

Hakemlik Süreci

Kör hakemlik süreci sonrası yayınlanmaya uygun bulunmuş ve kabul edilmiştir.

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ÖZGÜN ARAŞTIRMA

Batı Karadeniz Tıp Dergisi
Medical Journal of Western Black Sea

Med J West Black Sea 2023;7(1): 57-65
DOI: 10.29058/mjwbs.mjwbs.1251370

Kırmızı Kantaron *(Hypericum capitatum)* Bitkisi: Fenolik İçeriklerinin, Antioksidan Aktivitesinin Belirlenmesi ve Klinik İzolatlar Üzerinde Antimikrobiyal Etkinliğinin Araştırılması

Red Centaury *(Hypericum capitatum)*: Determination of Phenolic Content, Antioxidant Activity and Investigation of Antimicrobial Efficacy on Clinical Isolates

Şükran ÖZTÜRK[1], Yasin HAZER[2], Banu KAŞKATEPE[3], Hatice ÇÖLGEÇEN[4], Muhittin KULAK[5]

[1]Zonguldak Bülent Ecevit Üniversitesi, Eczacılık Fakültesi, Farmasötik Mikrobiyoloji Anabilim Dalı, Zonguldak, Türkiye
[2]Zonguldak Bülent Ecevit Üniversitesi, Eczacılık Fakültesi, Farmasötik Botanik Anabilim Dalı, Zonguldak, Türkiye
[3]Ankara Üniversitesi, Eczacılık Fakültesi, Farmasötik Mikrobiyoloji Anabilim Dalı, Ankara, Türkiye
[4]Zonguldak Bülent Ecevit Üniversitesi, Fen Fakültesi Biyoloji Bölümü, Zonguldak, Türkiye
[5]Iğdır Üniversitesi, Iğdır Teknik Bilimler Meslek Yüksekokulu, Iğdır, Türkiye

ORCID ID: Şükran Öztürk 0000-0003-2729-171X, Yasin Hazer 0000-0001-8870-0017, Banu Kaşkatepe 0000-0002-9722-4267, Hatice Çölgeçen 0000-0001-8246-4279, Muhittin Kulak 0000-0003-3673-9221

Bu makaleye yapılacak atıf: Öztürk Ş ve ark. Kırmızı kantaron *(hypericum capitatum)* bitkisi: fenolik içeriklerinin, antioksidan aktivitesinin belirlenmesi ve klinik izolatlar üzerinde antimikrobiyal etkinliğinin araştırılması. Med J West Black Sea. 2023;7(1):57-65.

Sorumlu Yazar
Şükran Öztürk

E-posta
sukranozturk79@gmail.com.

Geliş Tarihi
17.02.2023

Revizyon Tarihi
12.04.2023

Kabul Tarihi
14.04.2023

ÖZ

Amaç: Bu çalışmada, Kırmızı Kantaron, *Hypericum capitatum* var. *capitatum (H. capitatum)* bitkisinin fenolik içeriğinin ve antioksidan aktivitesinin belirlenmesi, standart suşlar ve klinik izolatlar üzerinde antimikrobiyal etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: *H. capitatum*'un, standart bakteri suşları ile kolistin dirençli *Acinetobacter baumannii (A. baumannii)* ve çok ilaca dirençli (ÇİD) A. baumannii klinik izolatları üzerindeki antimikrobiyal etki düzeylerine sıvı mikrodilüsyon testi (MİK) ile gerçekleştirilmiştir (ISO, 2006). Yüksek Performanslı Sıvı Kromatografisi (YPSK) ile bazı içerikleri aydınlatılan *H. capitatum* ekstraktının, tohum, gövde ve yaprak örneklerinde total fenol içeriği araştırılmıştır. DPPH (2,2-difenil-1-pikrilhidrazil) yöntemi ile antioksidan etkinlik tayini yapılmıştır.

Bulgular: Metanolle ekstrakte edilen bitkinin, Gram (+) bakterilere karşı *Staphylococcus aureus (S.aureus)* ATCC-29213 ve Metisilin dirençli *S. aureus* (MRSA) ATCC 43300 antimikrobiyal etkinliğinin 16 (mg/mL) olduğu saptanmıştır. Dirençli *A. baumannii* klinik izolatlarına karşı, 64-128 mg/mL MİK değerleri ile etkin olduğu tespit edilmiştir. YPSK ile bitkinin tohum kısmındaki içerikler ise, sırasıyla; şikimik asit (1720.42 ppm(mg/ml), kafeik asit (52.50 ppm(mg/ml), sinaminik asit, (14.217,61 ppm(mg/ml), rosmarinik asit (30,90 ppm(mg/ml) olarak belirlenmiştir. *H. capitatum* kısımlarına göre toplam fenolik madde miktarlarının, yaprak (155,93 mg/L), gövde (177,85 mg/L) ve tohum (344,22 mg/L) şeklinde farklılık gösterdiği tespit edilmiştir. DPPH İnhibisyon aktivitesi; tohum (%55.476 mg/mL), gövde (%57.318 mg/ml), yaprak (%53.241 mg/ml) BHA (Butil hidroksi anozil) ve BHT (Butil hidroksi tolüen) sırasıyla (%93.77 ve %88.62) askorbik asit ise (%95.21) olarak belirlenmiştir.

Sonuç: Fenolik içerikçe zengin olduğu görülen *H. capitatum*' un, antioksidan etkinlik sonuçları, farklı kısımlarının metanol ekstreleri orta derecede etkili serbest radikal gideren doğal bir antioksidan kaynağı olduğunu göstermiştir. Antimikrobiyal etkinlik sonuçları ise, standart suşlar ve özellikle klinikte tedavisinin zor olduğu bilinen dirençli *A. baumannii* izolatlarına karşı etkinliğinin umut vaat edici olduğu görülmüştür.

Anahtar Sözcükler: Antibakteriyel etki, Antioksidan etki, Fenolik içerikler, Hypericum capitatum

ABSTRACT

Aim: It was aimed in this study, to investigate its antimicrobial effect on standard strains and clinical isolates of *Hypericum capitatum var capitatum (H. capitatum)* and to determine the phenolic content and antioxidant activity plant.

Material and Methods: The antimicrobial effect of H. capitatum on standard bacterial strains and colistin-resistant) *Acinetobacter baumannii (A. baumannii)* and Multi Drug Resistant (MDR) *A. baumannii* clinical isolates were determined by broth microdilution test (MIC) (ISO,2006). The total phenol content of the *H. capitatum* extract, of which some contents were clarified by, was investigated in seed, stem, and leaf samples. Antioxidant activity was determined by the DPPH (2,2-diphenyl-1-picrylhydrazil) method.

Results: The plant extracted with methanol was found to have antimicrobial activity against Gram (+) bacteria (*Staphylococcus aureus* ATCC-29213 and Methicillin resistant *S. aureus* (MRSA) ATCC 43300 with 16 mg/mL). The efficacy against resistant *A. baumannii* clinical isolates was found to be effective between 64-128 mg/mL. The contents of the seed part of the *H. capitatum* plant by High liquid pressure chromatography (HPLC) method, were determined as shikimic acid (1720.42 ppm (mg/ml), Caffeic acid (52.50 ppm (mg/ml), Cinaminic acid, (14,217.61 ppm (mg/ml), Rosmarinic acid (30.90 ppm (mg/ml)) respectively. According to the H. capitatum plant parts, it was determined that the total amount of phenolic substances differed in the form of leaves (155.93 mg/L), stem (177.85 mg/L), and seeds (344.22 mg/L). Inhibition activity of DPPH was determined; seed (55,476%mg/mL), stem (57,318% mg/ml), leaf (53,241% mg/ml), BHA (Butyl hydroxy anosyl) and BHT (Butyl hydroxy toluene), respectively (93.77% and 88.62%) and ascorbic acid (95.21%).

Conclusion: The antioxidant activity results of *H. capitatum,* which was found to be rich in phenolic content, demonstrated that methanol extracts of different plant parts are a natural antioxidant source that moderately scavenges free radicals. When the antimicrobial efficacy results were evaluated, it was observed that its efficacy against standart strains and resistant A. baumannii isolates, which are known to be difficult to treat clinically, is promising.

Keywords: Antibacterial effect, Antioxidant effect, Phenolic contents, Hypericum capitatum

GİRİŞ

Ülkemizde ve dünyada antibiyotik direncinin giderek artış göstermesine bağlı olarak alternatif tedavi yöntemlerine eğilim ortaya çıkmıştır. Bu kapsamda bitkisel ekstrelerin birçok hastalık etkenini tedavi etmek için potansiyelleri araştırılmaktadır. Bitki bileşenlerinin tespiti ve antimikrobiyal etkinlik düzeylerinin belirlenmesi gittikçe önem kazanmaktadır. Bu sebeple uygun bitkilerin belirlenmesi ve içeriklerinin tespit edilerek antimikrobiyal aktivite tayinlerinin yapılmasıyla, bitkilerin tedavi sürecine katkıda bulunmaları için çalışmalar yapılmaktadır. Ülkemiz, farklı iklim ve ekolojik koşullara sahip olması, floranın çok sayıda bitki türü ve çeşitliliği içermesinden kaynaklı tıbbi amaçlı tüketilen birçok bitki türüne sahiptir (1). Bu bitkilerin birçoğunun antimikrobiyal etkileri olduğu gerek yurt dışında, gerek ülkemizde yapılan çalışmalarda bildirilmiştir (2-4).

Farklı amaçlar için kullandığımız kimyasal maddelerin, birçok istenmeyen yan etkisinin ortaya çıktığı ve gereksiz yere, uygunsuz dozlarda kullanılan kimyasalların da vücudumuzdaki direnç mekanizmalarını olumsuz yönde etkilediği bilinen bir gerçektir. Bu nedenle doğal ürünlere ve bunlardan elde edilmiş maddelere eğilim günden güne artmaktadır. Son yıllarda bitkisel ürünler ve etkinlikleri ile ilgili yapılan çalışmalardan ortaya çıkan olumlu sonuçlar da bu eğilimi destekler durumdadır. "Kan otu, mayasıl otu, binbirdelik otu, kılıç otu, koyun kıran" gibi farklı isimlerle anılan kantaron türleri (*Hypericum spp.*) ülkemizde doğal bir yayılıma sahiptir ve Türkiye Bitkileri Veri Servisi (TÜBİVES) (2013) verilerine göre 94 adet olarak bildirilmiştir (5,6). Yurtdışında St. John's Wort olarak bilinen kantaron ile yapılan farmakolojik çalışmalar bitkinin ve farklı ekstrelerinin antidepresan, antiinflamatuar, antimikrobiyal, antiviral aktivitelere sahip olduğunu göstermiştir (7).

Türkiye' de *Hypericum* cinsine ait 20 seksiyon ve 106 takson bildirilmiştir (8). 45 taksonun ise endemik olduğu bilinmektedir (9,10). Bu bitki cinsinin içerdiği sekonder metabolitler ekonomik bir değere sahip olduğu için dünya çapında önemli bir yer tutmaktadır (11,12).

Bilimsel çalışmalarla, kantaron türlerinin etkili aktif bileşenlerinin fenolik maddeler ve çeşitli terpenoidler olduğu ortaya konulmuş olup, kimyasal bileşenlerden en ilgi çekicilerin hiperforin ve hiperisin olduğu üzerine yoğunlaşılmıştır. Yapılan klinik çalışmalar kantaronun sakinleştirici ve antidepresan etkisinin bu maddelerden kaynaklandığını desteklemektedir (13). Uçucu yağlar, kantaron türlerinde az da olsa bulunan fitokimyasallardandır. Literatürde çok sayıda uçucu yağ bileşeni ortaya konulmuş olup, ülkemizde bulunan kantaron türlerindeki uçucu yağların en belirgin bileşiğinin α-pinene olduğu bildirilmiştir. Uçucu yağ oranı ve bileşenleri bitkilerin genetik yapılarına göre farklılık göstermekle birlikte, farklı yetişme koşulları, bitki kısımları, gelişme dönemi, hasat şekli ve sonrasındaki işlemlere göre de değişiklik gösterebilmektedirler (14).

Hypericum türleri (Guttiferae) geniş biyolojik özellikleri ve zengin fitokimyasal bileşiklere sahip olmalarıyla bitkisel kökenli farmasötik ilaçların geliştirilmesinde önemli bir yere sahiptir. Türler arasında *Hypericum capitatum CHOISY var. capitatum CHOISY,* Türkiye'nin Güneydoğu bölgesinde doğal olarak yayılış gösteren endemik bir tıbbi bitkidir. Günümüzde bitkisel ekstrelerin birçok hastalık etkenini tedavi etmek için kullanıldığı bilinmektedir.

Morfolojik olarak, *H. capitatum'* u ayırt etmede iki tanısal karakter vardır. *H. capitatum var. capitatum* yaprakları turuncu renklidir, sepali koyu kırmızıdır; diğeri ise, *H. capitatum var. luteum*, yaprakları, sarı ve sepali yeşil olarak rapor edilmiştir. Bu iki tür de Türkiye florasına aittir (15). *H. perforatum* (16) ve *H. perfoliatum* (17,18) 'un uçucu yağlarının farklı bileşimleri daha önce bildirilmiş olsa da, *H. humifusum ve H. pulchrum'un* (19) uçucu yağları hakkında çok az bilgi bulunmaktadır (20). Ülkemizde sadece doğal yayılış gösteren ve Doğu ve Güneydoğu Anadolu Bölgesinde yetişen, TÜBİVES (2013) kayıtlarına göre endemik olduğu bilinen *H. capitatum var capitatum* bitkisinin kimyasal yapısının ve antimikrobiyal aktivitesinin yeterli ölçüde çalışılmamış olması tıbbi amaçlı kullanımları için daha detaylı incelenmesinin gerekliliğini düşündürmektedir. Bu durum, endemik *H. capitatum* ile yapılacak çalışmaların önemini artırmaktadır. *Hypericum* türlerinin toprak üstü kısımlarında %0.05-0.3 naftodiantron türevleri (hiperisin, psödohiperisin, izohiperisin), flavonoitler (hiperozit, rutin, kersitrin, izokersitrin, kersetin, kemferol), biflavonoitler (biapigenin), floroglusinoller (hiperforin, adhiperforin), uçucu yağ (n-alkanlar, monoterpenler), kateşik ve kondanse tanenler (kateşin, epikateşin, lökosiyanidin), fenolik asitler (kafeik asit, klorojenik asit ve fendik asit), steroller (psitostcrol), ksantonlar (1,3,6,7 tetrahid- roksanton), fenilpropanoitler, A ve C vitamini gibi birçok biyoaktif bileşik içerdiği bildirilmiştir (21,22).

H. capitatum'un, yara iyileşme mekanizması için çok önemli olan antibakteriyel ve antioksidan özelliklere sahip olduğu bildirilmiştir (23).

Çalışmaya konu olan klinik izolatlardan biri Gram (-) bir bakteri türü ve birçok hastalık etkeni olarak bilinen *A. baumannii* tedavisi güç bir hastane enfeksiyon etkeni olarak klinikte büyük önem taşımaktadır. *A. baumannii* izolatlarına karşı oluşan antimikrobiyal direnç dünya çapında artmakta ve sıklıkla kombine terapi gerektirmektedir. Son yıllarda ÇİD suşların neden olduğu enfeksiyonların tedavisi için sınırlı sayıda antimikrobiyal ajan bulunması, yeni antimikrobiyal ajanların veya tedavi stratejilerinin keşfedilmesine olan eğilimi artırmıştır.

Tüm bu bilgiler göz önüne alınarak, bu çalışmada, kantaron türleri arasında Türkiye endemik *H. capitatum* kırmızı kantaron bitkisine ait ekstrelerin bazı sekonder metabolitlerinin kantitatif miktarları ile belirlenmiş olup aynı zamanda fenolik bileşikleri ve antioksidan etkinliği tespit edilmiştir. Bileşenleri belirlenmiş bitkinin gövde, yaprak ve çiçeklerinden elde edilen su, etanol, metanol, kloroform, asteon ile yapılan ekstraktlarının antimikrobiyal aktivitesinin Gram (-), ve (+) bakteriler ve klinik izolatlar üzerindeki etkinliği mikrodilüsyon yöntemi kullanılarak tayin edilmiştir. Bu amaçla yürütülen çalışmamızın, alternatif tedavi yöntemleri belirlemeye ve antibiyotik dirençli, klinikte tedavi güçlüğü bulunan bakterilerin inhibisyonu veya ortadan kaldırılması için yapılacak çalışmalara ışık tutacağı düşünülmektedir.

GEREÇ ve YÖNTEMLER

Bitkilerin Toplanması

H. capitatum (kırmızı kantaron) bitkisi, Güneydoğu Anadolu Bölgesi'nde sınırlı bir alanda yayılış gösteren bir tür olup, çiçeklenme dönemi olan Mayıs ayında Kilis ve çevresinden toplanmıştır.

Hypericum capitatum (kırmızı kantaron)

Antimikrobiyal Aktivite Tayini

Mikroorganizmalar

Çalışmada kullanılacak standart bakteri suşları Ankara Üniversitesi Eczacılık Fakültesi' nden temin edilmiştir. Araştırmada *Escherichia coli (E. coli) ATCC-25922, Staphylococcus aureus (S. aureus) ATCC-29213, Enterococcus fecalis (E. fecalis) ATCC-29212, Pseudomonas aeruginosa (P. aeruginosa) ATCC-27853 ve* metisilin dirençli *Staphylococcus aureus (MRSA) ATCC 43300* bakteri suşları kullanılmıştır. Kolistin dirençli ve ÇİD *A. baumannii* klinik izolatları ise Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi Mikrobiyoloji Laboratuvarındaki rutin örneklerden pasajlanarak temin edilmiştir.

Mikroorganizmaların Üretilmesi

Ankara Üniversitesi Eczacılık Fakültesi Farmasötik Mikrobiyoloji Laboratuvarı ve Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi Mikrobiyoloji Laboratuvarı kültür koleksiyonunda mevcut bulunan ve -80°C' de muhafaza edilen ATCC suşları ve klinik izolatlar stok kültürlerinden, steril koşullar altında öze yardımıyla taze hazırlanmış Mueller Hinton Agar (MHA) besiyerlerine pasajlanarak üretilmiştir. Bakteri inokülasyonu yapılan petriler 37°C'lik inkübatörde (Nüve, Türkiye) 18-24 saat süre ile inkübasyona bırakılmıştır. Suşlar iki kez aktifleştirildikten sonra çalışmada kullanılmıştır. Bakteri süspansiyonları 0.5 McFarland (1.5×10^8 CFU/ml) standart bulanıklıkta olacak şekilde EUCAST önerileri doğrultusunda hazırlanmıştır (24).

Sıvı Mikrodilüsyon Testi

Çalışmada, *Hypericum capitatum'un, E. coli ATCC-25922, S. aureus ATCC-29213, E. fecalis ATCC-29212, P. aeruginosa ATCC-27853, MRSA ATCC 43300* bakteri suşlarına ve dirençli *A. baumannii* klinik izolatlarına karşı antimikrobiyal etkinliğinin araştırılmasında EUCAST önerileri doğrultusunda sıvı mikrodilüsyon testi (MİK) kullanılmıştır. Plaklar 37° C'de 18-20 saat inkübe edildikten sonra değerlendirmeler EUCAST önerilerine göre yapılmıştır (24).

YPSK Analiz Yöntemi

YPSK-UV Analizi için Standartların Kromatogramı YPSK analizlerinde gerek hareketli fazın hazırlanmasında ve gerekse de fenolik bileşik standartlarının hazırlanmasında kullanılan kimyasallar YPSK saflığındadır. Elimizdeki farklı standartların kalibrasyon eğrisini oluşturmak için saflığında %100'lük MeOH kullanılarak 250 ppm, 100 ppm, 50 ppm, 25 ppm, 20 ppm, 10 ppm, 5 ppm ve 2,5 ppm olarak hazırlanmış ve kromatogramları çizilmiştir.

YPSK Analizlerinde Kullanılan Cihaz Shimadzu; Japonya markadır. Analizlerde kullanılan kolon C18 3µl 120 Å 4,6x150 mm'dir.

H. capitatum ait örnekler liyofilizatörde kurutularak, ekstrakte edilmiştir. Kurutulmuş gametofit kısımları belli miktarlarda tartılmış (Örn.100-400 mg gibi) ve tartılan numuneler toz haline getirilmiştir.

YPSK çalışma yöntemi, çıkış bileşiklerinin alıkonulma zamanlarına göre ayarlanarak uygulanmıştır (aynı parametrelerde çalışılmıştır). Numune 10 kat seyreltilerek cihaza verilmiştir. Sonuçlar 10 kat seyreltme göz önüne alınarak hesaplanmıştır (25, 26).

Total Fenol İçeriğinin Belirlenmesi

H. capitatum' un tohum, gövde ve yaprak örneklerinin liyafilizatör yardımıyla kuruması sağlanmış ve örnekler toz haline getirilerek 1'er gram olarak tartılmıştır. Etiketli erlenmayerlere 1g' lık toz örnekler ve 10 ml %80'lik Metanol (MeOH) eklenerek ve 26 ºC 180 rpm' de çalkalayıcıda bir saat çalkalamaya bırakılmıştır. Çalkalama işleminin tamamlanmasıyla ekstraksiyon çözeltisi balon jojelere dökülerek süzme işlemi yapılmıştır. Süzme işleminin ardından filtre kâğıtları üzerinde süzüntüden kalan kısımlar tekrar %80'lik 15 ml MeOH eklenerek 26 ºC 180 rpm' de 24 saat çalkalanmak üzere çalkalayıcıya yerleştirilmiştir. Balon jojeler içerisindeki %80'lik MeOH + ekstraktsiyon karışımları şilifli balonlara aktarılmış ve rotaevaporatör (BÜCHI, İsviçre) kullanılarak 45ºC banyoda %80'lik MeOH'ün uçurma işlemi yapılmıştır Uçurma işleminin ardından balonlarda kalan esktraktların kuru ağırlığını belirlemek için hassas terazide brüt ağırlıkları tartılarak balon dibine çökelen ekstraktı çözmek için 2 ml %99,9'luk MeOH dökülerek ultrasonik banyoda çözünmeleri sağlanmıştır. Çözünen 2 ml'lik ekstraktlar amber renkli viallere koyularak 4 ºC'de buzdolabında saklanmıştır.

Toplam Fenol Miktar Tayininde Tetra Marka T80+ UV/VIS Spektrofotometre Modeli kullanılmıştır.

