Selçuk Tıp Dergisi

Selcuk Medical Journal

Yıl/Year: 2025 Cilt/Volume: 41 Sayı/Issue:3

ISSN: 1017-6616 e-ISSN: 2149-8059

ELSEVIER Digital Commons™

NEU PRESS

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

ISSN: 1017-6616; **e-ISSN:** 2149-8059
Cilt/Volume: 41 **Sayı/Issue:** 3 **Yıl/Year:2025**

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

ISSN: 1017-6616; **e-ISSN:** 2149-8059
Cilt/Volume:41 **Sayı/Issue:** 3 **Yıl/Year:2025**

Sahibi/ Owner

Necmettin Erbakan Üniversitesi Rektörlüğü
Yaka Mah. Yeni Meram Cad. Kasım Halife Sok. No: 11/1 (A Blok) No:
11 (B Blok),Posta Kodu: 42090 Meram / KONYA/TÜRKİYE
Telefon : 0332 221 05 00
E-posta : bilgi@erbakan.edu.tr

Editör asistanı ve sekreter/ Editor assistant and Secreteriat

İlkay Kurt
Tlf: +90 332 223 62 54
E-Mail: ilkaykurt@mevlanamedsci.org

Yayıncı, Grafik ve Kapak tasarım/Publisher, Graphic and Cover design

NEU Press
Yaka Mah. Yeni Meram Cad. Kasım Halife Sok. No: 11/1 (A Blok) ,Meram / KONYA/TÜRKİYE
Tlf : +90 332 221 0 575, Mobil Tlf: 0 532 262 48 46
E-Mail: bilgi@neuyayin.com

Kapak ve Logo Tasarım/Cover and Logo designer: **Bünyamin Biçer**

Selçuk Tıp Dergisi; ULAKBİM/TR ve EBSCO, Inter-national Citation Index ve Türkiye Atıf Dizini tarafından indekslenmektedir

This journal is a member of, and subscribes to the principles of, the Committee on Publication Ethics (COPE)
www.publicationethics.org

Yayın Türü / Publication Type: Ulusal/Uluslararası Süreli Yayın; National/International periodical

Yayın Periyodu / Publication Period:Yılda dört kez (Mart, Haziran, Eylül ve Aralık) yayınlanır; Published fourth-annual (March, June,September and December)

Baskı Tarihi / Print Date: Eylül (September), 2025

Digital Commons™

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
ISSN: 1017-6616; **e-ISSN:** 2149-8059

YAZARLARA BİLGİ/YAZIM KURALLARI

Selçuk Tıp Dergisi (Selcuk Med J), Necmettin Erbakan Üniversitesi'nin bilimsel, bağımsız, hakemli, açık erişimli yayın organıdır. Tıp doktorları, araştırmacılar ve bilim adamlarından oluşan geniş bir kitleye hitap eden disiplinli bir dergidir. Temel amaç Tıp/Sağlık alanında, tanı ve tedavideki güncel gelişmelerin, cerrahi yenilikler ve bilim dünyasına katkıda bulunacak çalışmaların ulusal ve uluslararası literatürde paylaşımının sağlanmasıdır.

Selçuk Tıp Dergisi, tıp bilimine ve akademik çalışmalara katkısı olan, klinik ve deneysel çalışmaları, editöryal yazıları, klinik olgu bildirimlerini, teknik ve eğitici derlemeleri, orijinal görüntü raporlarını ve editöre mektupları yayınlar. Anket/mülakat çalışmaları; Editörün ilk değerlendirmesi sonucunda çok değerli bir katkı sunuyorsa değerlendirmeye alınabilir.

Dergi gönderim kurallarına ve dergi kapsamına uygun görülen, editöryal çalışmalar hariç tüm yazılar alanında uzman hakemlere bilimsel değerlendirme için gönderilir. En az iki hakem kararı aranır. Yayımlanan tüm makaleler çift taraflı kör akran değerlendirmesi sürecine tabidir. Uygunluğunu tartışılan çalışmalarda yardımcı editörler hakemlerin yorumlarını dikkate alarak kendi değerlendirmelerini eklerler. Gönderilen tüm yazılar için nihai karar Baş Editör'e aittir. Bütün makaleler için süreçlerin editör ve yayın kurulu tarafından en geç üç ay içerisinde sonuçlandırılması hedeflenir. Fakat elde olmayan gecikmelerden dolayı bu süre uzayabilir.

Yayın kurulu kararları ile belirlenen bazı konular hakkındaki yazılar, yayın kurulu üyelerinin tamamının incelemesine sunulur. İncelemeler sonucu oy çokluğuna ulaşan çalışmaların dergideki süreçleri devam edecektir. Yayın kurulu kararları dergi web sitesinde yayınlanmaktadır.

Yayına kabul edilen yazıların telif hakkı yazarlara aittir. Selçuk Tıp Dergisi, makaleyi ilk yayımlama hakkına sahiptir. Selçuk Tıp Dergisi, ilave olarak websitesinde bulunan telif hakları bildirim belgesinin de yazarlar tarafından onaylanarak imzalanmasını ve ıslak imzalı formun sisteme eklenmesini talep etmektedir. Dergi her yıl mart, haziran, eylül ve aralık aylarında olmak üzere dört sayı olarak yayımlanmaktadır. Derginin yayın dili İngilizcedir.

Gönderilen yazıların daha önce herhangi bir yerde/dergide yayınlanmamış olması ve yayın için başka bir dergiye gönderilmemiş olması gerekmektedir [Bilimsel kongrelerde sunulan sözlü bildiri ve posterler (özet ya da tam metin olabilir) bildirilmek kaydı ile hariçtir]. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal vb.) yazarlara aittir. Dergide yayımlanan yazılarda ifade edilen ifadeler veya görüşler yazarların görüşleri olup, editörlerin, yayın kurulu ve yayıncının görüşlerini yansıtmaz; editörler, yayın kurulu ve yayıncı, bu tür materyaller için herhangi bir sorumluluk veya yükümlülük kabul etmemektedir. Yazım kurallarına uygun olarak hazırlanmamış olan yazıların incelenmeye alınıp alınmaması Editör ve Editöryal Kurulun insiyatifindedir.

Tüm çalışmalarda etik kurul onayı ve bu onamın belgelendirilmesi gerekmektedir. Tüm çalışmalarda yazarların çalışmaya katkı düzeyi ve onayı bildirilmelidir. Çalışmada veri toplanması, deney aşaması, yazım ve dil düzenlemesi dahil olmak üzere herhangi bir aşamasında finansal çıkar çatışması olmadığı bildirilmelidir. Çalışmada varsa ticari sponsorluk bildirilmelidir. Selçuk Tıp Dergisi'nde intihal programı (iThendicate) kullanılmaktadır. Akademik atıf sınırını aşan benzerlik taşıyan makaleler ve yayın kurallarına uygun olarak hazırlanmamış makaleler değerlendirmeye alınmayacaktır. Dergi intihal tarama raporunu yazardan talep edeceği gibi kendisi de tarama yapabilir.

Derginin yayın politikası ve süreçleri Uluslararası Medikal Dergisi Editörleri Komitesi (International Committee of Medical Journal Editors-I**CMJE),** Dünya Tıbbi Editörler Derneği (World Association of Medical Editors-**WAME),** Bilim Editörleri Konseyi (Council of Science Editors-**CSE),** Avrupa Birliği Derneği Bilim Editörleri (European Association of Science Editors-**EASE)** ve Yayın Etiği Komitesi (Committee on Publication Ethics-**COPE)** ve Ulusal Bilgi Standartları Örgütü (National Information Standards Organization-**NISO)** yönergelerini takip eder. Dergimiz 'Şeffaflık ve Akademik Yayıncılık En İyi Uygulamalar İlkelerine' (Principles of Transparency and Best Practice in Scholarly Publishing) **(doaj.org/bestpractice)** uygundur. Yayın Kurulu, dergimize gönderilen çalışmalar hakkındaki intihal, atıf manipülasyonu ve veri sahteciliği iddia ve şüpheleri karşısında **COPE** kurallarına uygun olarak hareket edecektir.

Derginin Yayın Kurulu, itiraz ve şikâyet vakalarını, COPE rehberleri kapsamında işleme almaktadır. Yazarlar, itiraz ve şikayetleri için doğrudan baş editör veya editör/yayın kurulu ile temasa geçebilirler. İhtiyaç duyulduğunda Yayın Kurulu'nun kendi içinde çözemediği konular için tarafsız bir temsilci atanacaktır. İtiraz ve şikayetler için karar verme süreçlerinde nihai kararı Baş Editör verecektir. Yayıncı ve editör gerektiğinde düzeltmeler, açıklamalar, geri çekilmeler ve özürler yayınlamaya her zaman hazırdır.

Selçuk Tıp Dergisi ile ilgili tüm yazışmalar, makale gönderme, makalenin takibi, danışman raporları, düzeltmelerin yapılıp yüklenmesi, kabul yazısı gönderimi ve diğer tüm makale ile ilgili formların yüklenmesi **https://www. selcukmedj.org s**ayfasından yapılacaktır. Bu site üzerinden yüklenecek makaleler için kurallar aşağıda belirtilmiştir.

Selçuk Tıp Dergisi, ücretsiz, açık erişim politikası benimsemektedir. Bu bağlamda dergide yayınlanan tüm yazılar https://www. selcukmedj.org adresinden erişime açık olup yazarlardan hiçbir ek ücret talep edilmeyecektir.

Yazarlık

Selçuk Tıp Dergisi'ne gönderilen çalışmalarda yazar olarak listelenen herkesin ICMJE (www.icmje.org) tarafından önerilen yazarlık koşullarını karşılaması gerekmektedir. ICMJE, yazarların aşağıdaki 4 koşulu karşılamasını önermektedir:

- Çalışmanın konseptine/tasarımına; ya da çalışma için verilerin toplanmasına, analiz edilmesine ve yorumlanmasına önemli katkı sağlamış olmak;
- Yazı taslağını hazırlamış ya da önemli fikirsel içeriğin eleştirel incelemelerini yapmış olmak;
- Yazının yayından önceki son halini gözden geçirmiş ve onaylamış olmak;
- Çalışmanın herhangi bir bölümünün geçerliliği ve doğruluğuna ilişkin soruların uygun şekilde soruşturulduğunun ve çözümlendiğinin garantisini vermek amacıyla çalışmanın her yönünden sorumlu olmayı kabul etmek.

Yazar olarak belirtilen her kişi yazarlığın dört koşulunu karşılamalıdır ve bu dört koşulu karşılayan her kişi yazar olarak tanımlanmalıdır. Yazar olarak atanan tüm kişiler yazarlık için hak kazanmalı ve hak kazanan herkes listelenmelidir. Dört kriterin hepsini karşılamayan kişilere makalenin başlık sayfasında teşekkür edilmelidir. Finansman alımı, veri toplanması ya da araştırma grubunun genel gözetimi, kendi başlarına, yazarlığı haklı çıkarmaz. Bir ya da daha fazla yazar, çalışma başlangıcından yayınlanmış makaleye kadar, bütün olarak çalışmanın bütünlüğünün sorumluluğunu üstlenmelidir.Çok merkezli çalışmalarda yazarlık bir gruba atfedilir. Yazar olarak adlandırılan grubun tüm üyeleri, yukarıdaki yazarlık kriterlerini tam olarak karşılamalıdır. Bu kriterleri karşılamayan grup üyeleri, onayları ile birlikte listelenmelidir. Mali ve maddi destek de kabul edilmelidir.

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
ISSN: 1017-6616; **e-ISSN:** 2149-8059

Yazar Değişikliği Talepleri
Yazar listesindeki yazar isimlerinin eklenmesi, silinmesi veya yeniden düzenlenmesi ancak makale kabul edilmeden önce ve ancak dergi Editörü tarafından onaylandığı takdirde yapılabilir.
Böyle bir değişikliği talebi olursa Editör, sorumlu yazardan (a) yazar listesindeki değişikliğin nedeni ve (b) tüm yazarlardan eklemeyi kabul ettiklerine dair yazılı onay (e-posta), talep eder. Editör, yalnızca istisnai durumlarda, makale kabul edildikten sonra yazarların eklenmesini, silinmesini veya yeniden düzenlenmesini dikkate alacaktır.

Makale Yazımı
Orijinal araştırma makalesi kaleme alanlar, konuyu özgün bir şekilde ve nesnel bir tartışma ile ele almalıdır. Makale, başkalarının çalışmayı tekrarlamasına izin vermek için yeterli ayrıntı ve referansları içermelidir. Hileli veya bilerek yanlış beyanlar etik dışı davranış teşkil eder ve kabul edilemez.

Özgünlük
Yazar makalenin orijinal olduğu, daha önce başka bir yerde yayınlanmadığı ve başka bir yerde, başka bir dilde yayınlanmak üzere değerlendirmede olmadığı konusunda teminat sağlamalıdır. Makale yazımının yapay zekâ sistemleri kullanılarak yapıldığı çalışmalar kabul edilmemektedir. Yapay zekâ sistemleri, sadece yazıların dil düzenlemeleri için kullanılabilir.

Orijinal Kaynak Kullanımı ve Atıf Yapma
Yazarlar, tamamen özgün eserler yazdıklarından ve başkalarının eserlerini veya sözlerini kullanmışlarsa, bunun uygun şekilde alıntılandığından emin olmalıdır. Üçüncü taraflarla konuşma, yazışma veya tartışmalarda olduğu gibi özel olarak elde edilen bilgiler, kaynağın açık ve yazılı izni olmadan kullanılmamalıdır.

Veri Erişimi ve Muhafazası
Yazarlardan, editör incelemesi için makalelerini destekleyen araştırma verilerini sağlamaları ve/veya derginin açık veri gereksinimlerine uymaları istenebilir. Yazarlar, mümkünse, bu tür verilere kamu erişimi sağlamaya ve bu tür verileri yayınlandıktan sonra makul bir süre boyunca saklamaya hazır olmalıdır. Dergimiz, araştırma verilerinin TUBITAK'ın Aperta Portalı'na yüklenmesini tavsiye etmektedir.

Çoklu ve Eşzamanlı Yayın
Bir yazar aynı araştırmayı içeren makalesini birden fazla dergisinde yayımlamamalıdır. Aynı makalenin aynı anda birden fazla dergiye gönderilmesi etik dışı davranıştır. Bir yazar, özet şeklinde yayınlanmış olması dışında, daha önce yayınlanmış bir makaleyi başka bir dergide değerlendirilmek üzere sunmamalıdır.

Anket ve Mülakata Dayanan Çalışmaların Yayını ve Etik Kurul Onamları
Etik kurul izni gerektiren, tüm bilim dallarında yapılan araştırmalar için (etik kurul onayı alınmış olmalı, bu onay makalede belirtilmeli ve belgelendirilmelidir. Etik kurul izni gerektiren araştırmalarda, izinle ilgili bilgilere (kurul adı, tarih ve sayı no) yöntem bölümünde, ayrıca makalenin ilk/son sayfalarından birinde; olgu sunumlarında, bilgilendirilmiş gönüllü olur/onam formunun imzalatıldığına dair bilgiye makalede yer verilmelidir. Anket çalışmaları ve mülakata dayanan çalışmaların etik kurul onam belgeleri alınmış olmalı ve makale yüklenirken dergi sistemine eklenmelidir.

Çıkar Çatışması
Kişinin yaptığı işte çelişkiye düşmesine yol açacak, objektifliğini önemli oranda bozabilecek veya herhangi bir kişi ya da kuruluş lehine adil olmayan avantaj sağlayabilecek herhangi finansal ya da diğer tür çıkarlardır. Araştırmanın yürütülmesi ve makalenin hazırlanması sürecinde alınan tüm mali destek kaynakları ve sponsorların çalışmadaki rolü açıklanmalıdır. Finansman kaynağı yoksa bu da belirtilmelidir. Açıklanması gereken olası çıkar çatışması örnekleri arasında danışmanlıklar, maaş alımı, hibeler yer alır. Potansiyel çıkar çatışmaları mümkün olan en erken aşamada açıklanmalıdır.

Hata Bildirimi
Bir yazar yayınlanmış çalışmasında önemli bir hata veya yanlışlık fark ettiğinde, derhal dergiye bildirimde bulunmalıdır. Editör tarafından gerekli görüldüğü takdirde makaleyi geri çekmek veya düzeltmek için iş birliği yapmak da yazarın yükümlülüğüdür. Editör veya yayıncı, yayınlanan bir çalışmanın hata içerdiğini üçüncü bir şahıstan öğrenirse, yazarın konu hakkında editöre bilgi vermek de dahil olmak üzere editörle iş birliği yapması yazarın yükümlülüğüdür.

Görüntü Bütünlüğü
Bir görüntüde belirli bir özelliği geliştirmek, karartmak, taşımak, kaldırmak veya eklemek kabul edilemez. Yazarlar, dergi tarafından uygulanan grafik görseller için belirlenen politikaya uymalıdır.

Düzeltme ve Yayından Geri Çekme Talepleri
Selçuk Tıp Dergisi tarafından yayımlanan makaleler nihai versiyondur. Bu nedenle yayımlandıktan sonra düzeltme talepleri, Yayın Kurulu tarafından **COPE** yönergelerine göre değerlendirilir. Yayından geri çekme talepleri, makale kabulünden önce yapılmalıdır ve Editör Kurulu onayına tabidir. Makale kabulü sonrasında henüz yayınlanmadan önce bir geri çekme talebi olursa, gerekçesi ile birlikte baş editöre mail yolu ile ulaştırılmalıdır. Gerekçeler editör kurulu toplantısında değerlendirilerek nihai karar verilecek ve yazara mail yolu ile bildirilecektir. **Yayın aşamasına alınmış bir makalenin geri çekme talep başvuruları dikkate alınmayacaktır.** Yayımlanmadan önce çalışmasını geri çekme talebinde bulunmak isteyen yazar (lar), Geri çekme formunu doldurarak her bir yazarın ıslak imzası ile imzalanmış ve taratılmış halini editor@selcukmedj.org.tr adresi üzerinden e-posta aracılığıyla Baş Editör ve Editör kuruluna iletmekle yükümlüdür. Geri çekme formuna web sitemizin indirmeler sayfasından ulaşabilirsiniz(https://www.selcukmedj.org/tr-tr/indirmeler/). Editör Kurulu geri çekme bildirimini inceleyerek en geç 15 gün içerisinde dönüş sağlar.
Yazar isimleri, bağlantıları, makale başlıkları, özetler, anahtar kelimeler, herhangi bir bilgi yanlışı ve dijital nesne anımlayıcılardaki [digital object identifier (DOI)] yazım hataları, bir "erratum" ile düzeltilebilir.

Makale Değerlendirme Süreci
Dergiye gönderilen makalelerin hızlı bir şekilde değerlendirilmesi ve yayınlanması hedeflenmiştir. Tüm makaleler çift kör hakem değerlendirme sürecine tabidir. Makaleler, içerik, özgünlük, alandaki önem, istatistiksel analizin uygunluğu ve sonuçların çıkarılması için alanında uzman hakemler tarafından gözden geçirilecektir. En az iki hakem kararı aranacaktır. Hakemler arasında tutarsızlıklar olması durumunda, makale üçüncü ya da dördüncü bir hakeme gönderilebilecektir. Hakem kararları yardımcı editörler tarafından değerlendirilerek değerlendirme sonuçları baş editöre gönderilecektir. Gönderilen makalelerin kabulüne ilişkin nihai karar, baş editöre aittir.

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
ISSN: 1017-6616; e-ISSN: 2149-8059

Hakemler tarafından bildirilen ve yazarlar için faydalı oldukları değerlendirilen yorum ve değerlendirmeler yazarlara gönderilir. Hakemler tarafından yapılan talimat, itiraz ve talepler kesinlikle yerine getirilmelidir. Hakem(ler)e cevap dosyası ayrıca bir Word belgesi halinde oluşturulmalıdır. Yazının gözden geçirilmiş şekliyle yazarlar, bu dosyada, hakemlerin taleplerine uygun olarak atılan her adımı açık ve net bir şekilde belirtmelidir. Yazar açıklama notları, hakemlerin değerlendirme sırasına göre numaralandırılmış olarak listelenmelidir. Ayrıca makale içerisinde de gerekli değişiklikleri yapmalı ve bunları makale içerisinde belirterek (boyayarak), revize edilmiş makale ve hakem önerilerine verilmiş yanıtları içeren formlar https://www. selcukmedj.org adresinden titizlikle yüklenmelidir.

Yazıların Gönderilmesi

Yazarlar Yayın Hakları Bildirim Formunu sisteme yüklemelidir. Tüm yazışmalar sorumlu yazara gönderilecektir. İlgili sorumlu yazarın, tüm diğer yazışmalar için bir e-posta adresi bildirilmelidir. Yazarlar makalelerininin alındığından kendisine verilen numara ile haberdar edilirler. Bildirilen makale numarası yapılan tüm yazışmalarda kullanılmalıdır. Yazarlara beyan edilir ki; editör ofisinin ilk değerlendirmesi sonucu okuyucunun menfaatine dönük olarak makalelerin içeriği dolayısıyla makalesi geri iade edilebilir. Bu hızlı reddetme süreci, yazarın başka bir yerde makalesini yayınlanmasına olanak sağlar.
Selçuk Tıp Dergisi'ne makale gönderilmesi, tüm yazarların, derginin yayın politikalarını ve yayın etiğini okuduğu ve kabul ettiği anlamına gelir. Makale gönderimi ve ilgili diğer tüm işlemler https://www. selcukmedj.org adresinden online olarak yapılacaktır.

Yazıların Hazırlanması

Yazarların, materyallerini göndermeden önce aşağıdaki kuralları okumaları ve makalelerini bu kurallara uygun halde sisteme yüklemeleri gerekmektedir:

Genel yazı biçimi: Tüm makaleler, her tarafta 2,5 cm genişliğinde kenar boşlukları bulunan standart A4 boyutunda bir word dosyası kullanılarak yazılmalı, kaynaklar, resim şekil ya da tablolar metinde geçiş sırasına göre numaralandırılmalıdır. Metin, sol hizalı ve heceli satır sonları olmayan 12 puntolu bir fontta çift boşluk kullanılarak ve Times New Roman karakterinde yazılmalıdır. Kelimeler arasında ve cümle noktası sonrasında tek boşluk bırakmaya özen gösterilmelidir. Paragraf için sol girintiyi sekme tuşu ile bir kez tıklayarak ayarlanmalıdır. Ölçüm birimleri için Uluslararası Birimler Sistemi (SI) kullanılmalıdır. Makalenin tüm sayfaları sayfa sonunda numaralandırılmalıdır. Tüm yazılar yazım kurallarına uymalı, noktalama işaretlerine uygun olmalıdır.

Tüm makalelerde; Kapak sayfası, Ön yazı (cover letter), makale dosyası, Etik kurul onay Belgesi (kurumdan alınan), intihal analiz raporu, Şekiller ve Resimler, Telif Hakları Devir Formu, ve gerekli ise hasta onam formu ayrı dosyalar olarak yüklenmelidir.
Kaynaklar makale dosyasında, makale biter bitmez değil ayrı bir sayfada başlamalıdır. Tablolar, tablo açıklamaları, resim/şekiller ve resim/şekil açıklamaları ayrıca makale ana dosyasına kaynakların ardından ayrı bir sayfada eklenmelidir. Tablo/Resim/şekil açıklamaları; Tablo/Resim/şekillerin hemen altlarında olmalıdır.

Makale bölümleri hakkında

1-Kapak Sayfası: Makalenin İngilizce tam başlığı ve 50'den fazla karakter içermeyen kısa bir başlık, tüm yazarların açık şekilde adları ve soyadları, ORCID numaraları, kurumları, sorumlu yazar ismi iş veya cep telefonu, e-posta ve yazışma adresi belirtilmelidir.Makale daha önce tebliğ olarak sunulmuş ise tebliğ yeri ve tarihi belirtilmelidir. Yazarlar ve kurumları hakkındaki bilgiler başlık sayfası haricinde ana metinde (materyal metot bölümü dahil), tablolarda, şekillerde ve video dokümanlarında yer almamalıdır. Herhangi bir hibe ya da diğer destek kaynaklarının detayları, makalenin hazırlanmasına katkıda bulunan ancak yazarlık kriterlerini karşılamayan bireylere teşekkür bölümü de kapak sayfasına eklenmelidir.

2-Ana makale dosyası; Ana makale dosyası, yazar isimleri ve kurumları gibi bilgiler içermemelidir. Ana makale dosyası:
1. Başlık, 2. Özet ve Anahtar Kelimeler, 3. Makale ana metni, 4. Kaynaklar, 5. Tablolar ve açıklamaları, 6. Resim ve Şekil açıklamaları ile birlikte resim ve şekiller, 7. Alt yazılar şeklinde dizilmelidir.
Başlık: Makale Word dosyasında en baş kısımda makalenin yazım dilinde tek uzun başlığı yer almalıdır.
Özet: Editöre Mektup haricinde tüm yazılar özet içermelidir. Orijinal araştırma makalelerinin özetleri Amaç, Gereçler ve Yöntem, Bulgular ve Sonuç alt başlıklarını içermelidir. Özetler; kaynak, şekil veya tablo numarası içermemelidir. Sözcük sayısı ve özellikler için Tablo 1'deki veriler dikkate alınmalıdır.
Anahtar sözcükler:Özelerin sonunda en az üç ile en fazla beş anahtar sözcük bildirilmelidir. Anahtar sözcükler kısaltmalar olmaksızın tam olarak listelenmeli birbirinden virgül ya da noktalı virgül kullanılarak ayrılmalıdır. Anahtar kelimeler, "Tıbbi Konu Başlıklarına **(MESH)"** uygun olmalıdır (Bakınız: www.nlm.nih.gov/mesh/MBrowser.html).
Kısaltmalar:Özetlerde ve başlıklarda kısaltmalar kullanılmamalıdır. Makalede kullanılacak kısaltmalar, mümkünse ulusal veya uluslararası kabul görmüş olmalı, ilk kullanıldığında metin içinde tanımlanmalı ve parantez içinde yazılmalıdır. Daha sonra metin boyunca o kısaltma kullanılmalıdır. Yaygın olarak kabul edilen kısaltmalar ve kullanım için lütfen "Bilimsel Stil ve Biçim"e bakınız. (https://www.scientificstyleandformat.org/Home.html). Ana metinde Bir ticari markalı ilaç, ürün, donanım veya yazılım programı ana metinde yer aldığında, ürün bilgisi, ürünün adını, ürünün imalatçısını ve şirket ile şirket merkezinin bulunduğu ülkeyi aşağıdaki biçimde parantez içinde verilmelidir: "Discovery St PET / CT tarayıcı (General Electric, Milwaukee, WI, ABD).
Makale ana metni:
Giriş: Konuyu ve çalışmanın amacını açıklayacak spesifik bilgilere yer verilir.
Gereçler ve Yöntem: Çalışmanın gerçekleştirildiği yer, zaman ve çalışmanın planlanması ile kullanılan elemanlar ve yöntemler bildirilmelidir. Verilerin derlenmesi, hasta ve bireylerin özellikleri, deneysel çalışmanın özellikleri ve istatistiksel metotlar detaylı olarak açıklanmalıdır. Çalışmaya alınanlar ve çalışmayı yürütmek için kullanılan tüm yöntemler ayrıntılı olarak açıklanmalıdır. Kullanılan yeni veya modifiye yöntemler ayrıntılı olarak açıklanmalı kaynak belirtilmelidir. İlaçların ve kimyasal ajanların dozları, konsantrasyonları, verilme yolları ve süresi belirtilmelidir. Elde edilen verileri özetlemek ve önerilen hipotezi test etmek için kullanılan tüm istatistiksel yöntemlerin kısa bir raporu, istatistiksel olarak anlamlı farklılık için belirlenen p değeri ölçütleri de dahil olmak üzere bir alt başlık altında sunulmalıdır. Yapılan istatistiksel değerlendirme ayrıntılı olarak açıklanmalıdır. Olabildiğince standart istatistiksel yöntemler kullanılmalıdır. Nadiren kullanılmış veya yeni istatistiksel yöntemler kullanılmışsa konuya ilişkin ilgili referanslar belirtilmelidir. Gerekirse, olağandışı, karmaşık veya yeni istatistiksel yöntemlerle ilgili daha ayrıntılı açıklamalar, çevrimiçi ek veri olarak okuyucular için ayrı dosyalarda verilmelidir.
Bulgular: Elde edilen veriler istatistiksel sonuçları ile beraber ayrıntılı olarak verilmelidir. Bulgular şekiller ve tablolar ile desteklenmelidir. Rakam ve tablolarda verilen bilgilerin gerekli olmadıkça metinde tekrarlanmamasına özen gösterilmelidir.
Tartışma: Çalışmanın sonuçları literatür verileri ile karşılaştırılarak değerlendirilmeli, yerel ve/veya uluslararası kaynaklarla desteklenmelidir. Yazıyla alakasız veya gereksiz genel bilgiler eklenmemeli, yazının amacına uygun yeterli uzunlukta olmalıdır.
Kaynaklar: Kaynaklar ayrı bir sayfaya yazılmalıdır. Kaynaklar APA 7 sistemine uygun olarak belirtilmelidir. Buna göre, kaynak numaraları cümle sonuna nokta konmadan () içinde verilmeli, nokta daha sonra konulmalıdır. Kaynak yazar isimleri cümle içinde kullanılıyorsa ismin geçtiği ilk yerden sonra () içinde kaynak verilmelidir. Birden fazla kaynak numarası veriliyorsa arasına ",", ikiden daha fazla ardışık kaynak numarası veriliyor ise rakamları arasına "-" konmalıdır [ör. (1,2), (1-4) gibi. Yazar sayısı 3 ve daha azsa tüm yazarların ismi olmalı, 3'dan daha fazla ise ilk3 yazar yazılıp diğerleri için et al. kullanılmalıdır. Kaynaklar metindeki kullanılış sırasına göre numaralandırılıp listelenmelidir. Atıf doğruluğu, yazarın sorumluluğundadır. Kaynaklar orijinal yazım, aksan, noktalama vb. ile tam olarak uyumlu olmalıdır. Metin içindeki tüm kaynaklar belirtilmelidir. Kaynak listesinde mükerrer yazım yapılmamalıdır. Farklı yayın türleri için kaynak stilleri aşağıdaki örneklerde sunulmuştur:

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
ISSN: 1017-6616; e-ISSN: 2149-8059

Araştırma Makalesi:

- Mirza E, Oltulu R, Oltulu P, et al. Dry eye disease and ocular surface characteristics in patients with keratoconus. Saudi J Ophthalmol. 2022;36(1):117-21. doi: 10.4103/sjopt.sjopt_37_21.
- Vikse BE, Aasarød K, Bostad L, et al. Clinical prognostic factors in biopsy-proven benign nephrosclerosis. Nephrol Dial Transplant. 2003;18(3):517-23. doi: 10.1093/ndt/18.3.517.

Tek Yazarlı Kitaplar:

- Danovitch GM. Handbook of Kidney Transplantation. Boston: Little, Brown and Company (Inc.), 1996: 323-8.

Kitap Bölümü:

- Soysal Z, Albek E, Eke M. Fetüs hakları. Soysal Z, Çakalır C, ed. Adli Tıp, Cilt III,İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Yayınları, İstanbul, 1999:1635-50.
- Davison AM, Cameron JS, Grünfeld JP, et al. Mesengiocapillary glomerulonephritis In: Williams G, ed. Oxford Textbook of Clinical Nephrology.New York:Oxford University Press, 1998: 591- 613.

Baskıdan önce çevrim içi olarak yayımlanan dergi makalesi:

- Doğan GM, Sığırcı A, Akyay A, et al. A Rare Malignancy in an Adolescent: Desmoplastic Small Round Cell Tumor. Turkiye Klinikleri J Case Rep. 10.5336/caserep.2020-77722. Published online: 31 December 2020.
- Cai L, Yeh BM, Westphalen AC, et al. Adult living donor liver imaging.DiagnIntervRadiol. 2016 Feb 24.doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Toplantı Raporları:

- Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Bilimsel veya Teknik Rapor:

- Cusick M, Chew EY, Hoogwerf B, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Tez:

- Kaplan SI. Post-hospital home health care: elderly access and utilization (dissertation). St Louis (MO): Washington Univ; 1995.

Web sayfası ve Sosyal Medya araçları: Yazar. Başlık. Erişim linki: URL. Erişim tarihi ve yılı

3-Tablolar ve açıklamaları: Tablolar, ana makale metnine dahil edilmelidir, kaynak listesinden sonra sunulmalı ve ayrı bir sayfada olmalıdır. Ana metinde yer alan sıraya göre numaralandırılmalıdır. Her bir tablonun üzerine açıklayıcı bir başlık konulmalıdır. Tabloda kullanılan kısaltmalar, tablonun altında dipnotlarla tanımlanmalıdır (ana metin içerisinde tanımlanmış olsa bile). Tablolar kolay okunması için açık bir şekilde düzenlenmelidir. Tablolarda sunulan veriler, ana metinde sunulan verilerin tekrarı olmamalı, ancak ana metni desteklemelidir.

4-**Şekil ve Resimler:** Şekil, grafik ve resimler makale gönderim sistemi aracılığıyla ayrı dosyalar (TIFF veya JPEG formatında) halinde yüklenmeli ilaveten ana makale dosyasında ayrı bir sayfada tablolardan sonra ana metin içinde de gösterilmelidir. Sisteme ayrı olarak yüklenmeyen sadece makale içerisinde geçen resimler kabul edilmeyecektir. Şekil ve resimler mutlaka isimlendirilmeli ve numaralandırılmalı, metin içinde sıralamaya dikkat edilerek belirtilmelidir. Ana metine eklenecek resim, şekil ve grafik altına açıklamaları da eklenmelidir. Resimler minimum 300 dots per inch (dpi) çözünürlüğünde ve net olmalıdır. Şekil ve resim altlarında kısaltmalar kullanılmış ise, kısaltmaların açılımı alfabetik sıraya göre alt yazının altında belirtilmelidir. Mikroskobik resimlerde büyütme oranı ve tekniği açıklanmalıdır. Yayın kurulu, yazının özünü değiştirmeden gerekli gördüğü değişiklikleri yapabilir. Şekil alt birimleri olduğunda, alt birimler tek bir görüntü oluşturmak için birleştirilebilir. Şekiller, alt birimleri göstermek için işaretlenmeli ve her birinin açıklamaları (a, b, c, vb.) yazılmalıdır. Şekilleri desteklemek için kalın ve ince oklar, ok uçları, yıldızlar, yıldız işaretleri ve benzer işaretler kullanılabilir. Makale içeriği gibi şekiller de kör olmalıdır. Bir birey ya da kurumu tanımlayabilecek resimlerdeki olası bilgiler anonimleştirilmelidir. Hasta fotoğrafı paylaşımlarında kimliğin birebir tanınmamasına özen göstermeli, hastalığı belirlemeye yetecek yeterlilikte görüntü paylaşılmalıdır. Hastanın kimliğini açık eden resim paylaşımları için, hastanın resminin paylaşımına izin verdiği onam formu şarttır.

Tablo 1. Makale türlerine göre sınırlamalar

Makale türü	Sözcük sınırı	Özet sınırı	Kaynak sınırı	Tablo sınırı	Şekil sınırı
Araştırma makalesi	4000	300	50	6	6
Derleme	6000	300	85	6	10
Olgu sunumu	1500	200	15	3	5
Editöre mektup	1000	Özet yok	8	Tablo içermez	Şekil içermez
Editöryal	1000	Özet yok	20	3	3
Orijinal görüntü raporu	200	Özet yok	5	1	3

Makale Türleri

Selçuk Tıp Dergisi'nde aşağıda kısaca açıklanan makale türleri yayınlamaktadır:

Araştırma Makaleleri: Orijinal araştırmalara dayanan yeni sonuçlar sağlayan en önemli makale türüdür. Orijinal makalelerin ana metni Giriş, Yöntemler, Bulgular, Tartışma, Sonuç ve Kaynaklar alt başlıklarıyla yapılandırılmalıdır. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız. İstatistiksel analiz genellikle sonuçları desteklemek için gereklidir. İstatistiksel analizler uluslararası istatistik raporlama standartlarına uygun olarak yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983:7;1489–93). İstatistiksel analizler hakkında bilgi Materyaller ve Yöntemler bölümünde ayrı bir alt başlık ile sağlanmalı ve süreç boyunca kullanılan istatistiksel yazılım belirtilmelidir. Birimler Uluslararası Birimler Sistemine (SI) uygun olarak hazırlanmalıdır.
Makalenin kısıtlılıkları, sakıncalar ve eksik yönler, sonuç paragrafından önce Tartışma bölümünde belirtilmelidir.

Derleme Makaleleri: Yeterli sayıda bilimsel makaleyi tarayıp, konuyu bugünkü bilgi ve teknoloji düzeyinde özetleyen, değerlendirme yapan ve bulguları karşılaştırarak yorumlayan yazılar olmalıdır. Temel ve uygulamalı bilim alanlarında tüm gelişmeleri ile birlikte son bilimsel çalışmalardaki teknik ve uygulamalar değerlendirilir. Belirli bir alan hakkında kapsamlı bilgi sahibi olan ve bilimsel geçmişi yüksek atıf potansiyeli olan yazarlar tarafından hazırlanan derlemeler dergimiz tarafından kabul edilecektir. Bu yazarlardan makale kabul şekli davet yöntemiyle de olabilir. Ana metin Giriş, Klinik ve Araştırma Sonuçları ve Sonuç bölümlerini içermelidir. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Olgu Sunumları: Tanı ve tedavide zorluk teşkil eden, yeni tedaviler sunan veya literatürde yer almayan bilgileri ortaya koyan nadir olgu veya durumlar hakkında eğitici olgu sunumları dergimizde yayınlanmak için kabul edilir. Olgu sunumu, Giriş, Olgu Sunumu ve Tartışma ve Sonuç alt başlıklarını içermelidir.