Toplam Fenol Miktar Tayini Çözeltilerinin Hazırlanması

Ekstreler içerisindeki toplam fenol miktarı Folin-Ciocalta-eu yöntemine göre yapılmıştır (27). Hazırlanmış bitki ekstreleri, konsantrasyonları 2 mg/ml olacak şekilde %75'lik etanol (EtOH) ile çözülerek örnekten 20 µl alınmış, üzerine sırasıyla 1580 µl distile su, 100 µl Folin-Ciocalteau reaktifi ve 300 µl % 20'lik sodyum karbonat çözeltisi eklenmiştir. Kalibrasyon eğrisini oluşturabilmek için 15.62 mg/l, 31.25 mg/l, 62.5 mg/l, 125 mg/ml, 250 mg/l, 500 mg/l, 1000 mg/l konsantrasyonlarda gallik asit dilüsyonları hazırlanmış ve örnek yerine gallik asit dilüsyonları konularak diğer çözeltiler aynı miktarda ilave edilmiştir. Tüm örnekler 40°C'de 30 dakika inkübasyona bırakılarak süre sonunda absorbanslar 765 nm dalga boyunda kör olarak kullanılan etanole karşı spektrofotometrede okunmuştur. Gallik asit çözeltileri yardımıyla hazırlanan kalibrasyon eğrisine göre, örneğin absorbansı kullanılarak toplam fenol konsantrasyonu gallik asit eşdeğeri olarak hesaplanmıştır(R^2=0,9902).

GAE (mg/l) =

[(Numune Absorbans(765nm) Değeri + 0,0479) / (0.0008)]

Antioksidan Etkinlik Tayini

DPPH (2,2-difenil-1-pikrilhidrazil) çözeltisinin hazırlanması:

100 ml'lik erlenmayerin etrafı alümiyum folyo ile ışık almayacak şekilde sarılmıştır. Hassas terazide darası alınarak DPPH (Sigma-Aldrich) 2,4 gr tartılmış ve daha önce hazırlanmış 100 ml %70'lik MeOH ile çözülmüştür.

DPPH serbest radikali giderim aktivitesinin belirlenmesi işlemi için T80+ UV/VIS Spectrometer (Tetra Marka, USA) PG Instruments Modeli kullanılmıştır.

Flakonlarda bulunan 2000 µg/2ml, 1000 µg/2ml, 500 µg/2ml, 250 µg/2ml hazırlanan bitki ekstraksiyon çözeltileri, BHT, BHA, askorbik asit çözeltilerinin üzerine otomatik pipetle 2 ml DPPH eklenerek 30 dk karanlık dolapta oda sıcaklığında bekletilmiştir.

UV-Spektrofotometre' de ilk olarak blank zero gözüne 4 ml %99,9'luk MeOH disposable küvet koyularak autozero işlemi yapılmıştır. DPPH radikali ile reaksiyona giren dört farklı dilüsyondaki çözeltiler 1000 µg/ml 500 µg/ml, 250 µg/ml, 125 µg/ml olacak şekilde ayarlanmış ve kontrol olarak çözelti eklenmemiş olup DPPH olacak şekilde yerleştirilmiştir. UV-Spektrofotometre yazılımı programlanarak her gözde bulunan çözeltinin 517 nm absorbansta tekrarlı okuma işlemi yapılmıştır. Serbest radikal süpürme aktivitesi tayini

için absorbans değerleri aşağıdaki eşitliğe göre hesaplanmıştır.

% İnhibisyon = [(K. $A_{(517nm)}$ - Ö.$A_{(517nm)}$) / (K.$A_{(517\ nm)}$)] x 100

İstatistiksel Analiz

Çalışmada kullanılan çözücüler (Metanol: Sigma-Aldrich) analitik saflıktadır. Karşılaştırma amaçlı çözücü olarak saf su kullanılmış ve aynı analizler saf su ekstreleri için de gerçekleştirilmiştir. Sonuçlar tablo halinde sunulmuştur. Absorbans okumaları UV-VIS spektrofotometrede gerçekleştirilmiştir. Analizler tekrarlı yapılmış ve standart sapmalar sonuçlar ile birlikte verilmiştir.

Antimikrobiyal aktivite tayini için kullanılan çözücüler (Metanol: Sigma-Aldrich, Etanol, Merck, Aseton; Sigma- Aldrich, Kloroform; Merck) bitkiyi ekstrakte etmek için kullanılmıştır. Kullanılan tüm çözücüler ve saf su ile ekstrakte edilen bitkilerin antimikrobiyal etkinliği tabloda sunulmuştur.

Gallik asit, standart bir bileşik olarak kullanılır ve toplam fenoller, standart eğri denklemi kullanılarak mg/g gallik asit eşdeğeri olarak ifade edilir.

Kalibrasyon eğrisini oluşturabilmek için 15.62 mg/l, 31.25 mg/l, 62.5 mg/l, 125 mg/l, 250 mg/l, 500 mg/l ve 1000 mg/l konsantrasyonlarda gallik asit dilüsyonları hazırlandı ve örnek yerine gallik asit dilüsyonları konularak diğer çözeltiler aynı miktarda ilave edildi. Tüm örnekler 40°C'de 30 dakika inkübasyona bırakıldı. Süre sonunda absorbanslar 765 nm dalga boyunda kör olarak kullanılan etanole karşı spektrofotometrede okundu. Gallik asit çözeltileri yardımıyla hazırlanan kalibrasyon eğrisine göre, örneğin absorbansı kullanılarak toplam fenol mg/g gallik asit eşdeğeri olarak hesaplandı.

Tablo 1: YPSK Analiz Sonuçları

***Hypericum capitatum* Tohumu**	**Analiz Sonuçları**
Şikimik asit, ppm (mg/L)	1720,42
Kafeik asit, ppm (mg/L)	52,50
Sinnamik asit, ppm (mg/L)	14.217,61
Rosmarinik asit, ppm (mg/L)	30,90

BULGULAR

Çalışmada, *H. capitatum*' un ile bazı sekonder metabolitlerin tespit edilerek, mikrodilüsyon yöntemiyle antimikrobiyal etkinliğine bakılmıştır. Ayrıca bitki ekstraktlarının total fenol içeriği ve antioksidan etkinliği de uygun yöntemlerle belirlenmiştir.

YPSK Analiz Sonuçları

Hypericum türlerinde yapılan analizlerde literatür incelediğinde en başarılı ekstraksiyon metodu olarak metanol ekstraktları tercih edildiğinden çalışmamızda da bu ekstrakt kullanılmıştır. Çalışmamızda fenolik bileşiklerden Şikimik asit, Kafeik asit, Sinnamik asit, Rosmarinik asit incelenmiştir (Tablo 1).

H. capitatum bitkisinin tohum kısmına ait ekstraktında 14.217,61 ppm (mg/L) ile en yüksek oranda bulunan içerik Sinnamik asit olarak tanımlanmıştır. Sonrasında 1720,42 ppm (mg/L) ile Şikimik asit bitki ektraktındaki yüksek içeriklerinden biri olarak tespit edilmiştir.

Antimikrobiyal Etkinlik Sonuçları

H. capitatum' un standart suşlar üzerinde antibakteriyel etkinlik sonuçları (MİK) Tablo 2' de verilmiştir. Antibakteriyel etkinlikler incelendiğinde metanolle ekstrakte edilen bitkinin özellikle Gram (+) bakterilere karşı etkinliği olduğu belirlenmiştir (MİK 16-64 *µ*g/ml) (Tablo 2).

H. capitatum' un ÇİD ve kolistin dirençli *A. baumannii* klinik izolatları üzerinde antibakteriyel etkinlik sonuçları Tablo 3' de verilmiştir. Bu sonuçlar incelendiğinde ise, özellikle bitkinin gövde ve yaprak kısımlarının ÇİD izolatlara karşı antibakteriyel etkinliği dikkat çekmektedir (64 *mg/µL)*. Çiçek kısmının ise kolistin dirençli izolatlara karşı antibakteriyel etkinliği belirlenmiştir (128 *mg/µL)* (Tablo 3).

H. capitatum bitkisinin standart suşlar üzerindeki etkinlikleri değerlendirildiğinde, saf su ile yapılan bitki ekstraktında herhangi bir etkinlik bulunmazken, özellikle Gram pozitif bakterilerden *S. aureus* (*ATCC-29213)* ve MRSA (*ATCC 43300)* üzerinde metanol ve etanol ekstraktının 16 (*µ*g/mL)' lik Mik değerleriyle antimikrobiyal etkinliğe sahip olduğu görülmüştür. Gram negatif bakterilerden *E. fecalis* (*ATCC-*

Tablo 2: *H. capitatum' un* Standart Suşlar Üzerinde Antibakteriyel Etkinlik Sonuçları (MİK)

		MİK Değerleri (*µ*g/mL)				
No	**Ekstrakte Yöntemi**	**Metanol**	**Etanol**	**Aseton**	**Kloroform**	**Saf Su**
1	*E. coli ATCC-25922*	512	512	512	512	512
2	*S.aureus ATCC-29213*	16	16	32	32	512
3	*MRSA ATCC 43300*	16	64	64	128	512
4	*P.aeruginosa ATCC-27853*	512	512	512	512	512
5	*E. fecalis ATCC-29212*	128	64	64	128	512

29212)' in etanol ve aseton ile yapılan ekstraktı 64(*µ*g/mL) Mik değeri ile yine antimikrobiyal etkinlik göstermiştir. Dirençli *A. baumannii* klinik izolatları üzerinde yapılan antimikrobiyal etkinlik analizlerinde ise bitkinin yaprak kısmı ve gövde kısmından yapılan ekstraktın çok ilaca dirençli (ÇİD) *A. baumannii* klinik izolatları üzerinde 64 (*µ*g/mL) Mik değeri ile antimikrobiyal etkinliği tespit edilmiştir.

Toplam Fenolik Bileşen Miktarı Tayini Bulguları

Bitki kısımlarına göre toplam fenolik madde miktarlarının değişimi farklılık göstermektedir. Metanol ekstraktının fenolik ve flavonoid miktarlarının en zengin olduğu tespit edilmiştir. Metanol ekstraktından elde edilen toplam fenolik ve flavonoid miktarları yaprak, 155. 93 µg/mg ekstrakt gövde 177.85 µg/mg ekstrakt ve tohum 344.22 µg/mg olarak bulunmuştur.

H. capitatum bitkisinin tamamından hazırlanan, metanol ve su ekstraktlarının toplam fenolik ve flavonoid içerikleri belirlenmiştir (y=0,0008x+0,0479 R^2 = 0,9902). Test edilen ekstraktın fenolik içerikçe zengin olduğu görülen (Şekil 1) *H. capitatum' un* farklı kısımları ile sağlık alanında yapılacak farklı uygulama deneylerinde etki mekanizmalarının çalışılması önem kazanmaktadır.

H. capitatum bitkisinin tohum kısmına ait metanol ekstraktında 344.22 µg/mg lık fenolik bileşik içeriği ile bitkinin gövde ve yaprak kısmından daha yoğun olduğu görülmüştür.

Antioksidan Etki Sonuçları

H. capitatum bitkisinin toprak üstü (Herba) kısımlarından elde edilen özütlerinin DPPH radikal giderme aktivitelerinin yüzde (%) olarak hesaplamaları ise aşağıdaki denkleme göre yapılmıştır.

% İnhibisyon = [(K. $A_{(517nm)}$ - Ö.$A_{(517nm)}$) / (K.$A_{(517\ nm)}$)] x 100

Bu sonuçlara göre metanol ekstraktının DPPH serbest radikal yakalama deneyinde standart olarak kullanılan *H. capitatum* farklı bitki kısımlarının metanol ekstrelerinin, BHT (%88.62), BHA (%93.77) ve askorbik asit (%95.21) oranları ile yaprak (%53.241), tohum (% 55.476) ve gövde (%57.318) DPPH inhibisyon aktiviteleri değerlendirilmiş ve orta derecede etkili serbest radikal gideren doğal bir antioksidan kaynağı olduğu gösterilmiştir (Tablo 4).

H. capitatum bitkisinin yaprak tohum ve gövde kısımlarının metanol ekstrelerinin yaklaşık olarak %55 *(mg/ml)* DPPH İnhibisyon aktivitesi (%) ile orta dereceli antioksidan kaynağı olduğu belirlenmiştir.

TARTIŞMA

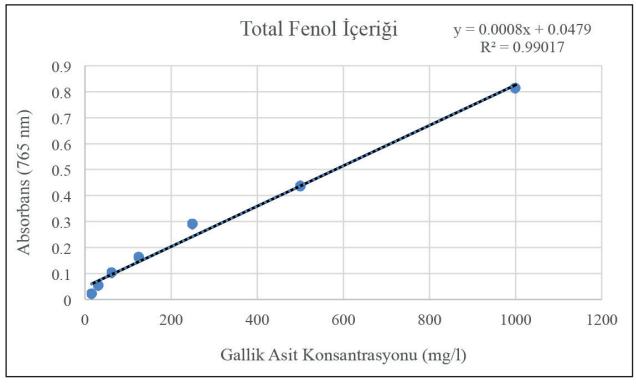
Günümüzde antibiyotik direncinin artışı ve bakteriyel enfeksiyonlar için tedavi seçeneklerinin kısıtlılığı dikkat çekicidir. Özellikle bitkisel içeriklerden fayda sağlamak konusunda yeni alanların oluşabilmesi ve bitki içeriklerinin farklı bakteriyel enfeksiyonlar ve farklı alanlar üzerindeki etkinliklerini

Tablo 3: *H. capitatum'un* Dirençli *Acinetobacter baumannii* Klinik İzolatları Üzerinde Antibakteriyel Etkinlik Sonuçları (MİK)

***A. baumannii Klinik İzolatlar,* (MIK mg/µL)**	**Sonuç**
Bitki Tohumu	
A. baumannii (Kolistin dirençli)	512
A. baumannii (Kolistin hariç ÇİD)	512
A. baumannii (Duyarlı)	512
E.coli ATCC 25922	512
Bitki Gövdesi	
A. baumannii (Kolistin dirençli)	256
A. baumannii (Kolistin hariç ÇİD)	64
A. baumannii (Duyarlı)	512
E.coli ATCC 25922	512
Bitki Çiçek kısmı	
A. baumannii (Kolistin dirençli)	128
A. baumannii (Kolistin hariç ÇİD)	512
A. baumannii (Duyarlı)	512
E.coli ATCC 25922	512
Bitki Yaprağı	
A. baumannii (Kolistin dirençli)	256
A. baumannii (Kolistin hariç ÇİD)	64
A. baumannii (Duyarlı)	512
E.coli ATCC 25922	512

Tablo 4: Antioksidan Etki Sonuçları

***H. capitatum* (mg/ml)**	**DPPH İnhibisyon aktivitesi (%)**
Tohum	55.476
Gövde	57.318
Yaprak	53.241
BHA	93.77
BHT	88.62
Askorbik Asit	95.21



Şekil 1: Gallik asidin artan derişimlerine karşılık ölçülen absorbans değerleri.

ortaya koymak için yapılan çalışmalar oldukça önem kazanmıştır. Çalışmamızda, *H. capitatum* bitkisinin standart bakteri suşları ve klinik izolatlara karşı antimikrobiyal etkinliği incelenmiştir. Aynı zamanda bitkinin YPSK yöntemi ile yapı aydınlatması yapılmış ve total fenol içerikleri ile antioksidan etkinliği araştırılmıştır. Çalışma sonuçları incelendiğinde, kırımızı kantaron (*H. capitatum*) bitkisinin özellikle bazı ekstraktlarının standart suşlar ve dirençli klinik izolatlar üzerindeki antibakteriyel etkinliği tespit edilmiştir. Diğer taraftan YPSK ile yapısal olarak aydınlatılması yapılan ve bitki içeriği ortaya konulan kırmızı kantaronun total fenol içeriği ve antioksidan etkinliği belirlenmiştir. Sonuçlar yorumlandığında, bitkinin total fenol bileşik açısından zengin ve özellikle metanol ekstraktının doğal bir antioksidan kaynağı olduğu tespit edilmiştir.

Şikimik asit biyolojik aktiviteler ve sentetik maddeler için önem arz eden bir fenolik asittir (28). Kafeik asit in vitro ortamda antioksidan ve antibakteriyel aktiviteye sahip olduğu bilinmekte ayrıca ateroskleroz ve kardiyovasküler hastalıkların önlenmesine katkıda bulunabileceği düşünülmektedir (29). Sinnamik asit, diş macunu, gargara sıvıları ve sakız içerisinde, temizlik malzemelerinde, deterjanlarda, şampuanlarda, parfümlerde ve kozmetikte de kullanılan bir bileşiktir (30). Rosmarinik asit antienflamatuar, antioksidan, antialerjik, antianjiyojenik, antitümör, antimikrobiyal, antiviral gibi biyolojik aktivitelerinden dolayı yoğun ilgi gören bir bileşiktir (31).

Yapılan çalışmalarda, Hypericum cinsinin birçok türünün bazı bakteriyel hastalıkların, mide ve bağırsak iltihaplarının tedavisinde Türk halk ilacı olarak kullanıldığı bilinmektedir. Birkaçı hariç bütün bitki özlerinin *S. aureus ve Mycobacterium smegmatis'e* karşı antimikrobiyal aktivite gösterdikleri belirtilmiştir (32). Sökmen vd. (1999), doku kültürü yöntemiyle çoğaltıp yetiştirdikleri *H. capitatum'un* magnezyum hidroksit (MgOH) özütünün düşük oranda HIV-1'e karşı antiretroviral aktivite gösterdiğini saptamışlardır (33).

Çırak vd. (2016) tarafından yapılan çalışmada *Hypericum* cinsinin bazı türlerinde sekonder metabolitlerinin (2,4- Dihidroksibenzoik asit, neoklorojenik asit, (+)-kateşin, klorojenik asit, kaffeik asit, mangiferin, epicatechin, rutin, hiperosid, isoquercitrin, avicularin, quercitrin, quercetin, 13, II8-biapigenin, amentoflavone, hiperforin, adhiperforin, pseudohiperisin, pseudohiperisin,) kantitatif tayinleri yapılmıştır (34).

Hypericum capitatum bitkilerinin toprak üstü kısımlarının uçucu yağ bileşenleri araştırılmış olup, GC/GC-MS analiz sonuçlarında 48 farklı bileşen tespit edilmiştir. Ana bileşenler α-pinene (%20,3), karyofillenoksit /%11.8), hekzadekanoikasit (%8,9), β-karyopilen (%6,5) ve undekan (%3,8) olarak belirlenmiştir (20). Yapılan diğer çalışmalarda ise, analiz edilen *H. capitatum* bitki örneklerinde, uçucu yağ bileşenleri ve ana bileşenlerin oranlarının bitkinin kısımlarına göre oldukça büyük farklılıklar göstermesi dikkat çekicidir. Bitkinin herba ve çiçek kısmındaki ana bileşen α-pinene olarak tespit edilmiş olup, oranlar sırasıyla (%43,589) ve (%71,897) olarak bulunmuştur (35,36). Kantaron bitkisinde kullanılan kısımların herba ve çiçek olduğu dikkate alındığında, kırmızı kantaronun (*H. capitatum*) ana bileşeninin α-pinene olduğu söylenebilir.

Çalışmamıza benzer şekilde, Boga vd., (2016) Hypericum türleriyle yaptıkları çalışmada Gram (-) ve Gram (+) bakteriler üzerinde disk difüzyon ve mikrodilusyon yöntemiyle antibakteriyel etkinliklerini incelemişler ve birçok Hypericum türünün Gram (+) bakterilerden *Streptococcus pyogenes ATCC19615 and S. aureus ATCC 25923*, Gram (-) bakterilerden ise *Pseudomonas aeruginosa ATCC 27853, E. coli ATCC 25922*, ve *Candida albicans ATCC 10231* üzerinde antimikrobiyal etkinliğinin olduğunu tespit etmişlerdir (37).

Yapılan çalışmalarda, *H. capitatum*'un *Bacillus cereus, S. aureus, Branhamella catarrhalis, Clostridium perfringens ve Candida albicans*' a karşı antimikrobiyal etkinlikleri bildirilmiştir. Ayrıca, bitkinin özleri HIV-I' e karşı hafif bir antiretroviral aktivite sergilediği belirtilmiştir (35). *H. capitatum* özleri, çeşitli çözücüler içinde, bu bitkiyi doğal bir serbest radikal temizleyici kaynağı olarak da bildirmişlerdir (38).

H. capitatum, farklı yerlerden toplandığında uçucu yağ bileşiminde benzer şekilde farklılıklar göstermiş, daha spesifik olarak spathulenol (%12,9) ve iso-longifolene (%11,2) veya alfa-pinen (%20,3) farklı koleksiyonlardan ana bileşenler olarak bildirilmiştir (38).

Bu çalışmada ise Türkiye' den Güneydoğu Anadolu Bölgesinde Kilis' den toplanan ve farklı bölümlerinin (yaprak, çiçek, tohum vb.) farklı çözücülerle ekstrakte edilen (metanol, etanol, aseton, kloroform vb) *H. capitatum* bitkisi incelenmiştir. YPSK ile analiz edilen *H. capitatum* bitkisinin tohum kısmında; şikimik asit (1720.42 ppm(mg/ml), kafeik asit (52.50 ppm(mg/ml), sinaminik asit, (14.217,61 ppm(mg/ml), ve rosmarinik asit (30,90 ppm(mg/ml) içerikleri tespit edilmiştir.

H. capitatum' un farklı kısımları ile sağlık alanında yapılacak farklı uygulama deneylerinde etki mekanizmalarının çalışılması önem kazanmaktadır.

Yapılan analizler sonucunda, kırmızı kantaron (*H. capitatum*) bitkisinin, standart bakteriler ve dirençli klinik izolatlar üzerindeki antimikrobiyal etkinliği tedavilere destek sağlayacak nitelikte bir kullanım alanı oluşturabileceği düşünülebilir. Ayrıca antioksidan etkinliği ve total fenol içeriğinin zengin olması da bu alanda kullanımını destekleyerek alternatif bir tedavi seçeneği olarak umut vaat edici olabilir. Sonuçlar, ÇİD ve kolistin dirençli *A. baumannii* enfeksiyonlarının kontrolü için *H. capitatum'* un potansiyel kullanımını olabileceğini göstermektedir. Bununla birlikte, insanda bakteriyel enfeksiyonlarla mücadelede kullanılma olasılığını doğrulamak için daha yeterli çalışmalar yapılmalıdır.

Bu sonuçlar doğrultusunda yapılan çalışmalar, ekonomik açıdan fayda sağlamakla birlikte bazı bakteriler üzerinde gereksiz ve yanlış antibiyotik kullanımının engellenmesine olanak sağlayarak, alternatif tedavi yöntemleri oluşturmak için bizlere ışık tutacaktır. *H. capitatum* kırmızı kantaron bitkisi ile hem Türkiye'de hem de dünyada kapsamlı çalışmalar olmadığı için çalışmamız, bu alanda yapılacak diğer çalışmalara temel teşkil edip katkı sağlayacaktır.

Teşekkür

Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi Mikrobiyoloji Laboratuvarı'ndan kültür koleksiyonundaki klinik izolatlarını paylaşan Uzm. Biyolog Sayın Eldan Subaşı'na ve Tıbbi Mikrobiyoloji Anabilimdalı Başkanı Prof. Dr. Sayın Füsun Cömert'e teşekkürlerimizi sunarız.

Yazar Katkı Beyanı

Fikir: **Şükran Öztürk, Yasin Hazer,** Tasarım: **Şükran Öztürk, Yasin Hazer, Banu Kaşkatepe,** Veri Toplama: **Şükran Öztürk, Yasin Hazer, Muhittin Kulak,** Analiz veya Yorumlama: **Şükran Öztürk, Yasin Hazer, Banu Kaşkatepe, Hatice Çölgeçen,** Literatür Taraması: **Şükran Öztürk, Banu Kaşkatepe, Yasin Hazer, Hatice Çölgeçen, Muhittin Kulak,** Makalenin Yazımı: **Şükran Öztürk, Yasin Hazer,** Onay: **Şükran Öztürk, Yasin Hazer, Banu Kaşkatepe, Muhittin Kulak, Hatice Çölgeçen.**

Çıkar Çatışması

Yazarlar herhangi bir çıkar çatışması beyan etmemektedir.

Finansal Destek

Bu çalışma, Zonguldak Bülent Ecevit Üniversitesi Bilimsel Araştırma Projeleri (BAP) tarafından 2018-43085703-01 No' lu proje desteğiyle yürütülmüş ve tamamlanmıştır.

Etik Kurul Onayı

Zonguldak Bülent Ecevit Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurul Başkanlığınca 08.02.2023 tarih ve 2023/05 sayılı karar ile onay almıştır.

Hakemlik Süreci

Kör hakemlik süreci sonrası yayınlamaya uygun bulunmuştur.

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ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2023;7(1): 66-74
DOI: 10.29058/mjwbs.1248606

Effects of Pilates Exercises to Depression and Sleep Quality on the Postpartum Period: A Randomized Controlled Study

Pilates Egzersizlerinin Doğum Sonu Dönemde Depresyon ve Uyku Kalitesine Etkisi: Randomize Kontrollü Bir Çalışma

Halil Ibrahim BULGUROGLU[1], Merve BULGUROGLU[1], Cansu GEVREK ASLAN[2]

[1]Ankara Medipol University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Ankara, Turkey
[2]Ankara Medipol University, Vocational School of Health Services, Department of Therapy and Rehabilitation, Programme of Physiotherapy, Ankara, Turkey

ORCID ID: Halil Ibrahim Bulguroglu 0000-0002-6767-7062, Merve Bulguroglu 0000-0002-5923-4720, Cansu Gevrek Aslan 0000-0003-0750-3033

Cite this article as: Bulguroglu HI et al. Effects of pilates exercises to depression and sleep quality on the postpartum period: A randomized controlled study. Med J West Black Sea. 2023;7(1):66-74.

Corresponding Author
Halil Ibrahim Bulguroglu

E-mail
fztibrahim@hotmail.com

Received
08.02.2023

Revision
09.04.2023

Accepted
11.04.2023

ABSTRACT

Aim: Postpartum is one of the most critical processes in women. Many changes occur in the female body during this process. Exercise is the easiest method to manage these changes. Our study aimed to understand how postpartum depression, sleep quality, and functional levels affect women who perform pilates exercises.

Material and Methods: In this randomized controlled study, 57 postpartum volunteer women between six weeks and six months, aged 25-38, with a single baby, were randomly included in 28 pilates and 29 control groups. The pilates group was given pilates exercises for one hour a day, two days a week for 12 weeks, by a physical therapist. The control group was given a home program consisting of relaxation and breathing exercises. Before and after the study, depression was evaluated using the Edinburgh Postpartum Depression Scale (EPDS), sleep quality, the Postpartum Sleep Quality Scale (PSQS), and postnatal functional levels, the Inventory of Functional Status After Childbirth (IFSAC) was evaluated using the questionnaire form-filling method.

Results: EPDS (8.71±1.42 versus 7.06±1.21, p=0.001), PSQS (25.69±3.40 versus 22.91±3.04, p=0.001), IFSAC (2.47±0.41 versus 2.93±0.21, p=0.001) scores statistically significant improvements were observed in pilates group. While the control group did not show a significant difference in depression levels (8.85±1.50 versus 8.95±1.23, p=0.479), statistically worsening of sleep quality (26.17±3.41 versus 27.59±2.94, p=0.009) and postpartum functional level parameters were observed (2.65±0.42 versus 2.48±0.46, p=0.016).

Conclusion: The results showed that 12-week pilates exercises applied during the postpartum period could improve postpartum women's functional levels, depression levels, and sleep quality.

Keywords: Pilates exercises, postpartum period, postpartum depression, sleep quality

ÖZ

Amaç: Doğum sonrası dönem kadınlar için en kritik süreçlerden biridir. Bu süreçte kadın vücudunda birçok değişiklik meydana gelir. Egzersiz, bu değişiklikleri yönetmenin en kolay yöntemidir. Çalışmamız, pilates egzersizi yapan kadınların doğum sonrası depresyon, uyku kalitesi ve fonksiyonel düzeylerinin nasıl etkilediğini anlamayı amaçlamaktadır.

Gereç ve Yöntemler: Randomize kontrollü çalışmamızda, 25-38 yaş arası, tek bebeği olan 28 pilates ve 29 kontrol grubunda rastgele olacak şekilde 57 postpartum gönüllü kadın dahil edildi. Pilates grubuna 12 hafta boyunca haftada iki gün, günde bir saat fizyoterapist tarafından pilates egzersizleri verildi. Kontrol grubuna gevşeme ve nefes egzersizlerinden oluşan 12 haftalık ev programı verildi. Çalışma

öncesi ve sonrasında doğum sonrası depresyon; Edinburgh Postpartum Depresyon Ölçeği ile (EPDÖ), uyku kalitesi; Postpartum Uyku Kalitesi Ölçeği (PUKÖ) ve fonksiyonel düzey; Doğum Sonrası Fonksiyonel Durum Envanteri (DSFDE) ile değerlendirildi.

Bulgular: Pilates grubunda EPDÖ (8,71±1,42'ye karşı 7,06±1,21, p=0,001), PUKÖ (25,69±3,40'a karşı 22,91±3,04, p=0,001), DSFDE (2,47±0,41'e karşı 2,93±0,21, p=0,001) skorlarında istatistiksel olarak anlamlı iyileşmeler gözlendi. Kontrol grubu depresyon düzeylerinde anlamlı fark göstermezken (8,85±1,50'ye karşı 8,95±1,23, p=0,479), uyku kalitesi (26,17±3,41'e karşı 27,59±2,94, p=0,009) ve doğum sonrası fonksiyonel düzey parametrelerinde istatistiksel olarak bozulmalar gözlendi (2,65±0,42'ye karşı 2,48±0,46, p=0,016).

Sonuç: Sonuçlar, doğum sonrası dönemde uygulanan 12 haftalık pilates egzersizlerinin kadınların postpartum fonksiyonel düzeylerini, depresyon düzeylerini ve uyku kalitelerini iyileştirebileceğini göstermiştir.

Anahtar Sözcükler: Pilates egzersizleri, postpartum dönem, postpartum depresyon, uyku kalitesi

INTRODUCTION

The postpartum period is when a new member joins the family, and the mother tries to adapt to her baby, postpartum discomforts, and changes in body image (1). Significant changes can be observed in postpartum mothers' physical and mental states (2). Especially women who experience motherhood for the first time, they may not be able to adapt to the changes that occur, and they may experience many significant disorders, especially depression and sleep disorders (3).

Postpartum depression, which affects 20% of postpartum women worldwide, is increasing day by day (4). It is known that there is a relationship between postpartum depression and functionality and sleep quality (3,5). Along with depressed mood in the postpartum period, frequent feeding at night and postpartum pain affect sleep quality (6). The National Sleep Foundation reports that most new parents have an insufficient sleep (7). Sleep problems cause mother to a lack of concentration, increased depression, and difficulties in daily activities (8). Disruption of the sleep cycle in the first period of motherhood can be considered normal, but if this cycle lasts for months or worsens, it may affect both infant care and self-care of the mother and reduce the mother-infant bond. New mothers' poor sleep quality and depressed mood increase the risk of anxiety and impair their functional levels (9). During this period, the mother needs special effort and energy for her new process (10). Mothers defined the postpartum period as a period that causes changes in their own and familial functions (2,5). The earlier the women can increase her functional status, the more her self-efficacy will increase (11). The functional status of women after childbirth gradually decreases. The decrease in this level of functionality may come to a level that will affect both maternal health and infant care (12). Especially the decrease in sleep duration and quality can reduce the energy of mothers in the next day (13). In this process, the functional levels of fathers, who are the biggest supporters of mothers, may also be negatively affected. This situation, which may cause an increase in depressive situations in the family, may worsen the process of the mother (14).

Inactivity, which is common in today's world, can increase the risk of various problems for new mothers. These problems can negatively affect postpartum women's depression, functional level, and sleep quality (15). Exercise increases the number of beta-endorphins, which increase energy and reduce feelings of anger, confusion, depression, fatigue, and irritability (16,17). Especially after the first birth, baby care and other problems may decrease the participation rate in exercise. It is known that regular physical activity during this period will accelerate the physical recovery of the mother and positively affect her mood and other problems (18). All these effects make it easier for mothers to perform their daily activities (19).

The published guidelines state that women should do moderate-intensity exercise for at least 150 minutes a week after giving birth (20). Given the processes in the postpartum period, the Pilates method is one of the most well-known and reliable exercise programs worldwide for babies and mothers (21-23). However few studies have examined the effect of pilates exercises on sleep quality and depression levels in the postpartum period (24-27). Ko et al. applied an exercise program consisting of yoga and pilates exercises for 12 weeks and stated that the depression levels of mothers decreased (24). In another study, it was observed that the level of depression in postpartum women decreased after performing an exercise program consisting of pilates and yoga exercises for ten weeks (25). A study concluded that pilates exercises performing for eight weeks increased sleep quality in postpartum women (26). In another study, eight pregnant women were given 8-week online pilates exercises during their pregnancy. Positive developments were observed in evaluating depression and sleep quality in the eighth week after birth (27). Methodological deficiencies are evident in all these studies, and it is emphasized in the results that methodologically strong, randomized controlled studies should be conducted in the future. Considering that the problems may increase with the decrease in the mother's functionality level (28), the functionality of the mother is indispensable for the mother-child relationship. In the literature, few studies evaluate the relationship between the functionality level of the mother and pilates exercises.

Therefore, this study aims to determine the effects of pilates exercises performed with a physiotherapist in the postpartum period on depression, sleep quality, and functional levels of women.

MATERIAL and METHODS

Participants

Sixty-three postpartum volunteer women who applied to physiotherapy unit between May and June 2022 agreed to participate in the study and had no problem exercising during the postpartum examinations performed by the obstetrician were invited to our study, which we planned as a randomized controlled study. Three women did not meet the inclusion criteria, and two declined to participate. In conclusion, our study started with fifty-eight postpartum women. One of the participants in the Pilates group did not complete the study due to personal reasons, and as a result, our study was completed fifty-seven postpartum. The flow of participants is illustrated in Figure 1 in line with the CONSORT 2010 guidelines (29). All methods related to our study, which we conducted in accordance with the Declaration of Helsinki, were performed according to the CONSORT 2010 guidelines (Clinical Trials.gov Number NCT05397808, First Posted: 31/05/2022). Ethics committee approval was obtained from Ankara Medipol University Non-Interventional Clinical Research Ethics Committee (dated 23/05/2022, decree no: 0108).

The inclusion criteria were defined as being between six weeks and six months postpartum, being between 25-38 years old, giving birth for the first time, having a single baby, having a vaginal delivery, and not having any birth anomaly in herself or the baby. Women with multiple pregnancies

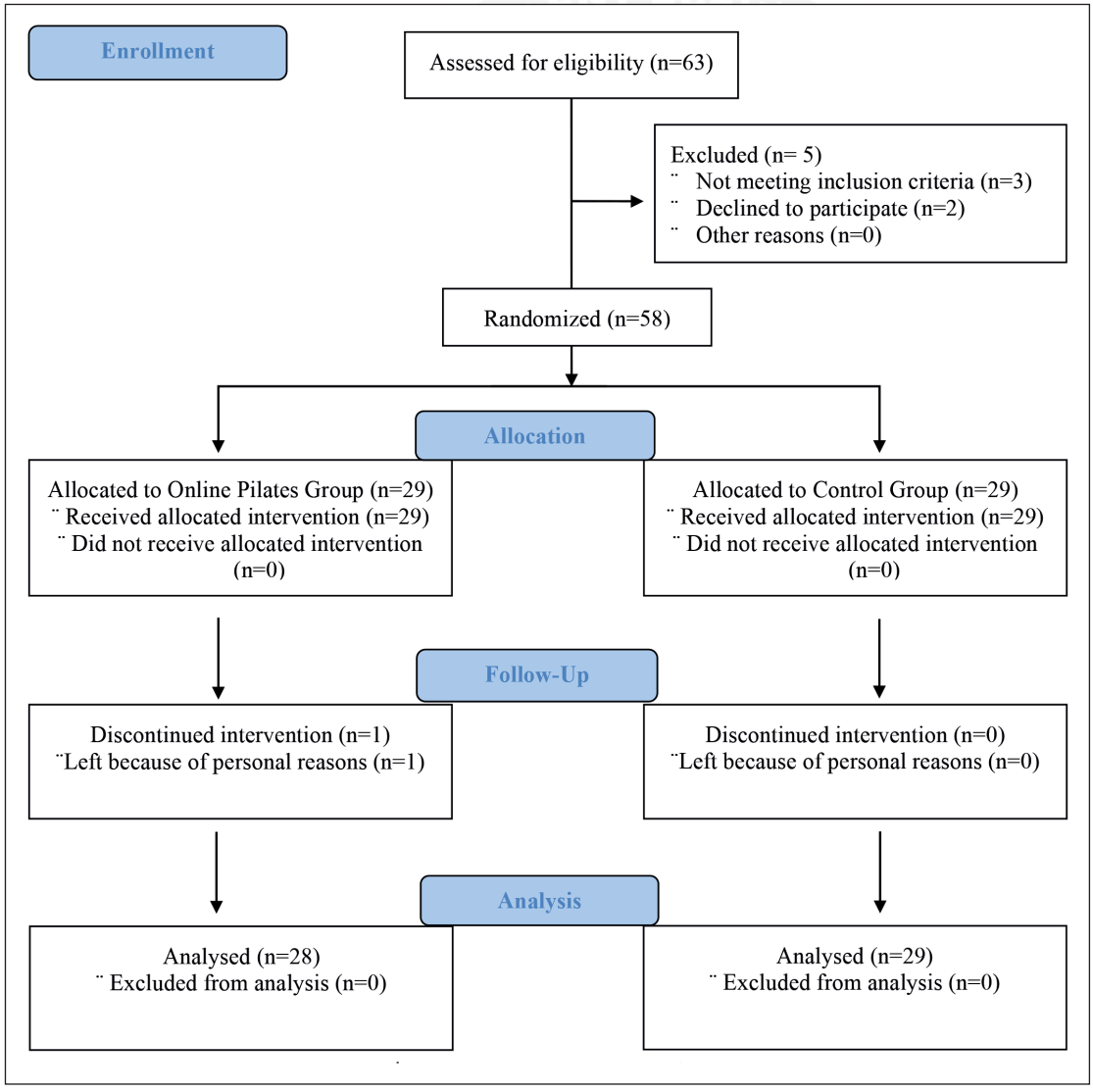

Figure 1: Flow diagram showing patient randomization and allocation processes.

and chronic diseases such as hemodynamically significant heart disease, restrictive lung diseases, diabetes, and hypertension were excluded from the study. Participants who participated in different activities or physiotherapy programs were excluded from the study.

In the power analysis to determine the sample size, to detect an effect size of Cohen's d=0.80 with 80 power (alpha=.05, two-tailed), G* Power version 3.1 suggested needing 26 participants per group in an independent samples t-test (30). 58 postpartum volunteer women (29 exercise group and 29 control group) were included in the study, considering the 10% dropout assumption.

Procedures

Before the study, its purpose and content were explained to the participants. Participants were assessed twice, at the beginning and end of the study, by an experienced blind physiotherapist. Randomization was performed with a program that generates random numbers (random.org) (24). Individuals who completed the initial assessment were randomly assigned to the pilates (PG) or control group (CG). The examiner and staff who performed the statistical analyses were blinded to the group assignment. In the final evaluation, the participants were asked not to report their participation in the training to the evaluator.

Intervention

Pilates training was performed by a certified, experienced, study-blind physiotherapist for one hour twice a week for 12 weeks. The exercise program recommended by the Australian Pilates and Physiotherapy Institute in the postpartum period was performed to the participants 30 minutes after breastfeeding (31). Pilates group was divided into two groups so that Pilates exercises could be applied more effectively. Pilates exercises were applied for 45 minutes. Before and after the exercises, 15-minute warm-up and cool-down exercises were given. The exercises applied within the scope of the Pilates exercise program are given in Table 1. In the first session, the basic principles and key elements of pilates were taught to the individuals, and they were asked to pay attention to them throughout the exercises. Visual and verbal imagery techniques were used during the exercise narrations. During the exercise, the individuals were carefully observed, and necessary corrections were made to the movements.

Table 1: Pilates exercises program

Movements	
1. Hundreds	2. Side Leg Lifts
3. Single Leg Circles	4. Arms Opening
5. Shoulder Bridge	6. Breaststroke Preparations
7. Single Leg Stretch	8. Swan
9. Clam	10. Swimming,
11. Sidekick	12. The Roll-Up.

The individuals in the control group were given relaxation and breathing exercises as part of a twelve-week home program. After the initial evaluation, a 50-minute program consisting of diaphragmatic breathing, expansion exercises, and respiratory control was given. Their first practice was done under the supervision of the instructor and it was ensured that they understood thoroughly. In the 4th, 8th, and 12th weeks, they were called by phone to check whether they adhered to the program.

Participants stated they should interrupt the exercises when side effects such as shortness of breath, dizziness, and weakness were observed. These effects did not occur in any of the participants during the process.

Outcome Measurements

The individuals included in the study were evaluated using data collection forms filled out through the questionnaires. The demographic information of the participants was recorded. Additionally, depression levels, postpartum sleep quality, and postpartum functional levels were evaluated.

Depression symptoms were the primary outcome of the study, and the Turkish version of the Edinburgh Postpartum Depression Scale (EPDS) was used to determine the postpartum depression levels of individuals (32). This scale determines the risk of depression in women in the postpartum period (33). The Cronbach's alpha value of the validity and reliability study of Aydın et al. was 0.72, while that of this study was 0.791. EPDS is a 10-item Likert-type self-report scale. Items 3, 5, 6, 7, 8, 9, and 10 gradually decrease strength and are scored as 3, 2, 1, and 0. Items 1, 2, and 4 are calculated as 0, 1, 2, and 3. The scale's total score is obtained by adding the item scores together. The lowest score on the scale is 0, and the highest score is 30. A score of 13 and above indicates a risk of depression.

Sleep Quality and Postnatal functional levels of individuals were secondary outcomes of the study, assessed by the Postpartum Sleep Quality Scale (PSQS) and Inventory of Functional Status After Childbirth (IFSAC) (34,35). The PSQS is a scale that measures women's sleep quality in the last two weeks postpartum. The items of the scale assess the duration of falling asleep, actual sleep time per night, difficulty falling asleep, waking up at midnight, waking up early in the morning, the effect of baby care and maternal physical state on sleep, feeling energetic throughout the day and satisfaction with sleep quality in the postpartum period. The items of the PSQS are scored between 0 and 4 on a 5-point Likert scale. The minimum score of the PSQS is 0, and the maximum available score is 56. Higher PSQS scores indicate worse sleep quality. The Turkish version of the scale

(36) was used in our study. The Cronbach's alpha value of the validity and reliability study of Boz and Selvi was 0.88, while that of this study was 0.91. The IFSAC consists of five subscales, including five dimensions of functional status and 36 four-point Likert-type questions to determine postpartum recovery. These include domestic, social, and community activities; baby care responsibilities; self-care; and professional activities. The total score was calculated by dividing the scores of all answered items by the number of answered items. Each question on the IFSAC was evaluated over four points (one to four). A high score (close to four) indicates high functional status. The Turkish version of the IFSAC was used in our study. The Cronbach's alpha value of the validity and reliability study of Ozkan and Sevil was 0.79, while that of this study was 0.834 (37).

Statistical Analysis

Statistical analyses were performed using SPSS software, version 26 (SPSS Inc. Chicago, IL, USA). Visual (histogram, probability graphs) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests) were used to determine whether the variables were normally distributed. Numerical variables with normal distribution are shown as mean ± standard deviation. Independent sample t test is used for demographic characteristics. The Repeated Measure ANOVA test was used to compare the data of the study and control groups that changed over time, and the paired-sample t-test was used for in-group comparisons. The statistical significance level was set at $p<0.05$ in all tests.

RESULTS

This study included 57 women. The two groups had similar demographic characteristics ($p>0.05$, Table 2). Although there was no statistical difference between the initial and twelve weeks postpartum BMI values of the pregnant women in both groups ($p>0.05$, Table 2), although the weeks progressed in the exercising group, the average BMI value of the participants decreased compared to the baseline (Table 2).

When the depression level results before and after the intervention were compared in the Pilates group, a statistically significant improvement was observed ($p<0.05$, effect size = 1.31, Table 3), while no difference was found in the control group ($p>0.05$, Table 3). When the sleep quality measurements before and after the Pilates group were compared, a statistically significant improvement was observed ($p<0.05$, effect size = 0.989, Table 3), while a statistically negative difference was found in the control group ($p<0.05$, Table 3). A statistically significant improvement was observed in the Pilates group before and after the measurements of the postpartum functional level parameters ($p<0.05$, effect size = 1.28, Table 3), while a statistically negative difference was found in the control group ($p<0.05$, Table 3).

In Table 4, a statistically significant difference was found with a large effect size in favor of the pilates group when the changes in the before and after depression level results of the study and control groups were compared ($F=39,753$; $p<0.001$, $\eta p2=0.429$).

In Table 4, a statistically significant difference was found with a large effect size in favor of the pilates group when the changes in the study and control groups before and

Table 2: Demographic characteristics of the groups

Characteristics*	Intervention (n= 28)	Control (n= 29)	p[a]
Age (years)	27.23±3.78	28.12 ± 3.52	0.321
Height (cm)	165±5.45	166±4.83	0.132
Weight (kg)	72 ± 4.8	74±5.11	0.674
BMI-1 (kg/cm²)	25.34 ± 4.81	25.89 ± 5.14	0.532
BMI-2 (kg/cm²)	24.21± 3.79	26.94± 4.92	0.187
Postpartum week	14.11± 5.79	15.03± 4.67	0.742

***Data are whown as mean±tandart deviation.**

a: Independent sample t test, **SD:** Standart deviation, **cm:** centimeters, **kg:** kilograms, **BMI:** body mass index, **PG:** Pilates group, **CG:** Control group, **n:** sample size.