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
ISSN: 1017-6616; e-ISSN: 2149-8059

İlginç ve sıra dışı resimler değerlendirme sürecinde bir avantajdır. Hasta tanımlayıcı resimlerde hasta kimliği açık ediliyorsa resmin paylaşımına izin veren hasta onamı mutlaka olmalıdır. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Editöre Mektuplar: Bu yazı türü, daha önce yayınlanmış bir makalenin önemli kısımlarını, gözden kaçan yönlerini veya eksik kısımlarını tartışır. Derginin dikkatini çekebilecek konular başta olmak üzere, okuyucuların dikkatini çekebilecek konular hakkında makaleler, özellikle eğitici konularda Editöre Mektup şeklinde sunulabilir. Okuyucular, yayınlanmış yazılar hakkındaki yorumlarını Editöre Mektup olarak da sunabilirler. Özet, Anahtar Sözcükler ve Tablolar, Şekiller, Görüntüler ve diğer medya eklenmemelidir. Metin alt başlıkları içermemelidir. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Editöryal: Tıbbın herhangi bir alanında bir görüşün açıklandığı ya da başkalarının görüşlerinin yayınlandığı, kısa makalelerdir. Normal bir dergi makalesine göre daha yaratıcı yazabilme olanağı sağlar. Dergide yakın zamanda yayınlanmış bir makale tartışılabilir, Tarihi materyal, Halk sağlığına dair konular, Sağlık politikaları, Tıp Eğitimi ve Tıpta teknolojik gelişmeler hakkındaki yazılar bu bölümde değerlendirilebilir. Tam bir derleme olamayacak bir konuda kısa derleme bu başlık altında değerlendirilebilir. Dergi editörü; okuyuculara kişisel mesaj iletmek, aynı sayıdaki bir makale ile ilgili yorum yapmak, okuyucunun dikkatini yeni gelişmelere çekmek isterse bu bölüme yazabilir. Bilimsel makalelerin tipik yazım bölümlerini içermez. Temel mesaj bir cümlede özetlenebilmelidir. Bu cümleyi editoryali yazmaya başlamadan belirlemek yazımı kolaylaştırır. Bu mesaj konusunda okuyucuyu ikna etmek için mantıklı bir tartışma yürütmelidir. Şekiller, Görüntüler ve diğer medya eklenebilir. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Orijinal Görüntü Raporu: Tıbbın her alanına ait ilgi çekici, tanımlayıcı veya eğitici görüntüler (ilustrasyon ya da Fotoğraf) birkaç satırlık açıklayıcı metin ve referanslarla birlikte bu bölümde değerlendirmeye sunulabilir. Makale uzunluğu 200 kelimeyi geçmemelidir. Özet, tartışma veya sonuca gerek yoktur ancak kısa bir başlık eklenmelidir. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Hakem Raporu Sonrasında Değerlendirme

Yazarlar hakem raporunda belirtilen düzeltme istenen konuları maddelendirerek bir cevap olarak kendilerine ayrılan cevap bölümüne yazmalıdırlar ve hakem (ler)e cevap başlıklı ek bir dosya şeklinde https://www. selcukmedj.org adresinden yüklenmelidir. Ayrıca makale içerisinde de gerekli değişiklikleri yapmalı ve bunları makale içerisinde belirterek (boyayarak) online olarak tekrar gönderilmelidir.

Son Kontrol

1. Yayın hakkı devir ve yazarlarla ilgili bildirilmesi gereken konular formu gereğince doldurulup imzalanmış,
2. Ana makale metni ve özetlerde gerekli kelime sayıları aşılmamış
3. Yeterli sayıda anahtar kelime eklenmiş,
4. Başlık uzun ve kısa başlık şeklinde yazılmış,
5. Kaynaklar kurallara uygun olarak yazılmış,
6. Tablo, resim ve şekillerde bütün kısaltmalar açıklanmış olmalıdır.

Online Yükleme Basamakları, https://www. selcukmedj.org sayfasında;

1. Makale türü *
2. Uzun Başlık *
3. Kısa başlık *
4. Özet*
5. Anahtar kelimeler *
6. Yüklenmesi gerekli bölümler (Kapak sayfası, Ön yazı (cover letter), makale dosyası, Etik kurul onay Belgesi (kurumdan alınan), intihal analiz raporu, Şekiller ve Resimler, Telif Hakları Bildirim Formu ve gerekli ise hasta onam formu şeklinde tamamlanmalıdır.

Dergi Sahibi
Necmettin Erbakan Üniversitesi Rektörlüğü

Yayıncı
Necmettin Erbakan Üniversitesi yayınları (Neü Press)
Yaka Mah. Yeni Meram Cad. Kasım Halife Sok. No: 11/1 (A Blok)
Meram / KONYA/TÜRKİYE
Tlf : +90 332 221 0 575
Mobil Tlf: 0 532 262 48 46
E-Mail: bilgi@neuyayin.com

Baş Editör
Prof. Dr. Pembe Oltulu
Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi Pataloji
Anabilim Dalı, Konya/Türkiye
Tel: 0 332 223 72 87
E-posta: editor@selcukmedj.org, pembeoltulu@gmail.com

Sekreter ve yazı işleri müdürü
İlkay Kurt
E-posta: info@selcukmedj.org , ilkayyildiz13@gmail.com

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
ISSN: 1017-6616; e-ISSN: 2149-8059

INFORMATION FOR AUTHORS/WRITING RULES

Selcuk Medical Journal is a scientific, independent, peer-reviewed, open access publication of Necmettin Erbakan University. It is a disciplinary journal that appeals to a wide audience of medical doctors, researchers and scientists. The main objective is to ensure that current developments in the field of medicine / health, diagnosis and treatment, surgical innovations and studies that will contribute to the world of science are shared in national and international literature.

Selcuk Medical Journal publishes clinical and experimental studies, editorials, short reports, clinical case reports, technical and educational reviews, original image reports with the latest developments in the field of medicine, visual questions of disease identification and letters to the editor that contribute to medical science and academic studies. In addition, reader questions and contributions regarding previously published articles and experimental studies are published briefly. All manuscripts, except for editorials, which are deemed appropriate for the journal submission rules and the scope of the journal, are sent to at least two reviewers who are experts in their fields for scientific evaluation. All published articles are subject to a double blind peer review process. For manuscripts whose suitability is discussed, associate editors add their own evaluations by taking into account the comments of the reviewers. The final decision for all submitted manuscripts belongs to the Editor-in-Chief. The editor and the editorial board aim to finalize the process for all manuscripts within three months. However, it may take longer due to unavoidable delays. Manuscripts on some topics determined by the editorial board are submitted to the review of all members of the editorial board. As a result of the reviews, the processes of the studies that reach the majority of votes will continue in the journal. Editorial board decisions are published on the journal website. The copyright of accepted manuscripts belongs to the authors. Selçuk Medical Journal holds the right of first publication of the article. Authors are required to read and approve the copyright agreement while uploading their manuscripts to the online system of Selcuk Medical Journal. The journal is published in four issues each year in March, June, September and December. The publication language of the journal is English.

The submitted manuscripts must not have been previously published in any other place/journal and must not have been sent to another journal for publication [Oral presentations and posters (abstract or full text) presented at scientific congresses are excluded, provided that they are notified]. All kinds of responsibilities (ethical, scientific, legal, etc.) of the articles published in the journal belong to the authors. Statements or opinions expressed in the articles published in the journal are the views of the authors and do not reflect the views of the editors, editorial board and publisher; the editors, editorial board and publisher do not accept any responsibility or liability for such materials. It is at the discretion of the Editor and Editorial Board whether or not to review manuscripts that are not prepared in accordance with the spelling rules.

Ethics committee approval and documentation of this approval are required in all studies. In all studies, the level of contribution and approval of the authors to the study should be reported. It should be reported that there is no financial conflict of interest at any stage of the study, including data collection, experimental phase, writing and language editing. Commercial sponsorship, if any, should be reported. The plagiarism program (iThenticate) is used in Selcuk Medical Journal. Articles with similarities exceeding the academic citation limit and articles that are not prepared in accordance with the publication rules will not be reviewed. The publication policy and processes of the journal follow the guidelines of the International Committee of Medical Journal Editors **(ICMJE),** World Association of Medical Editors **(WAME),** Council of Science Editors **(CSE),** European Association of Science Editors **(EASE),** Committee on Publication Ethics (**COPE)** and National Information Standards Organization (**NISO).** Our journal complies with the 'Principles of Transparency and Best Practice in Scholarly Publishing' **(doaj.org/bestpractice).** The Editorial Board will act in accordance with COPE rules in the face of allegations and suspicions of plagiarism, citation manipulation, and data falsification.

The Editorial Board of the journal processes appeals and complaints in accordance with the **COPE** guidelines. Authors may contact the Editor-in-Chief or the Editorial Board directly with their appeals and complaints. When needed, an impartial representative will be appointed for issues that the Editorial Board cannot resolve internally. The Editor-in-Chief will make the final decision in the decision-making process for objections and complaints. The publisher and editor are always ready to publish corrections, clarifications, retractions and apologies when necessary.

All correspondence related to Selcuk Medical Journal, paper submission, follow-up of the article, consultant reports, uploading corrections, sending acceptance letter and uploading all other forms related to the article will be made from **https://www.selcukmedj.org.** The rules for the articles to be uploaded via this site are stated below. Selcuk Medical Journal adopts a free, open access policy. In this context, all articles published in the journal will be available at https://www.selcukmedj.org and no additional fee will be charged to the authors.

Authorship

All authors listed as authors on manuscripts submitted to the Selcuk Medical Journal must meet the authorship requirements recommended by ICMJE (www.icmje.org). ICMJE recommends that authors meet the following 4 conditions:

- To contribute significantly to the conception/design of the study; or to the collection, analysis and interpretation of data for the study;
- To draft the manuscript or critically review the content;
- To review and approve the final version of the manuscript before publication;
- To agree to take responsibility for all aspects of the work to ensure that questions about the validity and accuracy of any part of the work have been properly investigated and resolved.

Each person designated as an author must meet the four conditions for authorship, and each person who meets these four conditions must be identified as an author. All persons designated as authors must be eligible for authorship, and all eligible persons must be listed. Individuals who do not meet all four criteria should be acknowledged on the title page of the article. Receipt of funding, data collection or general oversight of the research group do not, in themselves, justify authorship. One or more authors should take responsibility for the integrity of the study as a whole, from study inception to the published article.

In multicenter studies, authorship is attributed to a group. All members of the group named as authors must fully meet the above criteria for authorship. Group members who do not meet these criteria should be listed in the acknowledgments along with their consent. Financial and material support must also be acknowledged. All statements and opinions made in the articles reflect the views of the author(s). Authors submitting articles to the journal are deemed to have read these statements and accept the responsibility. All content is the responsibility of the authors. All financial and legal responsibility for the copyrights of tables, figures and other visual materials protected by national and international laws belongs to the authors. Authors are responsible for any legal action taken against the journal related to their articles.To clarify scientific contributions and responsibilities and any conflict of interest (COI) issues related to the manuscript, all sections of the Author Contribution Form must be completed by the corresponding author and the ICMJE Declaration of Potential Conflicts of Interest Form must be completed online by all authors. Both forms should be included in the manuscript at the time of the original submission. Author names will be published as listed on the Copyright Transfer Form. To protect all parties involved, no changes in affiliation or name changes will be made at a later date.

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
ISSN: 1017-6616; e-ISSN: 2149-8059

Requests for Author Change
Addition, deletion or rearrangement of author names in the author list can only be made before the manuscript is accepted and only if approved by the Editor of the journal.If such a change is requested, the Editor will request from the responsible author (a) the reason for the change in the author list and (b) written confirmation (e-mail) from all authors that they agree to the addition. Only in exceptional cases will the Editor consider the addition, deletion or reorganization of authors after the article has been accepted.

Article Writing
Authors of original research papers should address the topic in an original way and with an objective discussion. The paper should include sufficient detail and references to allow others to replicate the work. Fraudulent or knowingly false statements constitute unethical behavior and are unacceptable.

Originality
The author must ensure that the article is original, has not been previously published elsewhere and is not under consideration for publication elsewhere, in another language.

Using Original Sources and Citation
Authors should ensure that they are writing entirely original work and, if they have used the work or words of others, that it is properly cited. Privately obtained information, such as in conversations, correspondence or discussions with third parties, should not be used without the express written permission of the source.

Data Access and Preservation
Authors may be asked to provide research data supporting their articles for editorial review and/or to comply with the journal's open data requirements. Authors should be prepared to provide public access to such data, if possible, and to retain such data for a reasonable period after publication. The journal recommends uploading research data to TUBITAK's Aperta Portal.

Multiple and Simultaneous Submission
An author should not publish the same research article in more than one journal. It is unethical to submit the same article to more than one journal at the same time. An author should not submit a previously published article for consideration in another journal, except in the form of an abstract.

Publication of Studies Based on Surveys and Interviews
For research in all disciplines that require ethics committee approval, ethics committee approval must be obtained, this approval must be stated and documented in the article. In researches requiring ethics committee approval, information about the approval (name of the committee, date and number) should be included in the method section, as well as on one of the first/last pages of the article; in case reports, information on the signing of the informed consent form should be included in the article.

Conflict of Interest
Any financial or other interest that may cause the person to be conflicted in his or her work, significantly impair his or her objectivity, or provide an unfair advantage in favor of any person or organization. All sources of financial support received during the conduct of the research and preparation of the manuscript and the role of sponsors in the study should be disclosed. If there is no source of funding, this should also be indicated. Examples of potential conflicts of interest that should be disclosed include consultancies, salaries, grants. Potential conflicts of interest should be disclosed at the earliest possible stage.

Error Notification
When an author discovers a significant error or inaccuracy in his/her published work, he/she should notify the journal immediately. It is also the author's obligation to withdraw the manuscript or to cooperate in correcting it if deemed necessary by the editor. If the editor or publisher learns from a third party that a published paper contains an error, it is the author's obligation to cooperate with the editor, including informing the editor about the matter.

Image Integrity
It is not acceptable to enhance, darken, move, remove or add a specific feature in an image. Authors must adhere to the policy for graphic images implemented by the journal.

Requests for Correction and Withdrawal
The articles published by Selcuk Medical Journal are the final version. Therefore, requests for correction after publication are evaluated by the Editorial Board according to COPE guidelines. Requests for withdrawal from publication must be made before the article is accepted and are subject to the approval of the Editorial Board. If a retraction request is made after acceptance of the manuscript and before publication, it should be sent to the editor-in-chief via e-mail with the justification. The justifications will be evaluated at the editorial board meeting and the final decision will be made and the author will be notified by e-mail. Retraction requests will not be considered for an article that has been submitted for publication. Author(s) who wish to withdraw their manuscript before publication are obliged to fill out the withdrawal form and send it to the Editor-in-Chief and Editorial Board via e-mail at editor@selcukmedj.org.tr, signed and scanned with the wet signature of each author. You can access the withdrawal form from the downloads page of our website (https://www.selcukmedj.org/tr-tr/indirmeler/). The Editorial Board will review the withdrawal notification and respond within 15 days. Author names, affiliations, article titles, abstracts, keywords, any factual errors and typos in digital object identifiers (DOIs) can be corrected with an erratum.

Article Review Process
It is aimed to rapidly evaluate and publish the articles submitted to the journal. All articles are subject to a double-blind peer review process. Manuscripts will be reviewed by at least two impartial reviewers for content, originality, significance in the field, appropriateness of statistical analysis, and conclusions. In case of discrepancies between the reviewers, the manuscript may be sent to a third or fourth reviewer. The decisions of the reviewers will be evaluated by the associate editors and the evaluation results will be sent to the editor-in-chief. The final decision regarding the acceptance of submitted manuscripts rests with the editor-in-chief.
Comments and evaluations reported by the reviewers and evaluated as useful for the authors are sent to the authors. Instructions, objections and requests made by the referees must be strictly followed. The response file to the referee(s) should also be created as a Word document. In the revised version of the manuscript, the authors should clearly and concisely indicate in this file each step taken in accordance with the reviewers' requests. The author's annotations should be listed and numbered in the order of the reviewers' evaluation. They should also make the necessary changes in the manuscript and indicate them in the manuscript (by coloring), and the revised manuscript and the forms containing the responses to the referees' suggestions should be uploaded meticulously at **https://www.selcukmedj.org.**

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
ISSN: 1017-6616; e-ISSN: 2149-8059

Submission of Manuscript

Authors must upload the Notification of Publication Rights Form to the system. All correspondence will be sent to the corresponding author. The corresponding author should be provided with an e-mail address for all other correspondence. Authors will be notified of the receipt of their manuscripts by the number given to them. The article number should be used in all correspondence. Authors are advised that, following an initial evaluation by the editorial office, the manuscript may be returned due to its content in the best interest of the reader. This rapid rejection process allows the author to publish the article elsewhere. Submission of an article to Selcuk Medical Journal implies that all authors have read and accepted the journal's editorial policies and publication ethics. Manuscript submission and all other related procedures will be done online at https://www. selcukmedj.org.

Preparation of Manuscripts

Authors are required to read the following rules before submitting their materials and upload their manuscripts in accordance with these rules:

General writing style: All manuscripts should be written in a standard A4 size word document with 2.5 cm wide margins on all sides, and references, figures or tables should be numbered in the order of their occurrence in the text. The text should be written in Times New Roman font with double spaces in a 12-point font without left-aligned and syllabic line breaks. Please leave a single space between words and after the sentence point. The left indent for the paragraph should be set by clicking once with the tab key. The International System of Units (SI) should be used for units of measurement. All pages of the article should be numbered at the end of the page. All articles should follow the spelling rules and punctuation marks should be appropriate.

In all articles; Cover page, cover letter, article file, Ethics committee approval document (obtained from the institution), iThenticate analysis report, Figures and Images, Copyright Transfer Form, and patient consent form, if necessary, should be uploaded as separate files.
References should start on a separate page in the article file, not at the end of the article. Tables, table descriptions, images/figures and image/figure descriptions should also be added to the main article file on a separate page after the references. Table/Picture/figure descriptions should be immediately below the tables/ pictures/figures.

About article sections

1-Cover Page: The full title of the article in English and a short title containing no more than 50 characters, the full names and surnames of all authors, ORCID numbers, institutions, name of the corresponding author, work or mobile phone number, e-mail and correspondence address should be indicated. If the article has been previously presented as a paper, the place and date of the paper should be indicated. Information about the authors and their institutions should not be included in the main text (including the materials and methods section), tables, figures and video documents, except on the title page. Details of any grants or other sources of support and acknowledgments to individuals who contributed to the preparation of the manuscript but do not meet the criteria for authorship should also be included on the cover page.
2-Main article file: The main file should not contain information such as author names and institutions. Main article file should contain:
1. Title, 2. Abstract and Keywords, 3. Main text of the article, 4. References, 5. Tables and their descriptions, 6. Figures and figures with their descriptions, 7. Subtitles.
Title: At the very beginning of the article in the Word file, there should be a single long title of the article in written language.
Abstract: All manuscripts, except for Letters to the Editor, should include an abstract. Abstracts of original research articles should include the subtitles Objective, Materials and Methods, Results and Conclusion. Abstracts should not include reference, figure or table numbers. The data in Table 1 should be considered for word count and specifications.
Keywords: A minimum of three and a maximum of five keywords should be included at the end of the abstract. Keywords should be listed in full without abbreviations and separated by commas or semicolons. Keywords should conform to the "Medical Subject Headings (MESH)" (see: www.nlm.nih.gov/mesh/ MBrowser.html).
Abbreviations: Abbreviations should not be used in abstracts and titles. The abbreviations to be used in the article should be nationally or internationally recognized, if possible, and should be defined in the text and written in parentheses when first used. Then that abbreviation should be used throughout the text. For commonly accepted abbreviations and usage, please refer to "Scientific Style and Format" (https://www.scientificstyleandformat.org/Home.html). When a trademarked drug, product, hardware or software program is included in the main text, the product information should include the name of the product, the manufacturer of the product, and the company and country of headquarters in parentheses in the following format: "Discovery St PET / CT scanner (General Electric, Milwaukee, WI, USA).
Main text of the article:
Introduction; includes specific information to explain the topic and the purpose of the study.
Materials and Methods: The place, time and planning of the study and the elements and methods used should be reported. Data collection, characteristics of patients and individuals, characteristics of the experimental study and statistical methods should be explained in detail. The recruitment and all methods used to conduct the study should be described in detail. New or modified methods used should be described in detail and the source should be indicated. Doses, concentrations, routes and duration of administration of drugs and chemical agents should be specified. A brief report of all statistical methods used to summarize the data obtained and test the proposed hypothesis should be presented under a subheading, including the p-value criteria for statistically significant difference. The statistical evaluation performed should be described in detail. Standard statistical methods should be used whenever possible. If rarely used or new statistical methods are used, relevant references should be cited. If necessary, more detailed descriptions of unusual, complex or new statistical methods should be provided in separate files for readers as online supplementary data.
Findings: The data obtained should be given in detail with statistical results. Findings should be supported with figures and tables. Please do not repeat the information given in figures and tables in the text.
Discussion: The results of the study should be evaluated by comparing them with the literature and should be supported by local and/or international references. General information that is irrelevant or unnecessary should not be added and should be of sufficient length for the purpose of the article.
References: References should be written on a separate page. References should be cited according to the APA 7 system. Accordingly, reference numbers should be given in ( ) without a full stop at the end of the sentence, and the full stop should be placed afterwards. If the names of the source authors are used in a sentence, the reference should be given in ( ) after the first mention of the name. If more than one source number is given, "," should be placed between them, and if more than two consecutive source numbers are given, "-" should be placed between the numbers [e.g. (1,2), (1-4), etc.]. References should be numbered and listed in the order in which they are used in the text. Citation accuracy is the responsibility of the author. References must exactly match the original spelling, accent, punctuation, etc. All references in the text must be cited. There should be no duplicate spelling in the reference list. Reference styles for different types of publications are presented in the examples below:

Research Paper:

- Mirza E, Oltulu R, Oltulu P, et al. Dry eye disease and ocular surface characteristics in patients with keratoconus. Saudi J Ophthalmol. 2022;36(1):117-21. doi: 10.4103/sjopt.sjopt_37_21.
- Vikse BE, Aasarød K, Bostad L, et al. Clinical prognostic factors in biopsy-proven benign nephrosclerosis. Nephrol Dial Transplant. 2003;18(3):517-23. doi: 10.1093/ndt/18.3.517.

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
ISSN: 1017-6616; e-ISSN: 2149-8059

Single Author Books:
- Danovitch GM. Handbook of Kidney Transplantation. Boston: Little, Brown and Company (Inc.), 1996: 323-8.

Book Chapter:
- Soysal Z, Albek E, Eke M. Fetüs hakları. Soysal Z, Çakalır C, ed. Adli Tıp, Cilt III,İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Yayınları, İstanbul, 1999:1635-50.
- Davison AM, Cameron JS, Grünfeld JP, et al. Oxford Textbook of Clinical Nephrology. In: Williams G, ed. Mesengiocapillary glomerulonephritis. New York: Oxford University Press, 1998: 591- 613.
- **Journal article published online ahead of print:**
- Doğan GM, Sığırcı A, Akyay A, et al. A Rare Malignancy in an Adolescent: Desmoplastic Small Round Cell Tumor. Turkiye Klinikleri J Case Rep. 10.5336/caserep.2020-77722. Published online: 31 December 2020.
- Cai L, Yeh BM, Westphalen AC, et al. Adult living donor liver imaging.DiagnIntervRadiol. 2016 Feb 24.doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Meeting Reports:
- Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report:
- Cusick M, Chew EY, Hoogwerf B, A et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis:
- Kaplan SI. Post-hospital home health care: elderly access and utilization (dissertation). St Louis (MO): Washington Univ; 1995.

Website and Social Media Channels: Author. Title. Website: URL. Date and year

3-Tables and their descriptions: Tables should be included in the text of the main article, presented after the list of references and on a separate page. They should be numbered according to the order in the main text. A descriptive title should be placed above each table. Abbreviations used in the table should be defined in footnotes below the table (even if defined in the main text). Tables should be clearly organized for easy reading. The data presented in the tables should not repeat data presented in the main text, but should support the main text.

4-Figures and Images: Figures, graphics and images should be uploaded as separate files (TIFF or JPEG format) through the manuscript submission system and should also be shown in the main text after the tables on a separate page in the main file. Images that are not uploaded separately to the system and only included in the article will not be accepted. Figures and illustrations must be named and numbered, and must be cited in the text, paying attention to their order. Descriptions should be added under the pictures, figures and graphics to be added to the main text. Images should be clear with a minimum resolution of 300 dots per inch (dpi). If abbreviations are used in the captions of figures and images, the abbreviations should be indicated below the caption in alphabetical order. For microscopic images, the magnification ratio and technique should be explained. The editorial board may make changes it deems necessary without changing the essence of the manuscript. When figures have subunits, the subunits may be combined to form a single image. Figures should be labeled to indicate the subunits and descriptions (a, b, c, etc.) should be written for each. Thick and thin arrows, arrowheads, stars, asterisks and similar markings can be used to support figures. Like the content of the article, the figures should be blind. Possible information in images that could identify an individual or institution should be anonymized.

When sharing patient photos, ensure that the identity is not recognized one-to-one, and images sufficient to identify the disease should be shared. For sharing images that reveal the patient's identity, a consent form in which the patient authorizes the sharing of the image is necessary.

Table 1. Limitations according to article types

	limitation of article	abstract	references	Tables	Figures
Research Article	4000	300	50	6	6
Review	6000	300	85	6	10
Case Presentations	1500	200	15	3	5
Letters to the Editor	1000	(-)	8	(-)	(-)
Editorial	1000	(-)	20	3	3
Original Image Report	200	(-)	5	1	3

Article Types

Selcuk Medical Journal publishes the types of articles briefly described below:

Research Articles: This is the most important type of article that provides new results based on original research. The main text of original articles should be structured with the subheadings Introduction, Methods, Results, Discussion, Conclusion and References. Please refer to Table 1 for word count and specifications. Statistical analysis is often necessary to support leconclusions. Statistical analyses should be performed in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983:7;1489-93). Information on statistical analyses should be provided under a separate subheading in the Materials and Methods section and the statistical software used throughout the process should be indicated. Units should be prepared in accordance with the International System of Units (SI). Limitations, drawbacks and shortcomings of the article should be stated in the Discussion section before the conclusion paragraph.

Review Articles: Review articles should be articles that review a sufficient number of scientific articles, summarize the subject at the current level of knowledge and technology, evaluate and interpret the findings by comparing them. Techniques and applications in the latest scientific studies with all the developments in basic and applied sciences are evaluated. Reviews prepared by authors who have extensive knowledge of a particular field and have a scientific background with high citation potential will be accepted by our journal. Acceptance of manuscripts from these authors can also be by invitation. The main text should include Introduction, Clinical and Research Results and Conclusion. Please see Table 1 for word count and specifications.

Case Presentations: Educational case reports on rare cases or conditions that pose difficulties in diagnosis and treatment, offer new treatments or reveal information not included in the literature are accepted for publication in our journal. The case report should include the subheadings Introduction, Case Presentation and Discussion and Coclusion. Interesting and unusual pictures are an advantage in the evaluation process.

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
ISSN: 1017-6616; e-ISSN: 2149-8059

If patient identity is disclosed in patient-identifying pictures, patient consent must be provided to share the picture. Please see Table 1 for word count and specifications.

Letter to the Editor: This type of article discusses important parts, overlooked aspects or missing parts of a previously published article. Articles on topics that may attract the attention of the journal, especially on topics that may attract the attention of readers, especially on educational topics, can be submitted in the form of Letters to the Editor. Readers can also submit their comments on published articles as a Letter to the Editor. Abstract, Keywords and Tables, Figures, Images and other media should not be included. The text should not include subheadings. Please see Table 1 for word count and specifications.

Editorial: These are short articles in which an opinion is expressed or the opinions of others are published in any field of medicine. It provides the opportunity to write more creatively than a normal journal article. An article recently published in the journal can be discussed, historical material, public health issues, health policies, medical education and technological developments in medicine can be evaluated in this section. A short review on a subject that cannot be a complete review can be evaluated under this heading. Journal editor; If he/she wants to convey a personal message to the readers, comment on an article in the same issue, or draw the reader's attention to new developments, he/she can write in this section. It does not contain the typical writing sections of scientific articles. The basic message should be summarized in one sentence. Determining this sentence before starting to write the editorial makes writing easier. He/she must make a logical argument to convince the reader of this message. Shapes, Images and other media can be added. Please see Table 1 for word count and specifications.

Original Image Report: Interesting, descriptive or educational images (illustration or photography) from any field of medicine can be submitted for evaluation in this section, along with a few lines of explanatory text and references. Article length should not exceed 200 words. A summary, discussion, or conclusion is not required, but a brief title should be included. Please see Table 1 for word count and specifications.

Evaluation After Referee Report

Authors should itemize the issues for correction in the referee's report and write them as a reply to the referee(s) in the reply section allocated to them and upload it as an additional file titled reply to the referee(s) at https://www. selcukmedj.org. They should also make the necessary changes in the manuscript and indicate them in the manuscript (by coloring) and resubmit online.

Final Control

1. The form for transfer of publication rights and matters to be notified about authors has been duly completed and signed,
2. Required word counts are not exceeded in the main article text and abstracts
3. Enough keywords have been added,
4. The title is written as long and short title,
5. References are written in accordance with the rules,
6. All abbreviations in tables, pictures and figures should be explained.

Online Uploading Steps

via https://www. selcukmedj.org website;

1. Article type *
2. Long Title *
3. Short title *
4. Summary*
5. Keywords*
6. The required sections to be uploaded (Cover page, Cover letter, manuscript file, document of Ethics committee approval (obtained from the institution), identicate analysis report, Figures and Images, Copyright Form, and patient consent form if necessary.

Owner of Journal

Rectorate of Necmettin Erbakan University

Publisher

Necmettin Erbakan University Press (NEU Press)
Yaka Mah. Yeni Meram Cad. Kasım Halife Sok. No: 11/1 (A Blok)
Meram / KONYA/TÜRKİYE
Tlf : +90 332 221 0 575
Mobil Tlf: 0 532 262 48 46
E-Mail: bilgi@neuyayin.com

SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

ISSN: 1017-6616; e-ISSN: 2149-8059
Cilt/Volume:41 Sayı/Issue: 3 Yıl/Year:2025

İÇİNDEKİLER/CONTENTS

Araştırma Makalesi / Research Article

NEU PRESS

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2025.01868
Selcuk Med J 2025;41(3): 115-123

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Are diabetic Patients Adequately Educated About Their Disease?

Diyabet Hastalarının Hastalıklarıyla İlgili Eğitimi Yeterli mi?

Kubra Canarslan Demir[1], Burak Turgut[1], Simay Akyuz[2], Fatma Sena Konyalioglu[3]

[1]University of Health Sciences, Gulhane Training and Research Hospital, Department of Underwater and Hyperbaric Medicine, Ankara, Türkiye
[2]University of Health Sciences, Gulhane Faculty of Nursing, Ankara, Türkiye
[3]General Directorate of Health Promotion, Ministry of Health, Department of Monitoring and Evaluation, Ankara, Türkiye

ÖZET

Amaç: Diyabetik ayak ülserleri (DAÜ), diyabetin en ciddi ve maliyetli komplikasyonları arasında yer almakta; hastaların yaşam kalitesini önemli ölçüde düşürmekte ve hastaneye yatış ile ampütasyon riskini artırmaktadır. Bu çalışmanın amacı, DAÜ tanılı hastalarda diyabetik ayak öz bakım davranışları ile diyabet öz yönetim becerilerini değerlendirmektir.

Gereç ve Yöntem: Gözlemsel, kesitsel tipteki bu çalışma, üçüncü basamak bir hastanenin Sualtı Hekimliği ve Hiperbarik Tıp ile Diyabetik Ayak Polikliniklerine başvuran 228 DAÜ tanılı hasta ile gerçekleştirilmiştir. Hastaların demografik özellikleri, klinik verileri ve yara ile ilişkili değişkenler kaydedilmiştir. Diyabet Öz Yönetim Ölçeği (DSMS) ve Diyabetik Ayak Öz Bakım Davranışları Ölçeği (DFSBS) yüz yüze görüşme yöntemiyle uygulanmıştır. İstatistiksel analizler SPSS v25.0 programında yapılmış; anlamlılık düzeyi p<0,05 olarak kabul edilmiştir.

Bulgular: Katılımcıların yaş ortalaması 63,1±10,5 yıl olup, %72,4'ü kadındı. Hastaların %55,3'ü diyabetik ayak cerrahisi geçirmiş, %38'inde Wagner evre 4 yara saptanmıştır. Ortalama DSMS puanı 6,6±1,7; ortanca DFSBS puanı ise 28,0 (ÇKB: 9,0) olarak bulunmuştur. Eğitim düzeyi ile hem DSMS hem de DFSBS alt boyut puanları arasında anlamlı pozitif ilişki tespit edilmiştir (p<0,001). Diyet kontrol puanları, cerrahi öyküsü olan hastalarda ve Wagner evresi daha yüksek olanlarda anlamlı olarak daha yüksekti (sırasıyla p=0,019 ve p=0,003). Ancak, toplam DSMS veya DFSBS puanları ile Wagner evresi arasında anlamlı bir ilişki bulunmamıştır.

Sonuç: Gelişmiş öz bakım ve öz yönetim davranışları, daha yüksek eğitim düzeyi ile ilişkilidir ve diyabetik ayak komplikasyonlarının şiddetinden etkilenebilir. Hedefe yönelik eğitim programları hasta farkındalığını artırarak daha sağlıklı davranışları teşvik edebilir ve DAÜ'ye bağlı komplikasyonlar ile sağlık harcamalarını azaltabilir. Bu davranışların uzun dönem sonuçlar ve yaşam kalitesi üzerindeki doğrudan etkisini değerlendirmek için ileriye dönük uzunlamasına çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Ampütasyon, cerrahi, ayak ülseri, öz bakım, hemşirelik

ABSTRACT

Objective: Diabetic foot ulcers (DFU) are among the most severe and costly complications of diabetes, significantly affecting patients' quality of life and increasing the risk of hospitalization and amputation. This study aims to evaluate diabetic foot self-care behaviors and diabetes self-management skills in patients with DFUs.

Materials and Methods: This observational cross-sectional study was conducted with 228 patients diagnosed with DFUs who were admitted to the Underwater and Hyperbaric Medicine and Diabetic Foot Outpatient Clinics of a tertiary hospital. Patient demographic characteristics, clinical data, and wound-related variables were recorded. The Diabetes Self-Management Scale (DSMS) and Diabetic Foot Self-Care Behavior Scale (DFSBS) were administered via face-to-face interviews. Statistical analyses were performed using SPSS v25.0. P<0.05 was accepted as the statistical significance level.

Results: The mean age of participants was 63.1±10.5 years, and 72.4% were female. Among the patients, 55.3% had undergone diabetic foot surgery, and 38% had Wagner stage 4 wounds. The mean DSMS score was 6.6±1.7, and the median DFSBS score was 28.0 (IQR: 9.0). A significant positive relationship was found between education level and both DSMS and DFSBS subdimension scores (p<0.001). Dietary control scores were higher among patients who had undergone surgery and those with higher Wagner stages (p=0.019 and p=0.003, respectively). However, no significant correlation was observed between total DSMS or DFSBS scores and Wagner stage.

Conclusion: Improved self-care and self-management behaviors are associated with higher education levels and may be influenced by the severity of diabetic foot complications. Targeted educational interventions may enhance patient awareness, promote healthier behaviors, and potentially reduce DFU-related complications and healthcare costs. Further longitudinal studies are warranted to explore the direct impact of these behaviors on long-term outcomes and quality of life.

Keywords: Amputation, surgical, foot ulcer, self-care, nursing

INTRODUCTION

Diabetes mellitus is associated with serious microvascular and macrovascular complications, and diabetic foot ulcer (DFU) is among the most critical of these complications. The prevalence of DFU is reported to be 4–10%, with an annual incidence of 2.4–6.6%, and recurrence rates exceeding 50% within three years. As a chronic complication, DFU is one of the leading causes of hospitalization, amputation, and mortality in diabetic patients, and it has increasingly become a significant public health concern (1–4).

Geliş Tarihi/Received: 7 July/Temmuz 2025 **Kabul Tarihi/Accepted:** 25 September/Eylül 2025 **Yayın Tarihi/Published Online:** 28 September/Eylül 2025

Sorumlu Yazar/Corresponding Author: Kubra Canarslan Demir, University of Health Sciences, Gulhane Training and Research Hospital, Department of Underwater and Hyperbaric Medicine, Ankara, Türkiye
e-mail: drcanarslan@hotmail.com

Atıf yapmak için/ Cite this article as: Canarslan Demir K, Turgut B, Akyuz S, Konyalioglu FS. Are diabetic patients adequately educated about their disease? Selcuk Med J 2025;41(3): 115-123

Disclosure: *Author has no a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

DFU can be prevented not only by maintaining optimal glycemic control but also through effective foot care. In diabetic patients, management of risk factors for ulcer development, adherence to preventive measures, determination of appropriate follow-up intervals, and sustained compliance with these strategies play a critical role in both preventing ulcer formation and ensuring early treatment before infection occurs (5).