Table 3: A comparison of the previous and subsequent measurement of depression, sleep quality, and postnatal functional levels for pilates and control groups

Measurements*	Groups	Pre-test	Post-test	p[1]	Effect Size
EPDS (0-30)	PG	8.71±1.42	7.06±1.21	**0.001****	1.31
	CG	8.85±1.50	8.95±1.23	0.479	0.97
PSQS (0-56)	PG	25.69±3.40	22.91±3.04	**0.001****	0.989
	CG	26.17±3.41	27.59±2.94	**0.009****	0.528
IFSAC (0-4)	PG	2.47±0.41	2.93±0.21	**0.001****	1.28
	CG	2.65±0.42	2.48±0.46	**0.016****	0.485

***Data are whown as mean±tandart deviation.**

p < 0.05, **1: paired samples t-test. **SD:** Standart deviation, **PG:** Pilates group, **CG:** Control group, **EPDS:** Edinburgh Postpartum Depression Scale, **PSQS:** Postpartum Sleep Quality Scale, **IFSAC:** Inventory of Functional Status After Childbirth.

Table 4: Comparison of the data of the study and control groups that changed over time

Scales*	Groups	Pre-test	Post-test	p	ηp2
EPDS	PG	8.71±1.42	7.06±1.21	**<0.001****	0.429
	CG	8.85±1.50	8.95±1.23		
PSQS	PG	25.69±3.40	22.91±3.04	**<0.001****	0.375
	CG	26.17±3.41	27.59±2.94		
IFSAC	PG	2.47±0.41	2.93±0.21	**<0.001****	0.453
	CG	2.65±0.42	2.48±0.46		

***Data are whown as mean±tandart deviation.**

p < 0.05, Repeated Measures Anova Test, **ηp2: partial eta squared**, PG:** Pilates group, **CG:** Control group, **EPDS:** Edinburgh Postpartum Depression Scale, **PSQS:** Postpartum Sleep Quality Scale, **IFSAC:** Inventory of Functional Status After Childbirth.

after sleep quality measurement results were compared (F=31,865; p<0.001, ηp2=0.375). In Table 4 examined, a statistically significant difference was found with a large effect size in favor of the pilates group when the changes in the study before and after postpartum functional level results and control groups were compared (F=43,824; p<0.001, ηp2 =0.453).

DISCUSSION

This study showed that pilates exercises administered to postpartum women could reduce depression and improve sleep quality and postnatal functionality. Although few studies have shown the effects of pilates exercises specifically involved in the postpartum period on postpartum depression, studies have shown that exercise combinations, including pilates exercises, are effective in postpartum depression (24,25,27). In addition, it has been stated in the literature that women can benefit from cognitive behavioral therapy, interpersonal therapy, and psychodynamic psychotherapy (38) to reduce depression levels, and that education programs given in the prenatal period can also be effective (39).

In their study of 23 postpartum women, Ko et al. stated that the exercise program, including pilates and yoga exercises, had a statistically significant effect, especially in women with high depression levels (24). Another study using a combination of pilates, yoga, and elastic band exercises showed that postpartum depression decreased after ten weeks of training (25). Kim and Hyun showed that 8-week pilates training during pregnancy could be effective in the postpartum period (27). However, the most important limitations of these studies are the small number of participants in the research and the absence of a comparable control group. In addition, the inclusion criteria of these studies lacked an expression of the mode of delivery and trauma that may occur at birth. The mode of delivery and trauma that may occur during and after birth can seriously affect the level of depression in postpartum women (28). Therefore, to make our research more reliable, those who gave birth by cesarean section and traumas that occurred during or after delivery were excluded from our research. Previous studies report that regular exercise effectively manages stress, reduces depression, and improves personal self-esteem and body image (40). When pilates exercises are applied together with the breathing techniques in their nature, it helps individuals feel more energetic and fit (41). In addition, women may feel more alone during the new motherhood process. Socializing with other mothers and interacting with the instructor can reduce these feelings and reduce the level of depression (42). Therefore, we interfere that the decrease in depression levels in our study is because the women exercised regularly for 12 weeks and socialized with others during the exercise.

We observed that 12 weeks of pilates training improved the sleep quality of postpartum women. Although there is only one study in the literature on the effect of pilates exercises on postpartum sleep quality (26), methods such as cognitive behavioral therapy and light-dark therapy were found to be effective in reducing sleep problems (43).

Ashrafinia et al. observed that the sleep quality of postpartum women improved with eight weeks of pilates training in their study (26). They also emphasized the importance of pilates exercises to maintain physical and mental health postpartum. The most crucial difference between Ashrafia et al.'s and ours is that our study used a postpartum process specific sleep quality scale. Therefore, we think that sleep problems can be better examined, particularly during the postpartum period. In our study, we observed that the sleep quality of the pilates group improved positively, while that of the control group was negatively affected as the weeks progressed. It is common for the mother's sleep quality to deteriorate with the new period. The sleep problem seen during the new motherhood period is one of the critical problems that may affect the mother-baby and mother-family harmony that can be seen in the mother (44). In the literature, methods such as cognitive behavioral therapy and Light dark therapy have been used and found effective to reduce sleep problems (43). The improvement in sleep quality,

which is one of the essential parts of the result we obtained with our study, will also facilitate the daily life functions of mothers. Breathing exercises used in Pilates exercises help the individual calm down (45). In addition, the physical benefits of pilates exercises help the mother feel more vigorous and gain self-confidence (26). All of these may have helped improve the mother's sleep quality. In addition, pilates exercises comfort the mother by improving her mental health, contributing to increased sleep quality.

In our study, positive improvements were observed functional levels of mothers in the Pilates group at the end of 12 weeks. In contrast, functional levels of mothers in the control group worsened. Although there are no studies in the literature showing how exercise affects the postpartum functional level of the mother, few studies have shown the effects of various methods on the postpartum functional level (39,46-48). In these studies, postnatal and skills training approaches improve postnatal functional levels. In addition, It has been shown in the literature that physical activity during pregnancy and antenatal education may not affect postpartum functionality (39,49). Mothers with a high level of functionality also have a high level of maternal attachment. Social and psychological supports contribute to increasing functionality and motherly affection (48). It is also known that women with postpartum depression have a lower level of functionality (5). Pilates exercises reduce mothers' depression levels1 and increase their functional capacity by providing physical recovery (24,25). With the self-confidence provided by the training, the mother, moves more quickly. In addition, Pilates exercises minimize the painful problems seen in the postpartum period (50). All these developments may have increased the mother's level of functionality and allowed her to adapt to motherhood and her own life more quickly.

One of the strengths of our study was that it was a randomized controlled trial. Another strength of our study is that it is the first to evaluate the effect of exercise on the functional level of the mother. The questionnaires used in the study were pregnancy-specific, and the inclusion and exclusion criteria were well-defined compared to other studies. The most important limitation of our study is the lack of postpartum care training and exercise training. Another limitation of our study is that its relationship with IFSAC sub-dimensions was not examined. In addition, studies with larger samples are needed to examine the effects of different exercise methods on postpartum women. However, examining the effects of exercise programs that can be applied online in the postpartum period, considering the newborn baby and other situations, is necessary.

In conclusion, motherhood was one of the holiest periods for women. During this period, supporting the mother and ensuring the mother-child relationship is very important. This study shows the importance of pilates training for mothers to maintain their functions and social participation by gaining healthy habits. Therefore, our study can guide physiotherapists and the literature. Pilates exercise training reduces depression levels in postpartum women and increases sleep quality and functionality. Future studies should examine the effects of different exercise methods in postpartum women.

Acknowledgment

None.

Author Contributions

Concept: **Halil İbrahim Bulguroğlu,** Design: **Halil İbrahim Bulguroğlu,** Data collection or processing: **Merve Bulguroğlu, Cansu Gevrek Aslan,** Analysis or Interpretation: **Merve Bulguroğlu, Cansu Gevrek Aslan,** Literature search: **Halil İbrahim Bulguroğlu, Merve Bulguroğlu, Cansu Gevrek Aslan,** Writing: **Halil İbrahim Bulguroğlu, Merve Bulguroğlu, Cansu Gevrek Aslan.**

Conflicts of Interest

The authors have no conflicts of interest to declare.

Financial Support

This research was carried out without funding.

Ethical Approval

The research project was approved with the decision of Ankara Medipol University Non-Interventional Clinical Research Ethics Committee (dated 23/05/2022, decision no: 0108).

Review Process

Extremely peer-reviewed and accepted.

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ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2023;7(1): 75-80
DOI: 10.29058/mjwbs.1232968

The Role of Wrist Circumference (Regional Obesity Versus Local Swelling) in Conservatively Treated Distal Radius Fractures: A Single Center Experience

Konservatif Olarak Tedavi Edilen Distal Radius Kırıklarında El Bilek Çevresinin Rolü (Bölgesel Obeziteye Karşı Lokal Şişlik): Tek Merkez Deneyimi

Erdi ÖZDEMİR, Ozan ALTUN, Yılmaz ERGİŞİ, Uygar DAŞAR, Muhammed Nadir YALÇIN

Karabuk University Faculty of Medicine, Department of Orthopedics and Traumatology, Karabuk, Turkey

ORCID ID: Erdi Özdemir 0000-0002-3147-9355, Ozan Altun 0000-0002-0901-5247, Yılmaz Ergişi 0000-0003-2456-6802, Uygar Daşar 0000-0002-2039-7426, Muhammed Nadir Yalçın 0000-0003-3158-200X

Cite this article as: Özdemir E et al. The role of wrist circumference (regional obesity versus local swelling) in conservatively treated distal radius fractures: A single center experience. Med J West Black Sea. 2023;7(1):75-80.

Corresponding Author
Erdi Özdemir

E-mail
erdiozdemir@gmail.com

Received
12.01.2023
Revision
23.03.2023
Accepted
31.03.2023

ABSTRACT

Aim: Regional obesity around the wrist due to local excessive fat or local swelling due to edema has not been studied as a risk factor to predict the possibility of reduction loss during conservative treatment of distal radius fractures. We aimed to investigate the impact of wrist circumference on reduction loss risk in conservatively treated distal radius fractures.

Material and Methods: Patients with distal radius fractures who were conservatively in our institution between January 2021 and December 2021 are retrospectively reviewed. Patients' demographics, wrist circumference, radiographic parameters were obtained from hospital registry notes. Wrist circumference was measured with an unstretchable tape positioned on a line passing from lister tubercle of the distal radius and distal ulna. The difference in the wrist circumferences between the injured and uninjured extremities represented local swelling. The association of these factors with reduction loss was evaluated.

Results: A total of 73 consecutive patients (19 male, 54 female) with a mean age of 61.1 ± 12.9 were included. There were 18 reduction losses. There was no association with reduction loss between injured and uninjured wrist circumferences ($p>0.05$). However, local swelling, initial displacement at dorsal angulation and radial inclination, presence of dorsal comminution, and accompanying ulnar styloid fracture were associated with reduction loss ($p<0.05$). Local swelling had an odd ratio of 6.661 (1.848 – 24.006, p= 0.004).

Conclusion: Excessive local swelling is found to be a risk factor to predict reduction loss in conservative treatment of distal radius fractures while regional obesity is not.

Keywords: Wrist circumference, regional obesity, local fat, distal radius fracture, redisplacement

ÖZ

Amaç: Distal radius kırıklarının konservatif tedavisi sırasında redüksiyon kaybı olasılığını öngörmek için lokal aşırı yağ dokusuna bağlı bölgesel obezite veya ödeme bağlı lokal şişlik araştırılmamıştır. Konservatif olarak tedavi edilen distal radius kırıklarında bilek çevresinin redüksiyon kaybı riski üzerindeki etkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Ocak 2021-Aralık 2021 tarihleri arasında kliniğimizde konservatif olarak izlenen distal radius kırığı olan hastalar retrospektif olarak incelendi. Hastaların demografik bilgileri, bilek çevresi, radyografik parametreleri hastane kayıt notlarından elde edildi. Bilek çevresi, distal radius ve lister tüberkülü ve distal ulnadan geçen bir hat üzerinde konumlandırılan ve gerilemez bir bant ile

ölçüldü. Kırık ve sağlam ekstremiteler arasındaki el bilek çevrelerindeki fark, lokal şişlik olarak tanımlandı. Bu faktörlerin redüksiyon kaybı ile ilişkisi değerlendirildi.

Bulgular: Yaş ortalaması 61.1 ± 12.9 olan toplam 73 ardışık hasta (19 erkek, 54 kadın) çalışmaya dahil edildi. 18 adet redüksiyon kaybı görüldü. Kırık ve sağlam el bilek çevresi ölçüleri ile redüksiyon kaybı ile ilişki yoktu (p>0.05). Ancak lokal şişlik, dorsal açılanma ve radyal eğimdeki ilk yer değiştirme, dorsal parçalanma varlığı ve eşlik eden ulnar stiloid kırığı; redüksiyon kaybı ile ilişkiliydi (p<0.05). Lokal şişliğin odd oranı 6,661 idi (1,848 – 24,006, p= 0,004).

Sonuç: Aşırı lokal şişlik, distal radius kırıklarının konservatif tedavisinde redüksiyon kaybını öngörmek için bir risk faktörü olarak bulunurken, bölgesel obezite bulunmamıştır.

Anahtar Sözcükler: El bilek çapı, Bölgesel obezite, Bölgesel yağlanma, Distal radius kırığı, Redüksiyon kaybı.

INTRODUCTION

Distal radius fractures are one of the most common injuries that occur on the upper extremity worldwide. Distal radius fractures account for around 17% of all adult fractures diagnosed (1). These injuries are reported to affect more than 85.000 individuals per year in the United States. Its incidence is rising in older adulthood due to prolonged life expectancy and accompanying osteoporosis in this elderly population (2).

Several treatment options exist in the treatment of distal radius fractures. Closed reduction and casting is the mainstay of conservative treatment. However, reduction loss in the cast is the major drawback of this treatment modality in addition to slow functional recovery due to prolonged immobilization (3). The incidence of reduction loss was reported up to 64% in the previous literature (4). Open reduction and internal fixation is also well-established treatment for these injuries. Volar plates are the most popular fixation devices in surgical treatment (5). Although good functional outcomes have been reported after both conservative and surgical treatments, the ideal treatment modality is still being debated (6).

Several anthropometric indicators such as wrist circumference, waist circumference, waist to hip ratio, and body mass index (BMI) have been described to determine obesity. Although BMI is the most common method for the determination of obesity, it cannot differentiate body fat distribution (7). In recent studies, wrist circumference has been shown to be a better indicator than BMI in terms of defining the fat distribution (8, 9).

Reduction loss during conservative treatment of distal radius fractures is a frequent issue. Therefore, predictive factors for reduction loss have been extensively studied in the literature (3, 10). Lafontaine et al. described the former criteria for fracture instability including initial dorsal angulation above 20 degrees, dorsal comminution, intraarticular fracture, accompanying ulnar fracture and age over 60. Any fracture posing three or more criteria are considered unstable (11). Several studies confirmed these criteria (12) while some did not (10). In addition to these criteria, obesity is identified as a risk factor as well (13). Although the correlation of wrist circumference with obesity has been described (14), regional obesity around the wrist has not been studied yet as a risk factor for reduction loss. Furthermore, local swelling around the wrist is not an uncommon finding but is not quantified as a risk factor for reduction loss. Following these rationales, we hypothesized that wrist circumference in the contralateral extremity as a regional obesity marker and wrist circumference difference between the injured and contralateral extremity as a local swelling parameter could be a risk factor for reduction loss in the conservative treatment of distal radius fractures. The aim of this study is to investigate the impact of wrist circumference on reduction loss risk in distal radius fractures.

MATERIAL and METHODS

Patients who had distal radius fractures and were conservatively treated with closed reduction and casting in our institution between January 2021 and December 2021 are retrospectively reviewed. The protocol of the study was approved by the local ethics committee (2021/743). A written informed consent was obtained from each patient. The study was conducted in accordance with STROBE guidelines. Patients with neurovascular injury, open fractures, accompanying radius deformity, history of previous ipsilateral radius fractures, lost during follow-up, and aged below 18 were excluded.

Patients' demographics, BMI, and waist circumference was obtained from hospital registry records. Radiographic evaluation of the patients included fracture type according to AO (Arbeitsgemeinschaft für Osteosynthesefragen) classification, dorsal angulation and radial inclination of the fracture prior to closed reduction, presence of dorsal comminution and ulnar styloid fracture, cast index after closed reduction. Patients with excessive local swelling at the initial presentation were placed in a short arm splint to reduce swelling before close reduction and casting. The timing of the closed reduction was determined by the surgeon's preference.

AO classification was used to classify the distal radius fractures. AO classification groups extra-articular fractures as AO 23-A, partial articular fractures as AO 23-B, and complete articular fractures as AO 23-C (15).

Patients' wrist circumference of injured and uninjured extremities was recorded prior to closed reduction. Wrist circumference was measured with an unstretchable tape positioned on a line passing from the lister tubercle of the distal radius and distal ulna in a sitting position (14) (Figure 1). Local swelling was defined as the difference in the wrist circumference between the injured and uninjured extremities. Patients who had unacceptable reduction criteria (>10° dorsal angulation, radial shortening >3 mm, or intra-articular step-off) on weekly obtained radiographs were considered as loss of reduction (Figure 2). Patients' radiographs were obtained at 1st, 2nd, 3rd, and 6th weeks.

Descriptive statistics were expressed as mean and standard deviation (SD) for continuous numerical variables, categorical variables were expressed as number of patients and percentage. Distribution of variables was measured with the Kolmogorov-Smirnov test. Statistical analysis was performed with t-test to compare mean values. Categorical variables were compared with Pearson Chi-square test. A multiple logistic regression analysis was used to analyze relationship between risk factors and reduction loss. The results were considered statistically significant when the p-value was <0.05.

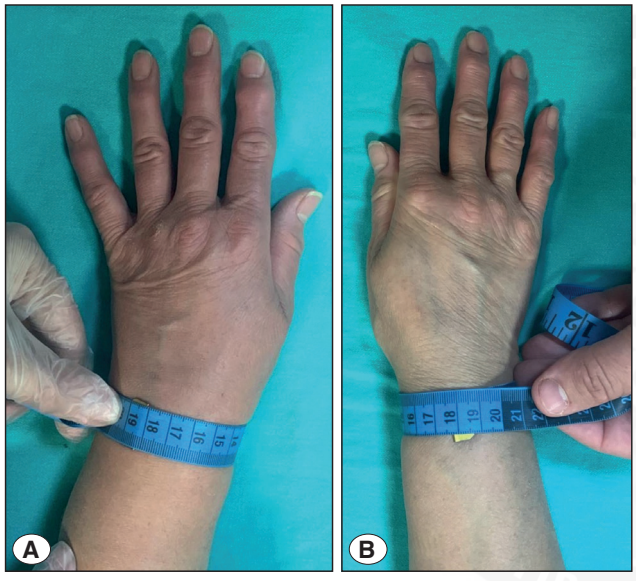

Figure 1: A) Measurement of wrist circumference on the injured and **B)** uninjured extremity.

RESULTS

A total of 73 consecutive patients (19 male, 54 female) with a mean age of 61.1 ± 12.9 were included in the study. During conservative treatment, 18 patients had reduction loss. Of these 18 reduction losses, 5 occurred in the first week while 13 occurred in the second week.

There was no statistical difference in age and gender, BMI, waist circumference, injured and uninjured wrist circumferences, cast index, or fracture type in patients who had reduction loss and whose reduction were maintained (p>0.05). However, local swelling was significantly higher in patients who had loss of reduction (2.1 ± 0.7 cm versus 1.2 ± 0.6, p<0.001). Initial displacement of the fracture including dorsal angulation and radial inclination, presence of dorsal comminution, and ulnar styloid fracture were associated with loss of reduction (p<0.05) (Table 1). Logistic regression analysis revealed local swelling had an odd ratio of 6.661 (1.848 – 24.006, p= 0.004). (Table 2).

DISCUSSION

Reduction loss after conservative treatment of distal radius fractures is a frequent problem (10). Identification of risk factors for reduction loss helps orthopedic surgeons in managing this injury in a more optimal manner. For that reason, risk factors for loss of reduction after conservative

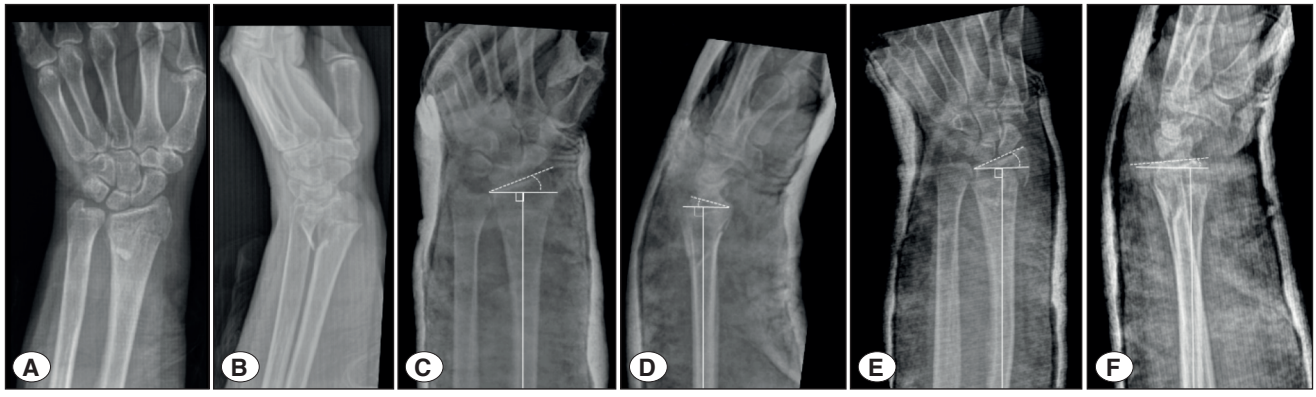

Figure 2: A) Anteroposterior (AP) and **B)** lateral radiographs of a 61-year-old female patient with AO type 23-A distal radius fracture. After closed reduction, **C)** AP radiograph showed 20° of radial inclination and **D)** lateral view showed 8° of volar tilt. At 2nd week follow-up, there was a reduction loss on **E)** AP and **F)** lateral views with 14° of radial inclination, 5° of dorsal angulation, and 4 mm of radial shortening.

Table 1: Demographics, wrist circumferences, and radiographic parameters between reduction loss and reduction maintained groups.

	Reduction loss (n=18)	Reduction maintained (n=55)	p
Age (years), mean ± SD	64.8 ± 12.2	59.5 ± 13.2	0.140
Gender (M/F)	3/15	16/39	0.297
BMI (kg/m^2), mean ± SD	29.6 ± 5.8	29.1 ± 5.9	0.729
Waist circumference (cm), mean ± SD	102.5 ± 11.2	102.3 ± 12.6	0.959
Uninjured contralateral wrist circumference (cm), mean±SD	17.6 ± 1.4	17.8 ± 2.2	0.704
Injured wrist circumference (cm), mean ± SD	19.8 ± 1.7	19.0 ± 2.4	0.245
Local swelling (cm), mean ± SD	2.1 ± 0.7	1.2 ± 0.6	<0.001
Cast index, mean ± SD	76.7 ± 10.3%	79.2 ± 5.9%	0.214
Fracture type (AO classification)			0.321
AO 23-A	14	32	
AO 23-B	2	10	
AO 23-C	2	13	
Dorsal angulation, mean ± SD	22.3° ± 7.0°	13.0° ± 13.0°	0.009
Dorsal comminution	11/18	16/55	0.015
Radial inclination, mean ± SD	17.1° ± 4.1°	20.0° ± 3.7°	0.006
Ulnar styloid fracture	14/18	18/55	0.001
Intra-articular fracture	4/18	24/55	0.105

M: Male, **F:** Female, **BMI:** Body mass index

Table 2: Multivariate regression analysis for risk factor of reduction loss.

	Odds ratio (95% confidence interval)	p
Local swelling	6.661 (1.848 – 24.006)	0.004
Ulnar styloid fracture	4.672 (0.984 – 2.222)	0.052
Female gender	2.881 (0.425 – 19.607)	0.278
Dorsal comminution	1.325 (0.253 – 6.939)	0.739
Dorsal angulation	1.003 (0.932 – 1.077)	0.939
Radial inclination	1.113 (0.892 – 1.388)	0.343

treatment of distal radius fractures have been extensively studied in the literature (12, 16). Although reduction loss has multifactorial causes, our study showed local swelling at the fractured wrist compared to the uninjured side significantly increased the reduction loss risk, however, there was no relation between contralateral wrist circumference as a regional obesity marker with reduction loss.

Obesity has also been shown as a risk factor for reduction loss in conservative treatment of distal radius fractures (13). In the previous literature investigating obesity as a risk factor for fracture displacement, it is commonly defined and stratified using BMI values of the patients (17). Furthermore, the association between wrist circumference and obesity has been documented (14). However, to the best of our knowledge, there is no previous study investigating the wrist circumference as an obesity parameter that could be a risk factor for loss of reduction after conservative treatment of the distal radius fracture. In this study, we have not found an association with contralateral wrist circumference as an obesity parameter with the reduction loss of distal radius fractures. Given the similar cast index values in reduction loss and maintained group, we may argue that proper casting techniques allowed manipulation of subcutaneous fat tissue around the wrist.

Local swelling around distal radius fracture is a common finding. Soft tissue edema after surgery of distal radius fractures is associated with prolonged pain and joint contracture (18). Several methods such as compression therapy (19), and intermittent pneumatic compression devices (20) have been described for the reduction of postoperative local tissue swelling. Although it is a well-known entity, quantitative analysis of local swelling has not been discussed in reduction loss after conservative treatment of distal radius fractures. We have found that local tissue swelling is significantly associated with reduction loss. We believe that manipulation of local swelling is challenging and sometimes impossible with casting techniques. Awareness of local swelling as a risk factor for reduction loss is important in decision making of distal radius fractures and could be considered as a relative surgical indication.

Reduction loss is a multifactorial entity in the conservative treatment of distal radius fractures. Several risk factors were identified which included but were not limited to accompanying ulnar styloid fracture, dorsal comminution, initial displacement, and older age (10). The univariate analysis of this study showed initial displacement, dorsal comminution, and accompanying ulnar styloid fracture are associated with an increased risk of reduction loss. Our findings were in line with the previous literature.

The incidence of reduction loss following conservative treatment of distal radius fractures was reported to be up to 64% (4). In this study, 18 of 73 (24.6%) patients had reduction loss. Of these 18 patients, 13 had reduction loss between the first- and second-week interval. Considering local swelling is the greatest risk factor in our series, we believe that the majority of the local swelling resolves between the first- and second-week interval. Orthopedic surgeons should be aware of this specific interval, especially in patients with excessive initial swelling.

There are several limitations of this study. First, this is a retrospective study. Second, the study was performed in a single institution therefore its results cannot be generalized to entire population. Third, although the method for wrist circumference measurement was clearly described in the literature (14), it has been not validated.

Excessive local swelling is found to be a risk factor to predict loss of reduction in conservative treatment of distal radius fractures while regional obesity is not. Local fatty tissue that increases wrist circumference can be manipulated with proper casting techniques, whereas edema cannot be managed optimally. Patients with excessive swelling may benefit from exchange casting following the resolution of edema.

Acknowledgment

None.

Author Contributions

Concept: **Erdi Özdemir, Ozan Altun, Yılmaz Ergişi, Uygar Daşar, Nadir Yalçın,** Design: **Erdi Özdemir, Ozan Altun, Yılmaz Ergişi, Uygar Daşar, Nadir Yalçın,** Data collection and processing: **Erdi Özdemir, Ozan Altun, Yılmaz Ergişi, Uygar Daşar, Nadir Yalçın,** Analysis and interpretation of data: **Erdi Özdemir, Ozan Altun, Yılmaz Ergişi, Uygar Daşar, Nadir Yalçın,** Literature review: **Erdi Özdemir, Ozan Altun, Yılmaz Ergişi, Uygar Daşar, Nadir Yalçın,** Writing of the manuscript: **Erdi Özdemir, Ozan Altun, Yılmaz Ergişi, Uygar Daşar, Nadir Yalçın.**

Conflicts of Interest

All the authors declare no conflict of interest.

Financial Support

None.

Ethical Approval

This study was approved by the local ethics committee of Karabuk University (no. 2021/743).

Review Process

Extremely peer-reviewed and accepted.

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ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2023;7(1): 81-91
DOI: 10.29058/mjwbs.1098894

Examining the Relationship between Adolescence Problems and Computer (Computer, Internet, Game) Addiction with Canonic Correlation Analysis in Turkish Generation K Adolescents: Ordu Province Center (Altinordu) Example

Türk K Kuşağı Ergenlerinde Ergenlik Sorunları ile Bilgisayar (Bilgisayar, İnternet, Oyun) Bağımlılığı Arasındaki İlişkinin Kanonik Korelasyon Analizi ile İncelenmesi: Ordu İl Merkez (Altınordu) Örneği

Nevin GÜNAYDIN[1], **Yeliz KAŞKO ARICI**[2]

[1]Ordu University, Faculty of Health Sciences, Department of Psychiatric Nursing, Ordu, Turkey
[2]Ordu University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, Ordu, Turkey

ORCID ID: Nevin Günaydın 0000-0002-5382-6354, Yeliz Kaşko Arıcı 0000-0001-6820-0381

Cite this article as: Günaydın N and Kaşko Arıcı Y. Examining the relationship between adolescence problems and computer (computer, internet, game) addiction with canonic correlation analysis in Turkish generation K adolescents: Ordu province center (Altinordu) example. Med J West Black Sea. 2023;7(1):81-91.

Corresponding Author
Nevin Günaydın

E-mail
nevin_altintas@yahoo.com.tr

Received
05.04.2022

Revision
28.12.2022

Accepted
03.01.2023

ABSTRACT

Aim: This study was conducted to examine the relationship between computer addiction (computer, internet, game addiction) and adolescent problems in Turkish generation K adolescents with correlation analysis.

Material and Methods: This study is a cross-sectional study. This research was carried out in three high schools in the city center of a city selected according to their success ranking in the high school entrance exam. In the study, a total of 665 students who received parental and student permission were included. Adolescents' Computer (computer/internet/game) Addiction Scale and Adolescence Problems Scanning List were used to gathering data. In the study, subscales of computer addiction scale for adolescence (computer, internet, game) were determined as Set 1, and subscales of adolescence problems scanning list (physical, social, relationship with the opposite sex and sexual information, psychological, future expectations) were determined as Set 2. Expected relationships between these Set 1 and Set 2 explained in an efficient manner by canonical weights and loadings.

Results: Three canonical variate pairs were ranging from 0.688 to 0.150. It was observed that the first and the second pairs were significant ($p<0.001$). In the Adolescents' Computer Addiction Scale, computer game addiction was the most significant parameter (1.064). In order to obtain high value for U1 canonical variate, while game addiction should be increased because of positively correlated, CA should be shrunk because of negatively correlated. Therefore, when the game addiction subscale is high and the computer and internet addiction subscales are low, it is expected that the psychological and social problems subscales will take high values. In the adolescence problems scanning list, psychological development problems were the most significant parameters (0.702). The value for V1 canonical variate increases with the increase of psychological development problems and social development problems. In contrast, the increase in the physical development problems reduces the value of the V1 canonical variable.

Conclusion: Present data revealed that there were positive and moderate correlations between computer addiction and adolescence problems of generation K. Canonical correlation analysis showed

that the adolescence problems had a significant variance in explaining the adolescent's computer (computer/internet/game) addiction, while the adolescent's computer addiction had significant variance in explaining the adolescence problems.

Keywords: Computer addiction, Internet addiction, Game addiction, Adolescence problems, Canonical correlation analysis

ÖZ

Amaç: Bu çalışma, Türk K kuşağı ergenlerinde bilgisayar bağımlılığı (bilgisayar, internet, oyun bağımlılığı) ile ergen sorunları arasındaki ilişkiyi korelasyon analizi ile incelemek amacıyla yapılmıştır.

Gereç ve Yöntemler: Bu çalışma kesitsel bir çalışmadır. Bu araştırma, lise giriş sınavı başarı sıralamasına göre seçilen bir il merkezindeki üç lisede gerçekleştirilmiştir. Araştırmada veli ve öğrenci izni alınan toplam 665 öğrenci çalışmaya dahil edilmiştir. Veri toplamak için Ergen Bilgisayar (bilgisayar/internet/oyun) Bağımlılığı Ölçeği ve Ergenlik Sorunları Tarama Listesi kullanılmıştır. Çalışmada ergenler için bilgisayar bağımlılığı ölçeğinin alt ölçekleri (bilgisayar, internet, oyun) Set 1 olarak belirlenmiş ve ergenlik sorunları tarama listesi (fiziksel, sosyal, karşı cinsle ilişki ve cinsel bilgiler, psikolojik, gelecek beklentileri) alt ölçekleri Set 2 olarak belirlenmiştir. Bu Set 1 ve Set 2 arasındaki beklenen ilişkiler kanonik ağırlıklar ve yüklemeler ile etkin bir şekilde açıklanmıştır.

Bulgular: Çalışmada, 0,688 ile 0,150 arasında değişen üç kanonik değişken çifti vardı. Birinci ve ikinci çiftlerin anlamlı olduğu gözlendi ($p<0,001$). Ergenlerin Bilgisayar Bağımlılığı Ölçeğinde bilgisayar oyunu bağımlılığı en önemli parametredir (1,064). U1 kanonik değişkeninin yüksek değer elde etmesi için pozitif korelasyon nedeniyle oyun bağımlılığının arttırılması, negatif korelasyon nedeniyle CA'nın küçültülmesi gerekmektedir. Dolayısıyla, oyun bağımlılığı alt ölçeği yüksek olduğunda, bilgisayar ve internet bağımlılığı alt ölçekleri ise düşük olduğunda psikolojik ve sosyal problemler alt ölçeklerinin yüksek değerler alması beklenmektedir. Ergenlik sorunları tarama listesinde psikolojik gelişim sorunları, en önemli parametre (0,702) idi. V1 kanonik değişkeninin değeri, psikolojik gelişim sorunları ve sosyal gelişim sorunları arttıkça artmaktadır. Buna karşılık fiziksel gelişim problemlerindeki artış V1 kanonik değişkeninin değerini düşürmektedir.

Sonuç: Mevcut veriler, bilgisayar bağımlılığı ile K kuşağı ergenlerinin ergenlik sorunları arasında pozitif ve orta düzeyde ilişki olduğunu ortaya koymuştur. Kanonik korelasyon analizi, ergenlik sorunlarının ergenin bilgisayar (bilgisayar/internet/oyun) bağımlılığını açıklamada önemli bir varyansa sahip olduğunu, ergenin bilgisayar bağımlılığının ise ergenlik sorunlarını açıklamada önemli bir varyansa sahip olduğunu göstermiştir.

Anahtar Sözcükler: Bilgisayar bağımlılığı, İnternet bağımlılığı, Oyun bağımlılığı, Ergenlik sorunları, Kanonik korelasyon analizi

INTRODUCTION

Internet and computer addiction is emerging as children and young adults increase their time on the internet (1). In the last 20 years, internet use and playing computer games by adolescents (including generation Z and K) has become a notable topic (2,3). Internet, computer, and game addiction were not included in DSM-4 (Diagnostic and Statistical Manual of Mental Disorders Version) as a separate diagnosis. In 2013, DSM-5 created a separate and temporary heading for internet addiction under the heading of "Internet Gaming Disorder" (4).

Intensive studies in this field have shown that the most important risk group in terms of addictions related to computers and the internet are adolescents as they have not yet reached sufficient psychological maturity (5,6). According to the World Health Organization, adolescence is between the ages of 10 and 19, when many physical, social, cognitive, and emotional changes are experienced, especially long-term goals and individual desires. It is the life cycle in which it is organized (7). Globally there are 1.2 billion adolescents aged from 10-19 years and they comprise 16% of the population of the whole world. More than half of all adolescents globally live in Asia (8). In the world in general, the majority of the prevalence of internet addictions comes from Asian countries. Internet use rates among adolescents are 21.2% in Vietnam, 6.2% in Japan, and 50% in Korea (9,10). It is also stated that the excessive internet use level among young people in OECD countries is 26% (more than 6 hours a day) (11). When Turkey's statistical agency of the 2020 data was evaluated according to age groups in terms of internet usage rates, it is seen that the highest usage level is between the ages of 16-24 (2.33% to 14%) (12, 13). In another source, the adolescent internet addiction rate in Turkey is reported to vary between 7.1 to 16% (14). It is reported that differences in the prevalence of internet-based technologies are due to differences in sampling, screening tests, and research designs (15).

When research conducted in recent years is examined, the use of internet-based devices seems to be emphasized that the cognitive development of children contributes to the development of memory, metacognition, and exploration and that today's young people are more connected than ever (11,16). Some studies on game addiction report that digital games improve the visual, attention skills of adolescents. Also, it promotes social connection and increases self-esteem (17,18). It can be said that this changing point of view also facilitates the orientation to computer and internet-based uses.

The most notable group among this more connected young generation is the "generation K adolescents". The generation born in the years from 1995-to 2002 is also named "Generation K" (19,20). Generation K partly includes Generation Z. This generation is also called "the generation of

producers, creators, and innovators" (21). This generation is anxious, pessimistic, and lack self-confidence due to encountering many negative events in the world through the internet, but are also reported to be quicker, more creative, more autonomous, more cautious, and more practical; in short, this is a generation of contradictions (19,20,22,23). Noreean Hertz stated that one of the three forces shaping generation K was technology, that technology was a must-have tool in the lives of this generation, and that this generation was "super social" and could "multi-scan and multi-task" (19,20,24). Young people in this age range had similar characteristics in every region of the world and were associated with the concepts of "technology, collapse, and danger".

The use of computer and internet-based technologies has turned into harm or an opportunity for adolescents, but by considering computer usage types together and multi-dimensionally; it is possible by gaining more information and awareness of its physical, cognitive, and psychosocial consequences. In the literature, it is seen that there are two basic perspectives explaining the concept of computer/internet addiction. The first of them considers computer and internet addiction together and deals with the characteristics of these two concepts with a common approach, and thinks that both of them emerge with the same characteristics (use time, tolerance…). The second opinion, based on the view that the activities done on the internet during the process, are gradually different, thinks that they should be handled separately since many different activities can be done (25). In the literature, no study evaluates computer/internet/game addiction and adolescence problems from a holistic perspective and together. Therefore in this study, to reveal the relational patterns between components of computer addiction (computer/internet/game addiction) and developmental problem areas in adolescents, the correlations between these two data sets were not dealt with in a one-to-one fashion but in multiple and holistically. Also, the aim was to investigate the correlations between these two datasets in depth using CCA. When investigating the correlations between scales with subdimensions, it is important to use CAA to reveal the true correlations (26). The aim of this research is to examine the relationship between puberty problems and computer (computer, internet, game) addiction in Turkish K generation adolescents by canonical correlation analysis and to determine which problem areas of adolescents contribute to explain computer addiction (computer, internet, games) of Turkish K generation adolescents.

MATERIAL and METHODS

Study Design

This descriptive and cross-sectional study was conducted to examine the relationship between computer addiction and adolescent problems in Turkish generation K adolescents holistically. The study was conducted in a city (Ordu) located in North Turkey. According to the information obtained from a Provincial Directorate of National Education, the high schools were classified based on three success levels (high, middle, and low). By drawing method, one high school from each success class was included in the study (Figure 1). The study was conducted in three high schools determined. The data were collected between 20 April and 2 June 2015 of the 2014-2015 academic year. Inclusion criteria; 1) Being born between 1996-2000, being a high school adolescent, 2) Not having any auditory or visual problems, 3) Volunteer to participate in the study

Sampling and Recruitment Procedures

According to the high school entrance exam results, schools are divided into 3 levels lower middle, and upper in terms of success level, and 1 high school from each success level was determined. A total of 2308 students, including 576 students from the high school determined for the lower achievement level, 1265 students from the high school determined for the medium success level, and 467 students from the high school determined for the upper success level, constituted the population of the study 2014 (Figure 1).

In the study, the power analysis was conducted (G*Power 3.1.9.2) and the number of students needed to be included in the study was determined as 651 with an effect size of 0.14, a significance level of .05, and a power of 0.90. Also, the sample width was estimated as 516 for α = 1% and ± 5 deviations, but for the power test, it was determined as 10% of the population width, ie 660 (27). For this reason, the sample of the project consisted of 665 students from the 9^{th}, 10^{th}, 11^{th}, and 12^{th}-grade students of these high schools, with a minimum of 25 students from each grade, using the simple random sampling method. The flow chart of the study is given in Figure 2.

In CCA, the sample size should be 10 times greater than the number of variables for reliable estimation of canonical loadings (28). The present sample size was already complying with this criterion (included almost 80 times greater than the number of variables).

Data Collection Tools

In this study, "Participation Information Form", "Adolescent's Computer Addiction Scale", and "Adolescence Problems Scanning List (APSL)" were used for measuring.

Dependent variables; Adolescence Problems Scanning List, Adolescent's Computer Addiction Scale (ACAS)

Independent variables: Sociodemographic characteristics

Participation Information Form: This form includes questions about age, gender, class, grade point average, parental education status, free time assessment, and computer and internet usage.

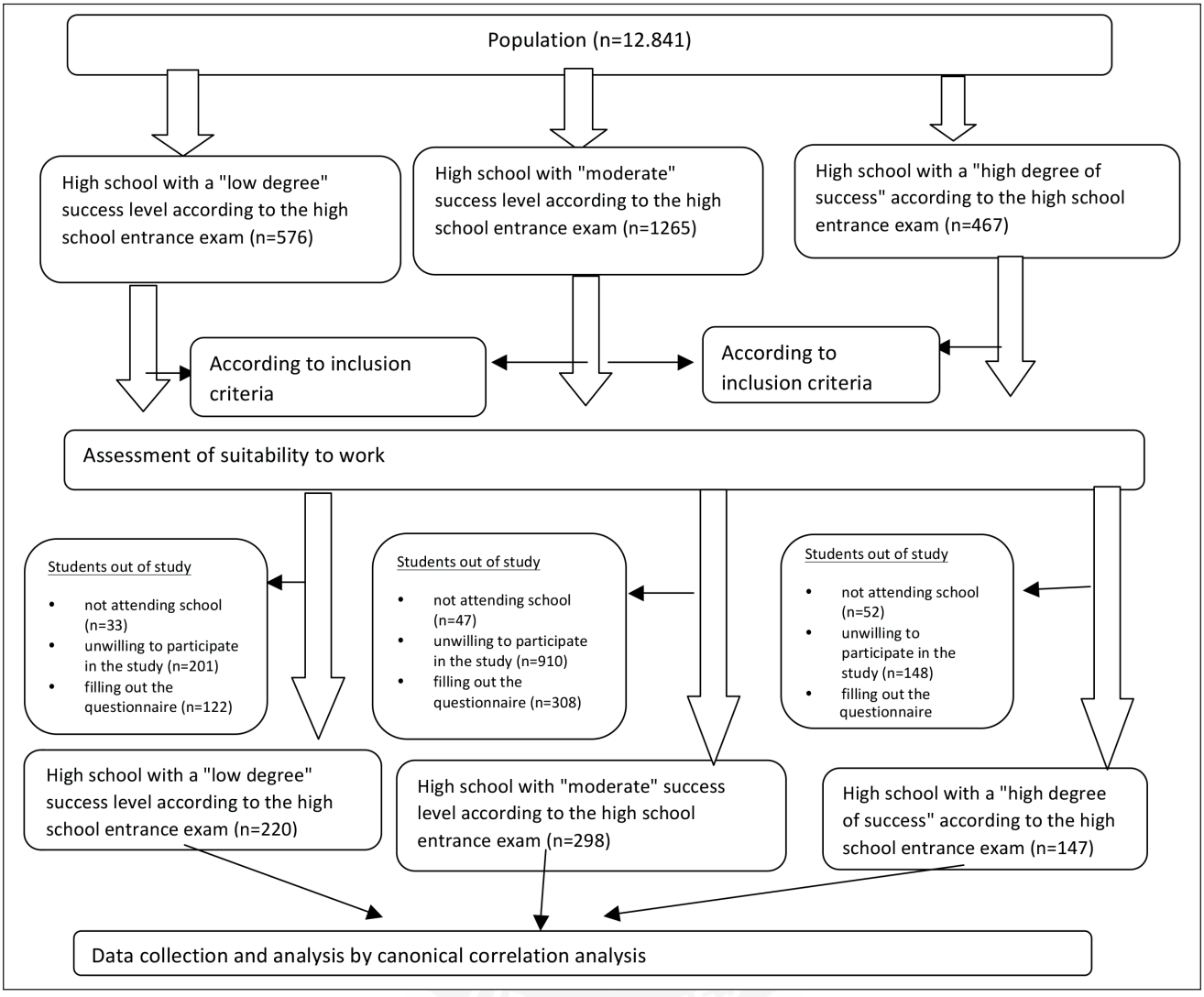

Figure 1: Research process chart

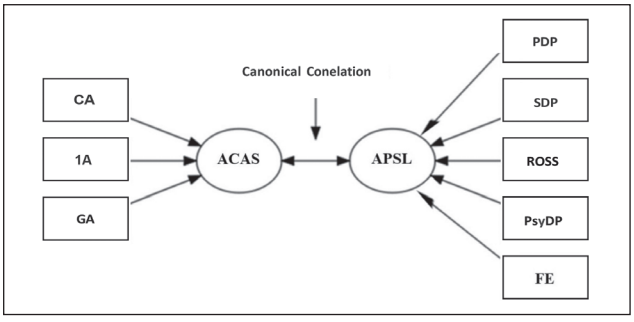

Figure 2: Graphical representation of a CCA of Set 1 and Set 2 constructs.