Self-management in diabetes refers to self-care behaviors that support adherence to medication use, medical nutrition therapy, and physical activity. For effective self-management, patients must acquire sufficient knowledge and develop self-care skills. Transforming these skills into a lifestyle is essential for maintaining blood glucose levels within the normal range and preventing complications (6). Supporting self-management in diabetic patients contributes to the regulation of metabolic control, improvement of quality of life, and prevention of complications. Conversely, poor metabolic control is closely associated with the development and progression of both microvascular and macrovascular complications (7).

Effective foot care requires adherence to basic principles aimed at maintaining hygiene, reducing the risk of infection, and enabling the early detection of complications. Regular cleaning, proper footwear selection, and self-examination of the feet play a crucial role in preventing injuries. Furthermore, educating patients about foot care enhances awareness and supports the preservation of long-term foot health. In patients with DFU, metabolic control and proper foot care are critical factors in the development and recurrence of ulcers; therefore, the evaluation of self-management and self-care behaviors is of great importance. Nevertheless, the self-management and self-care behaviors of patients with existing DFU, particularly in relation to ulcer recurrence prevention, remain insufficiently studied in the literature. This study aims to address this gap by evaluating self-care behaviors and diabetes self-management skills in patients with DFU, with the objective of identifying factors that may help reduce the risk of recurrence.

METHODS

The study was conducted with diabetic foot patients admitted to the Underwater Medicine and Hyperbaric Medicine Outpatient Clinic and the Diabetic Foot Outpatient Clinic. The demographic data and wound characteristics of the patients were recorded by the researchers. The Diabetes Self-Management Scale (DSMS) and Diabetic Foot Self-Care Behavior Scale (DFSBS) were filled out by a face-to-face interview technique.

Ethical Approval and Consent to Participate

This study was approved by the Clinical Research Ethics Committee (Protocol No:2022/160). All participants were informed about the purpose and procedures of the study, and written informed consent was obtained from each participant before data collection. In addition, permission was granted for the use of the questionnaires in the study. All procedures involving human participants were conducted in accordance with ethical standards, and written informed consent was obtained from each participant before enrollment. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria for the study

- The patient has applied to Underwater Medicine and Hyperbaric Medicine and/or Diabetic Foot Outpatient Clinic due to DFU.
- 18 years old or over
- Signing the informed consent form to participate in the study.
- Volunteering to participate in research

Exclusion criteria for the study

- Not signing the informed consent form to participate in the study.
- Being under 18 years old
- Not volunteering to participate in research.

The calculation of the sample size was done with the G*Power software (ver. 3.1.9.7). The minimum sample size was calculated as 204 participants by taking type 1 error 5%, type 2 error 20%, power of the study 80%, and effect size 0.35 from Cohen's table of constant values. In the event of data loss, it was deemed appropriate to reach 10% more people, resulting in a target of 225 participants.

Data Collection Forms

Demographic Data and Wound Characteristics Form

The age, gender, occupation, educational status, whether the patient had received hyperbaric oxygen therapy, history of surgical procedure, and Wagner stage of the wound were recorded on the "demographic data and wound characteristics" form.

Participant Recruitment and Data Collection

After obtaining ethical approval for the study, the sample consisted of individuals who presented to the diabetic foot outpatient clinic, met the inclusion and exclusion criteria, and agreed to participate in the study. After all participants were informed about the research, written informed consent was obtained, and data were collected through face-to-face interviews using a structured questionnaire. The interview with each participant lasted an average of 15 minutes. The data collection process, conducted between December 15, 2022, and February 1, 2023, was concluded upon reaching the target sample size, which was determined based on the sample size calculation.

Validity and Reliability of Instruments

The Diabetes Self-Management Scale (DSMS) and the Diabetic Foot Self-Care Behavior Scale (DFSBS) used in this study have been previously validated and tested for reliability, ensuring their appropriateness for use in this population (8,9).

Diabetes Self-Management Scale (DSMS)

It consists of 16 items and is a 4-point Likert-type. Items are scored with the options "does not apply to me" (0 points), "applies to me to some degree" (1 point), "applies to me to a considerable degree" (2 points), and "applies to me very much" (3 points). Participants are asked to rate the extent to which each statement applies to them with respect to the past eight weeks. The DSMS consists of four subscales. These are "glucose management" (items 1, 4, 6, 10, and 12); "dietary control" (items

2, 5, 9, and 13); "physical activity" (items 8,11, and 15), and "healthcare use" (items 3, 7, and 14). Item 16 requests an overall assessment of self-care. Seven of the items (items 1, 2, 3, 4, 6, 8, and 9) are scored straightforwardly, and nine of them (items 5, 7, 10, 11, 12, 13, 14, 15, and 16) are reverse-scored. The scale scoring is calculated as follows: [(Item total score from the total scale or sub-dimension) / (Maximum item total score that can be obtained from the total scale or sub-dimension) x 10]. If a non-skippable item (that has no "not required as a part of my treatment" option) is skipped, that item will be evaluated as -3 points. It is interpreted that as the score approaches 10 points, the level of diabetes self-management also increases. The scale does not have a defined cut-off value (9,10).

Diabetic Foot Self-Care Behavior Scale (DFSBS)

The scale has 7 items and 2 parts. While the items in the first part assess the behaviors exhibited by the patient over the course of the last week, the items in the second part assess the frequency of the particular foot self-care behaviors performed by the patient, ranging from 1 (never) to 5 (always). When calculating the total scale score, the number of items in Part 1 is categorized into 5 groups (0 days, 1-2 days, 3-4 days, 5-6 days, and 7 days). Thus, all items in the scale are rated on a 5-point Likert-type scale, indicating better foot care behavior. A minimum score of 7 and a maximum score of 35 can be obtained from the scale. The first sub-dimension of the DFSBS refers to self-care related to the feet, while the second sub-dimension refers to self-care related to the shoes (8,11). As the score obtained from the DFSBS scale increases, the level of self-care improves. The scale does not have a defined cut-off value.

Statistical Analysis

Analyses were evaluated using SPSS (v25, Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) package program. In this study, descriptive data were expressed as n (%) for categorical variables and mean±standard deviation (Mean±SD) or median (IQR) for numerical variables. The suitability of the numerical variables for normal distribution was determined using visual (histograms and probability graphs) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk

Table 1. Descriptive characteristics of the patients who participated in the study

	n (%) or Mean ± SD / Median (IQR)
Age	63.1±10.3
Gender	228 (100)
Female	165 (72.4)
Male	63 (27.6)
Employment status (n=228)	228 (100)
Working	53 (23.2)
Not working	144 (63.2)
Unknown	31 (13.6)
Education level (n=228)	228 (100)
Elementary school or lower	155 (68.0)
Middle school and higher	73 (32.0)
HBOT	222 (100.0)
Suggested	123 (55.4)
Not suggested	99 (44.6)
Surgical procedure	228 (100.0)
Do not have a history of surgical procedure	101 (44.7)
Have a history of surgical procedure	125 (55.3)
Type of surgical procedure	125 (100.0)
Digit amputation	113 (90.4)
Below-knee amputation (foot)	10 (8.0)
Above-knee amputation (foot)	2 (1.6)
Wagner stage of the wound	212 (100.0)†
Wagner 1	13 (6.1)
Wagner 2	69 (32.5)
Wagner 3	50 (23.5)
Wagner 4	80 (37.7)
DSMS	6.6±1.7
Glucose management	8.0 (3.3)
Dietary control	6.7 (3.3)
Physical activity	5.0 (3.3)
Healthcare use	6.7 (3.3)
DFSBS	28.0 (9.0)
Sub-dimension 1	16.0 (7.0)
Sub-dimension 2	11.0 (5.0)

† Due to rounding, some totals may not correspond with the sum of the separate figures. (HBOT – Hyperbaric Oxygen Treatment, DFSBS – Diabetic Foot Self-Care Behavior Scale, DSMS – Diabetes Self-Management Scale, SD – Standard Deviation, IQR – Interquartile Range)

tests) methods. For normally distributed variables, Student's t-test was used to compare the means between two groups, and one-way ANOVA analysis was used to compare more than two groups. For non-normally distributed variables, the Mann-Whitney U test was used for the comparison of two groups, and the Kruskal-Wallis test was used for the comparison of more than two groups. Spearman's correlation test was used to examine the relationship between continuous variables. P<0.05 was considered statistically significant in the analyses.

RESULTS

A total of 228 patients with DFU participated in the study, comprising 165 (72.4%) females and 63 (27.6%) males. The mean age of the patients was 63.1±10.5 years (min=23-max=96). While 63.2% of the patients were unemployed, 68.5% were either primary school graduates or illiterate. Hyperbaric oxygen therapy was recommended for 55.4% of the patients, and a surgical procedure was recommended for 55.3% of them. Digit amputation was performed in 90.4% of those who were recommended a surgical procedure. The mean score of the patients on the DSMS was 6.6±1.7, and the median score on the DFSBS was 28.0 (9.0) (Table 1). When the recommendation for HBOT was compared based on the Wagner Classification, the frequency of patients with Wagner wound stage ≥3 among those recommended for HBOT (63.6%) was significantly higher than those with stage ≤2 (40.3%) (p=0.001). (Table 2.)

No significant difference was observed in the scores obtained from the DSMS according to gender, age, and employment status. Those with a higher level of education had a significantly higher score in the DSMS than those with a lower level of education (p<0.001). Although patients who underwent diabetic foot surgery had higher DSMS scores than those who did not, the difference was not significant (p = 0.078). No significant difference was observed in the DSMS score according to the localization of the surgical procedure and the Wagner stage of the wound. No significant difference was found for the scores obtained from the DFSBS according to the variables of gender, age, employment status, educational status, history of surgical procedure, surgical procedure localization, and the Wagner stage of the wound (Table 3).

Table 2. Comparison of HBOT Recommendation Based on Wagner Classification

	Wagner Classification		
	≤2	**≥3**	**p-value***
HBOT	**n (%)**	**n (%)**	
Recommended	31 (40.3)	82 (63.6)	0,001
Not Recommended	46 (59.7)	47 (36.4)	

*Pearson's Chi-square test was applied, (HBOT – Hyperbaric Oxygen Treatment)

Table 3. Comparison of total scores of DSMS and DFSCB scales according to all parameters

	DSMS		**DFSBS**	
	Mean±SD	**p-value**	**Median (IQR)**	**p-value**
		Gender (n=228)		
Female	6.5±1.9	0.830[a]	28.0 (7.0)	0.388[c]
Male	6.6±1.7		28.0 (9.0)	
		Age (n=228)		
63 and younger	6.6±1.6	0.986[a]	28.0 (9.0)	0.787[c]
Older than 63	6.6±1.8		28.0 (9.0)	
		Employment status (n=228)		
Working	6.4±1.7	0.584[b]	29.0 (11.0)	0.341[d]
Not working	6.6±1.7		28.0 (9.0)	
Unknown	6.8±2.0		30.0 (7.0)	
		Education level (n=228)		
Elementary school or lower	6.3±1.7	<0.001[a]	28.0 (8.0)	0.308[c]
Middle school and higher	7.2±1.6		29.0 (9.5)	
		History of surgical procedure (n=226)		
Undergone	6.8±1.6	0.078[a]	28.0 (9.0)	0.485[c]
No surgery	6.4±1.8		28.0 (8.0)	
		Localization of the surgical procedure (n=125)		
Digit amputation	6.8±1.6	0.846[a]	28.0 (9.0)	0.953[c]
Below or above-knee amputation	6.7±2.3		28.5 (11.3)	
		Wagner stage of the wound (n=212)		
≤2	6.5±1.7	0.235[a]	29.0 (8.0)	0.378[c]
≥3	6.7±1.7		28.0 (10.0)	

[c]Mann-Whitney U test; [d]Kruskal-Wallis test (DFSCB – Diabetic Foot Self-Care Behavior Scale, DSMS – Diabetes Self-Management Scale, IQR – Interquartile Range)

Table 4. Comparison of the sub-dimensions of the DSMS according to all parameters

	Glucose management		Dietary control		Physical activity		Health-care use			
	Median (IQR)	p-value*	Median (IQR)	p-value*	Median (IQR)	p-value*	Median (IQR)	p-value*
Gender (n=228)								
Female	8.0 (3.3)	0.709	6.7 (3.3)	0.885	5.6 (3.9)	0.424	6.7 (3.3)	0.227
Male	8.0 (3.3)		6.7 (3.8)		4.4 (3.3)		6.7 (2.8)	
Age (n=228)								
63 and younger	8.0 (2.7)	0.245	6.7 (3.3)	0.262	5.6 (3.3)	0.833	6.7 (2.2)	0.196
Older than 63	8.0 (3.3)		6.7 (4.2)		4.4 (4.4)		6.7 (3.3)	
Employment status (n=228)**								
Working	7.3 (2.7)	0.157	6.7 (4.2)	0.676	4.4 (3.3)	0.839	6.7 (3.3)	0.810
Not working	8.0 (3.3)		6.7 (4.0)		5.0 (4.2)		6.7 (2.2)	
Unknown	8.0 (3.3)		5.8 (4.2)		5.6 (3.3)		6.7 (4.4)	
Education level (n=228)								
Elementary school or lower	7.3 (2.7)	<0.001	5.8 (4.2)	0.001	4.4 (4.4)	0.049	6.7 (2.2)	0.044
Middle school and higher	8.7 (2.7)		7.5 (3.3)		5.6 (3.3)		6.7 (2.2)	
History of surgical procedure (n=226)								
Undergone surgery	8.0 (3.3)	0.401	7.5 (4.2)	0.019	4.4 (3.3)	0.795	6.7 (3.3)	0.178
No surgery	8.0 (3.0)		5.8 (4.2)		5.6 (4.4)		6.7 (2.2)	
Localization of the surgical procedure (n=125)								
Digit amputation	8.0 (3.3)	0.333	7.5 (4.2)	0.527	4.4 (3.3)	0.980	6.7 (2.2)	0.070
Below and or above-knee amputation	9.0 (4.8)		8.3 (4.8)		5.6 (5.3)		6.1 (3.9)	
Wagner stage of the wound (n=212)								
≤2	8.0 (2.7)	0.652	5.8 (3.5)	0.003	5.6 (3.3)	0.273	6.7 (3.3)	0.906
≥3	8.0 (3.3)		7.5 (4.2)		4.4 (3.3)		6.7 (3.3)	

*Mann-Whitney U test, **Kruskal-Wallis test, (DSMS – Diabetes Self-Management Scale, IQR – Interquartile Range)

Table 5. Comparison of the sub-dimensions of the DFSBS according to all parameters

	DFSBS sub-dimension 1		DFSBS sub-dimension 2	
	Median (IQR)	p-value*	Median (IQR)	p-value*
Gender (n=228)				
Female	17.0 (6.0)	0.256	11.0 (5.0)	0.818
Male	16.0 (8.0)		12.0 (5.0)	
Age (n=228)				
63 and younger	17.0 (6.0)	0.767	11.0 (5.0)	0.836
Older than 63	16.0 (7.0)		12.0 (5.0)	
Employment status (n=228)**				
Working	16.0 (8.0)	0.330	12.0 (6.0)	0.225
Not working	16.0 (7.0)		11.0 (4.0)	
Unknown	17.0 (5.0)		12.0 (5.0)	
Education level (n=228)				
Elementary school or lower	16.0 (7.0)	0.853	11.0 (6.0)	0.030
Middle school and higher	16.0 (8.0)		12.0 (6.0)	
History of surgical procedure (n=226)				
Undergone surgery	17.0 (7.0)	0.847	12.0 (5.0)	0.063
No surgery	16.0 (6.5)		11.0 (5.0)	
Localization of the surgical procedure (n=125)				
Digit amputation	17.0 (6.5)	0.678	12.0 (5.0)	0.354
Below or above-knee amputation	17.0 (10.0)		13.0 (4.3)	
Wagner stage of the wound (n=212)				
≤2	17.0 (6.0)	0.175	11.0 (5.0)	0.953
≥3	16.0 (8.0)		12.0 (5.0)	

**Kruskal-Wallis test (DFSBS – Diabetic Foot Self-Care Behavior Scale, IQR –Interquartile Range)

Table 6. Correlation of scale scores with Wagner stage of the wound

		DSMS score	DFSBS score
Wagner stage of the wound	R-value	0.109	-0.060
	p-value	0.113	0.387

Spearman's rank correlation test was applied. (DFSCB – Diabetic Foot Self-Care Behavior Scale, DSMS – Diabetes Self-Management Scale)

The scores obtained from the sub-dimensions of the DSMS were also compared according to all parameters. Significant difference was found in all sub-dimension scores according to education level ($p<0.05$ for each sub-dimension). The scores of those with higher education levels were found to be higher in the sub-dimensions of the scale. The dietary control score of those who had undergone surgery was found to be higher than those who had not undergone surgery ($p=0.019$). The score obtained from the dietary control sub-dimension was significantly higher in patients with a higher Wagner stage compared to those with a lower Wagner stage ($p = 0.003$). (Table 4) When comparing patients with and without amputation according to education level, no significant difference was found between the groups ($p = 0.746$)

The scores obtained from the sub-dimensions of the DFSBS were also compared according to all parameters. The score obtained from the first sub-dimension of the DFSBS did not show a significant difference according to any variable. The score obtained from the second sub-dimension of the DFSBS showed a significant difference only according to the level of education ($p=0.030$). Those with a higher education level had higher scores in the second sub-dimension of the DFSBS. No significant correlation was observed between the DSMS and DFSBS scores and the Wagner stage. (Table 6)

DISCUSSION

In our study, socio-demographic and diabetic foot-related characteristics of 228 patients with foot ulcers and the relationship between diabetes self-management and diabetic foot self-care were examined. It was observed that as the patients' level of education increased, their scores of the DSMS and the second sub-dimension of the DFSBS increased. The subscale of the DSMS that measures dietary control yielded higher scores for those who underwent surgery compared to those who did not, and the dietary control score was also found to be significantly higher in patients with higher Wagner stage wounds compared to those with lower Wagner stage wounds.

The primary goal in the treatment of diabetes is to prevent complications and maintain quality of life. By ensuring self-management, it is possible to maintain the patient's well-being. The goal of diabetes self-management is to empower individuals to make lifestyle changes, adhere to medical nutrition therapy, maintain desired blood glucose levels, reduce or eliminate the symptoms of diabetes, prevent complications, and manage diabetes in a comprehensive way. For achieving this goal, self-management includes aspects such as knowledge, skills, decision-making, coping with stress, and cooperation with health professionals (12). Luo et al. conducted a meta-analysis of 45 studies to examine the factors affecting diabetes self-management in adult individuals with diabetes in China. As a result of this study, it was found that those with higher levels of education had better diabetes self-management (13). In a study conducted by Khalooei and Benrazavy to evaluate diabetes self-management and associated factors in patients with type 2 diabetes, which included 600 individuals with type 2 diabetes, it was found that those with higher education levels had higher diabetes self-management scores (14). According to our research findings, as the level of education increases, it is observed that the scores obtained from the DSMS significantly increase, which is consistent with the literature. This may be related to the fact that the higher the level of education, the easier it is to access information, put the learned information into practice, and increase the individual's awareness in the field of personal health management. It also suggests that increasing the level of social education may contribute positively to health self-management. In addition to sociodemographic characteristics, current physical examination findings and biochemical parameters are also critical in determining the prognosis of diabetic foot. In particular, renal failure, peripheral neuropathy, and HbA1c levels are significantly associated with amputation rates (15). Although our study primarily focused on self-management and self-care behaviors, it should not be overlooked that these clinical and biochemical indicators play a complementary role in shaping outcomes. For example, patients with poor glycemic control or concomitant renal dysfunction may experience more severe disease progression, which can influence their self-care priorities and engagement with healthcare services. Similarly, the presence of peripheral neuropathy may alter both symptom perception and the urgency of adopting protective behaviors. Considering these factors alongside sociodemographic characteristics could provide a more holistic understanding of the processes leading to adverse outcomes in diabetic foot. These parameters were not included in our study; however, future research should incorporate such clinical and biochemical variables to provide a more comprehensive understanding of the risks and self-management behaviors associated with diabetic foot.

In our study, although no significant difference was found, those who underwent surgery for DFU were found to have a higher DSMS score than those who did not undergo surgery. In addition, the dietary control score of those who had undergone surgery was higher than those who had not undergone surgery, and the dietary control subscale score of those with high Wagner stage was significantly higher than those with low Wagner stage. The study conducted by Aytemur and Inkaya aimed to examine the complication risk perception

and diabetes self-management skills of individuals with diabetes mellitus. That study sample consisted of 153 adults with diabetes mellitus. In that study, it was reported that self-management of individuals with diabetes mellitus was affected by sociodemographic and disease-related characteristics. In that study, it was observed that a high perception of complication risk in individuals with diabetes mellitus provided a positive increase in diabetes self-management (16). Becker et al. reported that individuals with DFU had poor physical activity but were good at self-monitoring of blood glucose and other diabetes self-management skills (17). There are also other studies supporting this finding (12,18). It is thought that individuals with complications pay more attention to nutrition, exercise, blood glucose monitoring, and health checks to prevent the progression of the existing condition, the development of new morbidities, and also against the possible risk of mortality. It is noteworthy that these behaviors are not exhibited until complications arise. In our study, since those who underwent surgery and those with high Wagner stage may have a higher risk perception of diabetes-related complications because of the reasons mentioned above, scores related to dietary control were higher in those groups than in those who did not undergo surgery and those with lower Wagner stage. In addition, those who underwent surgery for a wound also had higher overall DSMS scores than those who did not.

In our study, the mean score obtained from the DSMS, in which we evaluated diabetes self-management, was 6.6±1.7. In the study conducted in Germany in which the scale was developed, the average score obtained from the DSMS was found to be 6.8 (10). During the COVID-19 period, two studies conducted at primary care hospitals in Türkiye reported average DSMS scores of 5.3 and 5.6, respectively (16,19). When the international literature is reviewed, the average scale score of the patients in a study conducted in Iran was found to be 5.0. In studies examining the self-management levels of patients with diabetes in Uganda, Hungary, and Saudi Arabia, it was observed that the average scale scores ranged between 6.5-7.7 (20–23). DSMS includes behaviors such as regular medication use, adherence to a healthy diet, regular physical exercise, blood glucose monitoring, foot care, and compliance with medical check-ups. The successful management of diabetes aims to maintain blood glucose levels within the appropriate range. This will prevent the development of complications (24). The studies mentioned above included diabetic patients who were randomly selected from a specific population. In our study, we found that 55.3% of the patients had undergone surgery for diabetic foot, and 38% of the patients had foot ulcers at Wagner stage 4. At first glance, it might be expected that self-care would be lower in this population because of the development of complications, but the mean DSMS score of our study is higher than many studies in the literature. This may be due to the fact that patients have increased awareness of self-management in diabetes because they have DFU, which seriously affects their quality of life. In addition, as Wagner stages increase, tissue loss may also increase (25); therefore, patients should be cautious in self-management.

In our study, the median score obtained from the DFSBS was found to be 28.0. In a study conducted in Germany with 82 patients who had diabetes, the average score on the DFSBS was 21.9 (26). In a study conducted in Türkiye with 300 patients who had diabetes, the average of the DFSBS was found to be 23.89 (27). In another study, the DFSBS scores of patients with a history of foot ulcers were significantly higher DFSBS scores than those with no history of foot ulcers (11). The mean DFSBS score of our study was found to be higher when compared with the similar studies in the literature. The reason for this could be that all participants in our study had DFU, and the majority of our patients had undergone surgery, and their awareness of diabetic foot may be higher than other patients with diabetes.

The score obtained from the second sub-dimension of the DFSBS showed a significant difference according to the level of education. In a study involving 500 patients, similar to our study, it was found that patients with an academic education had a higher mean score in diabetic foot self-care (28). As the education level increases, patients' awareness of self-care behaviors also increases. Education level is associated with increased awareness and knowledge of health issues, which in turn enables greater emphasis on early intervention and foot health. Individuals with higher levels of education have better self-care skills and can adhere to treatment plans more effectively. The study conducted by Öztaş et al. concluded that patients with DFU have low levels of diabetes health literacy (29). Increased health literacy leads individuals with diabetes to approach foot problems in a more sensitive manner. These individuals may also have received more effective education on diabetic foot care by interacting with healthcare professionals. In conclusion, individuals with a higher level of education may have a more proactive and conscious approach to diabetic foot care. Therefore, it is possible that those with higher education levels scored higher on the second sub-dimension of the DFSBS.

In our study, no significant difference was observed between patients with and without amputation in terms of education level. This finding suggests that education level alone may not be a decisive factor in the development of amputation. Diabetic foot complications are the result of a multifactorial process influenced by various factors, including glycemic control, disease duration, comorbidities, regular follow-up, and appropriate foot care (30,31). Therefore, instead of focusing solely on educational status, comprehensive approaches aimed at enhancing patient awareness, ensuring continuous education, and promoting behavioral changes are considered more effective in reducing the risk of severe outcomes such as amputation (32).

The DSMS and DFSBS did not show a significant correlation with the Wagner stage of the wound. There was no study in the literature that compared the Wagner stage with the DSMS and DFSBS. Since the majority of our patients have undergone surgery, their current Wagner stages may be lower compared to previous Wagner stages. Therefore, a direct correlation between the Wagner stage and the DSMS and DFSBS may not

be expected.

Limitations

This study has several limitations that should be acknowledged. The single-center design of the study limits the generalizability of the findings to broader populations. In addition, important clinical and biochemical parameters such as HbA1c levels, renal function tests, peripheral neuropathy status, and duration of diabetes diagnosis were not assessed. Educational status and frequency of healthcare utilization were also not examined. Future studies with multi-center designs, longitudinal approaches, and objective data collection methods that incorporate these variables are needed to validate and expand upon the present findings.

CONCLUSION

Diabetic foot self-care and diabetes self-management are critical components for individuals with diabetes to reduce the risk of complications and improve health outcomes. By adopting practices such as regular foot inspections, appropriate moisturization, wearing suitable footwear, and early recognition of potential issues, patients can lower the risk of foot ulcers, infections, and related complications. Effective diabetes self-management, which includes regular monitoring of blood glucose levels, adherence to a healthy diet, consistent physical activity, and proper medication use, plays a pivotal role in maintaining glycemic control and preventing diabetes-related complications.

While this study did not directly assess quality of life, it demonstrated that patient education and increased awareness are associated with improved self-care and self-management behaviors, particularly among patients with higher levels of education. The findings suggest that enhancing patient education on diabetic foot care and diabetes management may indirectly contribute to a better quality of life by minimizing complications and reducing hospitalizations. Future studies are recommended to explore the direct impact of these behaviors on quality of life outcomes. Nevertheless, investing in educational programs on diabetic foot care and diabetes self-management has the potential to support better patient outcomes and alleviate the burden on healthcare systems, contributing to more sustainable healthcare solutions.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

Address correspondence to: *Kubra Canarslan Demir, University of Health Sciences, Gulhane Training and Research Hospital, Department of Underwater and Hyperbaric Medicine, Ankara, Türkiye*
e-mail: *drcanarslan@hotmail.com*

REFERENCES

1. Perez-Favila A, Martinez-Fierro ML, Rodriguez-Lazalde JG, et al. Current Therapeutic Strategies in Diabetic Foot Ulcers. Medicina (Mex). 2019; 25:55(11):714. doi: 10.3390/medicina55110714.
2. Boulton A, Armstrong D, Krisner R, et al. Diagnosis and Management of Diabetic Foot Complications. ADA Clin Compend. 2018; 2018(2):1–20. doi: 10.2337/db20182-1
3. Kim PJ, Steinberg JS. Complications of the diabetic foot. Endocrinol Metab Clin North Am. 2013;42(4):833–47.
4. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005;293;(2):217-228. doi:10.1001/jama.293.2.217
5. Wang X, Yuan CX, Xu B, et al. Diabetic foot ulcers: Classification, risk factors and management. World J Diabetes. 2022;15;13(12):1049–65. doi: 10.4239/wjd.v13.i12.1049
6. Funnell MM, Brown TL, Childs BP, et al. National Standards for Diabetes Self-Management Education. Diabetes Care. 2007;33(4):599-614. doi:10.1177/0145721707305880
7. Sturt J, Whitlock S, Hearnshaw H. Complex intervention development for diabetes self-management. J Adv Nurs. 2006;54(3):293–303. doi: 10.1111/j.1365-2648.2006.03819.x
8. Bakir E, Samancioglu S. Diyabetik Ayakta Öz Bakım Davranışı Ölçeği'nin Türkçe Geçerlilik ve Güvenilirliği. Karya J Health Sci. 2021;2(2):39-43. doi:10.52831/kjhs.894403
9. Eroğlu N, Sabuncu N. Diyabet Öz Yönetim Skalası'nın (DÖYS) Türk Toplumuna Uyarlanması: Geçerlik ve Güvenirlik Çalışması Adaptation Of Diabetes Self Management Questionnaire To Turkish Society: Validity and Reliability Study. 2019; 1.3: 1-6.
10. Schmitt A, Gahr A, Hermanns N, et al. The Diabetes Self-Management Questionnaire (DSMQ): development and evaluation of an instrument to assess diabetes self-care activities associated with glycaemic control. Health Qual Life Outcomes. 2013;11(1):138. doi:10.1186/1477-7525-11-138
11. Chin YF, Huang TT. Development and Validation of a Diabetes Foot Self-Care Behavior Scale. J Nurs Res. 2013;21(1):19–25. doi: 10.1097/jnr.0b013e3182828e59
12. Powers MA, Bardsley JK, Cypress M, et al. Diabetes Self-management Education and Support in Adults With Type 2 Diabetes: A Consensus Report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association. Diabetes Care. 2020;1;43(7):1636–49. doi: 10.2337/dci20-0023
13. Luo X, Liu T, Yuan X, et al. Factors Influencing Self-Management in Chinese Adults with Type 2 Diabetes: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2015; 10;12(9):11304–27. doi:10.3390/ijerph120911304
14. Khalooei A, Benrazavy L. Diabetes Self-management and Its Related Factors among Type 2 Diabetes Patients in Primary Health Care Settings of Kerman, Southeast Iran. J Pharm Res Int. 2019; 29;1–9. doi: 10.9734/jpri/2019/v29i430241
15. Ince B, Dadaci M, Arslan A, et al. Factors determining poor prognostic outcomes following diabetic hand infections. Pak J Med Sci. 2015;31(3):532–7. doi: 10.12669/pjms.313.6858.
16. Aytemur M, İnkaya B. Investigation of Diabetes Complication Risk Perception and Diabetes Self-Management Skills in Individuals with Diabetes. Turk J Diabetes Obes. 2022; 31;6(2):121–30. doi:10.25048/tudod.1099172
17. Becker J, Emmert-Fees K, Greiner G, et al. Associations between self-management behavior and sociodemographic and disease-related characteristics in elderly people with type 2 diabetes — New results from the population-based KORA studies in Germany.

Prim Care Diabetes. 2020;14(1) doi: 10.1016/j.pcd.2020.01.004.
18. Magee M, Bowling A, Copeland J, et al. The ABCs of Diabetes. Diabetes Educ. 2011;37(1):95–103. doi: 10.1177/0145721710392246.
19. Utli H, Vural Doğru B. The effect of the COVID-19 pandemic on self-management in patients with type 2 diabetics. Prim Care Diabetes. 2021;15(5):799–805. doi:10.1016/j.pcd.2021.07.009
20. Alodhayani A, Almutairi KM, Vinluan JM, et al. Association between self-care management practices and glycemic control of patients with type 2 diabetes mellitus in Saudi Arabia: A cross-sectional study. Saudi J Biol Sci. 2021;28(4):2460–5. doi:10.1016/j.sjbs.2021.01.047
21. Alruhaim HY, Almigbal TH, Almutairi JS, et al. The association between diabetes numeracy and diabetes self-management among Saudi adults with insulin-treated diabetes. Saudi Med J. 2021;42(5):517–25. doi:10.15537/smj.2021.42.5.20200422
22. Onyango JT, Namatovu JF, Besigye IK, et al. The relationship between perceived social support from family and diabetes self-management among patients in Uganda. Pan Afr Med J [Internet]. 2022 [cited 2025 Jul 9];41. Available from: https://www.panafrican-med-journal.com/content/article/41/279/full
23. Vincze, A., Losonczi, A. & Stauder, A. The validity of the diabetes self-management questionnaire (DSMQ) in Hungarian patients with type 2 diabetes. Health Qual Life Outcomes. 2020;18.1: 344.. doi:10.1186/s12955-020-01595-7
24. Ahola AJ, Groop P -H. Barriers to self-management of diabetes. Diabet Med. 2013;30(4):413–20. doi:10.1111/dme.12105
25. Akyüz S. Elevated HbA1c level associated with disease severity and surgical extension in diabetic foot patients. Turk J Trauma Emerg Surg. 2023;1013–8. doi: 10.14744/tjtes.2023.08939
26. Lecker L, Stevens M, Thienel F, et al. Validity and reliability of the German translation of the Diabetes Foot Self-Care Behavior Scale (DFSBS-D). PLOS ONE. 2022;3;17(6):e0269395. doi:10.1371/journal.pone.0269395
27. Karakurt P, Kasikci M. Validity and reliability of the Turkish version of the Diabetes Self-Care Scale. Int J Diabetes Dev Ctries. 2015;35(S2):148–56. doi:10.1007/s13410-014-0252-5
28. Hasanpour Dehkordi A, Chin Y, Huang T, et al. Psychometric evaluation of the Farsi version of the diabetes foot self-care behavior scale. J Foot Ankle Res. 2020;13(1). doi/10.1186/s13047-020-00437-5
29. Oztas B, Akyuz S, Oztas M, et al. Determination of Diabetes Health Literacy Levels of Patients Followed Up With Diabetic Foot Diagnosis: A Cross-Sectional Descriptive Study. The International Journal of Lower Extremity Wounds. 2023;0(0). doi:10.1177/15347346231179523
30. Armstrong DG, Tan TW, Boulton AJM, et al. Diabetic Foot Ulcers: A Review. JAMA. 2023;3;330(1):62–75. doi:10.1001/jama.2023.10578
31. Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on the management of diabetic foot ulcer. World J Diabetes. 2015;15;6(1):37–53. doi:10.4239/wjd.v6.i1.37
32. Bus SA, Lavery LA, Monteiro-Soares M, et al. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3269. doi:10.1002/dmrr.3269

NEU PRESS

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2025.01823
Selcuk Med J 2025;41(3): 124-130

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Effects of Biofeedback Treatment on Anal Incontinence Before Closing The Protective Ileostomy in Patients Undergoing Low Anterior Resection

Low Anterior Rezeksiyon Yapılan Hastalarda Koruyucu İleostominin Kapatılması Öncesinde Biofeedback Tedavinin Anal İnkontinans Üzerine Etkileri

Alper Varman[1], Tevfik Kucukkartallar[1], Murat Cakir[1], Mehmet Aykut Yildirim[1], Mustafa Senturk[1], Selman Alkan[1], Omer Kisi[2], Aslan Hasan Kocamaz[2], Abdulkadir Celik[3]

[1]Necmettin Erbakan University, Faculty of Medicine, Department of General Surgery, Konya, Türkiye
[2]Aksaray Training and Research Hospital, Department of General Surgery, Aksaray, Türkiye
[3]Uzunköprü State Hospital, Department of General Surgery, Edirne, Turkey, Türkiye

ÖZET

Amaç: Bu çalışma, anal sfinkterin pasif durumda olduğu dönemde (koruyucu ileostomi kapatılmadan önce) uygulanan biofeedback terapi yönteminin, rektum kanseri nedeniyle düşük anterior rezeksiyon ve koruyucu ileostomi yapılan hastalarda postoperatif inkontinans gelişimini önleme veya azaltma üzerindeki etkisini incelemeyi amaçlamaktadır. Bu bağlamda, biofeedback tedavisinin hem klinik semptomlar hem de anorektal manometri ölçüm parametreleri üzerindeki etkileri değerlendirilmiştir.
Gereçler ve Yöntem: Çalışmaya, Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi Genel Cerrahi Kliniği'nde düşük anterior rezeksiyon ve koruyucu ileostomi operasyonu geçiren hastalar dahil edilmiştir. Rastgele seçilen 40 hasta, her biri 20 kişiden oluşan iki gruba ayrılmıştır. Çalışma grubundaki hastalara, ileostomi kapatılmadan önce toplam dört hafta süresince, haftada iki seans olmak üzere biofeedback egzersiz tedavisi uygulanmıştır. Kontrol grubundaki hastalar ise bu tür bir terapi almamıştır. Koruyucu ileostomi kapatıldıktan iki hafta sonra her iki grup üzerinde anorektal manometri ölçümleri yapılmıştır. Ayrıca, Cleveland Clinic/Wexner İnkontinans Skoru , düşük anterior rezeksiyon sendromu skoru ve Cleveland Clinic tarafından geliştirilen Yaşam Kalitesi Anketi uygulanarak hastaların klinik durumları değerlendirilmiştir.
Bulgular: Biofeedback egzersiz tedavisi uygulanan hastalarda, koruyucu ileostomi kapatıldıktan sonra yapılan manometri ölçümlerinde "ortalama dinlenme basıncı" değerlerinin anlamlı derecede daha yüksek olduğu bulunmuştur. Düşük anterior rezeksiyon sendromu skorlamasına göre, çalışma grubunda inkontinans düzeyinin daha düşük olduğu, ayrıca gündüz dışkılama sıklığının daha az olduğu tespit edilmiştir. Bu bulgular, biofeedback terapisinin anal sfinkter üzerinde güçlendirici bir etkisi olabileceğini düşündürmektedir.
Sonuç: Çalışma sonucunda elde edilen veriler, koruyucu ileostomi kapatılmadan önce uygulanan biofeedback tedavisinin, postoperatif dönemde hastaların düşük anterior rezeksiyon sendromu semptomlarını iyileştirebildiğini ve bazı manometrik ölçüm parametrelerinde olumlu etkiler sağladığını ortaya koymaktadır. Bu sonuçlar, biofeedback terapisinin bu hasta grubu için umut verici bir tedavi yöntemi olabileceğini göstermektedir.