ACAS: Adolescent computer addiction, **CA:** Computer addiction, **IA:** Internet addiction, **GA:** Game addiction, **APSL:** Adolescent problem scanning list, **PDP:** Physical development problems, **SDP:** Social development problems, **ROSS:** Relationship with the opposite sex and sexual information, **PsyDP:** Phychological development Problems, **FE:** Future expectations.

Adolescent's Computer Addiction Scale (ACAS): The research used the subdimensions (computer/internet/game addiction) of the "Adolescent's Computer Addiction Scale" developed by Ayas, Çakır, and Horzum (2011) to determine computer, internet, and game addiction (29). As points on the scale increase, addiction related to the relevant area increases. With a three-factor structure, the scale includes a 24-item computer addiction, a 28-item internet addiction, and a 26-item game addiction subscale. However, validity and reliability studies determined that the two-factor structure of the 28-item internet addiction and 26-item game addiction subscales were valid and reliable. In samples providing validity, the researchers who developed the scale showed the computer addiction (CA) subscale could be used; in fact, all subdimensions could be independently and separately used. As a result, the Cronbach alpha values for the CA, internet addiction (IA), and game addiction

(GA) subdimensions were calculated and found to be 0.950, 0.937, and 0.974, respectively, so the subdimensions of the scale can be used.

Adolescence Problems Scanning List (APSL): The Adolescence Problems Screening List includes subsections about five problem areas of unique bodily development, social development, relations to the opposite gender and sexual information, psychological development, and future expectations in the adolescent period. Comprising a total of 55 items and it was prepared by Yılgör Tekelioğlu in 1993. The cumulative total for each subsection is obtained and divided by the number of items in the subsection to calculate the subsection points. Sections with high points are accepted as being more problematic areas (30,31). APSL has 5 subsections. These subsections are PDP (Physical Development Problems), SDP (Social Development Problems), ROSS (Relationship with the opposite sex and sexual information), PsyDP (Psychological Development Problems), and FE (Future Expectations).

Data Collection Process

A few days before starting the study, a "parent consent form" was distributed to the students in an envelope. Written consent from the parents and permission of the school administrators were obtained. The students were informed about the study and informed consent was obtained from the students. The questionnaires were then distributed and collected after an average of 10-12 minutes.

Statistical Analyses

Canonical correlation analysis (CCA) was used to identify the relationship between variables sets. Statistical calculations were performed with the SPSS v28 (IBM Inc., Chicago, IL, USA). Statistical significance was defined at $p<0.05$.

Canonical Correlation Analysis (CCA): In the bivariate correlation analysis, which determines the direction and degree of the relationship between two variables, it is assumed that the variables examined do not have sub-dimensions. However, if these variables have sets of sub-variables within them, CAA should be used instead of correlation analysis to determine the relationships between the sets of variables. In CCA, the relations between sub-dimensional variables, each variable set belonging to two variables are considered as a "latent variable" based on the measurement of indicator variables. In CCA, which is optimized by maximizing the linear correlation between two latent variables, there is more than one linear relationship with two variable sets and how many dimensions are required to explain this relationship is determined (32). For this reason, it is important to use CAA when examining the relationships between sub-dimensional scales in terms of revealing real relationships.

CCA, a multivariate statistical analysis method, is designed to determine the relationships between two groups of variables. It focuses on finding linear combinations of variables in these clusters that exhibit correlations. The pair of linear combinations with the strongest correlation forms the first canonical variable. The second canonical variable is a linear combination unrelated to the first canonical variable. Generally, the first couple is used to measure relationships (33,34).

Tools for the interpretation of CCA results are standardized canonical coefficients, canonical loads, and canonical cross-loadings. The canonical function can be interpreted by the sign and magnitude of the standardized canonical coefficients assigned to each variable in its respective canonical variable. Variables with larger coefficients contribute more to canonical variables, but these coefficients can be inflated due to the multicollinearity between variables. To explain the underlying structures, canonical loads are more appropriate than standardized canonical coefficients. Canonical cross-loads determine the relationship between the original variables and their opposites (35).

Let Set 1 (X) and Set 2 (Y) be two sets of variables containing p variables in set X: (X1, X2, X3, …., Xp) and set q variables in set Y: (Y1, Y2, Y3, …., Yq) where $p \leq q$. A series of linear combinations called U and V are defined; where U and V correspond to the set of linear combinations from X and Y, respectively (26). There were two sets of variables for the Adolescent's Computer Addiction Scale (X) and Adolescence Problems Scanning List (Y). Adolescents' Computer Addiction Scale included the subscales of ACAS (CA, IA, GA) and Adolescence Problems Scanning List included the subsections of APSL (DP, SDP, ROSS, PsyDP, FE). A graphical representation of a CCA with an Adolescent's Computer Addiction Scale and Adolescence Problems Scanning List is presented in Figure 2.

RESULTS

Of cases who participated in the study, 59.2% were female, 19.7% were in the 9th grade, 13.7% were in the 10th grade, 33.7% were in the 11th grade and 30.8% were in the 12th grade of them. While 28.1% of the students stated that they had the power-on password for their home computer. Similarly, 40.8% of the students stated that their computers had filter programs (Table 1).

It was calculated that the students spent 8.26 hours on the computer/internet on weekdays, 7.00 hours on weekends, and 14.57 hours in total, 40% of them had complaints from their families about spending too much time on the internet.

The descriptive statistics for the variables of the Adolescent's Computer Addiction Scale and Adolescence Problems Scanning List are provided in Table 2 and Pearson

correlation coefficients between the variables are provided in Table 3. As seen in Table 3, the highest correlation coefficient was between IA and CA (r=0.585, p<0.001). The CA variable has a significant degree of negative correlation with PsyDP (r=-0.216, p<0.001) and FE (r=-0.177, p<0.001). The IA variable has a significant degree of negative correlation with PsyDP (r=-0.186, p<0.001), SDP (r=-0.167, p<0.001), PDP (r=-0.149, p<0.01) and FE (r=-0.123, p<0.01). GA showed a significant degree of negative correlation with PDP (r=-0.246, p<0.001), ROSS (r=-0.181, p<0.001) and FE (r=-0.102, p<0.05). The other correlations between subscales and subsections of the ACAS and APSL were not found to be significant (p>0.05). The correlations between the Adolescent's Computer Addiction Scale formed of all

Table 1: Principle characteristics of the study group

Sociodemographic characteristics*		Findings
Gender	Female	393 (59.2)
	Male	271 (40.8)
Class	9th grade	224 (19.7)
	10th grade	91 (13.7)
	11th grade	131 (33.7)
	12th grade	205 (30.8)
Level of income	Less than minimum wage	46 (7.2)
	1000-2000TL	143 (22.4)
	>2000TL	450 (70.4)
Mother education status	Illiterate	28 (4.2)
	Literate	27 (4.1)
	Primary Education	252 (38.2)
	High School	119 (18.1)
	University	233 (35.4)
Father education status	Illiterate	16 (2.4)
	Literate	17 (2.6)
	Primary Education	156 (23.7)
	High School	145 (22.0)
	University	324 (49.2)

*Data are given as n (%)

Table 2: Descriptive statistics of the variables in Set 1 and Set 2

Scales*		Values
ACAS (Set 1)	CA	39.30± 17.72 (24.0-120.0)
	IA	41.55± 17.51 (28.0-120.0)
	GA	42.25± 24.43 (26.0-130.0)
APSL (Set 2)	PDP	7.38± 2.45 (0.0-10.0)
	SDP	5.25± 1.77 (0.0-8.0)
	ROSS	7.24± 1.70 (0.0-9.0)
	PsyDP	13.39± 3.82 (0.0-19.0)
	FE	4.80± 2.28 (0.0-9.0)

*Data are shown as mean ± standart deviation and minimum and maximum values. **ACAS:** Adolescent Computer Addiction Scale, **CA:** Computer Addiction, **IA:** Internet addiction, **GA:** Game addiction, **APSL:** Adolescent problem scanning list, **PDP:** Physical development problems, **SDP:** Social development problems, **ROSS:** Relationship with the opposite sex and sexual information, **PsyDP:** Phychological development problems, **FE:** Future expectations

Table 3: Pearson correlation coefficient matrix of the variables in Set 1 and Set 2

		CA	IA	GA	PDP	PDP	ROSS	PsyDP
IA	r	0.585						
	p	**<0.001**						
GA	r	0.461	0.383					
	p	**<0.001**	**<0.001**					
PDP	r	-0.043	-0.186	-0.246				
	p	0.343	**<0.001**	**<0.001**				
SDP	r	-0.046	-0.167	0.071	0.341			
	p	0.299	**<0.001**	0.104	**<0.001**			
ROSS	r	-0.069	-0.015	-0.181	0.436	0.480		
	p	0.130	0.752	**<0.001**	**<0.001**	**<0.001**		
PsyDP	r	-0.216	-0.149	0.029	0.382	0.562	0.422	
	p	**<0.001**	**0.001**	0.515	**<0.001**	**<0.001**	**<0.001**	
FE	r	-0.177	-0.123	-0.102	0.438	0.371	0.219	0.477
	p	**<0.001**	**0.007**	**0.020**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

CA: Computer addiction, **IA:** Internet addiction, **GA:** Game addiction, **PDP:** Physical development problems, **SDP:** Social development problems, **ROSS:** Relationship with the opposite sex and sexual information, **PsyDP:** Phychological development problems, **FE:** Future expectations

subdimensions of ACAS were positive and statistically significant ($p<0.001$). Similarly, the correlations between the Adolescence Problems Scanning List formed of all subdimensions of APSL were positive and statistically significant ($p<0.001$).

There were three different canonical variable pairs (U_iV_i) and canonical correlation coefficients between them. U and V canonical variate pairs varied between 0.688 - 0.150 in Table 4. Wilk's λ value revealed that the first canonical correlation (rU_1V_1=68.8%) between the first canonical variable pair was significant ($p<0.001$). The second canonical correlation (rU_2V_2=45.3%) of the second variable pair was also significant ($p<0.001$). Wilk's Lambda" shows the common variance amount shared by canonical variables and may be interpreted by R^2 in regression analysis (36). As a result, the shared common variance between the first canonical variable pair for ACAS (Adolescent's Computer Addiction Scale) and APSL (Adolescence Problems Scanning List) was 51% (1-0.490).

As can be seen in Table 5, in the final equations for U_1 and V_1, GA (1.064) of Adolescent's Computer Addiction Scale and PDP (0.702) of Adolescence Problems Scanning List had the greatest positive effect on canonical variates. For the Adolescents' Computer Addiction Scale, GA was the most important (1.064) parameter and it was respectively followed by CA (-0.830) and IA (-0.130). Except for IA, these parameters had great contributions. For a high U_1 canonical variate, GA should be raised because of positive correlations and CA should be reduced because of negative correlations. For Adolescence Problems Scanning List, PsyDP was the most significant parameter (0.702) and it was respectively followed by PDP (-0.653) and SDP (0.423). Loadings of PsyDP and SDP were positive. Thus, increasing V_1 canonical variate values were observed with increasing PsyDP and SDP. Contrarily, decreasing V_1 canonical variable values were observed with increasing PDP.

In Table 6, it is given what percentage of variability both Set1 and Set 2 explained in their own and other sets. In the first canonical variable pair, approximately 6.8% of the variance in the Set 1 was explained by the variables in the set 2. Approx 6.8% of the variance in Set 2 variables was also explained by Set 1.

Table 4: Canonical correlation coefficients

Canonical Variable	Canonical Correlation	Eigen Value	Wilk's Lambda	F	df	p
U_1V_1	0.688	0.586	0.490	18.127	15	**<0.001**
U_2V_2	0.453	0.259	0.777	11.369	8	**<0.001**
U_3V_3	0.150	0.023	0.977	2.601	3	0.052

Table 5: Standardized canonical coefficients and canonical loadings for Set 1 and Set 2

Scale	Subscales	Standardized Canonical Coefficients	Canonical Loadings	Cross Loadings
ACAS (Set 1)	CA	-0.830	-0.408	-0.248
	IA	-0.130	-0.037	-0.023
	GA	1.064	0.617	0.375
APSL (Set 2)	PDP	-0.653	-0.483	-0.294
	SDP	0.423	0.562	0.342
	ROSS	-0.293	-0.088	-0.054
	PsyDP	0.702	0.603	0.367
	FE	-0.066	0.033	0.020

ACAS: Adolescent Computer Addiction Scale, **CA:** Computer Addiction, **IA:** Internet Addiction, **GA:** Game Addiction, **APSL:** Adolescent Problem Scanning List, **PDP:** Physical Development Problems, **SDP:** Social Development Problems, **ROSS:** Relationship with the opposite sex and sexual information, **PsyDP:** Phychological Development Problems, **FE:** Future Expectations

Table 6: Proportion of variance explained

Canonical Variable	Set 1 by Self	Set 1 by Set 2	Set 2 by Self	Set 2 by Set 1
U_1V_1	0.183	0.068	0.184	0.068
U_2V_2	0.158	0.032	0.155	0.032
U_3V_3	0.659	0.015	0.313	0.007

DISCUSSION

This is the first study that examines the relationship between computer addiction and adolescent problems and sub-sections in adolescents of generation K with canonical correlation analysis. Previous research on the relationship between other factors and internet or computer addiction yielded conflicting findings. Canonical correlation analysis was used to examine the similarity between the two personality trait measures and conscientiousness and agreeableness, personality, in a study to see if personality traits can reliably predict excessive computer and internet use consistently, regardless of the personality trait measure. It has been discovered that these traits are crucial for comprehending the behaviors of technological addiction (37)

Since the average value of all five factors is above 0.50 in the adolescent problem screening list, it is observed that K generation adolescents have problems in these five areas. Again, the most problematic area was the relationships with the opposite sex (0.80±0.18), followed by physical (0.73±0.24) and psychological (0.70±0.20) problems, the least problematic area was the area of thoughts and expectations (0.53±0.25) determined. Again, in the computer, internet, game addiction scale (ACAS), it is seen that the highest average belongs to game addiction (42.25±24.45) (Table 2). In a study, friend problems were mostly found in the 9th grade (2.84±0.95), teacher problems in the 10th grade (3.04±1.01), and career choice problems in the 10th grade (2.89±0.95), and it was determined that students in the 9th grade (2.81±0.69) experience the problems of adolescence the most (38).

One of the aims of the study was to identify which of the subcomponents of the ACAS concept associated with APSL in adolescence predicted these concepts. The results of the analysis with this aim observed that the leading subdimension was GA. Gentile et al. state that we cannot explain pathological gameplay (game addiction) only with playing time. Griffiths et al. supported this view, in addition, they pointed out the need to lose control while playing the game and to examine negative psychological and physical consequences (39,40). In a study conducted with 154 children that examined the relationship between computer game addiction level and behavioral problems in children, a positive correlation is found between computer game addiction level and external behavioral problems, aggression, social problems, cautiousness problems, thought problems; and a negative correlation was found between the computer game addiction level and children's school competence ($p<0.05$) (41). In another study conducted with 221 students in Germany, it was determined that 6.3% of the students met the diagnostic criteria for behavioral addiction (game addiction), these adolescents showed limited cognitive flexibility, and used computer games as a mood management strategy (42). Results obtained related to GA confirm these characteristics of generation K who cannot view computer technologies from the outside and want computers to be part of all activities.

Another aim of the study was to determine which development problem areas of generation K adolescents contribute to explaining ACAS. In this context, high GA and IA in generation K adolescents were linked to PsyPD and SDP, while CA was linked to PDP. A study investigating the psychosocial variables predicting internet addiction in adolescents found variables like loneliness and perceived social support from a family affected internet addiction in adolescents and explained 7.3% of the total variance among variables affecting internet addiction (43). Another study using the "Brief Symptom Inventory" for psychological symptoms associated with internet addiction, found a moderate level positive significant correlation between internet addiction and psychological symptoms ($p<0.05$) (44). In a study of 1928 Norwegian adolescents aged 13-17 years, video game addiction is associated with depression, low academic achievement, and behavioral problems. (45). In a study conducted with 383 middle school students, it was determined that there is a low level of relationship between digital game addiction and gambling (games involving physical activity) scores and a high level of a positive significant relationship between aggression scores ($p<0.05$) (46). In another study on the subject, a highly significant positive correlation was found between social phobia and IGD (internet game disorder) ($p<0.001$) (18). A study by Dalbudak et.al. reported students may use the internet to cope by distancing themselves from negative emotions (47). In a study using canonical correlation analysis, it was discovered that perceived values (consumption values) were significantly correlated with mobile game addiction behavior. This study examined the relationship between mobile game addiction behaviors and perceived game value (benefit) of university students. Addiction to mobile games and behavior are closely related. This study offered some evidence that the perceived value (benefit) of a game may affect the behavior of mobile gaming addicts (48). These results show that GA is mainly associated with psychological and social problems.

In this study, the second prominent area of the APSL in the explanation of ACAS was SDP and it was observed to have a positive correlation. In a study on the subject, it was stated that the social development of children with high levels of computer game use slowed down, their self-confidence decreased, and their social anxiety levels and aggressive behaviors increased (49). Hertz reported that generation K especially conducted social relationships through social networks and as a result, many problems such as health, psychological and social relationship problems would be observed together (50). According to another study about social media use, young people spend more time using the internet and social media which negatively affects real-life

relationships and other areas (51). The cognitive-behavioral model of PIU suggests that certain online thoughts and behaviors are related to social anxiety. Therefore, it is imperative to look into the relationship between social anxiety and PIU. Additionally, there is a lack of research that considers the multidimensional character of PIU and social anxiety. Only the first of the canonical correlation functions calculated for men was found to be significant (Rc=0.43, =0.78, 29=64.7, p<0.001) and the overlapped variance was 19% in this study, which examined the relationships between social anxiety and PIU using canonical correlation analysis. Similarly, only the first canonical function—which accounted for 13% of the overlapping variance for females—was significant (Rc=0.36, =0.87, 29=33.9, p<0.001) (52). The findings obtained from the study and the literature confirm the relationship between computer addiction and problems in social relations.

In our study, one of the APSL contributing less to the explanation of ACAS was found to be PDP. Whereas some studies have reported high correlations between physical factors (sleep, nutrition, joints, eyes ...) and internet-based addictions (53). Studies have stated that excessive computer/internet use is reported to negatively affect eating habits and physical activity and cause excessive weight gain, eye disorders, exposure to radiation, and stance and skeletal structure disorders (54). In a study examining the relationship between BMI and sedentary life with 450 students, it was found that non-obese participants spent significantly less time using computers on weekends (p =0.04) and weekdays (p =0.025) than overweight/obese participants. As a result of logistic regression analysis, it was seen that those who use computers more than 4 hours a day on weekdays are probably overweight/obese (odds ratio: 5.79; p <0.003). (55).

Finally, the predictive role of adolescence problem areas (APSL) for the occurrence of or processes after the occurrence of computer addiction (ACAS) was analyzed and as a result of the analysis, it was determined that APSL played an explanatory role in the prediction of ACAS in generation K adolescents. Among the subdimensions of the ACAS for adolescents, it appeared there was a negative correlation between GA and CA, and IA. As a result, as GA increased, there was a fall determined in CA and IA. These results show that the subscales of ACAS interact with each other and change each other's points. In other words, the use of these subscales together for adolescent computer addiction explains higher rates than their separate use. In the literatüre, some experts in the literature consider that computer/internet-based behavior addiction should be dealt with together under the heading of computer addiction and is a psychophysiological disorder, while some stated that as different types of activities can be performed in internet environments, they should be dealt with separately (24,56,57).

Computer/internet/game addiction has effects on every individual, especially the K generation adolescents, who are today's adolescents. This study shows that the use of ACAS subscales together for adolescent computer addiction explains higher rates than their separate use. In other words, this study also shows that computer, internet, and game addiction interacts with all developmental problems of adolescents and this addiction should be handled not only with the psychological dimension but also with other adolescence problems. In this sense, mental health professionals should be effective in assessing addiction, not only in evaluation and treatment but also in preventative and protective approaches and they should address adolescence problems not only with their psychological dimensions but also with all dimensions.

The study results are limited to the generation K adolescents in the schools included in the study. Since the questionnaires are based on self-report, the answers are limited to the answers given by the students. The study results are limited to the internet addiction and adolescent problems examined in the study.

Acknowledgment

The authors would like to thank the Scientific Research Projects Coordination Unit of the Ordu University and the adolescents who gave their time to participate in this study as well as the administrators of the schools.

Author Contributions

Both authors have equal contributions.

Conflicts of Interest

We have no conflict of interest to declare.

Financial Support

This work was supported by the Ordu University Scientific Research Projects Unit as project number AR-1406.

Ethical Approval

The Ethics Committee of Ordu University approved the study protocol (ID 2015/10/04, 16 April 2015). Written permission was obtained from the Ordu Provincial Directorate of National Education before the survey started.

Review Process

Extremely peer-reviewed and accepted.

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OLGU SUNUMU

Batı Karadeniz Tıp Dergisi
Medical Journal of Western Black Sea

Med J West Black Sea 2023;7(1): 92-94
DOI: 10.29058/mjwbs.1209412

Ani Kardiyak Ölüm İçin Önemli Bir Risk Faktörü: Tip 2 Brugada Sendromu

An Important Risk Factor for Sudden Cardiac Death: Type 2 Brugada Syndrome

Burak ACEM, Merve OSOYDAN SATICI, Serdar ÖZDEMİR, Serkan Emre EROĞLU

Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim Araştırma Hastanesi, Acil Tıp Kliniği, İstanbul, Türkiye

ORCID ID: Burak Acem 0000-0002-9713-4966, Merve Osoydan Satıcı 0000-0002-3169-0724, Serdar Özdemir 0000-0002-6186-6110, Serkan Emre Eroğlu 0000-0002-3183-3713

Bu makaleye yapılacak atıf: Acem B ve ark. Ani kardiyak ölüm için önemli bir risk faktörü: Tip 2 brugada sendromu. Med J West Black Sea. 2023;7(1):92-94.

Sorumlu Yazar
Serdar Özdemir

E-posta
dr.serdar55@hotmail.com

Geliş Tarihi
25.12.2022

Revizyon Tarihi
18.02.2023

Kabul Tarihi
25.03.2023

ÖZ

Amaç: Brugada sendromunun hızlı ve doğru teşhisi, semptomatik hastalarda aritmiden kaynaklanan ani kardiyak ölüm riskinin yüksek olması nedeniyle çok önemlidir. Acil serviste Tip 2 Brugada EKG paterni tespit edilen bir olguyu, klinik tanı güçlüğü ve nadir görülmesi sebebi ile sunmayı ve tartışmayı amaçladık.

Olgu: Kırkdokuz yaşında erkek hasta acil servise 45 dakika önce başlayan sol göğüste ve epigastrik bölgede lokalize sıkıştırıcı tarzda göğüs ağrısıyla başvurdu. Tekrarlayan senkop öyküsü, ailede erken ölüm hikâyesi mevcuttu. Hız kontrolü sağlandıktan sonra çekilen EKG'sinde kalp tepe atımı 99/dk, V1-V2 derivasyonlarında ST segmentinde elevasyonu takiben 1mm'den fazla çökme ile karakterize 'eğer tipi' görünüm tespit edildi.