Anahtar Kelimeler: Fekal inkontinans, rektum kanseri, biofeedback tedavi

ABSTRACT

Objective: This study aimed to investigate whether biofeedback therapy performed while the anal sphincter was passive (before the closure of protective ileostomy) had any preventive or reducing effect on postoperative incontinence development in patients undergoing low anterior resection and protective ileostomy for rectal carcinoma. Additionally, the study sought to evaluate the impact of biofeedback therapy on anorectal manometry measurements, quality of life, and overall functional outcomes.
Materials and Methods: This study included patients who underwent low anterior resection and protective ileostomy at the General Surgery Clinic of Necmettin Erbakan University, Meram Medical Faculty. A total of 40 patients were randomly divided into two groups of 20 individuals each. The study group received biofeedback exercise therapy, which was administered twice a week for four consecutive weeks prior to the ileostomy closure. The control group did not receive any exercise therapy. Two weeks after the ileostomy closure, anorectal manometry measurements were performed for both groups. Clinical outcomes were assessed using the Cleveland Clinic/Wexner Incontinence Score , the low anterior resection syndrome score, and the Cleveland Clinic-developed Quality of Life Questionnaire.
Results: Patients who received biofeedback exercise therapy demonstrated higher "average resting pressure" in anorectal manometry measurements performed after ileostomy closure. According to the LARS scoring, the study group experienced less incontinence and a lower frequency of daytime defecation compared to the control group. These findings suggest a significant improvement in anal sphincter functionality.
Conclusion: The results of this study indicate that biofeedback therapy performed before ileostomy closure improves postoperative low anterior resection syndrome symptoms and enhances specific anorectal manometric parameters. These findings are promising and highlight the potential of biofeedback therapy as an effective intervention in this patient population.

Keywords: Fecal incontinence, rectal cancer, biofeedback therapy

Geliş Tarihi/Received: 1 February/Şubat 2025 **Kabul Tarihi/Accepted:** 19 September/Eylül 2025 **Yayın Tarihi/Published Online:** 28 September/Eylül 2025

Sorumlu Yazar/Corresponding Author: Alper Varman, Necmettin Erbakan University, Faculty of Medicine, Department of General Surgery, Konya, Türkiye
e-mail: alp.varman@gmil.com

Atıf yapmak için/ Cite this article as: Varman A, Kucukkartallar T, Cakir M, Yildirim MA, Senturk M, Alkan S, Kisi O, Kocamaz AH, Celik A. Effects of Biofeedback Treatment on Anal Incontinence Before Closing The Protective Ileostomy in Patients Undergoing Low Anterior Resection. Selcuk Med J 2025;41(3): 124-130

Disclosure: *Author has no a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Fecal incontinence can be defined as the decrease or loss of the anal sphincter's ability to control the discharge of solid, liquid and gaseous contents (1). It significantly impairs the quality of life of the patients. Guillaume et al. (2) reported the prevalence of fecal incontinence of varying degrees of severity as 18% in all age groups. However, fecal incontinence is mostly not reported as a complaint by patients since it is a private matter, patients may be embarrassed, or they may consider incontinence normal due to advanced age or previous surgery. Therefore, the actual prevalence rates are thought to be higher. Complaints such as changes in defecation frequency and anal incontinence may develop in patients who underwent low anterior resection (LAR) for rectal carcinoma (3). Multi-center studies have shown that low anterior resection syndrome (LARS), which is associated with symptoms such as incontinence, need for frequent defecation, and urge to defecate, develops in 80% of patients after undergoing LAR (4). Fecal incontinence has significant effects on the social and cultural life of individuals and has been reported to cause the development of fear of leaving home and avoidance of several outdoor social activities in several patients (5). Therefore, its diagnosis and treatment are of great importance for patients to be able to return to their social lives after the surgery and the medical treatments that they undergo and receive due to rectal carcinoma.

In the past, most of the studies on rectal carcinoma focused on local recurrence and mortality. In recent years, the development of surgical techniques, the widespread use of multidisciplinary treatment approaches and the decrease in mortality rates have led studies to focus on the functional results of treatment and quality of life. It has been shown that cancer-related depression adversely affects the general health and social relations of the person, and it is recommended to provide psychological support to cancer patients (6). Biofeedback therapy is an effective approach in the treatment of fecal incontinence after LAR (7). The combination of pelvic floor muscle physiotherapy and biofeedback therapy has been shown to be more effective than pelvic floor muscle physiotherapy alone (8). This study aimed to investigate the effects of biofeedback therapy performed when the anal sphincter was passive (before the closure of protective ileostomy) on postoperative incontinence development in patients who underwent LAR and protective ileostomy for rectal carcinoma.

MATERIALS AND METHODS

While planning our study, we found that there should be 21 cases in the study and control groups in the sample calculation we made using G Power version 3.1.9.3 with the parameters effect size: 0.8, a error: 0.05, b error: 0.20. Due to the fact that 2 of our cases exited during the study and the study budget was limited, we completed our study with 20 cases in the study and control groups. This study included patients undergoing LAR and protective ileostomy in the General Surgery Clinic of Necmettin Erbakan University, Meram Medical Faculty, between 01.02.2018 and 01.12.2018. This study was approved by Necmettin Erbakan University Meram Medical Faculty ethics committee with 05/01/2018 dated and 2017/1145 numbered decision and all procedures were conducted in accordance with the Declaration of Helsinki and local laws and regulations. All participants gave their written informed consent after the researchers explained the aim and course of the study. Oral assent was also obtained from all participants. As can be seen in the flow diagram, Patients were selected from locally advanced stage middle and lower rectal cancer cases with T3/T4 or lymph node involvement (Stage 2 or 3) in preoperative pelvic MRI imaging (Figure 1). Inclusion criteria for the study were: (1) age between 18 and 80 years, (2) histologically confirmed rectal adenocarcinoma requiring LAR and protective ileostomy, (3) clinical staging of T3/T4 or node-positive disease, (4) completion of neoadjuvant chemoradiotherapy, (5) ability to provide informed consent and participate in scheduled sessions. Patients with incomplete clinical data, refusal to participate, or noncompliance with scheduled interventions were excluded. All patients underwent low anterior resection and total mesorectal excision (LAR-TME) 4-6 weeks after receiving neoadjuvant chemoradiotherapy. History of previous pelvic surgery, history of urinary and/or fecal incontinence were accepted as exclusion criteria.

The patients were divided into two groups, each consisting of 20 people, using the 4-block randomization system. Patients who have undergone LAR operation and have a protective

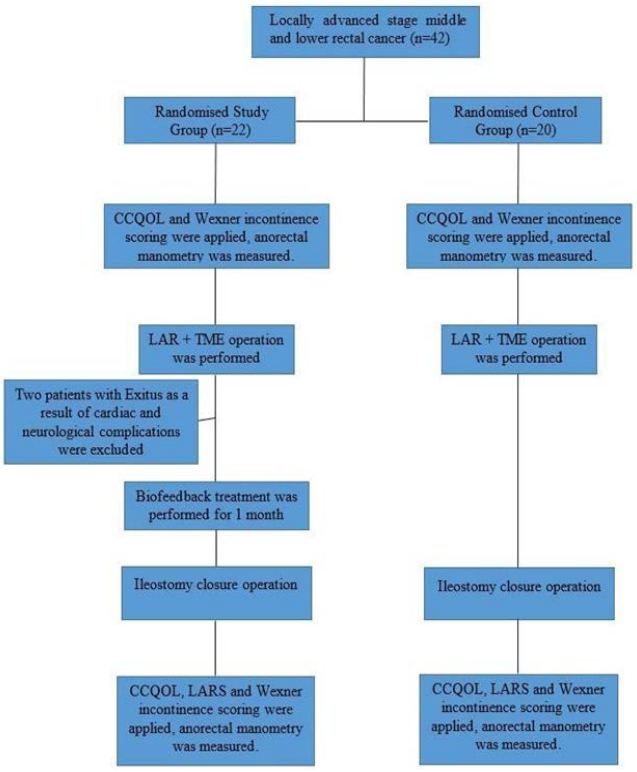


Figure 1. Flow Diagram

ileostomy do not defecate through the anus as long as their ileostomy is open. Therefore, they do not need fecal continence provided by the anal sphincter in their daily lives. For this reason, the anal sphincter will remain passive as long as the ileostomy remains open unless the patient is particularly exercising. 20 patients in the study group were called for exercises one month after LAR and were included in a four-week biofeedback therapy program. Exercises were done in two sessions a week, each lasting 30 minutes. The exercises were performed in the hospital accompanied by a nurse. The patients in the control group did not receive biofeedback therapy before ileostomy closure. Detailed information was provided to all patients included in the study, and their written consents were obtained.

Anorectal manometry, the Cleveland Clinic/Wexner Incontinence Score (CCIS) and Cleveland Clinic-developed Quality of Life Questionnaire (QOL) were preoperatively administered to both groups. Anorectal manometry measurement was performed using an eight-channel capillary perfusion system manometry device two weeks after protective ileostomy closure. In addition to the scales applied in the preoperative period, the Low Anterior Resection Syndrome scoring (LARS) was applied. Following the completion of the necessary documentation, independently of the present study, routine treatments of our clinic (biofeedback treatment and other necessary treatments) were provided to the patients in the control group with anal incontinence complaints.

Statistical Analysis

Statistical analysis was carried out using SPSS version 20.0 software. Descriptive data were expressed as number, percentage, and mean ± standard deviation. Categorical data was analyzed using the chi-square test. The Shapiro-Wilk test was used to determine whether the data followed a normal distribution. The independent t-test was for the analysis of normally distributed data, while the Mann-Whitney U test was used for the analysis of non-normally distributed data. A p-value of <0.05 was considered statistically significant. However, exact p-values were reported when possible to reflect the strength of association.

RESULTS

This study included a total of 42 patients undergoing LAR and protective ileostomy for rectal carcinoma in the General Surgery Clinic of Necmettin Erbakan University, Meram Medical Faculty, between February 2018 and December 2018. The patients were divided into two groups as: the study group and the control group. There were 22 and 20 individuals in the study and control groups, respectively. Two patients in the study group died during the study and were excluded. One patient with a history of heart valve replacement and receiving treatment for heart failure died due to the development of decompensated heart failure. One patient who developed Gulian Barre syndrome died while under treatment in the neurology intensive care unit.

Of the patients, 24 patients (60%) were male and 16 (40%) were female. There were 12 (60%) male and 8 (40%) female patients in the study group, whereas the control group included 11 (55%) male and 9 (45%) female patients. There was no statistically significant difference between the groups in terms of gender distribution (p: 0.757). The groups were similar in terms of age, anastomosis level, circular stapler diameter, and comorbidities. No difference was observed between the groups in terms of surgical procedure. 13 (65%) patients in the study group and 12 (60%) patients in the control group underwent laparoscopic surgery. For other patients, classical open surgery was performed with an anterior approach and none of the patients underwent robotic surgery (Table 1).

Scales and Scoring

The mean preoperative CCQOL score was 24.15 (19-30) in the study group and 25.40 (16-30) in the control group. The

Table 1. Comparison of the groups in terms of "age", "anastomosis level", "staple head""gender", "comorbidity" and "surgical procedure"

		Study group	Control group	Average ± Standard deviation		P value
Age	Study group	39	74	59,60 ± 10,99		0,708
	Control group	28	79	60,95 ± 11,60		
Anastomosis level	Study group	3	10	6,90 ± 1,83		0,384
	Control group	3	11	6,30 ± 2,43		
Stapler diameter	Study group	28	33	30,75 ± 2,38		0,574
	Control group	28	33	30,45 ± 2,19		
				Total Count	Total Percent	
Gender	Male	12	11	24	60,0	0,757
	Female	8	9	16	40,0	
Comorbiditiy	None	11	12	23	57,5	0,758
	Hypertension	5	3	8	20,0	
	Diabetes	1	3	4	10,0	
	COPD	1	1	2	5,0	
	Other	2	1	3	7,5	
Surgical procedure	Laparoscopic	13	12	25	62,5	0,752
	Laparotomy	7	8	15	37,5	

COPD: chronic obstructive pulmonary disease

mean preoperative Wexner incontinence score was 1.00 (0-4) in the study group and 2.15 (0-12) in the control group. There was no statistically significant difference between the study and control groups in terms of preoperative CCQOL scores and Wexner İncontinence scores (CCQOL: p=0.245, Wexner: p=0.232). The mean postoperative LARS score was 14.75 (4-19) in the study group and 25.75 (12-44) in the control group. The mean postoperative Wexner incontinence score was 3.45 (0-8) in the study group and 10.3 (4-18) in the control group. The postoperative LARS scores and Wexner incontinence scores of the control group were found to be significantly higher than those of the study group (LARS: p=0.001, Wexner: p=<0.001) (Table 2).

It was found that minor and major LARS symptoms were more common in the control group in the postoperative period (p = 0.022). In the postoperative period, minor LARS was observed in 2/20 (10%) cases and major LARS in 1/20 (5%) cases in the study group; In the control group, 4/20 (20%) cases had minor LARS and 7/20 (35%) cases had major LARS.

Manometric Measurements

All participants underwent anorectal manometry study both in the preoperative and postoperative periods and their mean resting pressure, maximum resting pressure (MRP), mean squeezing pressure, maximum squeezing

Table 2. Scales and Measures

		Minimum	Maximum	Average ± Standard deviation	P value
Preoperative CCQOL	Study group	19	30	24,15 ± 4,11	0,245
	Control group	16	30	25,40 ± 3,76	
Postoperative CCQOL	Study group	9	30	22,15 ± 5,98	0,957
	Control group	10	30	22,90 ± 4,78	
Postoperative LARS	Study group	4	39	14,75 ± 8,33	0,001
	Control group	12	44	25,75 ± 10,03	
Preoperative CCIS	Study group	0	4	1,00 ± 1,12	0,232
	Control group	0	12	2,15 ± 2,94	
Postoperative CCIS	Study group	0	8	3,45 ± 2,48	<0,001
	Control group	4	18	10,30 ± 4,18	

CCQOL: Cleveland clinical quality of life score, LARS: Low anterior resection syndrome score, CCIS: Wexner incontinence score

Table 3. Manometric Measurements

		Min.	Max.	Average Standard deviation	P value.	T value
ARP	Study group	37	75	57,65±11,35	0,308	1.034
	Control group	35	75	53,60±13,36		
Postoperative ARP	Study group	28	72	46,85±13,96	0,044	2.082
	Control group	13	67	37,65±13,98		
ASP	Study group	57	184	93,55±29,28	0,117	-1.602
	Control group	59	174	108,20±28,54		
Postoperaive ASP	Study group	44	129	78,25±24,01	0,106	1.672
	Control group	47	85	68,40±10,84		
MRP						
	Study group	49	102	76,80±16,44	0,305	-1,041
	Control group	42	126	83,45±23,35		
Postoperative MRP	Study group	38	107	66,10±17,84	0,521	0,647
	Control group	26	129	61,80±23,75		
MSP	Study group	87	298	179,45±59,34	0,776	0,512
	Control group	84	256	170,55±50,24		
Postoperative MSP	Study group	42	295	156,85±70,63	0,199	1,278
	Control group	61	282	131,00±56,51		
FACL	Study group	2,70	5,10	3,90±0,64	0,939	-0,077
	Control group	3,10	5,20	3,91±0,58		
Postoperative FACL	Study group	2,50	7,30	3,57±1,06	0,776	0,446
	Control group	2,00	4,50	3,44±0,75		
RAİR	Study group	12	33	19,45±5,59	0,080	-1,799
	Control group	11	34	23,00±6,83		
Postoperative RAİR	Study group	8	29	16,45±5,34	0,616	-1,430
	Control group	8	61	21,70±15,53		

ARP: Average resting pressure, ASP: Average squeezing pressure, MRP: Maximum resting pressure,
MSP: Maximum squeezing pressure, FACL: Functional anal canal length, RAIR: Rectoanal inhibitory reflex

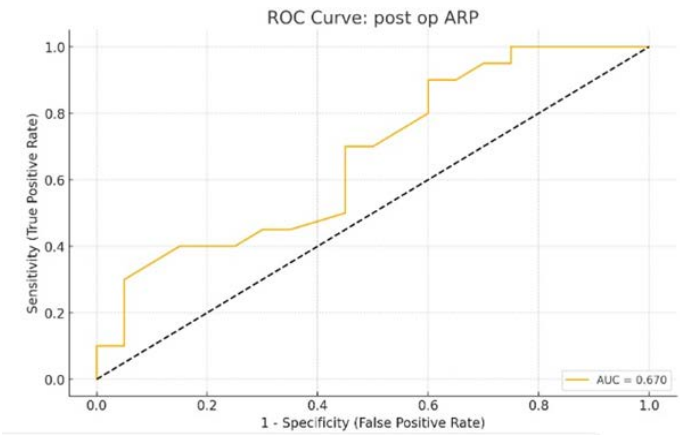


Figure 2. ROC Curve

pressure (MSP), functional anal canal length (FACL), and rectoanal inhibitory reflex (RAIR) were recorded. Preoperative manometric measurement values were similar between the groups. There was no statistically significant difference between postoperative average squeezing pressure values. The parameter of postoperative average resting pressure was found to be significantly lower in the control group (p=0.044, t=2.082) (Table 3). Receiver Operating Characteristic (ROC) analysis was performed to evaluate the discriminative performance of selected clinical parameters in distinguishing study and control groups. Postoperative average resting pressure showed a moderate predictive power with an AUC of 0.670. The optimal cut-off value was 33 mmHg, providing 90% sensitivity and 40% specificity. On the other hand, postoperative LARS score and QOL score yielded AUC values of 0.181 and 0.505, respectively, indicating low discriminative utility in this context. (Figure 2)

Univariate analysis for independent predictors

Postoperative mean Wexner incontinence scores showed a negative correlation with anastomosis level ($r = -0.476$, $p = 0.006$) and a positive correlation with age ($r = 0.392$, $p = 0.031$). These findings suggest that lower anastomosis level and older age may act as risk factors for higher incontinence scores. Since randomization was used, multivariate analysis was not applied.

DISCUSSION

Besides the complaints, such as the need for sudden defecation and various levels of incontinence, changes may occur in defecation habits and frequency of patients undergoing LAR for rectal carcinoma (3,4). The symptoms of incontinence, need for frequent defecation and urgent need for defecation are collectively referred to as anterior resection syndrome or LARS. Multicenter studies have shown that postoperative LARS develops in 80% of the patients (4,9). In a study by Wells et al. involving 277 patients, chemoradiotherapy, opening diverting diversion, surgeon's experience and low anastomosis level were reported to be effective in the development of LARS (10). Various anastomosis techniques have been studied in the literature to prevent LARS. In a study by Brown et al. including 2609 cases, the authors compared end-to-end coloanal anastomosis, colonic J-pouch, end-to-side anastomosis, and transverse coloplasty, and reported similar functional results in the long term(11). End-to-end coloanal anastomosis was preferred in all cases included in our study. There are studies in the literature investigating the usefulness of Kegel exercises for the treatment of incontinence and other functional disorders developing after pelvic surgery(12). However, the fact that these exercises are not performed under the supervision of a healthcare professional and, therefore, it cannot be determined if the patient does them correctly and effectively causes problems (13). At this point, biofeedback therapy comes to the fore as it is performed under the supervision of healthcare professionals; both visual and auditory feedback can be provided to the patient, and thus, the effectiveness of the exercise can be followed up.

There are different results in the literature regarding the duration of the biofeedback unit and the number of sessions. 6 sessions of treatment are recommended in ANMS-ESNM position paper and consensus guidelines on biofeedback therapy for anorectal disorders (14). In another article, a total of 10 sessions of treatment were applied, but the results were found to be insufficient (15). In our study, we preferred to apply a treatment protocol lasting 8 sessions. It was possible to extend the treatment period further, but we did not want the patients in the study to worry that their ileostomy closure operations were delayed because they were participating in this study. For this reason, we could not extend the treatment period any longer. Although our current results are clinically satisfactory, perhaps better results could have been obtained with longer treatment.

In the present study, anorectal manometric measurements were also performed in addition to LARS scoring and CCIS for clinical evaluation. Since the normal ranges of anorectal manometric measurement methods and results have not yet been fully standardized, their consistency is controversial. In a study by Pehl et al. involving a total of 703 cases consisting of individuals with fecal incontinence and healthy individuals, the authors reported the sensitivity of anorectal manometry as 91.4% and specificity as 62.5% (16). Yeap et al.(17) conducted a meta-analysis on a total of 1499 cases and reported the sensitivity and specificity of anorectal manometry as 80%. Bright et al. (18) reported that more realistic results could be obtained when manometric measurements were performed by mimicking physiological mechanisms. In their study, patients were asked to squeeze the anal sphincter, and a balloon that was inflated in the rectum was pulled out slowly, and patients were asked to prevent the balloon from coming out. The results of the measurement made with the help of balloons were found to be statistically significantly higher (16). The literature review has shown that anorectal manometry has acceptable accuracy, sensitivity and specificity in demonstrating defecation functions. However, the accuracy of the results is affected by the experience of the practitioner,

adequately informing the patient before the procedure, the environment conditions in which the test was carried out, the cooperation of the patient, and the mode of application of the test.

In a study by Laforest et al. involving 48 cases, patients undergoing LAR were divided into two groups and biofeedback therapy was administered to one group following ileostomy closure, whereas the other group did not receive the therapy (19). The authors found that both groups had similar Wexner scores. In the present study, the Wexner incontinence score was significantly higher in the control group compared to the study group. In a meta-analysis by Visser et al. biofeedback therapy was found to significantly reduce the symptoms and to improve the quality of life in patients with LARS symptoms (12). In the present study, the LARS score was found to be lower in the group receiving biofeedback therapy, in line with the literature. Performing exercises to strengthen continence with the application of biofeedback therapy may have increased the ability of the pelvic floor muscles to contract in a coordinated manner, although the maximum tightening pressure did not increase significantly. In addition, as a result of the manometric measurements made in the study group, it was determined that the mean resting pressure was higher than the control group. ARP and resting continence are largely formed by the internal sphincter (14). With the increase in internal sphincter function, resting continence may have increased in the study group, and as a result, symptoms such as frequent defecation and the need for urgent defecation may have decreased. We think that biofeedback treatment reduced the LARS score in the study group as a result of these mentioned effects.

In a study involving 169 patients, Pucciani (20) reported that LARS symptoms were more significant and the mean resting pressure was lower in patients who undergo pelvic surgery compared to those who did not underwent pelvic surgery. In the present study, the postoperative MRP, squeezing pressure, FACL and RAIR percentages of the study group and the control group were found to be similar, whereas the postoperative mean resting pressure was found to be significantly lower in the control group. Some of the results of this study are consistent with several studies in the literature, whereas some of them are inconsistent with the literature data. Different results are obtained in different studies. We attribute this to the fact that anorectal manometry measurement results could not have been fully standardized due to various factors such as the experience of the person performing the measurement, patient cooperation, and the features of the measurement device used. Internal sphincter is responsible for 80% of incontinence during the resting period. The mean resting pressure is known to give an idea about the resting continence, in which the internal sphincter is predominantly involved. The fact that the circular stapler shaft, which is advanced through the transanal route, traumatizes the internal sphincter due to excessive dilatation while passing through the anal sphincters may be another reason why the resting pressure is measured significantly lower.

There are studies reporting different results regarding the effects of anastomosis level and age on incontinence. In a study by Rasmussen et al., including 43 patients, the complaints of incontinence were found to increase as the anastomosis level decreased, but the patient age was found to have no effect on incontinence complaints (21). In another study of 27 patients undergoing rectal cancer surgery, continence was reported to be better after medium and high colorectal anastomoses compared to low coloanal anastomosis (22). The anastomosis level and patient age were found to be similar between the study and control groups in the present study. Anastomosis level was found to be positively correlated with the postoperative mean resting pressure, whereas it was negatively correlated with the postoperative Wexner score. This was an expected result and consistent with many similar studies in the literature. Unlike the Rasmussen study, there was a negative correlation between the patient's age and postoperative mean resting pressures in the present study. This may be due to the fact that the incidence of incontinence in the normal population increases with age in Türkiye.

ROC analysis suggested that among the studied variables, only postoperative average resting pressure had a moderate capacity to differentiate between the study and control groups. The optimal cut-off of 33 mmHg provided high sensitivity (90%) but relatively low specificity (40%). This finding supports the potential value of resting pressure as an objective manometric marker for treatment response, while LARS and QOL scores demonstrated limited diagnostic performance in this small sample.

Limitations

In addition to the small sample size and the absence of postoperative endoanal ultrasonography, other limitations of our study include its single-center design and the relatively short follow-up duration. Furthermore, although manometric measurements were used as objective parameters, the lack of long-term postoperative follow-up for recurrence of incontinence or symptom progression may have affected the generalizability of our findings.

CONCLUSION

In conclusion, the incidence of LARS following the LAR procedure is high and significantly impairs the patient's quality of life. This study investigated the effects of biofeedback therapy performed after LAR and before protective ileostomy closure when the anal sphincter was passive on postoperative incontinence, in other words, on LARS symptoms. There is still no standard treatment procedure regarding incontinence after LAR. Various treatment methods and schedules have been studied in the literature. As a result of our study, it was concluded that biofeedback therapy administered before ileostomy closure reduced the development of postoperative LARS and significantly improved the mean resting pressure. The results are promising, but the number of studies on the subject is limited. Therefore, there is a need for multi-center studies with a larger population group presenting long-term results for the development and standardization of the treatment modality recommended herein.

Use of Artificial Intelligence: No generative AI technologies were used in the writing, editing, or content generation of this manuscript.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

Address correspondence to: *Alper Varman, Necmettin Erbakan University, Faculty of Medicine, Department of General Surgery, Konya, Türkiye*
e-mail: *alp.varman@gmil.com*

REFERENCES

1. Bharucha AE, Knowles CH, Mack I, et al. Faecal incontinence in adults. Nat Rev Dis Primers. 2022;8(1):53. Published 2022 Aug 10. doi:10.1038/s41572-022-00381-7
2. Guillaume A, Salem AE, Garcia P, et al. Pathophysiology and Therapeutic Options for Fecal Incontinence. J Clin Gastroenterol. 2017;51(4):324-30. doi:10.1097/MCG.0000000000000797
3. Duman A, Ceviz C, Sönmez S, et al. Kolon Ve Rektum Kanseri Konusunda Klinik Araştırma Selçuk Üniv Tıp Derg. 1984 1-1 (59-70).
4. Dulskas A, Smolskas E, Kildusiene I, et al. Treatment possibilities for low anterior resection syndrome: A review of the literature. Int J Colorectal Dis. 2018;33(3):251-60. doi:10.1007/s00384-017-2954-x
5. Knol ME, Snijders HS, van der Heyden JT, et al. Fecal Incontinence: The Importance of a Structured Pathophysiological Model. J Anus Rectum Colon. 2022;6(1):58-66. Published 2022 Jan 28. doi:10.23922/jarc.2021-040
6. Kutlu R. Çivi S. Börüban MC. et al Depression and the Factors Affecting the Quality of Life in Cancer Patients. Selçuk Üniv Tıp Derg 2011;27(3):149-53.
7. Deb B, Prichard DO, Bharucha AE. Constipation and Fecal Incontinence in the Elderly. Curr Gastroenterol Rep. 2020;22(11):54. Published 2020 Aug 24. doi:10.1007/s11894-020-00791-1
8. Arnouk A, De E, Rehfuss A, et al. Physical, Complementary, and Alternative Medicine in the Treatment of Pelvic Floor Disorders. Curr Urol Rep. 2017;18(6):47. doi:10.1007/s11934-017-0694-7
9. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: Development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg. 2012;255(5):922-8. doi:10.1097/SLA.0b013e31824f1c21
10. Wells CI, Vather R, Chu MJ et al. Anterior resection syndrome--a risk factor analysis. J Gastrointest Surg. 2015;19(2):350-9. doi:10.1007/s11605-014-2679-x
11. Brown CJ, Fenech DS, McLeod RS. Reconstructive techniques after rectal resection for rectal cancer. Cochrane Database Syst Rev. 2008;2008(2):CD006040. Published 2008 Apr 16. doi:10.1002/14651858.CD006040.pub2
12. Visser WS, Te Riele WW, Boerma D, et al. Pelvic floor rehabilitation to improve functional outcome after a low anterior resection: A systematic review. Ann Coloproctol. 2014;30(3):109-14. doi:10.3393/ac.2014.30.3.109
13. Bø K. Can pelvic floor muscle training prevent and treat pelvic organ prolapse? Acta Obstet Gynecol Scand. 2006;85(3):263-8. doi:10.1080/00016340500486800
14. Rao SS, Benninga MA, Bharucha AE, et al. ANMS-ESNM position paper and consensus guidelines on biofeedback therapy for anorectal disorders. Neurogastroenterol Motil. 2015;27(5):594-09. doi:10.1111/nmo.12520
15. Lee BH, Kim N, Kang SB, et al. The Long-term Clinical Efficacy of Biofeedback Therapy for Patients With Constipation or Fecal Incontinence. J Neurogastroenterol Motil. 2010 Apr;16(2):177-85. doi: 10.5056/jnm.2010.16.2.177. Epub 2010 Apr 27. PMID: 20535349; PMCID: PMC2879852.
16. Pehl C, Seidl H, Scalercio N, et al. Accuracy of anorectal manometry in patients with fecal incontinence. Digestion. 2012;86(2):78-85. doi:10.1159/000338954
17. Yeap ZH, Simillis C, Qiu S, et al. Diagnostic accuracy of anorectal manometry for fecal incontinence: A meta-analysis. Acta Chir Belg. 2017;117(6):347-55. doi:10.1080/00015458.2017.1394674
18. Bright T, Kapoor R, Voyvodich F, et al. The use of a balloon catheter to improve evaluation in anorectal manometry. Colorectal Dis. 2005;7(1):4-7. doi:10.1111/j.1463-1318.2004.00698.x
19. Laforest A, Bretagnol F, Mouazan AS, et al. Functional disorders after rectal cancer resection: Does a rehabilitation programme improve anal continence and quality of life? Colorectal Dis. 2012;14(10):1231-7. doi:10.1111/j.1463-1318.2012.02956.x
20. Pucciani F. Post-surgical fecal incontinence. Updates Surg. 2018;70(4):477-84. doi:10.1007/s13304-017-0508-y
21. Rasmussen OO, Petersen IK, Christiansen J. Anorectal function following low anterior resection. Colorectal Dis. 2003;5(3):258-61. doi:10.1046/j.1463-1318.2003.00439.x
22. Di Matteo G, Mascagni D, Zeri KP, et al. Evaluation of anal function after surgery for rectal cancer. J Surg Oncol. 2000;74(1):11-14. doi:10.1002/1096-9098(200005)74:1<11::aid-jso3>3.0.co;2-d

NEU PRESS

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2025.01836
Selcuk Med J 2025;41(3): 131-135

OPEN

ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

The Investigation of Olfactory Function Related Quality of Life And Psychological Symptoms In Patients With Transfusion Dependent Beta Thalassemia

Transfüzyon Bağımlı Beta Talasemi Hastalarında Koku ile İlişkili Yaşam Kalitesi ve Psikolojik Semptomların İncelenmesi

Yasin Yilmaz[1], Doga Dalay[1], Zeynep Karakas[1]

[1]Istanbul University, Istanbul Medical Faculty, Department of Pediatrics, Division of Pediatric Hematology and Oncology, Istanbul, Türkiye

ÖZET

Amaç: Transfüzyon bağımlı beta talasemi hastalarının kronik hastalıkları nedeniyle psikolojik rahatsızlıkları olabilmekte ve bu durum yaşam kalitelerini olumsuz etkileyebilmektedir. Ayrıca koku alma fonksiyonundaki sorunlar yaşam kalitesini ve psikolojik durumunu olumsuz yönde etkileyebilmektedir. Çalışmamızda transfüzyon bağımlı beta talasemi hastalarında koku alma işlevine bağlı yaşam kalitesi ile psikolojik bozukluk belirtileri arasındaki ilişki araştırıldı.

Gereçler ve Yöntemler: Çalışmaya İstanbul Tıp Fakültesi Talasemi Merkezi'nde takip edilen 46 transfüzyon bağımlı beta talasemi hastası katıldı. Hastanın kendi bildirdiği koku alma işlevi ve koku almayla ilişkili yaşam kalitesini (ASOF) değerlendirmek için 12 maddelik anket ve depresyon ile anksiyete semptomlarını değerlendirmek için Hastane Anksiyete ve Depresyon Ölçeği (HAD) kullanıldı. İstatistiksel analiz SPSS (v23) programı ile yapıldı.

Bulgular: Çalışmaya katılan 46 hastanın yaş ortalaması 32,5±7,3 yıl idi. Hastaların bildirilen genel koku alma kapasitesi (BKK) puanı 8,8±1,3 bildirilen belirli kokuları alma kapasitesi (BKA) puanı 4,6 ± 0,5 ve bildirilen koku duyusu ile ilişkili yaşam kalitesi (KYK) puanı 4,7 ± 0,4 idi. HAD ölçeğine göre hastaların %22'sinde anksiyete belirtileri, %65'inde depresyon belirtileri vardı. Hastaların anksiyete puanları ve depresyon puanları ile genel koku alma kapasiteleri arasında anlamlı bir negatif korelasyon bulundu (p=0.02). Depresyon semptomları ve anksiyete semptomları olan hastalar daha düşük koku alma yeteneği gösterdi (p<0.05). Depresyon semptomları olan hastalarda koku alma ile ilgili yaşam kalitesi de önemli ölçüde azaldı (p<0.05). Deferasiroks (DFX) kullanan hastalar daha iyi koku alma yeteneği gösterdi (p<0.01).

Sonuç: Transfüzyon bağımlı beta talasemi hastalarının koku alma kapasitesi ile anksiyete ve depresyon skorları arasında anlamlı bir negatif korelasyon bulundu. Depresyon semptomları olan hastalarda, koku alma işleviyle ilişkili yaşam kalitesinin daha düşük olduğunu gösterildi. Şelasyon tipi, koku alma kapasitesi ile ilişkili görünmektedir.

Anahtar Kelimeler: Anksiyete, beta talasemi, hayat kalitesi, depresyon, koku bozukluğu

ABSTRACT

Objective: Transfusion-dependent beta thalassemia (TDBT) patients may be at risk for psychological symptoms due to chronic disease, which can burden their lives. Sense of smell problems may also accompany chronic disease and lead to qualityof life problems. his study examined the relationship between olfactory function, quality of life and psychological symptoms in transfusion-dependent beta-thalassemia patients.

Materials and Methods: Forty-six TDBT patients followed up at the Thalassemia Center of Istanbul Medical Faculty were included in the study. The 12-item self-reported olfactory function and olfactory quality of life assessment questionnaire (ASOF) and the Hospital Anxiety and Depression Scale (HAD) were used to screen olfactory function capacity, olfactory-related quality of life and psychological symptoms. Statistical analysis was performed with SPSS (v23) software.

Results: The mean age of the 46 participants was 32.5±7.3 years. The overall olfactory capacity score was 8.8±1.3, the specific olfactory capacity score was 4.6±0.5 and the odor-related quality of life score was 4.7±0.4. The HAD scale showed that 22% of the patients had anxiety symptoms and 65% had depression symptoms. There was a significant negative correlation between anxiety and depression scores and general olfactory capacity (p=0.02). Patients with depression symptoms and anxiety symptoms showed lower olfactory capacity (p<0.05). Olfactory quality of life was also significantly reduced in patients with depression symptoms (p<0.05). Patients receiving deferasirox (DFX) showed better olfactory capacity (p<0.01).

Conclusion: A significant negative correlation was found between olfactory capacity and anxiety and depression scores. Patients with symptoms of depression showed a decrease in quality of life related to olfactory function. Chelation type seems to be associated with olfactory capacity.

Keywords: Anxiety, beta thalassemia, quality of life, depression, olfactory dysfunction

Geliş Tarihi/Received: 18 February/Şubat 2025 **Kabul Tarihi/Accepted:** 28 August/Ağustos 2025 **Yayın Tarihi/Published Online:** 28 September/Eylül 2025

Sorumlu Yazar/Corresponding Author: Yasin Yılmaz, Istanbul University, Istanbul Medical Faculty, Department of Pediatrics, Division of Pediatric Hematology and Oncology, Istanbul, Türkiye
e-mail: dryasinyilmaz@gmail.com

Atıf yapmak için/ Cite this article as: Yilmaz Y, Dalay D, Karakas Z. The Investigation of Olfactory Function Related Quality of Life And Psychological Symptoms In Patients With Transfusion Dependent Beta Thalassemia. Selcuk Med J 2025;41(3): 131-135

Disclosure: *Author has no a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Thalassemia is a group of hemoglobinopathies resulting in mild to severe and life-threatening anemia. According to transfusion status, thalassemia syndromes are divided into Transfusion Dependent (TDT) and Non-Transfusion Dependent forms (1).

TDT patients need regular blood transfusions. TDT patients suffer from symptoms of the disease and transfusion complications such as endocrine dysfunction, heart failure and chronic liver disease (2). Psychological symptoms such as depression and anxiety are also common (3,4). Complication rate has started to decrease thanks to chelating agents (5).

Olfactory dysfunction was seen among patient with TDT (6). This sense is involved in nutrition and its deficiency results in diminishing the ability to distinguish spoiled foods, natural gas leaking, fire, and other environmental hazards (7). An intact olfactory function is necessary for a good quality of life. Moreover, olfactory dysfunction is associated with depression symptoms (8).

Studies on quality of life and psychological symptoms among patients with thalassemia are gradually increased (9). In this study, we examined the relationship between olfactory-related quality of life and symptoms of depression and anxiety in patients with TDT using questionnaires.

MATERIALS AND METHODS

Participants

A total of 46 patients (28 female and 18 male) with TDT were enrolled into study. All patients were administered regular blood transfusions. The 72% of patients received transfusions every 3 weeks. The 75% of patients used deferasirox (DFX), and 13% used deferiprone (DFP) and 10% used combination (DFX+DFP or DFO+DFP). The five patients didn't give information about trademark of chelator drug. The mean level of serum ferritin was 1559±1308.2 (median 1200 ng/mL).

Questionnaires

ASOF (The assessment of self-reported olfactory functioning and olfaction related quality of life)

The ASOF questionnaire was established by Pusswald et al. (10). ASOF includes olfactory-related quality of life scale (ORQ), self-reported functionality of perceiving specific odors scale (SRP) and subjective olfactory capability scale (SOC). It consists of 12 items of which one belongs to SOC, five items for SRP, and six items for ORQ scales.

SOC shows the smell function ability on a scale between 0 and 10 (with being 0 worst and 10 best smell score). A SOC score less than ≤3 demonstrates diminished sense of smell capabilities. SRP consists of 5 items and express the functionality of perceiving specific odors. A SRP score less than ≤2.9 reveals disorder in smelling odors. ORQ consists of six items and demonstrates smell-related quality of life. A ORQ score less than ≤3.7 are regarded as having olfactory-related issues in their quality of life. Turkish validation study was done by Saatci et al. (11). The ASOF questionnaire is easy to use and can provide information about psychological aspect of smell problem.

HAD (Hospital Anxiety and Depression Scale)

The HAD is a self-report questionnaire for screening the psychological symptoms (12). This questionnaire is used to screen the anxiety and depression symptoms of participants. It consists of 14 questions, 7 of them are related to anxiety and 7 of them are about depression. The Turkish validity trial was done by Aydemir et al. (13). The cut-off score is 7 for depression and 10 for anxiety in the Turkish validity form.

Procedure

Patients with TDT followed up at the Thalassemia Center of Istanbul Medical Faculty were asked to participate in this online survey. Patients' data were retrieved from the database and a letter containing the purpose of this study was sent. Forty-seven out of one hundred and six patients responded to the letter and completed the questionnaire. One patient did not fill out the form correctly, so the remaining 46 participants were included in the study.

Statistical Analysis

The SPSS 23.0 was performed for statistical analysis. Descriptive analysis was done. The student T test was done to make comparison between two groups of variables. Pearson analysis was performed for correlation. A value of $p<0.05$ was considered to be significant.

Ethical Approval

The ethical approval for this study was received from university ethic board (issue number 2022/2139). Study design and all procedure were done according to Helsinki Declaration.

RESULTS

Twenty-eight female and eighteen male TDT patients [mean age 32.5±7.3 years; range 15 – 47 years] were enrolled into study. The mean disease duration was 30.5±7.2 years. The median age of diagnosis was 9 months. The median age of starting regular transfusion was 12 months. The 67% of patients had splenectomy. Two of every three patients (65%) had endocrine complications (Table 1).

The SOC score of patient was 8.8 ± 1.3 (median 9). The SRP score was 4.6 ± 0.5 and ORQ score was 4.7 ± 0.4. None of patients showed hyposmia symptoms according to self-reported questionnaire (Table 2).

According to HAD (Hospital Anxiety and Depression Scale) results, the mean anxiety score was 7.6 ± 4.1 and when cut-off level 10 taken into account, 22% of patients showed anxiety symptoms. The mean depression score was 8.1 ± 4.1 and according to cut-off level of 7 score, 65% of patients demonstrated depression symptoms (Table 3).

There was negative significant correlation between subjective olfactory capability scale and depression and anxiety scores (p=0.02, r=-0.33; p=0.02, r=-0.34, respectively) (Table 4). The SOC score was significantly decreased among patients with depression signs compared to patients without depression signs (8.5 ± 1.5 vs 9.3 ± 0.8; p=0.01). The SRP score was significantly diminished in patients with depression symptoms compared to in patients without depression symptoms (4.5 ± 0.6 vs 4.8 ± 0.3, p=0.04). The ORQ score was also significantly decreased in patients with depression signs

Table 1. Sociodemographic and clinical data of participants

Characteristics	Study Group (n=46)
Gender	
Male	18 (%40)
Female	28 (%60)
Age	
mean ± SD years	32.5 ± 7.3
(median; min-max)	(31.5; 15-47)
Disease Duration	
mean ± SD years	30.5 ± 7.2
(median; min-max)	(30.5; 15-44)
Age of Diagnosis	
mean ± SD month	19.5±26.8
(median; min-max)	(9; 2-120)
Age of starting Regular Transfusion	
mean ± SD month	23.2±32.1
(median; min-max)	(12; 4-156)
Chelation Type	
DFO	1 (%2)
DFP	5 (%13)
Combination	4 (%10)
DFX-Ef	12 (%29)
DFX-Tb	19 (%46)
Splenectomy	
Yes	31 (%67)
No	15 (%33)
Ferritin Level	
mean ± SD ng/mL	1559.6±1308.2
(median; min-max)	(1200; 250-5600)
Pre-Transfusion Hgb	
mean ± SD	8.6±1.1
(median)	(8.6)
Transfusion Interval	
Every two weeks	5 (%11)
Every three weeks	33 (%72)
Every four weeks	8 (%17)
Endocrine Complications	(n=30; %65)
Osteoporosis	19 (%41)
Hypogonadism	10 (%21)
Diabetes	8 (%20)
Hypothyroidism	4 (%9)

SD: standard deviation; DFO: Deferoxamine; DFP: Deferiprone; DFX: deferasirox

Table 2. The assessment of self-reported olfactory functioning and olfaction related quality of life (ASOF) questionnaire results

Characteristics	Results (n=46)
Subjective Olfactory Capability scale (SOC) (mean ± SD)	8.8 ± 1.3
Self-Reported capability of Perceiving specific odors scale (SRP) (mean ± SD)	4.6 ± 0.5
Olfactory-Related Quality of life scale (ORQ) (mean ± SD)	4.7 ± 0.4

SD: standard deviation

Table 3. The Hospital Anxiety and Depression scale (HAD) results of participants

Characteristics	Results
Anxiety Score (mean ± SD)	7.6 ± 4.1
Anxiety Ratio (mean ± SD)	%22
Depression Score (mean ± SD)	8.1 ± 4.1
Depression Ratio (mean ± SD)	%65

SD: standard deviation

Table 4. The correlation between subjective olfactory capability scale and depression and anxiety scores of participants

Characteristics	Subjective Olfactory Capacity
Anxiety Score (7.6 ± 4.1)	r=-0.34, p=0.02
Depression Score (8.1 ± 4.1)	r=-0.33, p=0.02

Table 5. Olfactory function results of participants according to psychological symptoms

Characteristics		SOC	SRP	ORQ
Depression		p=0.01	p=0.04	p=0.02
		(mean ± SD)	(mean ± SD)	(mean ± SD)
	With	8.5 ± 1.5	4.5 ± 0.6	4.6 ± 0.5
	Without	9.3 ± 0.8	4.8 ± 0.3	4.9 ± 0.2
Anxiety		p=0.05	p=0.30	p=0.27
	With	7.9 ± 1.7	4.4 ± 0.7	4.4 ± 0.7
	Without	9.0 ± 1.1	4.7 ± 0.4	4.7 ± 0.3

Higher scores indicate better results; SOC: Subjective Olfactory Capability scale; SRP: Self-Reported capability of Perceiving specific odors scale; ORQ: Olfactory-Related Quality of life scale

Table 6. Olfactory function results of participants according to psychological symptom groups

Characteristics	Depression + Anxiety Group			
	Neither Depression nor Anxiety Mean	Either Depression or Anxiety Mean	Both Depression and Anxiety Mean	p value
SOC	9,3 ± 0.9	8,9 ± 1.2	7,6 ± 1.7	0.01
SRP	4,8 ± 0.3	4,6 ± 0.5	4,4 ± 0.8	0.13
ORQ	4,9 ± 0.2	4,7 ± 0.4	4,4 ± 0.8	0.08

SOC: Subjective Olfactory Capability scale; SRP: Self-Reported capability of Perceiving specific odors scale; ORQ: Olfactory-Related Quality of life scale

compared to in patients without depression symptoms (4.6 ± 0.5 vs 4.9 ± 0.2; p=0.02) (Table 5).

The mean SOC score was significantly decreased in patients with anxiety symptoms in comparison to in patients without anxiety symptoms (7.9 ± 1.7 vs 9.0 ± 1.1, p=0.05). The mean SRP score was 4.7± 0.4 in patients without anxiety symptoms and 4.4 ± 0.7 in patients with anxiety symptoms (p=0.30). The mean ORQ score was 4.7 ± 0.3 among patients without anxiety symptoms and 4.4 ± 0.7 in patients with anxiety symptoms (p=0.27) (Table 5).

There were 9 patients (20%) who showed both depression and anxiety symptoms and 15 patients (33%) who showed no depression or anxiety symptoms. SOC scores were gradually decreased from neither depression nor anxiety group towards both depression and anxiety group (p=0.01) (Table 6).

Olfactory function capability didn't significantly differ among patients with or without endocrine complications (9.1 w/o and 8.6 w; p=0.21). However, disease duration was associated with lower olfactory capability (r=-0.28, p=0.05).

Interestingly, patients using DFX only showed better olfactory capability compared to patients using other chelator (DFP, DFO and combination) (9.3 vs 7.5; p<0.01). Patients using DFX effervescing tablet showed tendency to have higher SRP score (specific odor capability) compared to patients using DFX film tablet (4.9 vs 4.6; p=0.09).

There was no relation between serum ferritin level, pre-transfusion level, splenectomy status and gender with olfactory capability.

DISCUSSION

In this study, we evaluated the relationship between subjective olfactory capacity and olfactory quality of life with depression and anxiety symptoms in patients with TDT. We found that a significant proportion of patients showed symptoms of depression. On the other hand, there was a very tight correlation between olfactory capacity and psychological symptoms (p=0.02, r=-0.33). Patients with both depression and anxiety symptoms had the lowest olfactory capacity. Olfactory quality of life was significantly reduced in patients with symptoms of depression. Chelation type was also associated with olfactory capacity.

Objective olfactory dysfunction was shown in patients with transfusion dependent thalassemia (6). Furthermore, olfactory impairment has been associated with difficulties in physical activities, limitations in daily life and impaired sense of general well-being. Therefore, the function of the olfactory system is closely linked to overall health.

Quality of life is one of main concern in thalassemia patients. Children with thalassemia showed lower quality of life in domains of physical, social, emotional and school (14,15). Another study also demonstrated lower quality of life in children with transfusion dependent thalassemia (16). A comprehensive study including both children and adult patients with thalassemia showed that children with thalassemia had lower quality of life compared to adults (17). Another study indicated that high ferritin level was negative predictor of quality of life in children (18).

Depression and anxiety are another main concern in thalassemia patients. Psychological symptoms are reported highly in chronic disorders and in thalassemia as well. Zolaly et al. (19) showed 60% depression rate and 50% anxiety rate in TDT patients. Adib-Hajbaghery et al. (20) also revealed high rate of depression and anxiety (60%). Maheri et al. (21) demonstrated lower depression (20%) and anxiety (25%) symptoms. Another study from Turkey (22) showed similar results (20% depression and 40% anxiety). Mohamadian et al. (23) emphasized the effect of behavioral therapy on depression and anxiety in their randomized trial.

Sense of smell is shown to be associated with quality of life and depression symptoms (8). Formerly, a tight connection between olfactory dysfunction and depression was shown in literature (24,25). Olfactory related quality of life disturbed in patients with olfactory dysfunction. On the other hand, it has been considered as a predictor of depressive symptoms in patients (8). In our study, we also showed a very close association between depression and anxiety symptoms with olfactory related quality of life. Moreover, olfactory capacity significantly decreased in patients showing depression and anxiety symptoms.

Limitation; The cross-sectional design of the study does not allow to conclude that odor-related quality of life may be a predictor of depressive symptoms in patients with thalassemia. Furthermore, the limited number of participants is also an important limitation. Another limitation is that the subjective test was not supported by an objective odor test. However, large prospective cohort studies investigating the cause-and-effect relationship between olfactory capacity, odor-related quality of life and psychological symptoms are needed to

clarify this point. The strength of this study is that we used standardized tests and questionnaires to assess psychological testing and olfactory quality of life.

CONCLUSION

This study demonstrated the relationship between olfactory function-related quality of life and psychological symptoms in patients with TDT. Although patients' subjective reports showed that olfactory capacity and olfactory-related quality of life were not affected, patients with depressive symptoms showed decreased olfactory function-related quality of life.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

Address correspondence to: *Yasin Yilmaz, Istanbul University, Istanbul Medical Faculty, Department of Pediatrics, Division of Pediatric Hematology and Oncology, Istanbul, Türkiye*
e-mail: *dryasinyilmaz@gmail.com*

REFERENCES

1. Origa R. Genetic basis, pathophysiology and diagnosis of thalassemias. In: Cappellini MD, Farmakis D, Porter J, Taher A, (eds). Guidelines for the management of transfusion dependent thalassemia (TDT), 4th edn. Nicosia:Thalassaemia International Federation (TIF) Publication, 2021; pp 20–36
2. Nemtsas P, Arnaoutoglou M, Perifanis V, et al. Neurological complications of beta-thalassemia. Ann Hematol. 2015;94(8):1261-65. doi: 10.1007/s00277-015-2378-z.
3. Khoury B, Musallam KM, Abi-Habib R, et al. Prevalence of depression and anxiety in adult patients with β-thalassemia major and intermedia. Int J Psychiatry Med. 2012;44(4):291-03. doi: 10.2190/PM.44.4.a.
4. Töret E, Karadaş NÖ, Gökçe NÖ, et al. Quality of Life and Depression in Turkish Patients with β-Thalassemia Major: A Cross-Sectional Study. Hemoglobin. 2018;42(5-6):326-29. doi: 10.1080/03630269.2018.1551231.
5. Borgna-Pignatti C. The life of patients with thalassemia major. Haematologica 2010;95(3):345-48. doi: 10.3324/haematol.2009.017228.
6. Yilmaz Y, Karakas Z, Uzun B, et al. Olfactory dysfunction and quality of life in patients with transfusion-dependent thalassemia. Eur Arch Otorhinolaryngol. 2017 ;274(9):3417-21. doi: 10.3324/haematol.2009.017228.
7. Doty RL. Olfactory dysfunction and its measurement in the clinic and workplace. Int Arch Occup Environ Health 2006;79(4): 268–82. doi: 10.1007/s00420-005-0055-6.
8. Liu DT, Prem B, Sharma G, et al. Depression Symptoms and Olfactory-related Quality of Life. Laryngoscope. 2022;132(9):1829-34. doi: 10.1002/lary.30122.
9. Amid A, Saliba AN, Taher AT, et al. Thalassaemia in children: from quality of care to quality of life.Arch Dis Child. 2015;100(11):1051-57. doi: 10.1136/archdischild-2014-308112.
10. Pusswald G, Auff E, Lehrner J. Development of a Brief Self-Report Inventory to Measure Olfactory Dysfunction and Quality of Life in Patients with Problems with the Sense of Smell. Chem. Percept. 2012; 5(1):292-99. doi:10.1007/s12078-012-9127-7
11. Saatçi Ö, Arıcı Düz Ö, Altundağ A. Reliability and Validity of the Turkish Version of the Questionnaire for the Assessment of Self-Reported Olfactory Functioning and Olfaction-Related Quality of Life. J Acad Res Med 2020;10(3):277-82. doi:10.4274/jarem.galenos.2020.3579
12. Zigmund AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67(6):361-70. doi: 10.1111/j.1600-0447.1983.tb09716.x.
13. Aydemir Ö, Güvenir T, Küey L, et al. Validity and reliability of Turkish version of Hospital Anxiety and Depression Scale. Turkish Journal of Psychiatry 1997;8(4):280-87.
14. Choudhry VP. Quality of Life in Thalassemia Major. Indian J Pediatr. 2018;85(11):957-58. doi: 10.1007/s12098-018-2792-z.
15. Chordiya K, Katewa V, Sharma P, et al. Quality of Life (QoL) and the Factors Affecting it in Transfusion-dependent Thalassemic Children. Indian J Pediatr. 2018;85(11):978-83. doi: 10.1007/s12098-018-2697-x.
16. Nashwan AJ, Yassin MA, Babu GDJ, et al. Quality of life among adolescents aged 14 to 18 years with Beta-Thalassemia Major (TM) in Qatar. Acta Biomed. 2018;89(2-S):16-26. doi: 10.23750/abm.v89i2-S.7083.
17. Etemad K, Mohseni P, Aghighi M, et al. Quality of Life and Related Factors in β-Thalassemia Patients. Hemoglobin. 2021;45(4):245-49. doi: 10.1080/03630269.2021.1965617.
18. Tuysuz G, Tayfun F. Health-related Quality of Life and its Predictors Among Transfusion-dependent Thalassemia Patients. J Pediatr Hematol Oncol. 2017;39(5):332-36. doi: 10.1097/MPH.0000000000000790.
19. Zolaly MA, Zolaly FM, Al Belowi L, et al. Depression, Anxiety, and Stress Symptoms in Patients with Beta Thalassemia Major in Almadinah Almunawwarah, Saudi Arabia. Cureus. 2020;12(11):e11367. doi: 10.7759/cureus.11367.
20. Adib-Hajbaghery M, Ahmadi M, Poormansouri S. Health Related Quality of Life, Depression, Anxiety and Stress in Patients with Beta-Thalassemia Major. Iran J Ped Hematol Oncol. 2015;5(4):193-05.
21. Maheri A, Sadeghi R, Shojaeizadeh D, et al. Depression, Anxiety, and Perceived Social Support among Adults with Beta-Thalassemia Major: Cross-Sectional Study. Korean J Fam Med. 2018;39(2):101-07. doi: 10.4082/kjfm.2018.39.2.101
22. Yengil E, Acipayam C, Kokacya MH, et al. Anxiety, depression and quality of life in patients with beta thalassemia major and their caregivers. Int J Clin Exp Med. 2014;7(8):2165-72.
23. Mohamadian F, Bagheri M, Hashemi MS, et al. The Effects of Cognitive Behavioral Therapy on Depression and Anxiety among Patients with Thalassemia: a Randomized Controlled Trial. J Caring Sci. 2018;7(4):219-24. doi: 10.15171/jcs.2018.033.
24. Kohli P, Soler ZM, Nguyen SA, et al. The association between olfaction and depression: a systematic review. Chem Senses. 2016;41(6):479-86. doi: 10.1093/chemse/bjw061.
25. Taalman H, Wallace C, Milev R. Olfactory functioning and depression: a systematic review. Front Psych. 2017;8:190. doi: 10.3389/fpsyt.2017.00190.

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
DOI:http:/dx.doi.org/10.30733/std.2025.01752
Selcuk Med J 2025;41(3): 136-141

OPEN

ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Serum Elebela Levels in Pulmonary Embolism

Akut Pulmoner Embolide Serum Elebela Düzeyleri

Filiz Alkan Baylan[1], Burcu Akkok[2], Yasarcan Baykisi[3], Cigdem Erdogan[3]

[1]Necmettin Erbakan University, Faculty of Medicine, Department of Biochemistry, Konya, Türkiye
[2]Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Department of Chest Diseases, Kahramanmaraş, Türkiye
[3]Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Department of Biochemistry, Kahramanmaraş, Türkiye

ÖZET

Amaç: Akut pulmoner emboli sık karşılaşılan ve yüksek mortaliteye sahip bir pulmoner vasküler hastalık olup tanısı için geliştirilmiş spesifik bir biyobelirteç henüz bulunmamaktadır. Çalışmamızda akut pulmoner emboli tanısı alan hastaların başvuru anındaki serum Elabela düzeylerini incelemeyi, oksidatif stres düzeyleri ile Elabela düzeylerinin ilişkisini ve Elabela'nın tanısal değerini araştırmayı amaçladık.

Gereçler ve Yöntem: Çalışmaya 41 akut pulmoner emboli hastası ve kontrol grubu için 37 sağlıklı birey dahil edildi. Tüm katılımcıların serumlarından Elabela, Total Antioksidan ve Oksidan Kapasite düzeyleri ölçülerek sonuçlar karşılaştırıldı.

Bulgular: Akut pulmoner emboli hastalarında kontrollere kıyasla Elabela düzeyleri anlamlı derecede düşük, total oksidan kapasite, total antioksidan kapasite ve oksidatif stres indeksi değerleri anlamlı derecede yüksekti. Elabela seviyeleri total oksidan kapasite ve oksidatif stres indeksi ile anlamlı korelasyon gösterdi. Elabela seviyeleri D-Dimer, Troponin I değerleri arasında korelasyon yoktu. Elabela için yapılan ROC eğrisi analizinde % 75,7 duyarlılık ve % 90,2 özgüllük ile akut pulmoner emboli tanısı için gerekli seviye 220,18 ng /L idi. Eğri altındaki alan 0,82 ve % 95 CI 0,72-0,94 idi (p<0,001).

Sonuç: Bu çalışmada akut pulmoner emboli hastalarında Elabela düzeylerinin azaldığını gösterdik. Ayrıca total oksidan kapasite ile serum Elabela seviyeleri arasında negatif bir korelasyon gözlemledik. Yapılan çalışmaların sonucunda Elabela-apelin/APJ sistemi ile trombosit agregasyonu ve aterotromboz arasındaki ilişki halen belirsizdir. Bu yolağın netleşmesiyle Elabela'nın insanlarda akut pulmoner emboli için tanısal biyobelirteç ve terapötik ajan olarak rolünü belirlenmesine imkan sağlanacaktır. Bunun için daha büyük ve daha kapsamlı çalışmalara ihtiyaç vardır. Klinik tanıya katkı sağlaması durumunda serum Elabela ölçümü hasta açısından daha kolay, daha hızlı ve daha az invaziv olabilir.

Anahtar Kelimeler: Pulmoner emboli, elabela, oksidatif stress

ABSTRACT

Objective: Acute pulmonary embolism is a common pulmonary vascular disease with high mortality, and there is no specific biomarker developed for its diagnosis yet. In our study, we aimed to examine the serum Elabela levels at the time of admission in patients diagnosed with acute pulmonary embolism and the relationship between oxidative stress and Elabela, and the diagnostic value of Elabela.

Materials and Method: Forty-one acute pulmonary embolism patients and thirty-seven healthy individuals for the control group were included in the study. Elabela, Total Antioxidant and Oxidant Capacity levels were measured from the serums of all participants and the results were compared.

Results: Elabela levels were significantly lower, total oxidant and antioxidant capacity and oxidative stress index values were significantly higher in acute pulmonary embolism patients compared to controls. Elabela levels showed a significant correlation with total oxidant capacity and oxidative stress index. There was no correlation between Elabela and D-Dimer and Troponin I values. In the ROC curve analysis for Elabela, the level required for the diagnosis was 220.18 ng /L with a sensitivity of 75.7% and a specificity of 90.2%. The area under the curve was 0.82 and 95% CI was 0.72-0.94 (p<0.001).

Conclusion: In this study, we showed that Elabela levels were reduced in patients with acute pulmonary embolism. We also observed a negative correlation between total oxidant capacity and serum Elabela levels. As a result of the studies, the relationship between the Elabela-apelin/APJ system and platelet aggregation and atherothrombosis is still unclear. The clarification of this pathway will allow the determination of the role of Elabela as a diagnostic biomarker and therapeutic agent for acute pulmonary embolism. For this, larger and more comprehensive studies are needed. Serum Elabela measurement may be easier, quicker and less invasive for the patient if it contributes to clinical diagnosis.

Keywords: Pulmonary embolism, elabela, oxidative stress

Geliş Tarihi/Received: 31 May/Mayıs 2024 **Kabul Tarihi/Accepted:** 10 March/Mart 2025 **Yayın Tarihi/Published Online:** 28 September/Eylül 2025

Sorumlu Yazar/Corresponding Author: Filiz Alkan Baylan, Necmettin Erbakan University, Faculty of Medicine, Department of Biochemistry, Konya, Türkiye
e-mail: drfilizalkan@gmail.com

Atıf yapmak için/ Cite this article as: Alkan Baylan F, Akkok B, Baykisi Y, Erdogan C. Serum Elebela Levels in Pulmonary Embolism. Selcuk Med J 2025;41(3): 136-141

Disclosure: *Author has no a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Acute pulmonary embolism (APE), together with deep vein thrombosis, is the clinical manifestation of venous thromboembolism (1). APE is the third most common acute cardiovascular condition (2) and its prevalence is increasing over time (3). Currently, APE diagnosis is primarily based on the combination of blood tests and imaging analyses. Although the D-dimer test, which has a high false-positive rate, is a good option to "exclude" APE, it is not good in terms of "diagnosis". Although computed tomography pulmonary angiography is reported as the 'gold standard', it is not suitable for regular clinical screening. Its use is limited in patients with renal failure and hypersensitivity to iodine-containing contrast agents (4-6). Therefore, other non-invasive, easy-to-detect and reliable biomarkers are still needed for the diagnosis of APE.

Apelin and Elabela are two peptide ligands for a class A G-protein coupled receptor called the apelin receptor (AR/APJ/APLNR). These ligands function by binding to this receptor, known as the apelinergic system (Apelin/APJ system). Binding of both endogenous peptides to APJ results in similar physiological effects (7,8). Elabela has been found to localize in adult endothelium, human stem cells, and kidneys (9). Several studies have also shown that Elabela is associated with vasodilation, myocardial contractility, and pulmonary arterial hypertension in animal models (10–12). Apelin and Elabela are known to have protective effects on the cardiovascular system. In human and animal models, Elabela administration has been shown to cause systemic vasodilation, resulting in a significant decrease in blood pressure (12,13). Elabela is thought to have this effect by blocking the renin-angiotensin-aldosterone system via the APJ receptor, which is 31% structurally similar to the angiotensin II type 1 receptor (10). Yavuz et al. have shown that Elabela levels are reduced in patients with total coronary occlusion and that there is a positive correlation between coronary collateral development and serum Elabela levels (14).

Studies have found that the Elabela-apelin/APJ system plays an important role in thrombosis-related diseases such as atherosclerosis, myocardial infarction, and cerebral infarction. However, there is no study investigating serum Elabela levels in APE patients with thrombosis as the pathological basis. Therefore, we aimed to investigate the difference between serum Elabela levels in healthy individuals and APE patients, whether Elabela can be a biomarker in the diagnosis of APE, and the relationship between serum Elabela levels and oxidative status.

MATERIALS AND METHOD

Patient Selection and Data Collection

This study was planned prospectively between July 2021 and January 2023. The study included 41 patients who were admitted to the chest diseases clinic of a tertiary referral hospital with the diagnosis of APE and 37 healthy individuals who met the exclusion criteria and did not have APE. The diagnosis of APE was confirmed by Computed tomography pulmonary angiography. In the study; congenital cardiomyopathy, severe heart valve disease, chronic liver disease, chronic kidney disease (GFR <60 ml/kg/min), thyroid dysfunction, atrial fibrillation, acute coronary syndrome, malignancy, active infection, autoimmune diseases, rheumatological diseases ≤18 and ≥ 85 years of age patients were accepted as exclusion criteria.

Acele et al. (15) found a difference in Elabela levels between patients with complete AV block and healthy individuals in a study they conducted on patients with complete AV block. In the power analysis conducted based on this study, the test power was 0.95 and the error was accepted as 0.05, and the sample size in terms of Elabela levels should include at least 8 patients for each group. The local ethics committee (Kahramanmaraş Sütçü İmam University Non-Interventional Clinical Research Ethics Committee, 03.02.2021/86) approved the study protocol implemented in accordance with the principles set out in the Declaration of Helsinki. All subjects signed written informed consent before starting the study.

Demographic data were recorded. Heart rate and systolic and diastolic blood pressure were measured. The remaining serums from the blood samples taken for routine tests from individuals in the control group and patients diagnosed with APE before starting the treatment were separated for the study. The separated serum samples were frozen at -80 °C until analysis. D-Dimer, one of the routine laboratory parameters; Cobas 8000 c702 (Roche Diagnostic, Germany) autoanalyzer and Troponin I was analyzed by Radiometer Aqt 90 (Bronshoj, Denmark).

Elabela Measurement

Elabela serum levels were determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Catolog No: NE010733101, NEPENTHE) with an automatic ELISA reader (Thermo Scientific, FINLAND) and a computer program (ScanIt for Multiscan FC 2.5.1) in accordance with the manufacturer's instructions. Sensitivity: 3.47 pg/L and assay range: 7 ng/L – 1500 ng/L. Intra-assay %CV was <8%, Inter-assay %CV was <10%. Results were determined as ng/L.

TOS, TAS Measurement

Total oxidant capacity: TOS levels were determined spectrophotometrically using Rel Assay commercial kits (Rel Assay Kit Diagnostics, Turkey). H_2O_2 was used as calibrator. Results were expressed as mol H_2O_2 equivalent/L.

Total antioxidant capacity: TAS levels were measured spectrophotometrically using Rel Assay commercial kits (Rel Assay Kit Diagnostics, Turkey). Trolox, a water-soluble vitamin E analog, was used as a calibrator. Results were expressed as mmol Trolox equivalent/L. Oxidative stress index (OSI) was calculated by dividing total oxidant capacity (TOS) by total antioxidant capacity (TAS) (16).

Statistical Analysis

Statistical analyses were performed using SPSS vn 22 program (IBM SPSS for Windows version 22, IBM Corporation, Armonk, NY, USA). Kolmogorov-Smirnov test was used to assess the conformity of the data to normal distribution. Independent T test was used for groups with normal distribution and Mann-Whitney U test was used for groups with non-normal distribution. Independent Chi-Square Test was used for age

and gender comparisons of the groups. Correlations between variables were evaluated with Spearman Correlation test. Diagnostic decision-making properties of elabela levels in predicting the disease were analyzed with ROC curve analysis. Descriptive variables were expressed as median (minimum-maximum) and mean±standard deviation, categorical data as percentage. P<0.05 was used for statistical significance.

RESULTS

The demographic characteristics of the acute pulmonary embolism and control groups are given in Table 1. The patient group in the study consisted of an older population, with the mean age of the APE patient group being 59.17 and the mean age of the control group being 36.94. There was no significant difference between the groups in terms of gender. Elabela levels were significantly lower, and TOS, TAS and OSI values were significantly higher in APE patients compared to controls (p value <0.001; <0.001; 0.47; <0.001, respectively) (Table 2) (Figure 1).

Elabela levels showed significant correlation with TOS and OSI (r= -0.423, r= -0.414; p= <0.001, respectively). There was no correlation between serum Elabela levels and D-Dimer, Troponin I values in APE patients. (Table 3) Serum D-Dimer levels in APE patients were 10.6±12.42 and Troponin I levels

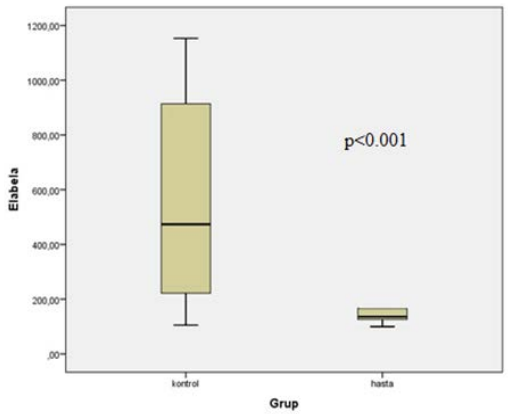


Figure 1. Levels of Correlation Between Study Groups Error bars indicate standard deviation.

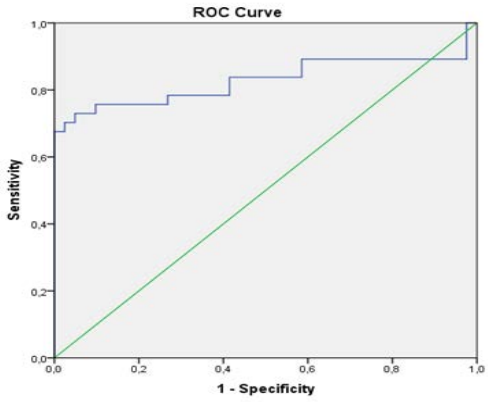


Figure 2. ROC Curve for Elabela in Acute Pulmonary Embolism (Area under the curve: 0.82)

Table 1. Demographic findings of the study population

	Patient Group (n= 41)	Control Group (n=37)	p Value
Gender (F/M)	14/27	11/26	0.676¥
Age (mean±standard deviation)	59.17±16.47	39.95±8,84	<0.001*α
Smoking (smoker/non-smoker)	11/30	16/21	0.128¥

*: indicates statistical significance ¥: Independent Chi-Square Test, α: Independent T Test

Table 2. Laboratory findings of the study population

	Patient (n= 41)	Control (n=37)	p Value
Elabela (ng/L) [median]	136.07 Q1=124.89 Q3=166.95	473.35 Q1=189.25 Q3=921.64	<0.001*β
TOS (μmol H_2O_2eq/L) [median]	41.45 Q1=14.56 Q3=65.55	5,91 Q1=3.02 Q3=8.94	<0.001*β
TAS (μmol Trolox eq/L) [median]	1.20 Q1=1.015 Q3=1.56	1.11 Q1=0.995 Q3=1.185	0.047*β
OSI (unitless) [median]	32.87 Q1=13.64 Q3=49.85	5,14 Q1=2.81 Q3=8.14	<0.001*β

TOS; Total Oxidant Status, TAS; Total Antioxidant Status, OSI; OSI; Oxidative Stress Index *: indicates statistical significance ¥: Independent Chi-Square Test, α: Independent T Test, β: Mann-Whitney U Test

Table 3. Correlation of plasma Elabela levels with clinical and laboratory parameters

Correlation	Correlation Coefficient (r Value)	Level
Elabela-TAS	-0.056	
Elabela-TOS	-0.423*	moderate
Elabela-OSI	-0.414*	moderate
Elabela-D-Dimer	-0.056	
Elabela-Troponin	0.098	
Elabela-CRP	0.099	
Elabela-Age	-0.449*	moderate
Elabela-SystolicTA	0.057	
Elabela-DiastolicTA	0.041	
Elabela-Pulse	0.042	

TOS; Total Oxidant Status, TAS; Total Antioxidant Status, OSI; OSI; Oxidative Stress Index *p <0.001 indicates statistical significance

were 0.28±0.42. In the ROC curve analysis for Elabela, the level required for APE diagnosis was 220.18 ng /L with 75.7% sensitivity and 90.2% specificity. The area under the curve was 0.82 and 95% CI was 0.72-0.94 (p<0.001) (Figure 2).

DISCUSSION

This study is the first to investigate serum Elabela levels in APE patients. The results of the study showed that serum Elabela levels were decreased in APE patients compared to healthy volunteers. In addition, TOS and OSI, which indicate total oxidative stress, were higher in APE patients and showed a negative correlation with serum Elabela levels.

In 1993, O'Dowd and colleagues identified a gene that they named APJ, which has an identity similar to the angiotensin II type 1 receptor (17). Later, in 1998, a new ligand, apelin, was discovered by Tatemoto and colleagues, which binds to this G protein-coupled receptor APJ (18). In the following years, other ligands such as Elabela and Tollder, which bind to APJ, were discovered and various physiological effects were investigated (19). Studies on the effects of apelin and Elabela on the cardiovascular system showed that they: i) contribute to the formation of the heart and angiogenesis during the embryogenic period; ii) have inotropic effects; iii) cause vasodilation in both the systemic and pulmonary vascular systems; iv) cause a decrease or slowing down of diseases that lead to cardiac hypertrophy and fibrosis; v) reduce peripheral vascular disease; and vi) they have shown to improve the clinical picture of heart failure and myocardial infarction (10). Therefore, it is thought that this could be a treatment method due to all these positive and cardiovascular protective effects (20).

Impaired endothelial function is associated with atherosclerosis. Elabela is mainly detected in fibroblasts and intact endothelial cells in the heart (21). Therefore, Elabela production decreases in impaired endothelial function. The low Elabela levels measured in the APE group in our study can be explained by the presence of impaired endothelial function. Yavuz et al. found low serum Elabela levels in chronic total occlusion patients with stable angina pectoris and associated them with impaired endothelial functions and impaired angiogenesis (14). In a study conducted in children with pulmonary stenosis, it was observed that serum Elabela levels were negatively correlated with the severity of pulmonary stenosis and that serum Elabela levels increased on the 3rd day after surgery in these children. In this study, it was stated that Elabela indicated right ventricular afterload (22). Human and mouse platelets express apelin and its receptor APJ. Apelin directly contributes to thrombin-mediated signaling pathways and platelet activation, secretion, and aggregation, but is ineffective against ADP- and thromboxane A2-mediated pathways. In an animal experiment, IV apelin given to rats was shown to cause excessive bleeding and prevent thrombosis. This study emphasized that apelin and/or APJ agonists may be potentially useful in antiplatelet therapies (23). Contrary to these data, some studies have shown that Elabela and other endogenous ligands such as apelin-12, -17, and -36 induce platelet aggregation and thrombosis (24). Again, some studies have detected high Elabela levels in MI patients with underlying thrombosis (25). In a study conducted in rats, apelin was shown to improve cardiac dysfunction after myocardial ischemic reperfusion injury by suppressing myocardial apoptosis and resisting oxidative effects through APJ receptor activation (26). A study reported that endogenous apelin in the pulmonary artery wall had no significant role in regulating pulmonary vascular tone in the acute phase of APE (27). In another study, no significant change was observed in the endogenous apelin level in the pulmonary artery wall in the early phase of APE, while an increase in apelin expression was observed in the bronchial epithelium (28). The levels of apelin 13, an adipokine that stimulates the APJ system like elabela, were examined in patients with pulmonary embolism, and higher apelin levels were detected in the patients compared to the healthy control group (29). In other words, there is no consensus on whether members of the APJ system such as elabela and apelin increase or decrease in either pulmonary embolism or other diseases. In the study conducted by Kavaklı et al., they found TOS and OSI values high in APE patients, but no significant difference was found in TAS values (30). The results of our study also supported this study. The negative correlation between TOS and serum Elabela levels indicates that Elabela levels decrease further with increasing oxidative load in patients, suggesting that this situation affects the pathogenesis of the disease.