Sonuç: Tip 1 Brugada paterni olan hastalara göre ani kardiyak ölüm açısından daha az riskli olarak kabul edilse de BrS EKG'si dinamik ve değişkendir, Tip 2 kısa sürede Tip 1'e dönüşebilir; bu nedenle gözden kaçırılmamalıdır.

Anahtar Sözcükler: Brugada sendromu, ventriküler taşikardi

ABSTRACT

Aim: Rapid and accurate diagnosis of Brugada syndrome is very important because of the high risk of sudden cardiac death from arrhythmia in symptomatic patients. We aimed to present and discuss a case in whom ECG pattern of Type 2 Brugada was detected in the emergency department due to clinical diagnosis difficulty and rarity.

Case: A forty-nine-year-old male patient presented to the emergency department with localized compressive chest pain in the left chest and epigastric region that started 45 minutes ago. There was a history of recurrent syncope and a family history of premature death. In his ECG, which was taken after the rate control was achieved, an 'if-type' appearance was detected, which is characterized by a peak heart rate of 99/min, and a depression of more than 1 mm following elevation in the ST segment in leads V1-V2.

Conclusion: Although Type 1 is considered to be less risky in terms of sudden cardiac death compared to patients with Brugada pattern, BrS ECG is dynamic and variable, Type 2 can turn into Type 1 in a short time; therefore it should not be overlooked.

Keywords: Brugada syndrome, ventricular tachycardia

GİRİŞ

Kardiyak acil durumlar, konjestif kalp yetmezliği, kardiyak tamponad, aritmojenik hastalık ve tromboembolik hastalık dahil olmak üzere çeşitli farklı hastalıkları içerir. Erişkin hastada göğüs ağrısı değerlendirilirken acil servis pratiğinde öncelikle akut koroner sendromların ekartasyonu hedeflenir (1). Bununla birlikte daha nadir görülen yaşamı tehdit eden patolojilerden Brugada sendromu da (BrS) acil servise göğüs ağrısı, malign aritmiler veya ani kardiyak ölüm ile başvurabilen bir patolojidir. Sendrom ilk olarak 1992'de vakalar temelinde tanımlanmış, dokümante edilmiş ventriküler fibrilasyon (VF), ventriküler taşikardi (VT), vagal olmayan senkop veya ani kardiyak ölüm gibi önemli klinik olaylarla ilişkili olan, kalpteki transmembran iyon kanallarındaki otozomal dominant bir genetik bozukluktur (2). Genel prevalansının 2–15/10.000 olduğu tahmin edilmektedir ve Güneydoğu Asya'da daha yüksek prevalans görülmektedir. Erkeklerde kadınlara göre yaklaşık 10:1 oranında daha sık görülür sahiptir ve genellikle daha şiddetli bir fenotip gösterirler (3).

Brugada Sendromlu hastalarının yaklaşık %20'sinde kardiyak Na+ kanallarını kodlayan SCN5A geninde mutasyon raporlanmıştır. Ca^{+} kanalları ve gliserol 3 fosfat dehidrojeaz 1 geninde de defektler raporlanmıştır (4). Tipik elektrokardiyogram (EKG) bulguları sağ dal bloğu ile V 1-3 derivasyonlarında karakteristik aşağı eğimli ST-segment yükselmesi ile belirgin bir J dalgasını takiben negatif T dalgasıdır ancak tüm hastalarda bu patognomonik Brugada işareti bulunmayabilir. Tip 2 ve Tip 3 Brugada paterni tanısal olmasa da spontan ya da provokatif testlerle Tip 1'e dönüşebileceğinden ileri değerlendirme gerektirir, bu sebeple EKG bulgularıın tanınması hayat kurtarıcıdır (5).

Acil serviste Tip 2 Brugada EKG paterni tespit edilen bir olguyu, klinik tanı güçlüğü ve nadir görülmesi sebebi ile sunmayı ve tartışmayı amaçladık.

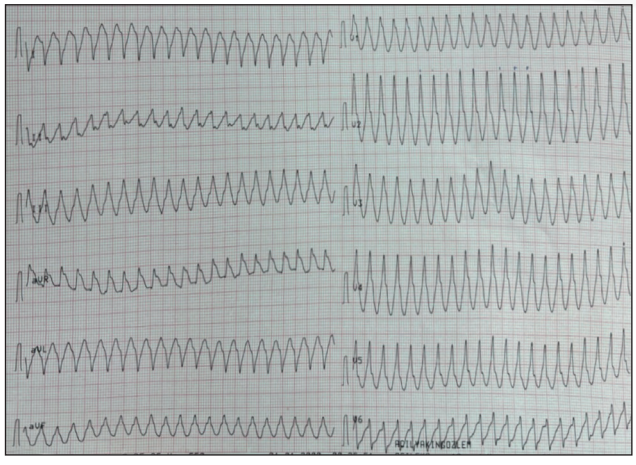
OLGU

Kırk dokuz yaşında erkek hasta acil servise 45 dakika önce başlayan sol göğüste ve epigastrik bölgede lokalize sıkıştırıcı tarzda göğüs ağrısıyla başvurdu. Tıbbi geçmişinde herhangi bir kronik hastalık öyküsü olmayan hastanın devamlı kullandığı bir ilacı olmadığı öğrenildi. Tekrarlayan senkop öyküsü, ailede erken ölüm hikâyesi mevcuttu.

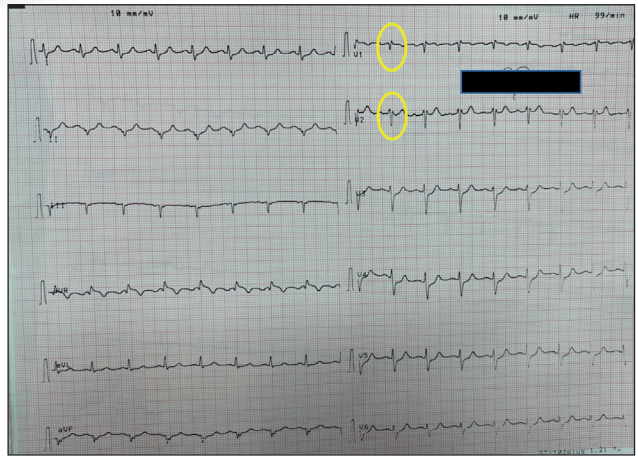
Fiziki muayenesinde bilinci açık, oryante ve koopere idi. Hastanın vital parametrelerinden kan basıncı 97/54 mm/Hg, nabız dakika sayısı 221 atım/dk, parmak ucu oksijen satürasyonu 94 (oda havası), ateş 36,7 °C, solunum sayısı 22/dk idi. Sistemik fizik muayenesi taşikardi dışında olağandı.

Kardiyak monitörize edilen hastanın çekilen EKG'sinde kalp tepe atımı 235/dk, QRS süresi 160 ms, prekordiyal derivasyonlarda pozitif konkordans ve RSR' kompleksi görülmesi üzerine ventriküler taşikardi düşünüldü (Şekil 1). Hastada hipotansiyon ve devam eden iskemik tarzda göğüs ağrısı olması sebebiyle unstabil taşiaritmi olarak değerlendirildi ve direkt akım kardiyoversiyon (DCCV) uygulanması planlandı. Hastanın midazolam 4 mg eşliğinde sedasyonu sağlanıp, DCCV 100 joule ile yapıldı ve normal sinüs ritmine dönüş sağlandı. Hız kontrolü sağlandıktan sonra çekilen EKG'sinde kalp tepe atımı 99/dk, V1-V2 derivasyonlarında ST segmentinde elevasyonu takiben 1mm'den fazla çökme ile karakterize 'eğer tipi' görünüm tespit edildi (Şekil 2).

Brugada Tip 2 paterni düşündüren hasta acil kardiyak değerlendirmeye alındı. Kardiyoloji uzmanı tarafından yapılan ekokardiyografide; ejeksiyon fraksiyonu (EF) % 45-50



Şekil 1: Hastanın başvuru anında çekilen EKG'sinde kalp tepe atımı 235/dk, QRS: 160ms, prekordiyal derivasyonlarda pozitif konkordans ve RSR' kompleksi ile prezante olan ventriküler taşikardi.



Şekil 2: Hastanın kardiyoversiyon sonrası çekilen EKG'sinde V1-V2 derivasyonlarında ST segmentinde elevasyonu takiben 1mm'den fazla çökme ile karakterize 'eğer tipi' görünüm

ve global duvar hipokinezi görüldü. Harici ciddi kapak patolojisi izlenmedi, sağ kalp boşlukları ve asendan aort normal olarak görüldü ve perikardiyal efüzyon izlenmedi.

Majör fizyolojik kardiyak patolojisi olmayan ve akut kalp yetmezliği kliniği olmayan hastaya, iskemik patolojilerin ekartasyonu açısından acil koroner anjiyografi planlandı. Koroner anjiografisinde sol koroner arterde plak ve sirkumfleks arterde orta bölgede dolunum defekti dışında patoloji görülmedi ve medikal tedavi kararı verildi. Laboratuvar bulgularında high sensitive troponin değerleri (hs-Tn) başlangıçta ve birinci saatte sırasıyla 12 ng/dL ve 81 ng/dL (normal değer 0-14 ng/dL) ölçüldü. Diğer biyokimyasal belirteçler (karaciğer ve böbrek fonksiyon testleri, sodyum, potasyum, klor, magnezyum, kalsiyum) ve enzimleri normal sınırda saptandı. Acil serviste yapılan ilk müdahalesinden sonra hemodinamisi stabil seyreden hasta BrS ön tanısı ile yoğun bakımda takibine alındı ve klinik stabilizasyon sonrası implantable kardiyak defibrilatör (ICD) uygulandı. Komplikasyon gelişmeksizin taburcu edildi.

TARTIŞMA

Genel popülasyonda, BrS prevalansının çok düşük olduğu bilinmekte iken; BrS her 10.000 kişiden 5'ini etkilemektedir. Ayrıca olguların 2/3'ünün tanı anında asemptomatik olduğu bildirilmiştir. Semptomatik olgularda ise pre-senkop, senkop, çeşitli aritmiler ve VT ve/veya VF gözlenebilmektedir (6). EKG paternindeki dinamik değişiklikler ve asemptomatik hastaların çokluğu nedeniyle, genel popülasyon üzerine hastalık yükünü tahmin etmek güç olmakla beraber; BrS'nin, yapısal kalp hastalığı olmayan bireylerde gözlenen ani kardiyak ölümlerin %20'sinden sorumlu olduğu düşünülmektedir. Ani kardiyak ölüm ve hayatı tehdit eden aritmi riski nedeniyle tanı almış hastalarda kanıtlanmış tek tedavi yöntemi ICD yerleştirilmesidir (7). Nadir gözlenen ancak hayatı tehdit eden BrS tanısının mevcudiyeti nedeniyle, olgumuzun klinisyenlere BrS'ye ilişkin hatırlatıcı ve dikkat çekici nitelikte olduğunu düşünmekteyiz.

Avrupa Kardiyoloji Derneğinin (European Society of Cardiology [ESC]) güncel tanımına göre BrS EKG paterni (tip 1); 2., 3. veya 4. interkostal boşluğa yerleştirilen, ≥ 1 sağ prekordiyal derivasyonda (V1 ve/veya V2) kendiliğinden veya provokatif ilaç testinden sonra ortaya çıkan ≥ 2 mm ST-segment yükselmesi ile karakterizedir. ST elevasyonunu takiben negatif T dalgası izlenmektedir. Tanısal olmayan ancak BrS düşündüren ve ileri tetkik gerektiren tip 2 EKG paterninde ise eğer şekilli ST elevasyonu (J noktasında ≥ 2 mm) gözlenmektedir. Tip 2 EKG paterninde BrS tanısı, kendiliğinden veya indüksiyon (sodyum kanal blokerleri aracılığıyla gerçekleştirilen) sonucu tip 1 EKG paternine dönüşüm göründüğünde konabilmektedir. Bu gerçek aynı zamanda prognoz açısından da önemlilik arz etmektedir. Tip 1 EKG paterni kendiliğinden gözlenmeyen hastalar daha iyi prognoza sahip iken, aritmik olaylar ve ani kardiyak ölüm yine de ortaya çıkabilmektedir (3). Klinik stabilizasyon ve tip 2 EKG paterni gözlenmesi öncesinde DCCV gerektiren, klinik stabilizasyon sonrası ise ICD planlanan olgumuz; tip 2 EKG paterninin klinik önemi ve progresyonuna ilişkin kayda değer bir olgu niteliğindedir.

Brugada Sendromunun hızlı ve doğru teşhisi, semptomatik hastalarda aritmiden kaynaklanan ani kardiyak ölüm riskinin yüksek olması nedeniyle çok önemlidir. Özellikle Tip 2 Brugada EKG'lerini tanımak zor olabilmektedir. Tip 1 Brugada paterni olan hastalara göre ani kardiyak ölüm açısından daha az riskli olarak kabul edilse de BrS EKG'si dinamik ve değişkendir, Tip 2 kısa sürede Tip 1'e dönüşebilir; bu nedenle gözden kaçırılmamalıdır.

Teşekkür

Yazımızın hazırlanmasında sağladığı teknik destekten dolayı uzman Doktor İbrahim Altunok'a teşekkür ederiz

Yazar Katkı Beyanı

Yazarların eşit katkıları vardır

Çıkar Çatışması

Çıkar çatışması bulunmamaktadır.

Finansal Destek

Finansal destek bulunmamaktadır.

Etik Kurul Onayı

Olgu sunumu yapıldığından etik kurul oluru gerekmemiştir. Hastadan sözlü ve yazılı onam alınmıştır.

Hakemlik Süreci

Kör hakemlik süreci sonrası yayınlanmaya uygun bulunmuş ve kabul edilmiştir.

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CASE REPORT

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2023;7(1): 95-98
DOI: 10.29058/mjwbs.1243354

Pilomatricoma of the Upper Extremities: A Case Report

Üst Ekstremite Yerleşimli Pilomatrikoma: Olgu Sunumu

Yusuf Doruk BİLGİLİ[1], Gülden TAŞOVA YILMAZ[2]

[1]Balıkesir Bandırma Training and Research Hospital, Department of Pediatric Surgery, Balıkesir, Turkey
[2]Balıkesir Bandırma Training and Research Hospital, Department of Pathology, Balıkesir, Turkey

ORCID ID: Yusuf Doruk Bilgili 0000-0002-3965-885X, Gülden Taşova Yılmaz 0000-0001-8921-3704

Cite this article as: Bilgili YD and Taşova Yılmaz G. Pilomatricoma of the upper extremities: A case report. Med J West Black Sea. 2023;7(1):95-98.

Corresponding Author
Yusuf Doruk Bilgili

E-mail
y.doruk.bilgili@gmail.com

Received
27.01.2023

Revision
08.04.2023

Accepted
08.04.2023

ABSTRACT

Pilomatricoma is a benign skin tumor, which is generally spotted in neck region along with the head. Isolated lesions are the usual detected. Malignant transformations are considered as seldom occurrences. A 17-year-old boy with a pilomatricoma on his left arm was presented as our case in this study. On ultrasonography, the hypoechoic solid lesion with calcification spots defined 15x8 mm sized, well-defined margins localized in the subcutaneous fatty tissue. Definitive diagnosis is made by histopathology. From histopathological point of view, shadow or ghost cells are characteristic. Pilomatricoma should be taken into consideration in the differential diagnosis of superficial or subcutaneous, painless masses of head, neck and extremities. Surgical excision is curative and the recurrent rate is low.

Keywords: Benign tumor, Pediatric, Pilomatricoma, Pilomatrixoma, Skin lesions

ÖZ

Pilomatrikoma, genellikle baş ve boyun bölgesinde yerleşim gösteren iyi huylu bir deri tümörüdür. Genellikle izole bir lezyon olarak görülür ve nadiren malign seyreder. Bu yazıda sol kolunda pilomatrikoma saptanan 17 yaşındaki erkek olgu incelenmiştir. USG'de cilt altı yağlı dokuda lokalize düzgün sınırlı 15x8 mm boyutlu mm'lik kalsifik odaklar içeren hipoekoik solid lezyon izlenmiştir. Pilomatrikomanın kesin tanısı histopatolojik olarak konulur. Histopatolojik incelemede gölge ve hayalet hücrelerin görülmesi karakteristiktir. Baş, boyun ve ekstremitelerde cilt altı yüzeyel yerleşimli ağrısız kitle ile karşılaşıldığında pilomatrikoma ayırıcı tanıda değerlendirilmelidir. Cerrahi eksizyon tam kür sağlamaktadır ve nüks oranı düşüktür.

Anahtar Sözcükler: İyi huylu tümör, Pediatrik, Pilomatrikoma, Pilomatriksoma, Deri lezyonları

INTRODUCTION

Pilomatricomas (PMX) are benign, cutaneous tumors of the hair matrix cells (1). A pilomatricoma is typically present as a superficial, mobile, small, hard mass. The most commonly, it presents as a single lump found on head or neck with varying sizes from 0.5 to 3 cm in diameter (2,3). Pilomatricomas may be found in all age groups with bimodal peaks in those under 20 years and a second less significant peak between 50-65 years of age (4). It demonstrates a higher prevalence in female (3). It is the second most common superficial tumor excised in children (5). This lesion is considered relatively common. According to the study by Marrogi et al., PMX accounts for one of every 500 specimens submitted by dermatologists (6). Complications of PMX are uncommon. However occasionally they grow to giant size and malignity has been very rarely reported.

A firm, slow growing, and non-tender are the most frequent clinical features encountered. Superficial tumors develop a bluish-gray hue, and occasionally protuberant, red nodules are present. Showing a central whitish or grayish-blue structureless area on dermoscopy may suggest PMX. If the nature of the skin lesions is unclear, ultrasound scan might be recommended. Fine-needle aspiration cytology can be a useful method to diagnose PMX including pediatric patients (7).

Management of PMX is marginal excision and histopathological examination is required for definitive diagnosis (1). The tumor is encompassed of a basaloid proliferation resembling the hair matrix cells, which matures into structureless esosinophilic cells lacking nuclei called shadow cells. The shadow cell area signifies differentiation towards the hair cortex. Frequently there are areas of calcification within the shadow cell regions. For PMX and most benign skin tumors, surgical removal is the most preferred treatment. They do not disappear by themselves, and if incompletely removed, they might recur.

Our aim was to keep PMX in mind during the differential diagnosis of subcutaneous mass lesions that do not match the lymph node localization in the childhood.

CASE REPORT

A 17-year-old boy was presented with a one-year-old enlarging skin lesion on his left arm. He denied any history of trauma, fever, weight loss, tingling or fatigue. According to the patient he had contact with animals in the village. Last year he felt his extremities cold. The patient did not report pain or any other symptoms. Physical examination was unremarkable except for a 20x10 mm solid, painless mass over the left arm. It was superficial and easily mobile. Laboratory parameters were normal (Table 1).

Table 1: Laboratory parameters

Parameters	Range	Values
White blood cells ($10^3/\mu$L)	4.27-9.84	4.630
Hemoglobin (g/dL)	10.2-13.4	17.3
Platelet ($10^3/\mu$L)	144-597	276
Neutrophils (%)	22.4-74.5	56.2
Eosinophils (%)	0-4.7	2..1
Lymphocytes (%)	15.5-68.6	33..9
Glucose (mg/dL)	74-106	89
Urea (mg/dL)	16.6-48.5	17.9
Creatinine (mg/dL)	0.4-0.6	0.98
Alanine transaminase (U/L)	0-41	17
Aspartate aminotransferase (U/L)	0-40	29
Alkaline phosphatase (U/L)	142-335	100
Lactate dehydrogenase (U/L)	120-300	223
Creatine Kinase (U/L)	20-200	99
Calcium (mg/dL)	8.8-10.8	10.9
Fosfor (mg/dL)	2.7-4.9	3.3
Magnesium (mg/dL)	1.58-2.55	2.1
Cholesterol (mg/dL)	0-200	148
Triglycerides (mg/dL)	0-200	74
HDL Cholesterol (mg/dL)	35-75	45
LDL Cholesterol (mg/dL)	0-130	88
Serum iron (μg/DL)	33-193	171
Sodium (mmol/L)	136-145	137
Potassium (mmol/L)	3.5-5.1	4.8
Chloride (mmol/L)	98-107	100
Blood urea nitrogen (mg/dL)	6-20	8.4
C-Reactive Protein (mg/dL)	0-0.5	0

On ultrasonography, the hypoechoic solid lesion with calcification spots defined 15x8 mm sized, well-defined margins localized in the subcutaneous fatty tissue. There was no vascularization in the lesion. Radiologically, these results suggested benign lesions.

Under general anesthesia, the lesions were excised (Figure 1). After cross-sectioned, it was seen that it had yellow-orange colored calcified areas in places. Histopathologically, the lesion has typical basaloid cells (Figure 2), ghost cells (Figure 3) and calcification. The patient was discharged on same day, recovered well and is in perfect health.

DISCUSSION

Pilomatricomas is a neoplasm of the hair follicle matrix cells. Towards the end of 19th century, Malherbe and Chenantais first described it as a “calcifying epithelioma” thought to be

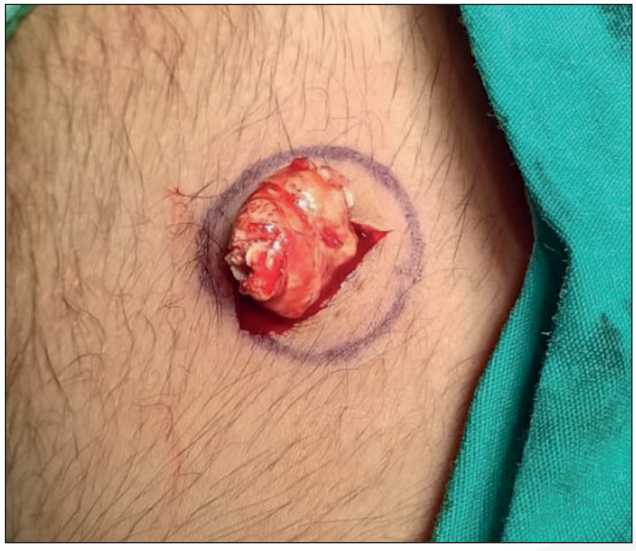

Figure 1: Encapsulated solid mass removed thorough left arm.

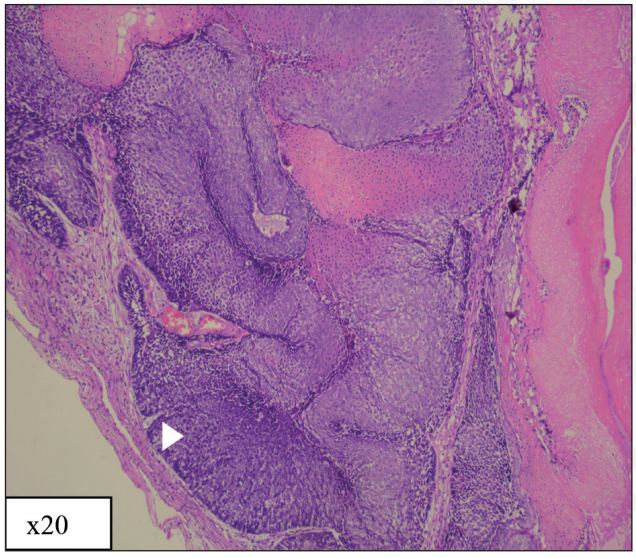

Figure 2: Basaloid cells area is seen where indicated by the black arrow. Slide stained with hematoxylin and eosin (x20).

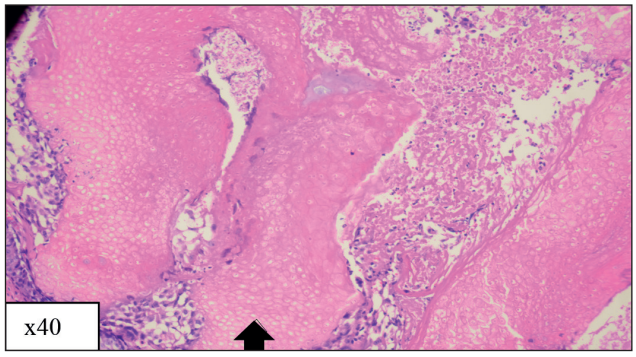

Figure 3: "Ghost cells" is seen where indicated by the black arrow. Slide stained with hematoxylin and eosin (x40).

of sebaceous gland origin (8). Forbis and Helwig examined the cortex of hair follicle and describes it as cell of origin. After this elucidation, PMX term has been proposed by them in '61 (9). The etiopathogenesis of PMX is unknown. Literature shows it is associated with trauma, β-catenin mutations, polyoma virus and genetic disorders such as xeroderma pigmentosum, myotonic dystrophy Gardner syndrome, Turner syndrome, basal cell nevus syndrome (2-4). Moehlenbeck's statistical study, which analyzed 140,000 skin tumor samples at their department of dermatology, showed an incidence of 0.12% of PMX (10). In society, 97% of PMX seen in white people (11). Gender distribution demonstrates a female predominance (4).

The head and neck regions are the most typical areas to locate these lesions. It is more likely to find PMX within the head region compared to the neck region. Within the head region specifically, the tumor locations in decreasing order are the cheek, periorbital and periauricular areas (4). They have also been described in various upper and low extremity locations. No cases have been reported on soles, palms or genital region (12). Clinically, PMX can be present as a solid mass, mobile attached to the skin. It can be present with overlying normal skin or with reddish and bluish tint (4). In this case, characteristics of palpation outcome of a superficial firm nodule are painlessness, or tenderness.

The differential diagnosis for PMX is varied. The differential diagnosis includes dermoid cyst, epidermal inclusion cyst, lipoma, hemangiomas, ossified hematoma, osteoma cutis, degenerating fibroxanthoma and foreign body reaction. Pilomatricomas may be mistaken for these lesions. According to literature, it has been emphasized that "tent sign" and "teeter-totter" findings may be useful in distinguishing PMX from other lesions. Stretching of the skin over the tumor shows the "tent sign" with multiple facets and angles, a pathognomonic sign for PMX (13). Pressing on one edge of the lesion causes the opposite edge to bulge from the skin like a "teeter-totter" (14). Imaging methods are used preoperatively in cases where a definitive diagnosis cannot be made. In this case, ultrasound as first option for us since it is a noninvasive tool, relatively quick, cost effective and sedative-free. It can demonstrate the degree of calcification, position and the continuity of the lesion deeper structures. There are also articles in which CT an MRI are used in the diagnosis phase (15,16).

On fine needle aspiration, the diagnosis of PMX may be extremely difficult. The presence of the complete spectrum of PMX cytological characteristics, such as basaloid cells, calcium deposits, naked nuclei, shadow ("ghost"), and giant cells, inflammatory background, allows a significant well-done preoperative diagnosis (17). In our case, demonstrated a characteristic histologic appearance including shadow (or ''ghost'') cells, basaloid cells and areas of calcification.

In pediatric patients, PMX is now considered as a more familiar diagnosis for cysts. In the past, it was not widely known on cytology.

Surgical excision remains the gold standard of treatment with low recurrence rates during the follow-up period (4). In cases with tumor adherence to the dermis, the overlying skin might be excised. Tumor size does not correlate with prognosis, although recurrence may occur if incompletely excised. If a lesion recurs after excision or rapidly enlarges, it should be excised due to malignant potential or possible misdiagnosis (18).

Hair matrix cell originated benign tumors are pilomatricomas that mostly appear in children. It should be taken into consideration in the differential diagnosis of superficial or subcutaneous masses in children. Imaging studies are generally not necessary unless the symptoms or lesion's location warrants such diagnostic assessments.

Acknowledgment

We thank to both aut authors for contribution to desing, concept, data collection, interpretation, writing and preparing the manuscript.

Author Contributions

Concept, design, validation, writing-original draft preparation, methodology, writing review and editing: **Yusuf Doruk Bilgi,** Data analysis: **Gülden Taşova Yılmaz.** The final version article has been read and approved by all authors.

Conflicts of Interest

There is no conflict of interest.

Financial Support

No financial support has been accepted for this study to avoid potential impacts on its outcome.

Ethical Approval and Consent

Not available.

Review Process

Extremely peer-reviewed and accepted.

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OLGU SUNUMU

Batı Karadeniz Tıp Dergisi
Medical Journal of Western Black Sea

Med J West Black Sea 2023;7(1): 99-101
DOI: 10.29058/mjwbs.1136494

Nadir Görülen Bir Vaka: Dyke-Davidoff-Masson Sendromu

A Rarely Seen Case Report: Dyke-Davidoff-Masson Syndrome

Öznur ADIGÜZEL AKMAN[1], Ayşenur DOĞRU[2], Ayşe KARTAL[3]

[1]Karadeniz Ereğli Devlet Hastanesi, Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları Bölümü, Zonguldak, Türkiye
[2]Çumra Devlet Hastanesi, Çocuk Sağlığı ve Hastalıkları Bölümü, Konya, Türkiye
[3]Ankara Bilkent Şehir Hastanesi, Çocuk Nörolojisi Anabilim Dalı, Ankara, Türkiye

ORCID ID: Öznur Adıgüzel Akman 0000-0001-8196-6664, Ayşenur Doğru 0000-0001-8091-8417, Ayşe Kartal 0000-0002-7775-8747

Bu makaleye yapılacak atıf: Adıgüzel Akman Ö ve ark. Nadir görülen bir vaka: Dyke-davidoff-masson sendromu. Med J West Black Sea. 2023;7(1):99-101.

Sorumlu Yazar
Öznur Adıgüzel Akman

E-posta
oznuradiguzel58@gmail.com

Geliş Tarihi
19.12.2022

Revizyon Tarihi
08.04.2023

Kabul Tarihi
09.04.2023

ÖZ

Dyke-Davidoff-Masson sendromu (DDMS) ilk kez 1933 yılında Dyke, Davidoff ve Masson tarafından tanımlanan, sıklıkla çocukluk döneminde ortaya çıkan, nöbet, hemipleji/ hemiparezi, zihinsel yetersizlik, serebral hemiatrofi, fasiyal asimetri, kalvaryal kalınlaşma, frontal sinüslerin hiperpnömatizasyonuyla karakterize nadir görülen bir sendromdur. Bu vakada, fokal epilepsi ve hemiparezi tanısı ile izlenen, eşlik eden fasiyal asimetri, zihinsel yetersizlik ve kraniyal görüntülemesinde DDMS ile uyumlu bulguları olan 15 yaşında bir kız hasta sunularak serebral hemiatrofi ayırıcı tanısında DDMS düşünülmesi gerektiği vurgulanmak istenmiştir. DDMS'nin tedavisi semptomatiktir ve tedavi epileptik nöbetler, hemiparezi veya hemipleji ve öğrenme güçlüğü gibi sorunlara yönelik olmalıdır. Sonuç olarak, epilepsi tanısı ile izlenen hastaların nörolojik muayenesinde fasial asimetri ve hemiparezi saptanması durumunda mutlaka kranyal MRG yapılmalı ve görüntülemede serebral hemiatrofi, kafatası kemiklerinde kalınlaşma gibi bulguların eşlik etmesi durumunda DDMS de aklımıza gelmeli ve diğer serebral hemiatrofi yapan nedenlerle ayırıcı tanı yapılmalıdır.

Anahtar Sözcükler: Dyke-Davidoff-Masson sendromu, serebral hemiatrofi, epilepsi, fasiyal asimetri, zihinsel yetersizlik

ABSTRACT

Dyke-Davidoff-Masson syndrome (DDMS) was first described by Dyke, Davidoff and Masson in 1933. It is a rarely-observed syndrome characterized by seizures, hemiplegia/hemiparesis, intellectual disability, cerebral hemi-atrophy, facial asymmetry, calvarial thickening, and hyperpneumatization of the frontal sinuses, frequently emerging in the childhood period. In this case, a 15-year old girl monitored for focal epilepsy and hemiparesis diagnosis with accompanying facial asymmetry, intellectual disability and findings compatible with DDMS on cranial imaging is presented to emphasize the need to consider DDMS in differential diagnosis of cerebral hemi-atrophy. The treatment for DDMS is symptomatic and treatment should target problems like epileptic seizures, hemiparesis or hemiplegia and learning difficulties. In conclusion, if neurological examination of patients monitored for epilepsy diagnosis identifies facial asymmetry and hemiparesis, cranial MRI should definitely be performed. If accompanied by findings like cerebral hemi-atrophy and thickening of the skull bones on imaging, DDMS should come to mind and differential diagnosis should be performed for other causes of cerebral hemi-atrophy.

Keywords: Dyke-Davidoff-Masson syndrome, cerebral hemi-atrophy, epilepsy, facial asymmetry, intellectual disability

GİRİŞ

Dyke-Davidoff-Masson Sendromu (DDMS) kontrlateral hemipleji/hemiparezi, epileptik nöbetler, fasiyal asimetri, öğrenme güçlüğü ya da zihinsel yetersizlik ile seyreden; serebral hemiatrofi, kalvaryal kalınlaşma ve paranazal sinüslerde hiperpnömatizasyonun eşlik ettiği kalıtsal olmayan, oldukça nadir görülen bir sendromdur (1,2). Prenatal dönemde geçirilmiş enfeksiyonlar, vasküler oklüzyon, damarsal anomaliler konjenital formuna neden olurken, doğum travması, beyin tümörü, uzamış febril nöbetler, iskemi ya da intrakraniyal kanamalar edinsel formuna neden olur (3).

Bu vakada, fokal epilepsi ve hemiparezi tanısı ile izlenen, eşlik eden fasiyal asimetri, zihinsel yetersizlik ve kraniyal görüntülemesinde DDMS ile uyumlu bulguları olan 15 yaşında bir kız hasta sunularak serebral hemiatrofi ayırıcı tanısında DDMS düşünülmesi gerektiği vurgulanmak istenmiştir.

OLGU

Onbeş yaşında kız hasta epilepsi, sol hemiparezi ve zihinsel yetersizlik nedeniyle ailesi tarafından polikliniğe getirildi. Annesinden alınan öyküye göre ilk kez üç aylıkken başlayan sol kol ve bacaktan başlayıp tüm vücuda yayılan nöbetler nedeniyle hastaneye yatırıldığı, o dönemde menenjit tanısı aldığı ve fenobarbital tedavisi ile taburcu edildiği, üç yaşında fenobarbital tedavisinin sonlandırıldığı, 12 yaşında nöbetlerinin tekrarlaması üzerine karbamazepin tedavisinin başlandığı öğrenildi. Özgeçmişinden miadında sezaryen ile 2860 gr olarak doğduğu, doğumda herhangi bir asfiksi bulgusu bulunmadığı, nöromotor gelişim basamaklarının yaşıtlarının gerisinde olduğu öğrenildi. Soygeçmişine bakıldığında ailede epilepsi veya başka bir nörolojik hastalık öyküsü olmadığı saptandı. Anne ile baba arasında akrabalık yoktu.

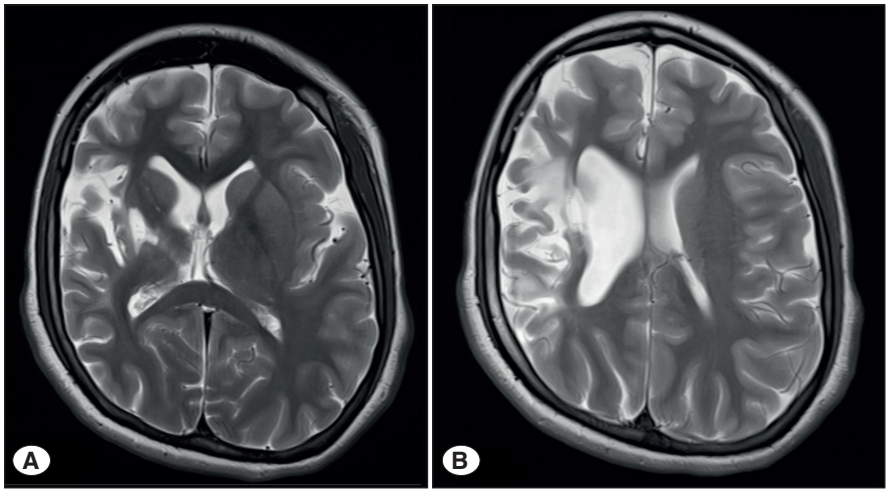
Olgunun yapılan fizik muayenesinde genel durumu iyi, bilinci açık, pupiller normoizokorik, yüz asimetrisi, solda her iki ekstremitede derin tendon reflekslerinde artış ve sol hemiparezi bulguları mevcuttu. Serebellar testlerinde herhangi bir anormallik yoktu. Bilişsel gelişiminin ise yaşıtlarıyla uyumlu olmadığı gözlendi.

Laboratuvar değerlendirmeleri sonucunda, hemogram, biyokimya tetkikleri, tiroid fonksiyon testleri normaldi (Tablo 1). Elektroensefalografisi jeneralize epileptik bozukluk ile uyumluydu. Yapılan WISC-R testi sonucunda bilişsel, sosyal, duygusal gelişiminin yaşıtlarının gerisinde olduğu saptandı.

Kranial manyetik rezonans görüntülemede (MRG) sağ serebral hemisferde ve bazal ganglionlarda diffüz atrofi (Şekil 1A), hacim kaybına sekonder sağ lateral ventrikülde genişleme, sağ hemikalvariyal kemik yapılarında kalınlaşma (Şekil 1B) ve frontal sinüslerin havalanmasında artış saptandı. Sol hemiparezi, sağ serebral hemiatrofi, fasiyal

Tablo 1: Laboratuvar değerleri

	Sonuçlar	Referans aralığı
Hemoglobin (g/dl)	12.8	12-15.5
Aspartat Transaminaz (U/L)	10	0-35
Alanin Aminotransferaz (U/L)	16	0-33
Kan üre azotu (mg/dl)	30	16.6-48.5
Kreatinin (mg/dl)	0.71	0.5-0.9
Ürik asit (mg/dl)	3.7	2.4-5.7
Sodyum (mmol/L)	136	135-145
Potasyum (mmol/L)	4.68	3.7-4.9
Kalsiyum (mg/dl)	9.9	8.8-10.6
Magnezyum (mg/dl)	1.96	1.9-2.7
Klor (mmol/L)	104	101-109
Tiroid stimülan hormon (mU/L)	0.921	0.38-5.33
Serbest T3 (ng/L)	3.47	2.6-4.37
Serbest T4 (ng/dl)	0.85	0.61-1.12



Şekil 1: A) Aksiyel T2 ağırlıklı manyetik rezonans görüntülemede sağ serebral hemisferde ve bazal ganglionlarda diffüz atrofi izlenmektedir. **B)** Aksiyel T2 ağırlıklı manyetik rezonans görüntülemede hacim kaybına sekonder sağ lateral ventrikülde genişleme ve sağ hemikalvariyal kemik yapılarında kalınlaşma izlenmektedir.

asimetri, zihinsel yetersizlik bulguları ve epilepsisi olan hastaya DDMS tanısı konuldu. Hemiparezisine yönelik fizyoterapi almakta olan olguya özel eğitim önerildi ve ayaktan takibe alındı.

TARTIŞMA

Dyke, Davidoff ve Masson tarafından ilk kez 1933 yılında tanımlanan DDMS, sıklıkla çocukluk döneminde ortaya çıkan, nöbet, hemipleji/ hemiparezi, zihinsel yetersizlik, serebral hemiatrofi, fasiyal asimetri, kalvaryal kalınlaşma, frontal sinüslerin hiperpnömatizasyonuyla karakterize nadir görülen bir sendromdur (4). Olgumuzda da sağ serebral hemiatrofi, aynı taraf frontal sinüslerde genişleme, fasiyal asimetri, zihinsel yetersizlik ve epilepsi mevcuttu.

Sendrom ilk olarak 1939 yılında tanımlanmış olsa da 1939 yılında serebral hemiatrofinin konjenital ve edinsel olarak iki tipi belirlenmiştir. Konjenital tipinde genellikle beyin maturasyonunun tamamlanmasından önce meydana gelen intrauterin vasküler oklüzyonlar neden olur ve bu olgularda semptomlar perinatal dönemde ya da bebeklik çağında ortaya çıkabilir (5).

Edinsel DDMS nedenleri arasında intraserebral hemoraji, enfeksiyon, travma, beyin tümörleri, iskemi, uzamış febril nöbetler sayılabilir (3). Olgumuzun üç aylıkken menenjit nedeniyle hastanede tedavi alması edinsel tip olabileceğini düşündürmektedir. Güven ve ark. tarafından tekrarlı fokal nöbet ve zihinsel yetersizlik ile başvuran, görüntülemede hipokampal atrofi, sağ serebral hemiatrofi, kontrlateral serebellar atrofi ve serebral venöz sinüslerin boyutunda asimetri gözlenen, altı aylıkken menenjit öyküsü olan 45 yaş erkek bir olgu bildirilmiştir (2).

Dyke-Davidoff-Masson sendromlu hastalarda zihinsel yetersizlik, epileptik nöbetlere eşlik eden bir durumdur ve sıklığının %15-20 arasında olduğu bildirilmiştir (6). Bizim olgumuzda da yapılan testler sonucunda orta derecede zihinsel yetersizlik saptandı.

Dyke-Davidoff-Masson sendromunun ayırıcı tanısında serebral hemiatrofinin görüldüğü Sturge-Weber sendromu, Rassmussen ensefaliti, hemimegalensefali, Silver sendromu gibi hastalıklar da unutulmamalıdır. Sturge-Weber sendromu, konvülsiyon, hemiparezi, hemipleji ve zihinsel yetersizlik görülmesi ile bu sendroma benzeyebilir. Ancak cilt ve göz bulgularının yanında tomografi ile ilk aylarda saptanabilen giral kalsifikasyonlar hastalığın tanınmasında kolaylık sağlar. Rasmussen ensefalitinde klinik tabloya daha çok fokal status epileptikus hakimdir ve epileptik nöbetler medikal tedaviye dirençli seyreder. Hemimegalensefalide ise etkilenen beyin yarısında ventriküller dilate değil ufak görünümlü olması ile ayırt edicidir. Silver sendromunda ise hastalar dismorfik fasiyal bulgular (düşük kulak, küçük üçgen yüz) kısa boy, serçe parmağında içe eğiklik gibi yapısal değişikliklere sahiptir.

Dyke-Davidoff-Masson sendromunun tedavisi semptomatiktir. Tedavide epileptik nöbetler, hemiparezi veya hemipleji ve eşlik eden öğrenme güçlüğü gibi problemlere yönelik olmaktadır. Özetle, epilepsi tanısı ile takipte olan hastaların nörolojik muayenesinde fasiyal asimetri ve hemiparezi saptanması durumunda mutlaka kranyal MRG yapılması ve görüntülemede serebral hemiatrofi, kafatası kemiklerinin kalınlaşması gibi bulguların eşlik etmesi durumunda DDMS de düşünülmeli ve diğer serebral hemiatrofi nedenleriyle ayırıcı tanısı yapılmalıdır.

Teşekkür

Radyolojik görüntülerin raporlanması ve yorumlanması sürecindeki emeklerinden dolayı Selçuk Üniversitesi Tıp Fakültesi Radyoloji Anabilim Dalı ve ekibine, ayrıca Uzm Dr. Zeynep Yüceler Şener'e teşekkür ederiz.

Yazar Katkı Beyanı

Yazarlar eşit katkıda bulunmuştur.

Çıkar Çatışması

Yazarlar arası herhangi bir çıkar çatışması yoktur. Bu olgu, 4-7 Aralık 2019 1. Uluslararası Rûmi Pediatri Kongresi'nde (IRUPEC 2019) poster olarak sunulmuştur.

Finansal Destek

Finansal destek bulunmamaktadır.

Etik Kurul Onayı

Olgu sunumu nedeniyle etik kurul oluru gerekmemiştir. Hasta ve vasisinden yazılı ve sözlü onam alınmıştır.

Hakemlik Süreci

Kör hakemlik süreci sonrası yayınlanmaya uygun bulunmuş ve kabul edilmiştir.

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DR. HASAN BAKLA
DÖNEM BİRİNCİSİ


TIP
FAKÜLTESİ

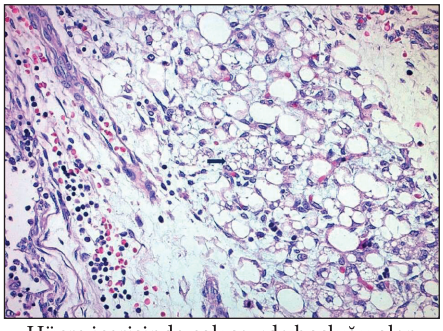
Cilt/Vol 7 • Sayı/Number 1 Nisan/April 2023

ISSN 2587-0335 / EISSN 2587-0572

Türkiye Diyabet ve Obezite Dergisi

Turkish Journal of Diabetes and Obesity

Zonguldak Bülent Ecevit Üniversitesi Obezite ve Diyabet Uygulama ve Araştırma Merkezi Yayın Organıdır



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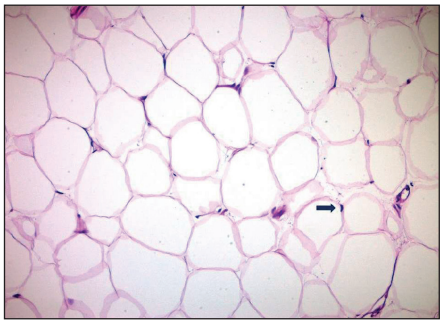

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