In conclusion; in this study, we showed that Elabela levels are decreased in APE patients. We also observed a negative

correlation between total oxidant capacity and serum Elabela levels. As a result of the studies, the relationship between Elabela-apelin/APJ system and platelet aggregation and atherothrombosis is still unclear. Clarification of this pathway will allow the determination of the role of Elabela as a diagnostic biomarker and therapeutic agent for APE in humans. Larger and more comprehensive studies are needed for this. Serum Elabela measurement may be easier, faster and less invasive for the patient if it contributes to clinical diagnosis.

Limitations

This study has some limitations. First, the sample size was relatively small. The other is that since the ages of the individuals in the control and patient groups were different, it was not clear whether the measured parameters varied depending on age.

Acknowledgements

This study was supported by the Kahramanmaraş Sütçü İmam University Scientific Research Projects (KSÜBAP) Unit (Project No: 2021/3-4YLS)

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

Address correspondence to: *Filiz Alkan Baylan, Necmettin Erbakan University, Faculty of Medicine, Department of Biochemistry, Konya, Türkiye*
e-mail: *drfilizalkan@gmail.com*

REFERENCES

1. Konstatinides SV, Meyer G, Becattini C, et al. ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2019;41(4):543–603. doi: 10.1093/eurheartj/ehz405.
2. Raskob GE, Angchaisuksiri P, Blanco AN, et al. ISTH Steering Committee for World Thrombosis Day. Thrombosis: A major contributor to global disease burden. Arterioscler Thromb Vasc Biol.2014;34:2363–71. doi: 10.1161/ATVBAHA.114.304488.
3. Keller K, Hobohm L, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J.2020;41(4):522-9. doi: 10.1093/eurheartj/ehz236.
4. Chien CH, Shih FC, Chen CY, et al. Unenhanced multidetector computed tomography findings in acute central pulmonary embolism. BMC Med Imaging. 2019;19(1):65. doi: 10.1186/s12880-019-0364-y.
5. den Exter PL, van der Hulle T, Klok FA, et al. Advances in the diagnosis and management of acute pulmonary embolism. Thromb Res. 2014;133(2):10-6. doi: 10.1016/S0049-3848(14)50002-3.
6. Karakuş H, Poyraz N. Pulmonary Angiography with Low Dose Contrast Media in 64-Slice CT: A Feasibility Study. Selcuk Med J. 2021;37(1):64-9. doi: 10.30733/std.2020.01464.
7. Chng SC, Ho L, Tian J, et al. ELABELA: A hormone essential for heart development signals via the apelin receptor. Dev Cell. 2013;27:672–80. doi: 10.1016/j.devcel.2013.11.002.
8. Read C, Nyimanu D, Williams TL, et al. International union of basic and clinical pharmacology. CVII. Structure and pharmacology of the apelin receptor with a recommendation that Elabela/Toddler is a second endogenous peptide ligand. Pharmacol Rev. 2019;71:467–502. doi: 10.1124/pr.119.017533.
9. Sunjaya AP, Sunjaya AF, Ferdinal F. Apela/Elabela/Toddler: New perspectives in molecular mechanism of heart failure. Glob Cardiol Sci Pract. 2019:e201915. doi: 10.21542/gcsp.2019.15.
10. Zhang Y, Wang Y, Lou Y, et al. Elabela, a newly discovered APJ ligand: Similarities and differences with apelin. Peptides. 2018:109:23–32. doi: 10.1016/j.peptides.2018.09.006.
11. Sharma B, Ho L, Ford GH, et al. Alternative progenitor cells compensate to rebuild the coronary vasculature in Elabela- and APJ-deficient hearts. Dev Cell. 2017;42:655–66e653. doi: 10.1016/j.devcel.2017.08.008.
12. Yang P, Read C, Kuc RE, et al. Elabela/Toddler is an endogenous agonist of the apelin APJ receptor in the adult cardiovascular system, and exogenous administration of the peptide compensates for the downregulation of its expression in pulmonary arterial hypertension. Circulation. 2017;135:1160–73. doi: 10.1161/CIRCULATIONAHA.116.023218.
13. Murza A, Sainsily X, Coquerel D, et al. Discovery and structure-activity relationship of a bioactive fragment of ELABELA that modulates vascular and cardiac functions. J. Med. Chem. 2016;59:2962-72. doi: 10.1021/acs.jmedchem.5b01549.
14. Yavuz F, Kaplan M. Association Between Serum Elabela Levels and Chronic Totally Occlusion in Patients with Stable Angina Pectoris. Arq Bras Cardiol. 2021;117(3):503-10. doi: 10.36660/abc.20200492.
15. Acele A, Bulut A, Donmez Y; et al. Serum Elabela Level Significantly Increased in Patients with Complete Heart Block. Braz J Cardiovasc Surg. 2020;35(5):683-8. doi: 10.21470/1678-9741-2019-0461.
16. Yumru M, Savas H.A, Kalenderoglu A, et al. Oxidative imbalance in bipolar disorder subtypes: A comparative study. Progress in Neuro-Psychopharmacology and Biological Psychiatry.2009;33(6): 1070-4. doi: 10.1016/j.pnpbp.2009.06.005.
17. O'Dowd BF, Heiber M, Chan A, et al. A human gene that shows identity with the gene encoding the angiotensin receptor is located on chromosome 11. Gene. 1993;136(1-2):355-60. doi: 10.1016/0378-1119(93)90495-o.
18. Tatemoto K, Hosoya M, Habata Y, et al. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor, Biochem Biophys. Res Commun. 1998;251(2);471–6. doi: 10.1006/bbrc.1998.9489.
19. Chng SC, Ho L, Tian J, et al. ELABELA: a hormone essential for heart development signals via the apelin receptor, Dev. Cell. 2013;27(6):672–80. doi: 10.1016/j.devcel.2013.11.002.
20. Li L, Zhou Q, Li X, et al. Elabela-APJ axis: a novel therapy target for cardiovascular diseases. Acta Biochim Biophys Sin (Shanghai).2017;49(11):1042-3. doi: 10.1093/abbs/gmx098.
21. Xu J, Chen L, Jiang Z, et al. Biological functions of Elabela, a novel endogenous ligand of APJ receptor. J Cell Physiol. 2018;233(9):6472-82. doi: 10.1002/jcp.26492.
22. Wang J, Zhou Y, Wang Q, et al. Elabela: A Novel Biomarker for Right Ventricular Pressure Overload in Children With Pulmonary Stenosis or Pulmonary Atresia With Intact Ventricular Septum. Front Cardiovasc Med. 2020;12(7).581848. doi: 10.3389/fcvm.2020.581848.
23. Adam F, Khatib AM, Lopez JJ, et al. Apelin: An antithrombotic factor that inhibits platelet function. Blood. 2016;18;127(7):908-20. doi: 10.1182/blood-2014-05-578781.
24. Chen Z, Luo X, Liu M, et al. Elabela-apelin-12, 17, 36/APJ system

promotes platelet aggregation and thrombosis via activating the PANX1-P2X7 signaling pathway. J Cell Biochem. 2023;124(4):586-605. doi: 10.1002/jcb.30392.
25. Dönmez Y, Acele A. Increased Elabela levels in the acute ST segment elevation myocardial infarction patients. Medicine (Baltimore). 2019;98(43):e17645. doi: 10.1097/MD.0000000000017645.
26. Zeng XJ, Zhang LK, Wang HX, et al. Apelin protects heart against ischemia/reperfusion injury in rat. Peptides.2009;30(6):1144-52. doi: 10.1016/j.peptides.2009.02.010.
27. Andersen CU, Markvardsen LH, Hilberg O, et al. Pulmonary apelin levels and effects in rats with hypoxic pulmonary hypertension. Respir Med. 2009;103(11):1663-71. doi: 10.1016/j.rmed.2009.05.011.
28. Feng JH, Li WM, Wu XP, et al. Hemodynamic effect of apelin in a canine model of acute pulmonary thromboembolism. Peptides. 2010;31(9);1772-8. doi: 10.1016/j.peptides.2010.06.004.
29. Sen HS, Kaplan I, Abakay O, et al. Serum Apelin 13 Levels in Patients With Pulmonary Embolism. Clin Appl Thromb Hemost. 2016;22(6):543-7. doi: 10.1177/1076029615572467.
30. Kavaklı HS, Celik GK, Ahmedalı A, et al. Importance of Oxidative Stress in Pathogenesis and its Value in Diagnosis of Pulmonary Embolism Patients. JAEM. 2012;19-22. doi:10.5152/jaem.2012.015.

NEU PRESS

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2025.01881
Selcuk Med J 2025;41(3): 142-151

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

The Evaluation of Nasal Polyps in Terms of Smoking, Proliferative Processes, and Inflammation: Cross-Sectional Study

Nazal Poliplerin Sigara İçimi, Proliferatif Süreç ve Enflamasyon Açısından Değerlendirilmesi: Kesitsel Çalışma

Ethem Omeroglu[1], Ayse Nur Ugur Kilinc[1], Zeynep Bayramoglu[2], Yasar Unlu[1]

[1]Konya City Hospital, Pathology, Konya, Türkiye
[2]Dokuz Eylul University, Pathology, İzmir, Türkiye

ÖZET

Amaç: Bu çalışmada Türk toplumunda Nazal poliplerin (NP) sigara içimi, proliferatif süreçler ve enflamasyon ile ilişkisini histopatolojik ve klinik parametreler doğrultusunda detaylı bir şekilde değerlendirmeyi amaçladık.

Gereçler ve Yöntem: Mart-Ağustos 2021 tarihleri arasında hastanemizde endoskopik sinüs cerrahisi yapılan 36'sı erkek, 19'u kadın toplam 55 nazal polip hastasının patolojik materyalleri incelendi. Hematoksilin ve Eozin (H&E) boyama ile histolojik alt tipler skuamöz metaplazi, epiteliyal hiperplazi gibi histolojik değişikliklerin değerlendirilmesi yapıldı. Ayrıca eozinofil, nötrofil, lenfosit oranları ve yoğunluğu gibi çeşitli inflamatuar durumları değerlendirildi. Bununla birlikte, dokularda sigara içimi ile ilgili gelişebilecek proliferatif değişiklikler immünohistokimya (IHK) yöntemi ile Ki-67 ve p53 boyama değerlendirmeleri yapılarak araştırıldı. Hastane sisteminden elde edilen klinik bilgiler, laboratuvar sonuçları ve Lund-Mackay sınıflaması verileri dahil edildi. Çalışmada R 4.2.2 programı kullanılarak Ki-Kare ve Fisher testleri ile T-testi analizleri gerçekleştirildi.

Bulgular: Hastaların yaş ortalaması 37,22±16.96'dir. Bunlardan 34'ü (61,82%) sigara içmezken, 21'i (38,18%) sigara içmekteydi. Sonuçlarımızda sigara içenlerde ve Lund-Mackay sınıflaması puanı yüksek olanlarda eozinofilik infiltrasyon ile anlamlı bir ilişki gösterdi ($p<0.05$). Ayrıca, Lund-Mackay puanı yüksek olanlarda eozinofilik ve lenfoplazmositik inflamasyon türleri ile de anlamlı korelasyon saptandı ($p<0.05$). Nazal poliplerde skuamöz metaplazinin bulunması ile Ki-67 ve p53 immünhistokimyasal boyanma skorları arasında anlamlı ilişki bulunurken, epiteliyal hiperplazi ile bu değerler arasında ilişki bulunmadı.

Sonuç: Çalışmamızda nazal polip hastalarında sigara içimi ile Lund-Mackay sınıflaması sonuçları, inflamasyon tipi ve eozinofilik inflamasyon arasında ilişkiyi gösterdik. Ayrıca, proliferatif belirteçler olan Ki-67 ve p53 bulguları ile metaplazik değişiklikler ve epitel hiperplazi gelişimi arasında korelasyon tespit edildi. Türk toplumunda NP'lerdeki eozinofilik inflamasyon dereceleri Asya ve Avrupa toplumları arasında bir noktada olduğu sonucuna varıldı.

Anahtar Kelimeler: Nazal polip, proliferatif süreç, sigara içimi, Ki-67, p53

ABSTRACT

Objective: This study aimed to evaluate the relationship between nasal polyps (NP) in the Turkish population and smoking, proliferative processes, and inflammation, based on histopathological and clinical parameters.

Materials and Methods: Nasal polyp materials from 36 male and 19 female patients who underwent endoscopic sinus surgery at our hospital between March and August 2021 were examined. Histological changes, such as histological subtypes, squamous metaplasia, and epithelial hyperplasia, were evaluated using Hematoxylin and Eosin (H&E) staining. Various inflammatory conditions, such as the proportions and density of eosinophils, neutrophils, and lymphocytes, were also assessed. Furthermore, proliferative changes in tissues related to smoking were investigated using immunohistochemistry (IHC) using Ki-67 and p53 data. Clinical information obtained from the hospital system, laboratory results, and Lund-Mackay classification data were included. In the study, Chi-square and Fisher's tests, as well as t-test analyses, were performed using the R 4.2.2 program.

Results: Thirty-four (61.82%) of the patients were non-smokers, while 21 (38.18%) were smokers. Our results showed a significant association between eosinophilic infiltration in smokers and those with high Lund-Mackay classification scores ($p<0.05$). Furthermore, a significant association was found with eosinophilic and lymphoplasmacytic inflammation types in those with high Lund-Mackay scores ($p<0.05$). While there was a significant association between the presence of squamous metaplasia in nasal polyps and Ki-67 and p53 immunohistochemical staining scores, no association was found between these values and epithelial hyperplasia. **Conclusion:** In our study, we demonstrated the relationship between smoking and Lund-Mackay classification results, inflammation type, and eosinophilic inflammation in patients with nasal polyps. Additionally, an association was found between the proliferative markers Ki-67 and p53 and the development of metaplastic changes and epithelial hyperplasia. It was concluded that the degree of eosinophilic inflammation in NPs in the Turkish population appears to be intermediate between those of Asian and European populations.

Keywords: Inflammation, nasal polyp, proliferative processes, smoking, Ki-67, p53

Geliş Tarihi/Received: 17 August/Ağustos 2025 **Kabul Tarihi/Accepted:** 25 September/Eylül 2025 **Yayın Tarihi/Published Online:** 28 September/Eylül 2025

Sorumlu Yazar/Corresponding Author: Ayse Nur Ugur Kilinc, Konya City Hospital, Pathology, Konya, Türkiye
e-mail: aysenurugur@hotmail.com

Atıf yapmak için/ Cite this article as: Omeroglu E, Ugur Kilinc AN, Bayramoglu Z, Unlu Y. The Evaluation of Nasal Polyps in Terms of Smoking, Proliferative Processes, and Inflammation: Cross-Sectional Study. Selcuk Med J 2025;41(3): 142-151

Disclosure: *Author has no a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Nasal polyps (NPs) are nonneoplastic, chronic inflammatory growths in sinonasal tissues and are seen in 2-4% of the population (1,2). In NPs, there are histological developments in the form of epithelial proliferation, squamous metaplasia, thickening of the basal membrane, inflammation, and vascular and glandular proliferation (1,3). Genetic factors, anatomical disorders, allergic inflammations, infections, mastocytosis, and environmental factors play a role in the etiopathogenesis of NPs under the headings of proliferative processes, and infective-immunological and genetic conditions (4,5). NPs are more common among males and adults due to the intensity of smoking and higher exposure to occupational chemicals (6). Recurrence is observed in 15-40% after polypectomy (7).

Smoking is an important environmental factor, and it has been reported that NPs are more commonly seen in smokers than non-smokers, respond less to surgery, and have a higher recurrence rate (5,8). Smoking increases the aggravation of eosinophilic inflammation and inflammatory responses, decreases mucociliary clearance, and paves the way for the formation of polyps (9-11). Proinflammatory mediators and inflammatory cells may contribute to the formation of polyps (12). Reducing immune resistance is also considered to lead to NPs. Most individuals with NPs have an increased level of immunoglobulin E (IgE) and reveal skin test positivity against inhalant allergens (9). Potent regulatory molecules are increased in NPs (13). Despite the prevalence of polyps, sinonasal cancers account for less than 1% of all malignancies (14). Malignancy development in inverted papillomas (IPs) is 10%, whereas it is very rare in NPs (15).

Fewer eosinophils have been shown to exist in the nasal mucosa normally (16). The eosinophil activation contributes to the formation and development of polyps. Eosinophils have also been demonstrated to be effective on CD-3-positive cells (17). T lymphocytes are involved in the pathogenesis of diffuse and chronic rhinosinusitis. In polyps, polymorphonuclear neutrophils (PMNs) also participate in inflammation at various rates. It is known that eosinophilic chronic rhinosinusitis with NPs (CRSwNP) responds well to steroid therapy, but non-eosinophilic cases are resistant to the therapy with steroids (12). In addition, nasal polyps refractory to more than eight weeks of appropriate local therapy or more than two courses of systemic steroid therapy are the most acceptable indication for surgery. Furthermore, biologics (i.e., Dupilumab, Benralizumab, Omalizumab, and Mepolizumab) are a treatment option in patients who do not respond to topical medical therapy or cannot tolerate surgery (18).

Epithelial hyperplasia, squamous metaplasia, and hyperplasia of goblet cells are witnessed as remodeling in the sinonasal mucosal epithelium (1). Smoking leads to more squamous metaplasia than airways (5). A tumor suppressor protein, p53, plays a key role in maintaining the integrity of the genetic code by screening for likely mutations and is responsible for repairing the damaged DNA and inducing apoptosis of mutated cells (12,19). On the other hand, Ki-67 is a proliferation marker and generally increases inflammation and carcinogenic processes (20). About 3800 chemical and carcinogenic substances have been detected in cigarette smoke (21).

In our study, we aimed to evaluate NPs in terms of smoking, proliferation processes, and inflammation in the Turkish population. In this context, we immunohistochemically investigated in detail the histological subtypes, types, and grades of inflammation, eosinophil inflammation grading, formation of eosinophilic aggregates, PMNs, and lymphocyte infiltration through the staining of Ki-67 and p53.

MATERIAL AND METHODS

Design and ethical approval

Approval was obtained from the Ethics Committee of Hamidiye Health Sciences University (Date and number: 02/19/2021-2021/7). Informed consent was also obtained from the participants. All procedures in this study adhered to the ethical standards of the institutional and national research committees and conformed to the principles of the Declaration of Helsinki and its later amendments.

Patients and samples

In our study, 55 patients (36 males and 19 females) undergoing endoscopic sinus surgery between March and August 2021 were evaluated at Konya City Hospital, University of Health Sciences, Konya, Turkiye.

The study plan was applied to the patients who applied to our hospital with complaints of nasal polyps and underwent surgery. Patients with unavailable demographic data or without adequate pathologic specimens were excluded from the study Demographic data (age and gender), hemogram values including eosinophil (%), polymorphonuclear neutrophils (%), lymphocyte (%), monocyte (%), basophil (%), Red blood cell (M/Ul), Hemoglobin (g/Dl), hematocrit (%), MCV (fL), MCH (pg), MCHC (g/dl) values and smoking status(smoking history or not) were obtained from data from the hospital. All patients were evaluated with the Lund-Mackay classification (22).

While 23 (41.81%) of the patients were <35 years old, 32 (58.18%) were ≥ 35 years old. Of the smokers, 10 (47.62 9%) smoked for more than 20 years, 8 (38.09%) smoked for less than 5 years, and the remaining 3 (14.29%) smoked for 5-20 pack-years.

IHC and H&E staining

The tissues of NPs were prepared by cutting 4-5 micron-thick sections for the hematoxylin-eosin and immunohistochemistry (IHC) studies. Anti-Ki-67 and anti-p53 were stained according to protocols. Anti-Ki-67 antibody for immunohistochemistry (Mouse monoclonal, Biogenex, The Hague, The Netherlands), Anti-p53 (Mouse monoclonal, Zeta, Sierra Madre, CA, USA.

To grade eosinophils and PMNs, the counts were classified as Grade 0 (G0) if the count was 0, G1 between 1-2, G2 between 3-10, G3 between 11-30, and G4 if the count was >30 in 5 high-power fields (HPF). Even so, the eosinophil infiltration in tissues was evaluated as <10% and >10% of the inflammation. While the histological types were also grouped as edematous, fibroinflammatory, angioectatic, and glandular, the types of inflammation were grouped as lymphocytic,

lymphoplasmacytic, and eosinophilic. In terms of stromal degeneration and fibrosis, the severity of inflammation was evaluated as mild (1), moderate (2), and severe (3). Also, the presence of eosinophilic aggregates, lymphocyte infiltration, squamous metaplasia, epithelial hyperplasia, and goblet cells was evaluated with the presence and absence (0/1). For Ki-67 and p53, no staining was considered as G0, between 1-25 cells as G1, between 25-50 cells as G2, and >50 cells were evaluated as G3. Preliminary evaluation was made regarding the presence and intensity of staining in preparations stained with Ki-67 and p53 of the cases at x20 magnification. Then, epithelial cells, which were considered positive for nuclear staining, were counted in all areas at x40 magnification. Absence of staining in all areas was evaluated as G0, and according to the number of positively stained cells, 1-25 cells were evaluated as G1, 25-50 cells as G2, and >50 cells as G3.

Ulceration in the epithelium, infarction in the stroma, hemorrhage, and cystic changes were evaluated as degeneration. The presence of hyalinized connective tissue in the stroma and fibrosis was evaluated with H&E. In 6 suspicious cases, evaluation was performed using Masson Trichrome (blue staining).

Lund-Mackay classification

In chronic rhinosinusitis, the Lund-Mackay classification is used radiologically. The six subdivisions of the paranasal sinuses, including the maxillary sinus, anterior ethmoid sinuses, posterior ethmoid sinuses, sphenoid sinus, frontal sinus, and osteomeatal complex, are divided into 12 regions when evaluated as right and left. Mucosal inflammation or fluid collection of the sinus is scored as (0) completely radiolucent, (1) partially radiolucent, or (2) completely radiopaque. In addition, mild mucosal thickening without fluid collection is scored 0; mild mucosal thickening with fluid collection causing a partial radiolucent appearance is scored 1; and moderate or severe mucosal thickening without fluid collection causing a partial radiolucent appearance without complete radiopaque is scored 1. In addition, since the osteomeatal complex is a difficult region to grade, it is scored as 0, no obstruction, and 2, obstruction. As a result of these evaluations, all sinuses are completely radiolucent: 0; all sinuses are completely radiopaque: 24, and a total bilateral Lund-Mackay score is determined. Based on the Lund-Mackay scoring system, patients with scores of 1–12 were categorized into the low-score group (A), whereas those with scores of 13–22 were categorized into the high-score group (B).

Statistical Method

Descriptive statistics were presented as mean ± standard deviation for quantitative variables and as frequency and percentage for categorical variables. For comparisons between categorical variables, Chi-Square or Fisher's Exact Tests were used as appropriate. For normally distributed numerical variables, Student's t-test or analysis of variance (ANOVA) was applied. All analyses were performed using R software (version 4.2.2). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

The average age range of the study population was 37.22±16.96 (ranging between 7- 77 years). Of 55 patients, 36 (65.45%) were males and 19 (34.55%) were females, and while 34 (61.82%) were non-smokers, 21 (38.18%) were smokers. The package-years of smoking were 6.79±12.64 (ranging from 0 to 45 years). Histopathological evaluation of nasal polyps revealed that the majority of cases were of the edematous type (80%), followed by angioectatic (7.27%), glandular (7.27%), and fibroinflammatory types (5.45%). Regarding the type of inflammation, lymphoplasmacytic infiltration was most common (54.55%), while eosinophilic (30.91%) and lymphocytic inflammation (14.55%) were less frequent. The severity of inflammation was predominantly moderate (44.45%), with mild (30.91%) and severe inflammation (23.64%) observed in fewer cases. Eosinophilic infiltration ≥10% was present in 56.36% of the samples. According to the grading of eosinophilic inflammation, Grade 3 was most frequent (25.45%), followed by Grade 1 (23.64%), Grade 2 (16.36%), and Grade 0 (5.45%). Eosinophilic aggregates were detected in 52.73% of cases. In addition, neutrophilic inflammation was identified in 63.64% of specimens, while lymphoid aggregates were less common (18.18%). Evaluation of other histopathological parameters showed that macrophage counts <5 were more frequent (60%) than ≥5 (40%). Epithelial hyperplasia was observed in 36.36% of cases, mucosal ulceration in 58.18%, and squamous metaplasia in 45.45%. Goblet cells were preserved in most cases (78.18%), and subepithelial edema was identified in 54.55%. Concerning stromal changes, stromal degeneration was most commonly observed at Grade 2 (36.36%) and Grade 3 (34.55%), while Grade 1 (20%) and Grade 0 (9.09%) were less frequent. Stromal fibrosis was predominantly absent or mild

Table 1. Findings related to smoking status and the Lund-Mackay classification

Smoking Status	Sex	Low (Group A: 1–12) n (%)	High (Group B: 13–22) n (%)	Total n (%)	p-value1
Non-Smoking	Female	7 (12.72)	11 (20.00)	18 (32.72)	
	Male	8 (14.54)	8 (14.54)	16 (29.08)	
	Total	15 (27.26)	19 (34.54)	34 (61.80)	0.9270
Smoking	Female	0 (0.00)	1 (1.81)	1 (1.81)	
	Male	9 (16.36)	11 (20.00)	20 (36.36)	
	Total	9 (16.36)	12 (21.81)	21 (38.17)	
Overall Total	24 (43.62)	31 (56.38)	55 (100.00)		

Abbreviations: N, number; %, percent. [1]Pearson's Chi-squared test.

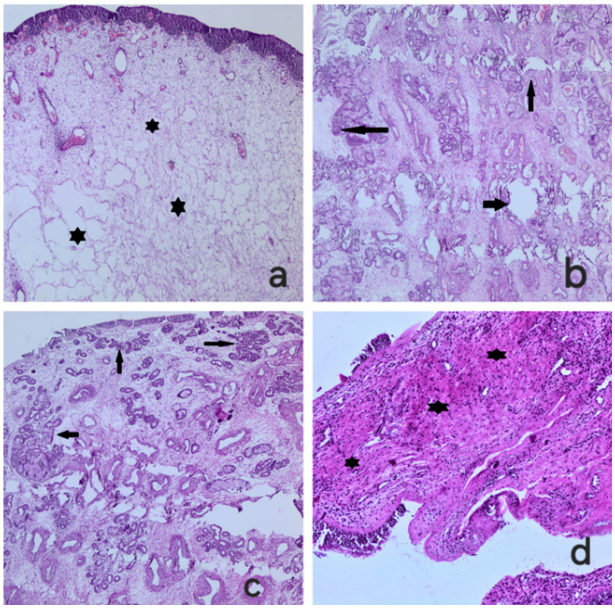


Figure 1. Histological subtypes of nasal polyps: A- Edematous, widespread edematous changes in the stroma (stars), H&E x100; B- Angioectatic, vascular structures with wide lumens between glands (arrows), H&E x150; C- Glandular, increased number of glandular building communities (arrows), H&E x100; D- Fibroinflammatory, Inflammation in diffuse fibrotic stroma (stars), H&E x100
Abbreviations: H&E: Hematoxylin & Eosin

(41.82% for both Grade 0 and Grade 1), whereas Grade 2 and Grade 3 changes were found in 9.09% and 7.27% of cases, respectively (Figure 1). According to Lund-Mackay's findings, the patients were divided into two groups: low, 31 (% 53.37%), and high, 24 (% 46.63%). The smoking status in both groups is shown in Table 1.

Those with higher scores of the Lund Mackay classification were more likely to have the eosinophilic and lymphoplasmacytic types of inflammation, and a significant association was detected between those types of inflammation (p=0.0306). Among those with higher scores of the Lund-Mackay criteria, eosinophilic aggregates were observed at a higher rate (64.52%), and the rate of inflammatory >10% was higher than 70.97%, a significant associate with was found between those parameters (p=0.0466, p=0.0131, respectively). A significant association was found between the scoring (p=0.0324) and the increase in blood eosinophil values among the patients with higher Lund-Mackay scores that displayed higher blood eosinophil values. Even so, no significant relationship was detected between this scoring and other histopathological changes, proliferative processes, rates of Ki-67 and p53, and other blood values (p>0.05). Given the comparisons between smokers and non-smokers, the fact that eosinophil aggregates were more marked (p=0.0236), and the rate of inflammatory

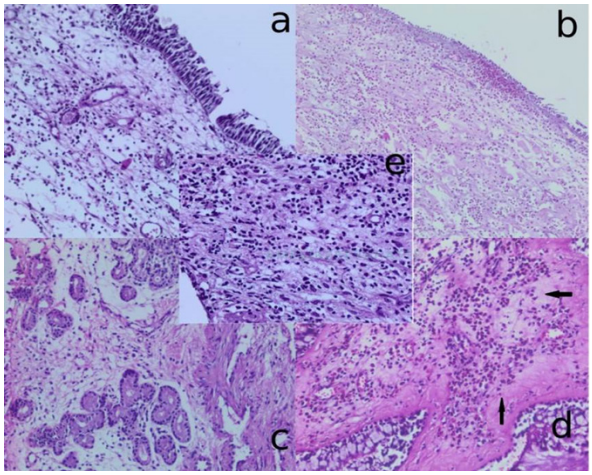


Figure 2. Inflammatory features of nasal polyps: A- Lymphoplasmacytic, H&E x100; B-Eosinophilic, H&E x100; C- Lymphocytic, H&E x100; D- Eosinophilic aggregate, densely eosinophilic cells form distinct clusters (arrows), H&E x200; E- Neutrophilic, H&E x200
Abbreviations: H&E: Hematoxylin & Eosin

cells was eosinophilic >10% (p=0.0318) among smokers suggested that there was a significant relationship between high hemoglobin values (p=0.0408), high hematocrit values (p=0.0256) (Figure 2), and mean corpuscular hemoglobin (MCH) values (p=0.0296). No significant association was found between smoking status and other histopathological changes, proliferative processes, rates of Ki-67 and p53, and other blood values (p>0.05).

Various histological findings of histological eosinophilic grading and aggregates were determined to be prominent, and some blood values were also found to be high. Significant correlations were observed between eosinophilic grade and blood eosinophil (p=0.0013), neutrophil (p=0.0014), and lymphocyte counts (p=0.0200). Similarly, the presence of eosinophilic aggregates correlated with these three blood parameters (p=0.0012, p=0.0003, and p=0.0032, respectively). In addition, with the higher rates of eosinophilic aggregates in smokers, all these significant relationships are shown in Tables 2 and 3. No significant association was detected between the out-of-histological and other blood values of these two entities and the scores of Ki-67 and p53 (p>0.05) (Table 4). The differences in Figure 4 and the scoring results of Ki-67 IHC staining in Table 4 were evaluated, and a trend was observed (p=0.0563), but it did not reach statistical significance.

Due to the presence of higher values of Ki-67 in the cases with squamous metaplasia, while a significant association was found between the values of Ki-67 and squamous metaplasia (p=0.0032), no significant association was seen between Ki-67 and epithelial hyperplasia (p=0.2897) (Figure 3). Given the assessment of the differences (Figure 5) and scoring results of p53 IHC staining (Table 4), a significant association was found in the patients with squamous metaplasia due to higher values

Table 2. Association of Clinicopathological Parameters with Eosinophilic Aggregate

Variable Parameter	Category	Eosinophilic Aggregate Present (N,%)	Eosinophilic Aggregate Absent (N,%)	p – value1
Smoking	Yes	7 (24.14%)	14 (53.85%)	p=0.0236
	No	22 (75.86%)	12 (46.15%)	
Degree of Inflammation	Mild	2 (6.90%)	15 (57.69%)	p=0.0002
	Moderate	18 (62.07%)	7 (26.92%)	
	Severe	9 (31.03%)	4 (15.38%)	
Type of Inflammation	Lymphocytic	2(6.90%)	6 (23.08%)	p<0.0001
	Lymphoplasmacytic	10 (34.48%)	20 (76.92%)	
	Eosinophilic	17 (58.625)	0 (0.00%)	
Eosinophilic Grade	Grade 0	0 (0.00%)	3 (11.54%)	p<0.0001
	Grade 1	0 (0.00%)	13 (44.83%)	
	Grade 2	0(0.00%)	9 (34.62%)	
	Grade 3	13 (50.00%)	1 (3.85%)	
	Grade 4	16 (55.17%)	0 (0.00%)	
Eosinophil Inflammation >10%	Yes	28 (96.55%)	3 (11.54%)	p<0.0001
	No	1 (3.45%)	23 (88.46%)	
Neutrophilic Inflammation	Yes	23 (79.31%)	12 (46.15%)	P=0.0107
	No	6 (20.69%)	14 (53.85 %)	

Abbreviations: N, number; %, percent. [1]Pearson's Chi-Squared Test.

Table 3. Association of Clinicopathological Parameters with Eosinophilic Grade

Variable	Category	Eosinophilic Grade 0 (N,%)	Eosinophilic Grade 1 (N,%)	Eosinophilic Grade 2 (N,%)	Eosinophilic Grade 3 (N,%)	Eosinophilic Grade 4 (N,%)	p – value1
Smoking	Yes	2 (66.67%)	7 (53.85%)	5(55.56%)	3(21.43%)	4(25.00%)	0.1728
	No	1 (33.33%)	6(46.15%)	4(44.44%)	11(78.57%)	12(75.00%)	
Degree of Inflammation	Mild	3(100.00%)	8 (61.54%)	4(44.44%)	1(7.14%)	1(6.25%)	0.0046
	Moderate	0(00.00%)	4 (30.77%)	3(33.33%)	9(64.29%)	9(56.25%)	
	Severe	0(00.00%)	1 (7.69%)	2(22.22%)	4(28.57%)	6(37.50%)	
Type of Inflammation	Lympho-plasmacytic	2 (66.67%)	8 (61.54%)	9(100.00%)	8(57.14%)	3(18.75%)	<.0001
	Eosinophilic	0(00.00%)	0 (00.00%)	0(00.00%)	4(28.57%)	13(81.25%)	
	Lymphocytic	1 (33.33%)	5(38.46%)	0(00.00%)	2(14.29%)	0(00.00%)	
Eosinophilic Aggregate	Yes	0 (0.00%)	0(00.00%)	0(00.00%)	13(92.16%)	16(100.00%)	<0.0001
	No	3(100.0%)	13(100.0%)	9(100.00%)	1(7.14%)	0(00.00%)	
Eosinophil Inflammation >10%	Yes	0(00.00%)	0(00.00%)	2(22.22%)	13(92.86%)	16(100.00%)	<0.0001
	No	3 (100.0%)	13(100.0%)	7(77.78%)	1(7.14%)	0(00.00%)	
Neutrophilic Inflammation	Yes	1(33.33%)	6(46.15%)	4(44.44%)	13(92.86%)	11(68.75%)	0.0460
	No	2(66.67%)	7(53.85%)	5(55.56%)	1(7.14%)	5(31.25%)	

Abbreviations: N, number; %, percent. [1]Pearson's Chi-Squared Test.

Table 4. Scoring values of immunohistochemical staining of Ki-67, p53, and the relationship between smoking

	Grade 0 (N,%)	Grade 1(N,%)	Grade 2(N,%)	Grade 3(N,%)	p – value1
Ki-67 Values n (%)	13 (23.63)	14 (25.45)	20 (36.36)	8 (14.54)	
Smoking	4 (7.27)	4 (7.27)	8 (14.54)	5 (9.09)	0.410
Non-smoking	9 (16.36)	10 (18.18)	12 (21.81)	3 (5.45)	
p53 Values n (%)	27 (49.09)	19 (34.54)	8 (36.36)	1 (14.54)	
Smoking	10 (18.18)	7 (12.72)	3(5.45)	1(1.81)	0,648
Non-smoking	17 (30.90)	12 (21.81)	5 (9.09)	0 (0.00)	

Abbreviations: N, number; %, percent. [1]Pearson's Chi-squared test.

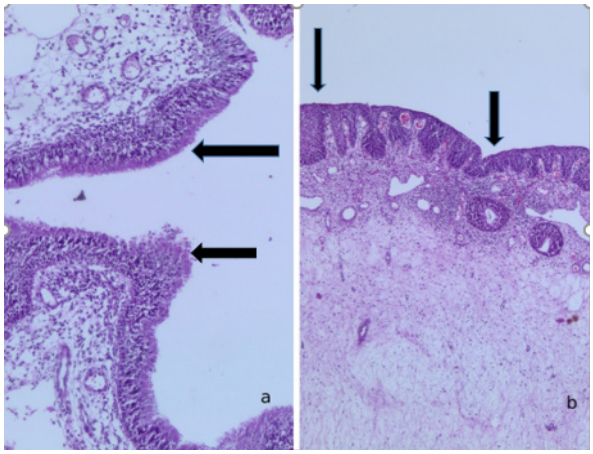


Figure 3. A- Epithelial hyperplasia, increased number and order of pseudostratified columnar epithelium (arrows), H&E x200; B- Squamous metaplasia, transformation of pseudostratified columnar epithelium into squamous epithelium (arrows), H&E x100
Abbreviations: H&E: Hematoxylin & Eosin

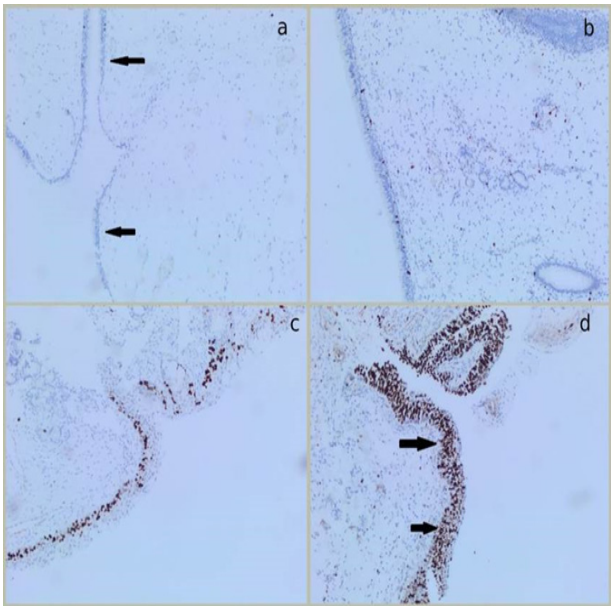


Figure 4. Ki-67 Scoring: A- Grade 0. No staining with Ki-67 in epithelial cells (arrows), Ki-67 x100; B- Grade 1, Ki-67 x100; C- Grade 2, Ki-67 x100; D- Grade 3, Strong staining with Ki-67 in epithelial cells (arrows), Ki-67 x200

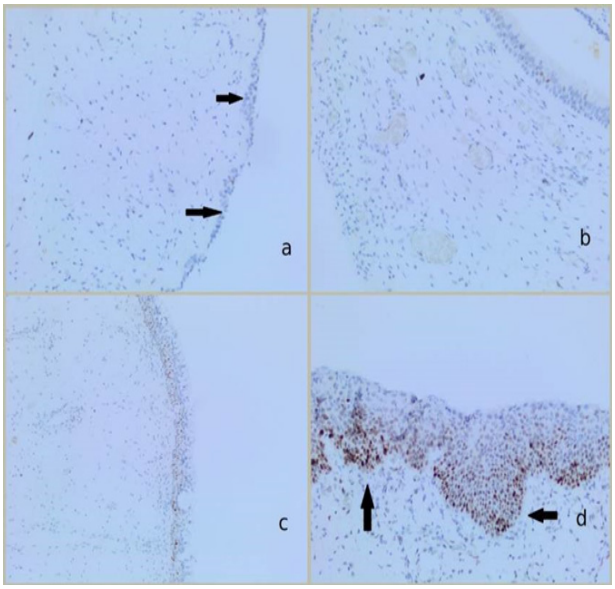


Figure 5. p53 Scoring: A- Grade 0. No staining with p53 in epithelial cells (arrows) p53 100X; B- Grade 1, p53 x100; C- Grade 2, p53 x100; D- Grade 3, Strong staining with p53 in epithelial cells (arrows), p53 x200

of p53 scores (p=0.0237). Even so, no significant relationship was detected between epithelial hyperplasia and values of p53 scores (p=0.0847).

DISCUSSION

NPs are among the commonly encountered phenomena in the community [1]. Here, we aimed to carry out a wide-parameter study including the inflammatory-proliferative processes and also the clinical-radiological evaluations of NPs. In addition, we strove to demonstrate the place of Turkish society between Asian and European societies regarding the evaluations of eosinophilic inflammation. Due to a higher rate of smoking and greater exposure to environmental pollution, NPs are more commonly encountered in males. In a study with 172 patients, the rate of the development of polyps was found to be 1.72 times higher in males than in females (23). In our study, this rate was detected to be 1.89 times higher among male patients. It is considered that the difference has decreased due to the increased exposure to environmental pollution. In the study carried out by Erbek et al. with 125 patients, no significant relationship was detected between smoking status and the diameter of NPs, paranasal NPs. Scores of computed tomography (CT), total IgE levels, and blood eosinophil levels (24). In our study, there was no significant relationship between the evaluations of similar parameters and the Lund-Mackay scoring of smoking.

Studies investigating the relationship between smoking status, inflammation, and NPs have also generally found similar results to each other. In the study by Lee et al., chronic smoking was emphasized to aggravate the eosinophilic inflammation and formation of NPs (25-27). In two separate studies by Kule et

al. and Li et al., however, it was demonstrated that the number of total inflammatory cells and PMNs increased in the NPs of cigarette smokers (5,27). In a study, it was shown that serum IgE, Th2 cytokines, N-cadherin, α-SMA, and vimentin increased, while E-cadherin levels decreased in smokers compared to non-smokers (28). In our study, no significant association was determined between smoking status and other findings related to inflammatory cells, except for the evaluations of eosinophilic infiltration. Even so, various values of complete blood count, such as hemoglobin, hematocrit, and MCH, were found to be higher in cigarette smokers.

In studies of the airway, a significant association has been shown between smoking and squamous metaplasia. However, in different studies, controversial findings have been reported. In the study by Kule et al., squamous metaplasia and hyperplasia of goblet cells were found to be significantly higher in smokers, compared to non-smokers (5). Likewise, Li et al. also reached identical findings in the study carried out with 48 patients (29). In a study of 285 people, including smokers, quitters, and non-smokers, it was shown that smokers had more squamous hyperplasia, metaplasia, and basement membrane thickness (27). Contrary to the findings mentioned above, Gao et al. stated that smoking did not affect the development of squamous metaplasia in NPs (1). Parallel to this, in our study, there was no significant relationship between smoking status and the development of squamous metaplasia and epithelial hyperplasia.

In routine pathologic practices, the Sydney classification systems, such as numerous benefits have been achieved in terms of the clinical-pathological association, with classification used in reporting gastritis can also be recommended for NPs [30]. In addition, clinical and age-related information on atypia, dysplasia, and cancer development in NPs can be collected, as in some large studies, although not seen in our study (2,31). In the diagnoses of NP in routine histopathological examinations, in general, various parameters (Table 3) such as the histological types of the polyps, type of inflammation, and rate of eosinophilic inflammation can be specified in interpreting the report. Thanks to this standard practice, a larger series of data can be acquired for the treatment, follow-up, and clinicopathological features of further studies.

Studies related to the Lund-Mackay classification and pathological findings are limited. Tezer et al. found no statistically significant association between the Lund-Mackay classification and the evaluation of Ki-67 (32). Erbek et al. did not detect a significant relationship between smoking status and the Lund-Mackay classification (24). In our study, while no significant relationship was detected between the scores of the Lund-Mackay classification, smoking status, and rates of p53 and Ki-67, a significant relationship was revealed between the inflammatory characteristics of polyps, eosinophil inflammation and formation of aggregates, and blood eosinophil values. Studies have found a high rate of eosinophilic cells in NPs in Europe. In two studies, one with 107 patients, conducted by Hellquist, and the other with 123 patients, these rates were found to be 86% and 83% (33). This rate has also been found to be 80%-90% in non-European Western societies and 98% in North Africa (34,35). Unlike Western societies, the rate of eosinophilic polyps has been found to be lower in Asian societies, including South Korea (9). In a study conducted in Malaysia, the rate of neutrophil-predominant polyps in the country was demonstrated as 67.2% (36). In various recent comparative studies in South Korea between 1993 and 2011, the rates of eosinophilic NPs have been demonstrated to increase (9). The socioeconomic and environmental conditions (bacterial superantigens, smoking, dust, climate changes, fungal infections, etc.) of Asian societies are increasingly similar to those of Europe. Because of these, the prevalence of eosinophilic polyps is also increasing among Asian populations (9,33). In fact, in an old study, the rate of eosinophil infiltration in NPs was found to be 92.3% in Japanese, as high as among Europeans (37). In the study by Yu et al., the ratio of the eosinophil-dominant phenotype of CRSwNP increased significantly (38).

There are more significant challenges in the treatment of non-eosinophilic polyps compared to eosinophilic polyps. In different studies, it has been stated that there will be differences in treatment regimens since the etiologies of NPs may be different in the Caucasian and Asian populations. In the method used in the Asian population, more antibiotics are needed to treat NPs, and there is less response to steroids (39,40). Eosinophilic NPs have a poorer prognosis than other groups due to reasons such as increased serum eosinophilia, atopic presentation and more widespread disease. A study has shown that all these parameters have been shown to have adverse effects (39). The rate of the least part of the inflammation was eosinophilic in 31 (56.36%) of the polyps evaluated in our study; with such a rate, our country ranks between the values of the Asian and European populations in terms of eosinophilic infiltration in NPs. In the study conducted by Ikeda et al., the serum eosinophil values and recurrence rates were found to be higher in the eosinophilic groups, compared to the other two groups. In addition, the symptomatic and CT scores, and the expressions of eotaxin, interleukin-17A, MUC5AC, and CD68 were also detected to be high [40]. High IgE levels have been found in the serum of patients with CRSwNPs (41). It has also been reported that treatment is more difficult in patients with a high eosinophilic aggregate/infiltration ratio (42).

In our study, a significant association was also determined between eosinophilic grades and blood eosinophil values. In various studies, the effects of lymphocytic factors and PMNs on the formation of polyps and eosinophilic inflammation were also investigated. Cho et al. emphasized that, as well as the presence of eosinophils in 80% of the cases with NPs in the tissues, the inflammation of T helper-2 cells is present in Western countries. Although now increasing in distant Asian countries, the rate is approximately between 35-45% (42). The Japanese population showed a significant association between CD4 and IL-17A (Th17) cells in terms of eosinophil count and mucosal remodeling. In previous studies, a moderate number of PMNs was shown to be present in eosinophilic CRSwNPs (39). In our study, a significant association was found between

neutrophil inflammation in NPs, blood neutrophil values, and eosinophilic infiltration criteria. In their study, Enache et al. demonstrated a higher proportion of lymphocytes in NP tissues compared to normal tissues. They reported that most of the lymphocytes in NPs were CD8 positive (44). In our study, however, a significant association was detected between the levels of blood lymphocytes and eosinophilic infiltration criteria.

P53 and Ki-67 studies in NPs and IPs were compared with more malignant conditions. Based on the literature, the number of studies investigating NPs and the effects of smoking on NPs is limited. An increase is also observed in the cells in the positive S-phase via Ki-67 staining in NPs (14). In the study that evaluated the diagnosis of NPs or IPs, a significant association was found in both with Ki-67 staining (45). In the study by Karagianni et al., the amount of Ki-67 staining showed an increase in the epithelium of patients with NPs, compared to the controls (46). However, in the study, no difference was found in terms of Ki-67 index values between recurrence of NPs (24,23). Haznedar et al. reported that Ki-67 also has an immunostimulant effect in their study (47). Barouh et al. didn't find any significant difference in proliferative cell nuclear antigen (PCNA) expression between nasal polyps and chronic rhinosinusitis [18]. In our study, the activity of Ki-67 was 76.36% in polyps. While there was a significant relationship between Ki-67 expression and squamous metaplasia, there was no significance between epithelial hyperplasia.

Encoding c-Jun, p63, vascular endothelial growth factor (VEGF), and IL-19, a large number of promoting genes associated with aberrant remodeling patterns have been found in NPs (48). In a study, the levels of IL-17, TNF-alpha, and rafftin, which are remodeling factors, were increased, especially in patients with nasal polyps who were smokers (48). Katori et al. demonstrated the expression of p53 in 11 (38%) of 29 patients with NP [49]. In two studies, p53 and Ki-67 were found to be more expressed in squamous cell carcinomas than in IPs (50). In a study where Sham et al. investigated NPs, the focal immunoreactivity of p53 was found as 19% in IPs and 40% in NPs (51). Contrary to the findings in other studies, the study evaluated 35 patients with NPs and IPs and detected that no significant association was present (44). When evaluating all these data, it should be taken into consideration that only smoking increases p53, p21, and Ki-67 values (52). In the study, staining rates of p53 in imprint smears of patients with NPs were determined as 50% for polyps, 60% for simple hyperplasia, 80% for significant hyperplasia, and 0% for metaplasia (53). However, while p53 expression was observed at a rate of 50.01% in NPs, a significant relationship between p53 expression and squamous metaplasia, and an insignificant relationship between epithelial hyperplasia were found in our study. The retrospective nature of this study means that the clinical outcome of patients, such as relapsed cases or response to drug treatment, was not investigated, which is one of the limitations of the present study.

CONCLUSIONS

In conclusion, the outcomes of the present study related to smoking status and evaluations through the Lund-Mackay classification revealed that there was an association between the inflammation types of polyps and data on eosinophilic inflammation in NPs. This is different from the findings of previous studies investigating Ki-67 and p53 at a higher rate in IPs and nasal squamous cell carcinomas, but at a limited rate in NPs; a significant relationship was shown between the scoring values of Ki-67 and p53, and squamous metaplasia, one of the proliferative processes. It was also concluded that the eosinophilic inflammation data in the polyps in the Turkish population were between those in the Asian and European populations. In the pathological reporting of NPs, with the advent of such methods as the "Sydney Gastritis Scoring" in gastritis, extensive data can be

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

Address correspondence to: *Ayse Nur Ugur Kilinc, Konya City Hospital Pathology, Konya, Türkiye*
e-mail: *aysenurugur@hotmail.com*

REFERENCES

1. Gao T, Ng CL, Li C, et al. Smoking is an independent association of squamous metaplasia in Chinese nasal polyps. Int Forum Allergy Rhinol. 2016;6(1):66-74. doi:10.1002/alr.. 21662
2. Perić A, Stoiljkov M, Đokić D, et al. Epithelial squamous metaplasia and dysplasia in inflammatory nasal polyps: An observational study. Ear Nose Throat J. 2021;100(2):NP120-4. doi:10.1177/01455613211000232
3. Brescia G, Alessandrini L, Giacomelli L, et al. A classification of chronic rhinosinusitis with nasal polyps based on structured histopathology. Histopathology. 2020;76(2):296-307. doi:10.1111/his 13972
4. Wang Y, Song X, Jin M, et al. Characterization of the Immune Microenvironment and Identification of Biomarkers in Chronic Rhinosinusitis with Nasal Polyps Using Single-Cell RNA Sequencing and Transcriptome Analysis. Journal of Inflammation Research. 2024;253-77. doi: 10.2147/JIR.S328813
5. Kule ZG, Habesoglu TE, Somay A, et al. Histopathological characteristics of nasal polyps in smokers and non-smokers. Journal of Craniofacial Surgery. 2014;25(3):946-9.doi 10.1097/SCS.0000000000000589
6. Vaitkus J, Vitkauskienė A, Simuntis R, et al. Chronic rhinosinusitis with nasal polyps: Age and disease severity differences in the levels of inflammatory markers. Medicina. 2021;57(3):282.doi: 10.3390/medicina57030282
7. Bao X, Liu B, Jiang Y, et al. Loss of SENP3 mediated the formation of nasal polyps in nasal mucosal inflammation by increasing alternatively activated macrophages. Immunity, Inflammation and Disease. 2023;11(2):e781.doi: 10.1002/iid3.781
8. Fageeh YA, Basurrah MA, Hakami KT, et al. Risk factors for recurrence of chronic rhinosinusitis with nasal polyps after endoscopic sinus surgery: A retrospective study. Saudi Medical Journal. 2023;44(12):1254.doi: 10.15537/smj.2023.44.12.20230650
9. Kim SJ, Lee KH, Kim SW, et al. Changes in histological features

of nasal polyps in a Korean population over 17 years. Otolaryngology-Head and Neck Surgery. 2013;149(3):431-7.doi: 10.1177/0194599813493334
10. Ueha R, Ueha S, Kondo K, et al. Effects of cigarette smoke on the nasal respiratory and olfactory mucosa in allergic rhinitis mice. Frontiers in Neuroscience. 2020;14:126.doi: 10.3389/fnins.2020.00126
11. Mahmud A, Salisu AD, Kolo ES, et al. Impact of smoking on nasal mucociliary clearance time in Kano metropolis, Nigeria. World Journal of Otorhinolaryngology-Head and Neck Surgery. 2023;9(01):53-8.doi: 10.1016/j.wjorl.2023.02.004
12. Pant H, Hughes A, Miljkovic D, et al. Accumulation of effector memory CD8+ T cells in nasal polyps. American Journal of Rhinology & Allergy. 2013;27(5):e117-26. doi:10.2500/ajra.2013.27.4075
13. Liu Y, Sha J, Meng C, et al. The Role of Small Extracellular Vesicles and MicroRNAs in the Diagnosis and Treatment of Allergic Rhinitis and Nasal Polyps. Mediators of Inflammation. 2022, 4428617, 9 pages. doi: 10.1155/2022/4428617
14. Sarkar S, Saha R, Das M, et al. Sinonasal polyps: A diagnostic challenge. Bengal Journal of Otolaryngology and Head Neck Surgery. 2019;27(3):243-50.DOI: 10.5005/jp-journals-10011-1344
15. Lee HY, Lee HK, Kim SJ. Squamous Cell Carcinoma In Situ Originating From Nasal Polyps With Human Papillomavirus 51 Infection: A Case Report. Ear, Nose & Throat Journal. 2021;100(10_suppl):1054S-7S.doi: 10.1177/01455613211004994
16. Soklic TK, Silar M, Rijavec M, et al. CD3+ CD4– CD8– mucosal T cells are associated with uncontrolled chronic rhinosinusitis with nasal polyps. Journal of Allergy and Clinical Immunology. 2019;143(3):1235-7.doi: 10.1016/j.jaci.2018.07.017
17. Iordache A, Balica NC, Horhat ID, et al. Allergic rhinitis associated with nasal polyps and rhinosinusitis–histopathological and immunohistochemical study. Romanian Journal of Morphology and Embryology. 2022;63(2):413.doi: 10.47162/RJME.63.2.09
18. BAROUH, Alireza; NADOUSHAN, Mohammadreza Jalali; SOLTANIPUR, Masood. Comparison of proliferating Cell Nuclear Antigen (PCNA) expression among nasal polyp and chronic Rhinosinusitis. Acta Otorrinolaringologica (English Edition), 2024, 75.5: 310-315.doi: 10.1016/j.otoeng.2024.04.007
19. Vadivel Gnanasundram S, Bonczek O, Wang L, et al. p53 mRNA metabolism links with the DNA damage response. Genes. 2021;12(9):1446.doi: 10.3390/genes12091446
20. Andrés-Sánchez N, Fisher D, Krasinska L. Physiological functions and roles in cancer of the proliferation marker Ki-67. Journal of Cell Science. 2022;135(11):jcs258932.doi: 10.1242/jcs.258932
21. Lagunas-Rangel FA, Linnea-Niemi JV, Kudłak B, et al. Role of the synergistic interactions of environmental pollutants in the development of cancer. GeoHealth. 2022;6(4):e2021GH000552. doi: 10.1029/2021GH000552
22. Güneş S, Akidil AÖ, Erdem İ, et al. Correlation of Retention Cyst and Rhinosinusitis. Bakirkoy Tip Dergisi. 2019;15(1):65.doi: 10.4274/bakirkoymedj.galenos.2018.72122
23. Brescia G, Contro G, Ruaro A, et al. Sex and age-related differences in chronic rhinosinusitis with nasal polyps electing ESS. American Journal of Otolaryngology. 2022;43(2):103342.doi: 10.1016/j.amjoto.2021.103342
24. Erbek SS, Erbek SE, Budakoğlu IŞ, Cakmak O. The relationship between smoking and nasal polyposis. Kulak Burun Bogaz Ihtisas Dergisi: KBB= Journal of Ear, Nose, and Throat. 2008;18(4):216-20. doi: 10.24953/kbbtr.2008.4.216
25. Lee KI, Kim DW, Kim EH, et al. Cigarette smoke promotes eosinophilic inflammation, airway remodeling, and nasal polyps in a murine polyp model. American Journal of Rhinology & Allergy. 2014;28(3):208-14.doi: 10.2500/ajra.2014.28.4103
26. Lou H, Zhang N, Bachert C, et al. Highlights of eosinophilic chronic rhinosinusitis with nasal polyps in definition, prognosis, and advancement. International Forum of Allergy & Rhinology. 2018 Nov (Vol. 8, No. 11, pp. 1218-1225).doi: 10.1002/alr.22176
27. Kuhar HN, Ganti A, Brown HJ, et al. Histopathologic influences of comorbid smoking status in chronic rhinosinusitis. American Journal of Rhinology & Allergy. 2020 Nov;34(6):775-83.doi: 10.1177/1945892420957209
28. Xie L, Liu AG, Peng LY, et al. Expression of E-prostanoid receptors in nasal polyp tissues of smoking and nonsmoking patients with chronic rhinosinusitis. PloS One. 2018;13(7):e0200989.doi: 10.1371/journal.pone.0200989
29. Lee KI, Han Y, Ryu JS, et al. Tobacco Smoking Could Accentuate Epithelial-Mesenchymal Transition and Th2-Type Response in Patients With Chronic Rhinosinusitis With Nasal Polyps. Immune Network. 2022 Aug;22(4):e35.doi: 10.4110/in.2022.22.e35
30. Şenocak Taşçı E, Akbaş T. The Relationship between the Sydney Classification and the First-Line Treatment Efficacy in Helicobacter-Associated Gastritis. Medical Principles and Practice. 2020 Dec 9;29(6):551-7.doi: 10.1159/000512806
31. Kim HJ, Ahn HS, Kang T, et al. Nasal polyps and future risk of head and neck cancer: A nationwide population-based cohort study. J Allergy Clin Immunol. 2019;144(4):1004–10. doi:10.1016/j.jaci.2019.06.019
32. Tezer İ, Şanlı A, Sarısoy B, et al. Comparison of epithelial cell proliferation and physical examination findings of nasal polyps. Elektronik Kulak Burun Boğaz Baş Boyun Cerrahisi Dergisi. 2006;5(3):118-21. doi:10.5152/kbbihtisas.2006.118-121
33. Jeong WJ, Lee CH, Cho SH, et al. Eosinophilic allergic polyp: A clinically oriented concept of nasal polyp. Otolaryngology-Head and Neck Surgery. 2011;144(2):241-6.doi: 10.1177/0194599810387355
34. Laidlaw TM, Prussin C, Panettieri RA, et al. Dexpramipexole depletes blood and tissue eosinophils in nasal polyps with no change in polyp size. The Laryngoscope. 2019;129(2): E61-6.doi: 10.1002/lary.27353
35. Darouassi Y, Azami MA, El-Akhiri M, et al. Endotype of Chronic Rhinosinusitis with Nasal Polyps in Morocco. Head and Neck Pathology, 16(4), 1130-3.doi: 10.1007/s12105-022-01596-4
36. Syuhada O, Shalini P, Lim WK, et al. Malaysian Nasal Polyps: Eosinophil or Neutrophil-Predominant. Medicine & Health (Universiti Kebangsaan Malaysia). 2016;11(1).doi: 10.1111/mha.12205
37. Morinaka S, Nakamura H. Inflammatory cells in nasal mucosa and nasal polyps. Auris Nasus Larynx. 2000;27(1):59-64.doi: 10.1016/S0385-8146(99)00047-5
38. Yu J, Xian M, Piao Y, et al. Changes in clinical and histological characteristics of nasal polyps in northern China over the past 2–3 decades. International Archives of Allergy and Immunology. 2021;182(7):615-24.doi: 10.1159/000514981
39. Ikeda K, Shiozawa A, Ono N, et al. Subclassification of chronic rhinosinusitis with nasal polyp based on eosinophil and neutrophil. The Laryngoscope. 2013;123(11): E1-9.doi: 10.1002/lary.23985
40. Yang SK, Kim JW, Won TB, et al. Differences in Clinical and Immunological Characteristics According to the Various Criteria for Tissue Eosinophilia in Chronic Rhinosinusitis With Nasal Polyps. Clinical and Experimental Otorhinolaryngology. 2023;16(4):359.doi: 10.21053/ceo.2022.02108
41. Lee K, Choi IH, Lee H, et al. Association of cotinine-verified

cigarette exposure with chronic rhinosinusitis in Korean adults. International Journal of Environmental Research and Public Health. 2020;17(21):8291.doi: 10.3390/ijerph17218291
42. Cui Y, Wang K, Shi J, et al. Endotyping Difficult-to-Treat Chronic Rhinosinusitis with Nasal Polyps by Structured Histopathology. International Archives of Allergy and Immunology. 2023;184(10):1036-46.doi: 10.1159/000529706
43. Ryu G, Kim HY, Jung YG, et al. Endotypes of Asian chronic rhinosinusitis with nasal polyps: A narrative review. Precision and Future Medicine. 2022;6(3):170-6.doi: 10.20517/pfm.2022.26
44. Enache I, Ioniţă E, Anghelina F, et al. Involvement of inflammatory cells in chronic rhinosinusitis with nasal polyps. Romanian Journal of Morphology and Embryology. 2020;61(3):871.doi: 10.47162/RJME.61.3.02
45. Mumbuc S, Karakok M, Baglam T, et al. Immunohistochemical analysis of PCNA, Ki67, and p53 in nasal polyposis and sinonasal inverted papillomas. Journal of International Medical Research. 2007;35(2):237-41.doi: 10.1177/147323000703500206
46. Karagianni F, Kataki A, Koniaris E, et al. Distinctive expression profiles of Caveolin-1 and Notch-1 protein in patients with nasal polyps or sinonasal inverted papillomas. Pathology-Research and Practice. 2018;214(12):2004-10.doi: 10.1016/j.prp.2018.08.007
47. Haznedar B, Kaplan Ö, Aşır F, et al. Immune activity of Ki-67 during nasal polyp development. Eur Rev Med Pharmacol Sci. 2023;27(6):2759-64.doi: 10.26355/eurrev_202304_31828
48. Yu XM, Li CW, Li YY, et al. Down-regulation of EMP 1 is associated with epithelial hyperplasia and metaplasia in nasal polyps. Histopathology. 2013;63(5):686-95.doi: 10.1111/his.12200
49. Lin YT, Tsai MH, Su YY, et al. Expression of Major Lipid Raft Protein Raftlin in Chronic Rhinosinusitis with Nasal Polyps in Smoking and Non-Smoking Patients Correlated with Interleukin-17 and Tumor Necrosis Factor-α Levels. Biomolecules. 2022;12(9):1316. doi: 10.3390/biom12091316
50. Wang MJ, Noel JE. Etiology of sinonasal inverted papilloma: A narrative review. World journal of otorhinolaryngology-head and neck surgery. 2017;3(01):54-8.doi:10.1016/j.wjorl.2017.01.004
51. Oncel S, Cosgul T, Calli A, et al. Evaluation of p53, p63, p21, p27, ki-67 in paranasal sinus squamous cell carcinoma and inverted papilloma. Indian Journal of Otolaryngology and Head & Neck Surgery. 2011;63:172-7. DOI: 10.1007/s12070-011-0163-0
52. Sham CL, To KF, Chan PK, et al. Prevalence of human papillomavirus, Epstein–Barr virus, p21, and p53 expression in sinonasal inverted papilloma, nasal polyp, and hypertrophied turbinate in Hong Kong patients. Head & Neck. 2012;34(4):520–33. doi: 10.1002/hed.21772
53. Ingle RR, Setzen G, Koltai PJ, et al. p53 protein expression in benign lesions of the upper respiratory tract. Arch Otolaryngol Head Neck Surg. 1997;123(3):297-300. doi:10.1001/archotol.1997.01900030071009

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
DOI:http:/dx.doi.org/10.30733/std.2025.01746
Selcuk Med J 2025;41(3): 152-157

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

The Role of Plasma Calprotectin Levels in Patients with Severe Mitral Regurgitation

Şiddetli Mitral Yetersizliği Olan Hastalarda Plazma Kalprotektin Düzeylerinin Rolü

Ahmet Seyfeddin Gurbuz[1], Semi Ozturk[2], Alev Kilicgedik[3], Ahmet Taha Sahin[4], Ali Yaman[5]

[1]Necmettin Erbakan University, Faculty of Medicine, Department of Cardiology, Konya, Türkiye
[2]Haseki Training and Research Hospital, Department of Cardiology, Istanbul, Türkiye
[3]Kosuyolu Training and Research Hospital, Department of Cardiology, Istanbul, Türkiye
[4]Beyhekim Training and Research Hospital, Department of Cardiology, Konya, Türkiye
[5]Marmara University School of Medicine, Department of Biochemistry, Istanbul, Türkiye

ÖZET

Amaç: Kalprotektin, fagositlerin sitoplazmasında bulunan ve inflamatuar yanıtta ekstrasellüler matrikse salınan bir proteindir. Önceki çalışmalar, kalp yetersizliği ve akut koroner sendromlu hastalarda plazma kalprotektin düzeylerinin yüksek olduğunu göstermiştir. Bu çalışmada, plazma kalprotektin düzeylerinin fonksiyonel ve dejeneratif mitral yetersizliği etiyolojilerine göre farklılık gösterip göstermediği araştırıldı.
Yöntem: Çalışmaya şiddetli fonksiyonel mitral yetersizliği (FMY) tanısı alan 24 hasta, şiddetli dejeneratif mitral yetersizliği (DMY) tanısı alan 36 hasta ve 22 sağlıklı kontrol dahil edildi. Tüm katılımcılara ekokardiyografi uygulandı. Plazma kalprotektin düzeyleri enzyme-linked immunosorbent assay (ELISA) yöntemiyle ölçüldü.
Bulgular: Yaş, cinsiyet ve kardiyovasküler risk faktörleri açısından gruplar arasında anlamlı farklılık saptanmadı. Plazma kalprotektin düzeyleri FMY grubunda hem DMY grubuna hem de kontrol grubuna göre anlamlı derecede yüksek bulundu (sırasıyla p<0.001 ve p=0.002).
Sonuç: Bulgularımız, şiddetli FMY hastalarında plazma calprotectin düzeylerinin belirgin şekilde arttığını göstermektedir. Kalprotektin düzeyleri, mitral yetersizliğinden ziyade kalp yetersizliği ile daha fazla ilişkili görünmektedir.

Anahtar Kelimeler: Kalp yetersizliği, mitral yetersizliği, kalprotektin, akut koroner sendrom

ABSTRACT

Introduction: Calprotectin is an inflammatory protein complex which is stored in the cytosol of phagocytes and released into extracellular matrix during inflammatory response. Previous studies demonstrated that levels of plasma calprotectin were higher in patients with heart failure and acute coronary syndrome. We aimed to investigate whether levels of plasma calprotectin differed between two different etiologies of mitral regurgitation; functional and degenerative mitral regurgitation.
Methods: A total of 24 patients diagnosed with severe functional mitral regurgitation (FMR), 36 patients diagnosed with severe degenerative mitral regurgitation (DMR), and 22 control subjects were prospectively enrolled in this study. All participants underwent echocardiographic examinations. Plasma calprotectin levels were quantified using an enzyme-linked immunosorbent assay (ELISA) test kit.
Results: Age, gender, and cardiovascular risk factors did not exhibit significant differences between the FMR, DMR, and control groups. Plasma calprotectin levels were found to be higher in the FMR group compared to both the DMR group and the control group (p <0.001 and p= 0.002, respectively).
Conclusion: Our research revealed elevated plasma calprotectin levels among individuals diagnosed with severe FMR. It appears that calprotectin levels are influenced more by heart failure rather than specifically by mitral regurgitation.

Keywords: Heart failure, mitral regurgitation, calprotectin, acute coronary syndrome

INTRODUCTION

Primary mitral regurgitation constitutes the vast majority of mitral regurgitation (MR). Degenerative disease, rheumatic valve disease, senile degeneration and infective endocarditis are most common causes of primary MR (1). Degenerative disease is characterized as a spectrum that induces leaflet prolapse, whereby infiltrative or dysplastic alterations in tissue lead to elongation or disruption of the mitral valve chordae. Degenerative MR is a broad spectrum of diseases ranging from fibroelastic deficiency to Barlow's disease. Pressure and volume overload trigger cardiac remodeling which initially serves as a compensatory mechanism in primary MR. Left ventricular (LV) dysfunction and marked LV enlargement are associated with an unfavorable outcome in primary MR.

Geliş Tarihi/Received: 24 May/Mayıs 2024 **Kabul Tarihi/Accepted:** 26 June/Haziran 2025 **Yayın Tarihi/Published Online:** 28 September/Eylül 2025

Sorumlu Yazar/Corresponding Author: Ahmet Taha Şahin, Beyhekim Training and Research Hospital, Department of Cardiology, Konya, Türkiye
e-mail: drtahasahin@yahoo.com

Atıf yapmak için/ Cite this article as: Gurbuz AS, Ozturk S, Kilicgedik A, Sahin AT, Yaman A. The Role of Plasma Calprotectin Levels in Patients with Severe Mitral Regurgitation. Selcuk Med J 2025;41(3): 152-157

Disclosure: *Author has no a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

Functional mitral regurgitation resulting from papillary muscle dysfunction associated with mitral annular dilation and/or LV dysfunction is a common condition in heart failure (HF) patients. In conjunction with elevated atrial pressure, there is a concurrent rise in left ventricular end-diastolic pressure, precipitating the progressive dilation of the left ventricle. Incidence of functional MR (FMR) increased due to increase in atherosclerotic coronary syndromes despite widespread availability of percutaneous coronary interventions. FMR has a poor prognosis since it is associated with HF. Chronic inflammation after acute coronary syndromes leads to cardiac remodeling which causes further progression of HF and FMR. Several inflammatory biomarkers were shown to be associated with cardiac remodeling and prognosis in HF patients (2). Calprotectin, alternatively recognized as S100A8/A9, myeloid-related protein 8/14 (MRP-8/14), calgranulin A/B, and leukocyte L1 antigen complex, denotes an inflammation-associated protein complex localized within the cytosol of neutrophils and monocytes. Calprotectin is released into extracellular matrix during inflammatory response (3).The extracellular calprotectin stimulates innate immune system via activating receptor of advanced glycation end products (RAGE) which consequently causes myocardial inflammation and HF (4). Previous studies demonstrated that calprotectin is associated with acute coronary syndromes (5-7). Elevated plasma calprotectin levels have been correlated with an unfavorable prognosis among individuals diagnosed with myocardial infarction (8). Several studies showed that level of plasma calprotectin was not only higher in patients with HF but also associated with severity of HF(9,10). Although association of calprotectin and HF is evident, association with different pathogenesis of mitral valve has not been studied yet. FMR is more related with inflammation, atherosclerosis and HF, whereas DMR seems to be less related. These substantial differences in pathogenesis of mitral valve disease raise suspicion about relationship between these two distinct etiologies and calprotectin. We aimed to investigate, for the first time, whether levels of plasma calprotectin differed between two different etiologies of mitral regurgitation: functional and degenerative MR (DMR).

MATERIALS AND METHODS

Compliance with Ethical Standards:

The study was reviewed and approved by the institutional research ethics board (Approval Number: 2024/4802), adhering to the principles of the Helsinki Declaration. Written informed consent was obtained from all participants. Artificial intelligence-supported technologies were not used in the study.

Study population

The study enrolled 60 patients diagnosed with severe MR who were referred for echocardiographic assessment. A control group consisting of 22 subjects without MR and possessing normal left ventricular ejection fraction (LVEF) was included for comparison. The patients were categorized into groups: DMR (n=36), FMR (n=24), and the control group (n=22)

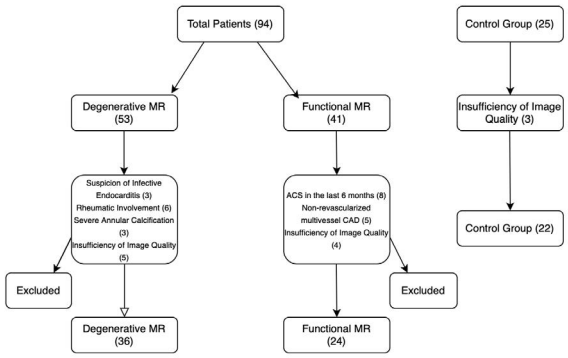


Figure 1. Flow diagram of the participants in the study

as depicted in Figure 1. Exclusion criteria involved patients with a history of acute coronary syndrome within the previous six months. Additionally, significant coronary artery disease (CAD) was ruled out either through coronary angiography or myocardial perfusion scintigraphy (MPS) among patients in the DMR group and the control group. Patients presenting with primary MR attributed to causes such as rheumatic etiology or mitral annular calcification, as well as those with infective endocarditis, were excluded from the study. Ethical approval was obtained from the local ethics committee.

Measurement of Calprotectin Levels

Blood samples were collected from the antecubital vein of patients 15 minutes prior to echocardiographic examination to determine plasma calprotectin levels and other hematological parameters. For calprotectin analysis, blood was drawn into pyrogen-free tubes containing EDTA and then centrifuged at 3000 revolutions per minute (rpm) for 10 minutes. The resultant plasma was stored at -70°C until further analysis. Plasma calprotectin levels were quantified using an enzyme-linked immunosorbent assay (ELISA) test kit (CALPROLAB Calprotectin ELISA (ALP); Calpro AS, Lysaker, Norway). Complete blood count (CBC) analysis was performed using a Beckman Coulter HMX-AL instrument (Brea, CA, USA).

Echocardiography

All patients underwent examination by the same experienced echocardiographer, who remained blinded to the study protocol. Standard echocardiographic assessments were conducted using a 1 to 5 MHz X5-1 transducer (iE33, Philips Healthcare, Inc., Andover, MA). Left ventricular end-diastolic (LVEDD) and end-systolic diameters (LVESD) were measured from the parasternal long-axis view utilizing M-mode imaging. Left ventricular ejection fraction (LVEF) was calculated using Simpson's Formula (11). Mitral inflow velocities were assessed using pulsed-wave Doppler, with recording of E and A wave velocities. The E/A ratio was subsequently calculated. Tricuspid annular plane systolic excursion (TAPSE) was measured using M-Mode, while the tricuspid annulus peak systolic velocity (Sm) was recorded using tissue Doppler imaging (TDI) in the apical four-chamber view to assess right ventricular function.

Left ventricular circumferential and longitudinal strain parameters (LV-GCS, LV-GLS) were evaluated utilizing 2D speckle-tracking imaging. The severity of mitral regurgitation (MR) was quantified by determining mitral regurgitant volume (RV) and effective regurgitant orifice area (EROA), following recommended guidelines (12). MR was classified as severe if RV was greater than 60 mL/beat or EROA exceeded 0.4 cm^2 (1). FMR were graded according to 2021 ESC/EACTS Guidelines for the management of valvular heart disease (1). However, in light of discrepancies in the determination of severe FMR between the 2020 AHA/ACC and ESC/EACTS guidelines, the severe FMR group was reclassified into high overload and low overload subgroups. The high overload group was defined as having an effective regurgitant orifice area (EROA) of ≥0.4 cm^2 or a regurgitant volume (RV) of ≥ 60 ml/beat, while the low overload group was characterized by an EROA of 0.2-0.4 cm^2 or an RV of 30-60 ml/beat (1,13). This arbitrary reclassification enabled us to comprehend similar RVs in both groups.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics 16.0 (SPSS, Chicago, IL) software. Sample size determination was based on previous studies with similar methodologies and patient populations. While no formal power analysis was conducted, the sample size was considered adequate to detect meaningful differences based on prior literature. Due to the rarity of the condition and the strict inclusion criteria, the final sample size was determined by the number of eligible patients within the study period. Continuous variables were expressed as mean and standard deviation, while categorical variables were presented as percentages. The conformity of the data to normal distribution was evaluated with the Shapiro-Wilk test. Categorical variables were compared using the Chi-Square or Fisher's Exact test as appropriate. The distribution of numerical data in 3 independent groups showing normal distribution was evaluated with ANOVA and Tukey's post hoc test, and if the variances were not homogeneous, with Welch and Tamhane post hoc test. The distribution of numerical data in 3 independent groups showing normal distribution was evaluated with Kruskal Wallis test. Dunn Bonferroni test was used in post hoc analysis of data with significant Kruskal Wallis test results. The relationship between numerical data was evaluated with the Pearson Correlation test. Receiver operating characteristic (ROC) curve analysis was employed to determine the optimal cut-off level for plasma calprotectin values in predicting severe FMR. Additionally, linear regression analysis was performed to identify predictors of plasma calprotectin levels. A p-value <0.05 was considered statistically significant for all results.

RESULTS

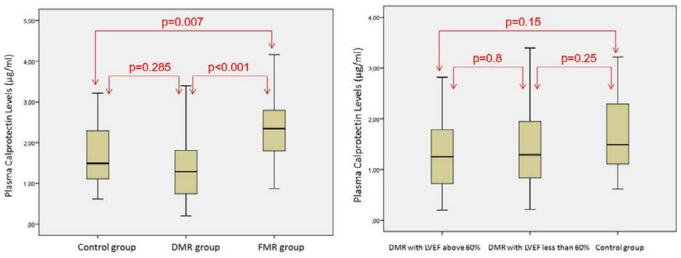
Twenty-four patients diagnosed with FMR and 36 patients diagnosed with DMR were prospectively enrolled in the study. Demographic, clinical, echocardiographic, and laboratory characteristics of the study population are presented in Table 1. There was no statistically significant difference observed between the control group and the study groups regarding

Table 1. Demographic, clinical, echocardiographic and laboratory characteristics of study population

	Control Group n:22	DMR n:36	FMR n:24	p value	Post hoc p1	p2	p3
Age, years	51.6±9.3	51.9±15.5	56.5±15.4	0.161			
Sex, Male (%)	14 (63.6)	27 (75.0)	19 (79.2)	0.468			
Hypertension (%)	4 (18.2)	11 (30.6)	8 (33.3)	0.471			
Diabetes Mellitus (%)	5 (22.7)	9 (25.0)	8 (33.3)	0.681			
Dyslipidemia (%)	4 (18.2)	8 (22.2)	7 (29.2)	0.667			
Urea (mg/dl)	31.4±5.8	34.3±11.3	67.8±51.2	0.018	0.674	0.022	0.045
Creatinine (mg/dl)	0.81±0.17	0.85±0.26	1.21±0.8	0.340			
Hemoglobin (mg/dl)	13.9±0.86	13.9±2.1	12.8±2.3	0.250			
Platelet(1000/mm^3)	264.4±52.3	214.4±38.5	199.6±95.5	0.026	0.059	0.007	0.271
Leukocyte(1000/mm^3)	8.1±1.6	7.5±2.3	9.6±3.7	0.073			
LV-ESD (cm)	2.9±0.43	3.51±0.66	5.16±0.75	<0.001	0.001	<0.001	<0.001
LV-EDD (cm)	4.73±0.45	5.76±0.75	6.53±0.83	<0.001	<0.001	<0.001	<0.001
LV-EF (%)	64.7±2.5	57.4±8.2	32.8±6.9	<0.001	0.016	<0.001	<0.001
LV-GCS (%)	-23.4±4.9	-19.4±5.8	-10.4±4.2	<0.001	0.030	<0.001	<0.001
LV-GLS (%)	-19.8±2.6	-16.9±5.6	-9.3±3.8	<0.001	0.036	<0.001	<0.001
LA diameter (cm)	3.29±0.38	4.17±0.75	4.66±0.75	<0.001	<0.001	<0.001	0.051
E/A ratio	0.9±0.3	1.75±0.55	2.2±0.96	<0.001	<0.001	<0.001	0.436
Tapse (mm)	25.9±4.8	25±5.3	17.7±4.5	<0.001	0.789	<0.001	<0.001
Sm (cm/s)	15±2.8	15.6±3.5	10.1±2.5	<0.001	0.790	<0.001	<0.001
ERO (mm^2)		68.5±27.6	32.2±9.5	<0.001			
RV (ml/beat)		94.2±30.8	49.4±13.5	<0.001			
Calprotectin (µg/ml)	1.70±0.79	1.36±0.78	2.45±0.85	<0.001	0.285	0.007	<0.001

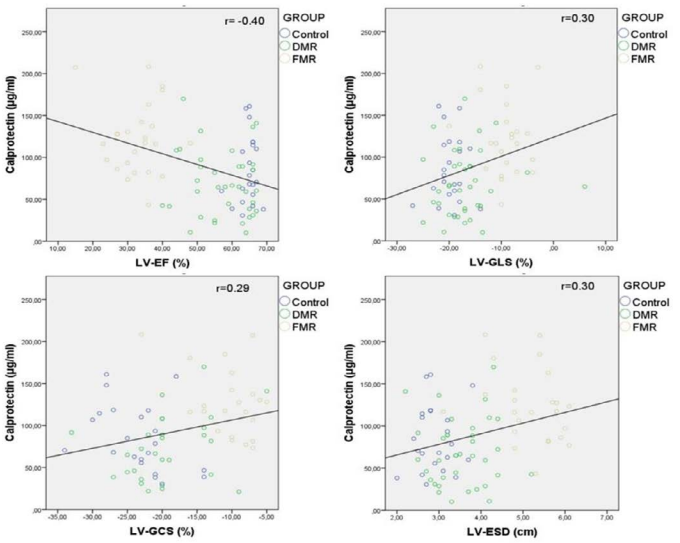
LV-EDD: left ventricle end-diastolic diameter; LV-ESD: left ventricle end-systolic diameter; LV-EF: left ventricle ejection fraction; LV-GCS: global circumferential left ventricular strain; LV-GLS: global longitudinal left ventricular strain; LA: left atrium; LAVI: left atrial volume index; Tapse: tricuspid annular plane systolic excursion; ERO: effective regurgitant orifice area; RV: regurgitant volume; p1: p value between controls and DMR; p2:p value between controls and FMR; p3: p value between DMR and FMR

age and gender distribution (p= 0.161, p= 0.468, respectively). Additionally, cardiovascular risk factors such as hypertension, diabetes mellitus, and dyslipidemia did not differ significantly between the groups (p= 0.471, p= 0.681, p= 0.667, respectively). Three patients in the DMR group and six patients in the FMR group exhibited a functional capacity of Class III according to the New York Heart Association (NYHA) Classification System, while the remaining MR patients were classified as NYHA Class II (p= 0.137). All patients with FMR had history of CAD and 10 (45%) had atrial fibrillation (AF). AF did not exist in DMR and control group. LVEDD and LVESD were largest in FMR group and smallest in control group (p<0.001 for all). LVEF, LV-GLS and LV-GCS were worst in FMR group and best in control group (p<0.001 for all). Left atrium (LA) diameter was largest in FMR group (p<0.001) and smallest in control group. E/A ratio was higher in FMR and DMR groups than control (p<0.001). FMR group had the worst right ventricle systolic function (TAPSE and Sm) (p<0.001 for all), although no difference existed between DMR group and controls (p>0.05). ERO and RV were larger in DMR group compared with FMR group (p<0.001). Plasma calprotectin levels were (1.70±0.79 µg/ml in control group; 1.36±0.78µg/ml in DMR group; 2.45±0.85 µg/ml in FMR group) higher in FMR group compared with DMR group and control (p<0.001, p=0.007; respectively), however no difference was present between DMR group and control (p=0.285) (Figure 2). Plasma calprotectin levels negatively correlated with LVEF (r=-0.40, p<0.001), TAPSE (r=-0.38, p=0.001) and Sm (r=-0.31, p=0.006), and positively correlated with LVESD (r=0.30, p=0.006), LV-GLS (r=0.30, p=0.007), LV-GCS (r=0.29, p=0.02) (Figure 3 and 4) in all study group. In FMR group, presence of AF did not have effect on plasma calprotectin levels (p=0.2 between FMR patients with and without AF). FMR group was dichotomized as high (EROA ≥0.4 cm^2, RV ≥ 60 ml/beat) and low (EROA: 0.2-0.4 cm^2, RV: 30-60 ml/beat) overload groups. Plasma calprotectin levels did not differ between high and low overload groups (2.48±1.04 µg/ml in high group (n: 10), 2.43±0.71 µg/ml in low group (n: 14), p=0.87). Plasma calprotectin levels were higher in high overload FMR group (n: 10) compared with DMR group and control (p<0.001, p=0.01; respectively). In ROC analysis, a cut-point of 1.85 µg/ml identified the patients with FMR in this study population (area under curve (AUC) =0.797, 95% CI 0.69- 0.89) (Figure 5). Plasma



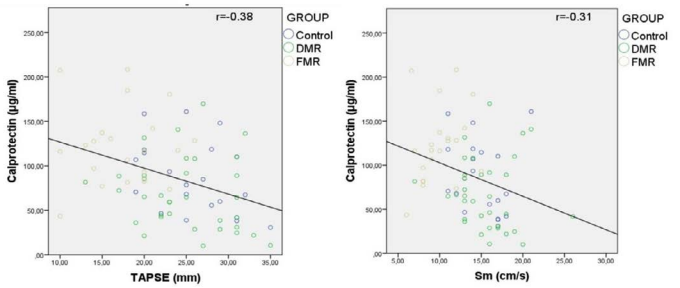
DMR: Degenerative Mitral Regurgitation FMR: Functional Mitral Regurgitation LVEF: Left Ventricular Ejection Fraction

Figure 2. Plasma calprotectin levels of control and MR groups.



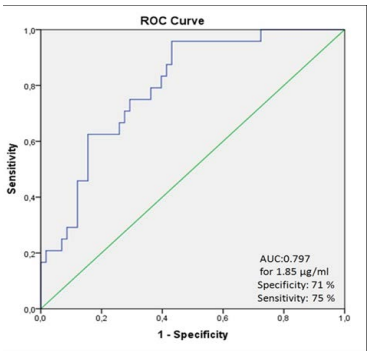
DMR: Degenerative Mitral Regurgitation FMR: Functional Mitral Regurgitation LVEF: Left Ventricular Ejection Fraction LV-GLS: Left Ventricular Global Longitudinal Strain LV-GCS: Left Ventricular Global Circumferential Strain LV-ESD: Left Ventricular End-Systolic Diameter

Figure 3. Correlation between plasma calprotectin level and left ventricle functions.



DMR: Degenerative Mitral Regurgitation FMR: Functional Mitral Regurgitation TAPSE: Tricuspid Annular Plane Systolic Excursion Sm: Systolic Myocardial Velocity

Figure 4. Correlation between plasma calprotectin level and right ventricle functions.



ROC: Receiver Operating Characteristic FMR: Functional Mitral Regurgitation

Figure 5. ROC curve of plasma calprotectin level for prediction of FMR.

Table 2. Linear regression analysis to identify independent predictors of calprotectin

	B	t	p
EF	-1.913	-4.543	<0.001
Severe MR (presence)	-15.912	-1.168	0.246
LA diameter	-11.977	-1.556	0.124
Age	0.131	0.374	0.709
Sex (male)	2.544	0.233	0.816

B: Unstandardized Coefficient EF: Ejection Fraction MR: Mitral Regurgitation LA: Left Atrium

calprotectin level of higher than 1.85 µg/ml demonstrated FMR with a sensitivity of 75%, a specificity of 71%. A linear regression model was constructed to estimate the calprotectin parameter from demographic and echocardiographic parameters. The patient group (combining DMR and FMR) was included versus the control group. According to the results of the linear regression analysis performed to determine the independent determinants of the calprotectin index, the LV EF parameter was determined to be an independent determinant of the calprotectin index (Table 2).

DISCUSSION

Calprotectin is a heterodimeric protein complex comprising two calcium-binding proteins. It is released from the cytosol of phagocytes into the extracellular matrix during inflammatory responses. Extracellular calprotectin plays a role in mediating inflammatory activity in endothelial cells, potentially through interaction with the RAGE. Experimental studies have demonstrated that activation of RAGE leads to the development of sustained myocardial inflammation and heart failure (4). Previous studies have indicated a positive correlation between calprotectin levels and high-sensitivity C-reactive protein (hsCRP), an established predictor of morbidity and mortality in heart failure (HF). These findings support the hypothesis of heightened inflammatory activity in HF (9). Previous studies have shown that calprotectin level was associated not only with the presence of HF and but also the severity (NHYA Classification) (9). Although calprotectin level was a predictor of one year mortality in elderly patients with HF, no correlation between calprotectin level and EF was demonstrated (10). BNP, a marker of cardiomyocyte stretch, was independent predictor of long-term mortality in patients with DMR (14). Previous studies demonstrated no association between NT-pro B-Type Natriuretic Peptide (NT-BNP) and calprotectin in patients with CHF (9). This finding concluded that inflammation is not related to stretching of cardiomyocytes. Additionally, sustained release of calprotectin contributes to development of post-ischemic HF through activation of RAGE (4). Studies have shown that calprotectin levels are elevated in patients with CAD. Calprotectin level was higher in acute coronary syndromes (ACS) compared with stable angina. Additional prognostic value of calprotectin was demonstrated in myocardial infarction(5-8,15). Present study found that plasma calprotectin level was higher in patients with severe FMR compared with patients with severe DMR and control group. High level of calprotectin in patients with FMR may be associated with presence of heart failure and coronary artery disease in this patient group. Additionally, the comparable plasma calprotectin levels in both high and low overload groups of FMR suggest that, in our study, MR-related volume overload does not affect the plasma calprotectin levels. Our findings indicate that volume overload, resulting in cardiomyocyte stretching, did not have an effect on calprotectin levels in patients with severe FMR. Atrial functional mitral regurgitation (AFMR) is a recognized subtype of secondary MR, often associated with atrial fibrillation (AF). In our study, 45% of the FMR group had AF, which may suggest a significant proportion of AFMR. Although we did not specifically classify AFMR, this condition might contribute to elevated plasma calprotectin levels due to chronic atrial inflammation and remodeling. Future studies should differentiate between AFMR and ventricular functional MR to assess their distinct impact on inflammatory biomarkers like calprotectin.

In contrast to the findings of other studies, our study demonstrated a correlation between EF and calprotectin levels in all study groups and in all MR patients. We also demonstrated that the right ventricular systolic function (TAPSE, Sm) was correlated with calprotectin levels in our study. Although previous study has shown that calprotectin level is higher in patients with AF, independent of heart failure, we did not demonstrate association between AF and calprotectin levels in patients with severe FMR (16). In patients with severe DMR without HF and CAD, we demonstrated that stretching of cardiomyocytes due to severe mitral regurgitation did not have an effect on calprotectin levels. Increased calprotectin levels in patients with severe FMR were related to heart failure. Further large-scale and comprehensive studies are needed to validate the reliability of calprotectin as an inflammatory biomarker in mitral regurgitation. Additionally, the underlying pathophysiological mechanisms involving calprotectin require further elucidation.

Limitations

The primary limitation of our study is the small sample size. Furthermore, since our study exclusively focused on patients with severe MR, there is a lack of sufficient comparable data between severe and mild or moderate MR cases. Additionally, the absence of BNP and an inflammatory marker such as C-reactive protein (CRP) in our study limits the comparison of these markers with calprotectin, which could further elucidate pathophysiological relationships. Moreover, the grading of MR using proximal isovelocity surface area (PISA) measurements may lead to overestimation of the severity of regurgitant

volume (RV) and effective regurgitant orifice area (EROA) in DMR patients.

Another limitation is the lack of differentiation between atrial functional MR (AFMR) and ventricular functional MR in the FMR group, particularly given that 45% of the patients had AF. Future studies should stratify FMR patients based on AFMR status to better understand the relationship between AF, MR subtype, and inflammatory markers such as calprotectin. This study acknowledges the potential confounding effects of CAD and AF on inflammation markers. Since CAD and AF were more prevalent in the FMR group, it is possible that observed differences in inflammation levels may not be solely attributable to mitral regurgitation itself. A multivariate regression analysis was not performed to adjust for these confounders, which represents a limitation of the study. Future studies with larger sample sizes and comprehensive statistical adjustments are needed to further clarify these associations.

CONCLUSION

Our study demonstrated elevated plasma calprotectin levels in patients diagnosed with severe FMR, whereas there was no significant increase observed in patients with severe DMR. Therefore, it appears that calprotectin levels are influenced more prominently by heart failure rather than by the presence of mitral regurgitation.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

Address correspondence to: *Ahmet Taha Şahin, Beyhekim Training and Research Hospital, Department of Cardiology, Konya, Türkiye*
e-mail: *drtahasahin@yahoo.com*

REFERENCES

1. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Rev Esp Cardiol (Engl Ed). 2022 Jun;75(6):524. doi: 10.1016/j.rec.2022.05.006.
2. Gruson D, Ahn SA, Rousseau MF. Biomarkers of inflammation and cardiac remodeling: The quest of relevant companions for the risk stratification of heart failure patients is still ongoing. Biochem Med (Zagreb). 2011;21(3):254-63. doi: 10.11613/bm.2011.035.
3. Hessian PA, Edgeworth J, Hogg N. MRP-8 and MRP-14, two abundant Ca(2+)-binding proteins of neutrophils and monocytes. J Leukoc Biol. 1993 Feb;53(2):197-204.
4. Volz HC, Laohachewin D, Seidel C, et al. S100A8/A9 aggravates post-ischemic heart failure through activation of RAGE-dependent NF-κB signaling. Basic Res Cardiol. 2012 Mar;107(2):250. doi: 10.1007/s00395-012-0250-z.
5. Healy AM, Pickard MD, Pradhan AD, et al. Platelet expression profiling and clinical validation of myeloid-related protein-14 as a novel determinant of cardiovascular events. Circulation. 2006 May 16;113(19):2278-84. doi: 10.1161/CIRCULATIONAHA.105.607333.
6. Altwegg LA, Neidhart M, Hersberger M, et al. Myeloid-related protein 8/14 complex is released by monocytes and granulocytes at the site of coronary occlusion: A novel, early, and sensitive marker of acute coronary syndromes. Eur Heart J. 2007 Apr;28(8):941-8. doi: 10.1093/eurheartj/ehm078.
7. Morrow DA, Wang Y, Croce K, et al. Myeloid-related protein 8/14 and the risk of cardiovascular death or myocardial infarction after an acute coronary syndrome in the Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction (PROVE IT-TIMI 22) trial. Am Heart J. 2008 Jan;155(1):49-55. doi: 10.1016/j.ahj.2007.08.018.
8. Jensen LJ, Pedersen S, Bjerre M, et al. Plasma calprotectin predicts mortality in patients with ST segment elevation myocardial infarction treated with primary percutaneous coronary intervention. J Interv Cardiol. 2010 Apr;23(2):123-9. doi: 10.1111/j.1540-8183.2010.00532.x.
9. Jensen LJ, Kistorp C, Bjerre M, et al. Plasma calprotectin levels reflect disease severity in patients with chronic heart failure. Eur J Prev Cardiol. 2012 Oct;19(5):999-1004. doi: 10.1177/1741826711421078.
10. Ma LP, Haugen E, Ikemoto M, et al. S100A8/A9 complex as a new biomarker in prediction of mortality in elderly patients with severe heart failure. Int J Cardiol. 2012 Feb 23;155(1):26-32. doi: 10.1016/j.ijcard.2011.01.082.
11. Feigenbaum H, Armstrong WF, Ayan T. Feigenbaum's Echocardiography. 6th ed. Philadelphia: Lippincotts Williams&Wilkins; 2005. p. 355
12. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003 Jul;16(7):777-802. doi: 10.1016/S0894-7317(03)00335-3.
13. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021 Feb 2;143(5):e35-e71. doi: 10.1161/CIR.0000000000000932.
14. Clavel MA, Tribouilloy C, Vanoverschelde JL, et al. Association of B-Type Natriuretic Peptide With Survival in Patients With Degenerative Mitral Regurgitation. J Am Coll Cardiol. 2016 Sep 20;68(12):1297-307. doi: 10.1016/j.jacc.2016.06.047.
15. Peng WH, Jian WX, Li HL, et al. Increased serum myeloid-related protein 8/14 level is associated with atherosclerosis in type 2 diabetic patients. Cardiovasc Diabetol. 2011 May 18;10:41. doi: 10.1186/1475-2840-10-41.
16. Bruhn LV, Lauridsen KG, Schmidt AS, et al. Elevated calprotectin in patients with atrial fibrillation with and without heart failure. Scand J Clin Lab Invest. 2017 May;77(3):210-215. doi: 10.1080/00365513.2017.1292364.

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
DOI:http:/dx.doi.org/10.30733/std.2025.01826
Selcuk Med J 2025;41(3): 158-164

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Is Diminished Ovarian Reserve Associated with Poor Perinatal Outcomes? A Retrospective Cohort Study

Azalmış Over Rezervi Kötü Perinatal Sonuçlarla İlişkili midir? Retrospektif Bir Kohort Çalışması

Dilay Gok Korucu[1], Fatih Akkus[2]

[1]University of Health Sciences, Konya City Hospital, Department of Obstetrics and Gynecology, IVF Unit, Konya, Türkiye
[2]Kütahya City Hospital, Department of Obstetrics and Gynecology, Division of Perinatology, Kütahya, Türkiye

ÖZET
Amaç: İntrasitoplazmik sperm enjeksiyonu (ICSI) tedavisi gören kadınlarda düşük over rezervinin (DOR) olumsuz perinatal sonuçlarla ilişkili olup olmadığını araştırmak.
Gereç ve Yöntemler: Bu retrospektif kohort çalışması bir hastanenin in vitro fertilizasyon (IVF) Ünitesinde yürütülmüş ve 2019-2022 yılları arasındaki kayıtlar analiz edilmiştir. Çalışmada DOR nedeni ile IVF uygulanıp canlı doğum yapan 26 hasta ile ve kontrol grubu olarak erkek faktörü nedeni ile IVF uygulanıp canlı doğum yapan 63 kadının doğum verileri incelenmiştir. Analiz edilen sonuçlar arasında erken doğum (ED), düşük doğum ağırlığı (DDA), erken membran rüptürü (EMR), hipertansif gebelik bozuklukları (GHB), gestasyonel diyabet (GDM), abruptio plasenta, intrahepatik gebelik kolestazı, konjenital anomali ve sezaryen oranı yer almaktadır. Gruplar yaş ve vücut kitle indeksi (VKİ) açısından eşleştirilmiştir. İstatistiksel analizler DOR ile perinatal komplikasyonlar arasındaki ilişkiyi değerlendirmek için lojistik regresyonu içermektedir.
Bulgular: DOR'lu kadınlar birkaç temel alanda önemli ölçüde daha kötü perinatal sonuçlar göstermiştir. Doğum ağırlıkları DOR grubunda kontrol grubuna kıyasla anlamlı derecede düşüktür [2.300 (900-4.000) gr vs. 3.150 (900-4.100) gr, p = 0.011]. Ayrıca, 34 haftadan önce erken doğum oranı DOR grubunda belirgin şekilde daha yüksektir (%29.6' ya karşı %11.1, p = 0.031) ve 3.36'lık bir olasılık oranı (%95 GA: 1.07-10.53) ile önemli ölçüde yüksek bir riske işaret etmektedir. EMR' de DOR grubunda belirgin şekilde daha yaygındı (%25.9' a karşı %7.9, p = 0.021). Buna karşılık, GHB (%14.8' e karşı %12.7, p = 0.787) ve GDM (%7.4'e karşı %6.3, p = 0.854) oranlarında önemli bir farklılık görülmemiştir. Plasental ablasyo, intrahepatik kolestaz ve konjenital anomaliler dahil olmak üzere diğer komplikasyonlar gruplar arasında benzerdi.
Sonuç: DOR, artmış DDA, ED ve EMR riskleri ile ilişkilidir. Bu bulgular, perinatal sonuçları iyileştirmek için DOR'lu kadınlar için özel yönetimin önemini vurgulamaktadır.

Anahtar Kelimeler: Over rezervi, perinatal sonuçlar, intrasitoplazmik sperm enjeksiyonu, düşük doğum ağırlığı

ABSTRACT
Objective: To investigate whether diminished ovarian reserve (DOR) is associated with adverse perinatal outcomes in women undergoing intracytoplasmic sperm injection (ICSI) treatment.
Materials and Methods: This retrospective cohort study was performed in the In Vitro Fertilization (IVF) Unit of a hospital, examining records spanning from 2019 to 2022. The study involved 26 women diagnosed with DOR who achieved live births through ICSI. These patients were compared to a control group of 63 women who underwent IVF treatment due to male factor infertility, also resulting in live births. Outcomes analyzed included preterm birth (PTB), low birth weight (LBW), preterm premature rupture of membranes (PPROM), hypertensive disorders of pregnancy (HDP), gestational diabetes (GDM), abruptio placenta, intrahepatic cholestasis of pregnancy, congenital anomaly, c-section rate. The groups were matched by age and body mass index (BMI). Statistical analyses included logistic regression to evaluate the association between DOR and perinatal complications.
Results: Women with DOR demonstrated significantly poorer outcomes in several key areas. Birth weights were significantly lower in the DOR group compared to controls [2.300 (900–4.000) gr vs. 3.150 (900–4.100) gr, p = 0.011]. Additionally, the rate of PTB before 34 weeks was markedly higher in the DOR group (29.6% vs. 11.1%, p = 0.031), with an odds ratio of 3.36 (95% CI: 1.07–10.53), indicating a significantly elevated risk. PPROM was also notably more prevalent in the DOR group (25.9% vs. 7.9%, p = 0.021). In contrast, rates of HDP (14.8% vs. 12.7%, p = 0.787) and GDM (7.4% vs. 6.3%, p = 0.854) showed no significant differences. Other complications, including placental abruption, intrahepatic cholestasis, and congenital anomalies, were similar between the groups.
Conclusion: DOR is associated with increased risks of LBW, PTB, and PPROM. These findings emphasize the importance of tailored management for women with DOR to improve perinatal outcomes.

Keywords: Ovarian reserve, perinatal outcomes, intracytoplasmic sperm injection, low birth weight

Geliş Tarihi/Received: 5 February/Şubat 2025 **Kabul Tarihi/Accepted:** 28 August/Ağustos 2025 **Yayın Tarihi/Published Online:** 28 September/Eylül 2025

Sorumlu Yazar/Corresponding Author: Dilay Gok Korucu, University of Health Sciences, Konya City Hospital,Department of Obstetrics and Gynecology, IVF Unit, Konya, Türkiye
e-mail: dilaygok@yahoo.com

Atıf yapmak için/ Cite this article as: Korucu Gok D, Akkus F. Is Diminished Ovarian Reserve Associated with Poor Perinatal Outcomes? A Retrospective Cohort Study. Selcuk Med J 2025;41(3): 158-164

Disclosure: *Author has no a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Diminished ovarian reserve (DOR) is a clinical condition characterized by a diminished response to ovarian stimulation during assisted reproductive treatments (ART), often resulting in lower oocyte retrieval, using high gonadotropin doses, decreased implantation rates, and challenges in achieving a successful pregnancy (1). The prevalence of DOR is increasing, partly due to delayed childbearing, which exposes more women to the natural decline in ovarian function. An estimate of 9–24% of women undergoing In Vitro Fertilization (IVF) are poor ovarian responders (2).

The outcome of an IVF cycle is significantly influenced by the ovarian response to gonadotrophin stimulation, among various other factors (3). A suboptimal ovarian response not only correlates with lower success rates in IVF treatments but also poses a heightened risk of obstetric and perinatal complications (4) in subsequent pregnancies when compared to alternative methods like intrauterine insemination (5).

The relationship between DOR and adverse maternal and neonatal outcomes remains a subject of ongoing debate. Several studies researched that women with poor ovarian response may be at increased risk of gestational diabetes (GDM), hypertensive disorders of pregnancy (HDP), preterm birth (PTB), and other complications (6, 7). For instance, Li et al., observed that certain Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) groups, particularly older women with low ovarian reserve, showed higher incidences of GDM, HDP, and first-trimester pregnancy loss compared to women with normal ovarian function (6). On the other hand, some evidence contradicts these findings. Jin et al., reported that among women under 38 years of age, DOR did not increase the likelihood of maternal complications or adverse neonatal outcomes such as low birth weight (LBW) or PTB in singleton pregnancies (7). The discrepancies in the literature may be attributed to differences in study populations, methodologies, and the criteria used to define DOR. For example, while some studies focus on older women undergoing ART, others investigate younger populations with varying degrees of ovarian reserve. Moreover, confounding factors such as age, body mass index (BMI), and preexisting medical conditions often complicate the interpretation of results.

Despite these difficulties, which can make IVF seem like a last resort, infertile couples need to weigh its disadvantages against the chances of success and the possibility of achieving a live birth. This underscores the importance of conducting further research and in-depth studies on the subject. This study aims to evaluate whether DOR is associated with poorer perinatal outcomes, including adverse maternal and neonatal complications. Understanding these associations is critical for informing clinical management and improving outcomes in this growing patient population.

MATERIALS METHODS

This research involved a retrospective cohort of women who achieved a singleton live birth following fresh embryo transfer during intracytoplasmic sperm injection (ICSI) cycles at the University of Health Sciences Konya City Hospital IVF Unit, from 2019 to 2022. The outcome of 26 live birth patients who underwent ICSI due to DOR, were compared with the obstetric and perinatal outcomes of 63 live birth patients who underwent ICSI due to male factor as a control group. To exclude maternal factors, we included patients who underwent ICSI due to male factor and had a singleton live birth after fresh single embryo transfer as a control group. The controls were matched by age and BMI. Complications for mothers and newborns were compared between the DOR group and the control group.

Inclusion criteria for the study were; patients who underwent ICSI due to DOR and achieved live births as the study group (n=26) and patients who underwent ICSI due to male factor and achieved live births, as the control group (n=63). At the same time, patients who had a single fresh 3rd or 5th day embryo transfer and had a single live birth. Exclusion criteria; Patients over 40 years of age, due to age-related perinatal and obstetric risks, patients with systemic diseases, endometrioma/endometriosis, polycystic ovary syndrome, patients with more than 1 embryo transfer, frozen embryo transfer cycles. Information about the patients was obtained from infertility files and computerized data. Each participant in this study signed a written informed consent. Ethical approval of this manuscript was obtained from Karatay University Faculty of Medicine (Date: 26.12.2024, number: 2024/008).

Patients born at 24 weeks and over were accepted as live births. Among the maternal and neonatal complications analyzed were HDP, PTB, preterm premature rupture of membranes (PPROM), LBW, GDM and abruptio placenta, intrahepatic cholestasis, c- section rate, fetal anomaly. Patients defined as, DOR if two out of these three criteria were met; 1) Anti-Müllerian Hormone (AMH) < 1.2 ng/mL, 2) Antral Follicle Count (AFC) < 7 on days 2–4 of the menstrual cycle, 3) basal serum Follicle-Stimulating Hormone (FSH) > 10 U/L. Patients with hypertensive disorders were diagnosed according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria (8). In the current study, HDP includes gestational hypertension and pre-eclampsia and excludes chronic hypertension. PTB is characterized by a live birth occurring before 37 weeks of pregnancy. LBW is identified when a full-term newborn's birth weight is under 2500 grams. The diagnosis of GDM according to WHO criteria is made when one or more of the following criteria are met: fasting plasma glucose ≥ 7.0 mmol/l; 2-hour plasma glucose ≥ 11.1 mmol/l following a 75 g oral glucose load; random plasma glucose ≥ 11.1 mmol/l in the presence of diabetes symptoms (9). Intrahepatic cholestasis of pregnancy is characterized by pruritus and an elevation in serum bile acid concentrations, typically developing in the late second and/or third trimester and rapidly resolving after delivery (10).

Ovarian stimulation protocol

Basal hormone profiles were assessed on the 2nd or 3rd day of menstruation for all patients. To rule out persistent cysts, transvaginal ultrasonography was performed. Patients were administered either a fixed or flexible short antagonist protocol,

with individualized doses of recombinant Follicle-Stimulating Hormone (recFSH) (Gonal f, Merck, Italy) or recFSH+Human Menopausal Gonadotropin (HMG) (75-150 IU of Merional, IBSA, Switzerland) initiated on the 2nd or 3rd day of the cycle based on BMI. Patients were recalled every 2-3 days for transvaginal folliculometry, and measurements of Luteinizing Hormone (LH), estradiol, and progesterone. Upon the dominant follicle exceeding 12mm, a Gonadotropin-Releasing Hormone (GnRH) antagonist (Cetrorelix, Merck, Italy) was added for flexible antagonist protocol. GnRH antagonist (Cetrorelix, Merck, Italy) was added on day 6th day of stimulation in patients using a fix antagonist protocol. When follicles reached a size of 17-18mm, final maturation was induced with recHCG (Ovitrelle, Merck, Italy). Oocyte retrieval was conducted under anesthesia 34-36 hours after triggering. All patients underwent standard ICSI with Metaphase II (MII) oocytes. The highest-quality embryos from day 3 or day 5 were transferred using a soft catheter under ultrasound guidance. Post-transfer, patients received routine luteal support of 3x200mg intravaginal progesterone (Progestan caps, Koçak Farma, Istanbul). Patients were invited back to the hospital for a pregnancy test 12 days following the transfer.

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY, USA). The conformity of continuous variables to normal distribution was evaluated by Kolmogorov-Smirnov test and histograms. Continuous variables showing normal distribution were expressed as mean ± standard deviation (Mean ± SD) and continuous variables not showing normal distribution were expressed as median (Min-Max). Categorical variables were expressed as n (%). In intergroup comparisons, Independent t-test was used for variables with normal distribution and Mann-Whitney U test was used for variables without normal distribution. Chi-square test or Fisher exact test was used when appropriate for analyses of categorical variables. Logistic regression analysis was performed to evaluate the risk factors for PPROM. The results of the regression analysis are reported with odds ratios (odds ratios, OR) and 95% confidence intervals (confidence intervals, CI). In all statistical tests, a value of $p < 0.05$ was accepted as the limit of statistical significance. Patients born at 24 weeks and over were accepted as live births.

RESULTS

A comparison was made of the demographic and hormonal characteristics of the DOR and control groups (Table 1). The analysis revealed no statistically significant differences in age (33.63 ± 5.09 years vs. 32.89 ± 4.04 years, p = 0.464) or BMI [23.67 (20.00-33.00) kg/m2 vs. 23.80 (19.45-30.05) kg/m2, p = 0.476] between the groups. However, a significant difference was observed in antral follicle count (AFC) [5.00 (2.00-12.00) vs. 11.00 (8.00-13.00), p = 0.001] and antimüllerian hormone (AMH) levels (0.92 ± 0.36 ng/mL vs. 3.04 ± 0.96 ng/mL, p = 0.001) were significantly lower in the DOR group compared to the control group.

The total FSH dose required was significantly higher in the DOR group (2834.26 ± 606.07 IU vs. 1826.19 ± 338.15 IU, p = 0.001), while serum estradiol levels on the hCG day were

Table 1. Comparison of clinical and hormonal parameters between DOR and controls

Variables	DOR (n=27)	Control Group (n=63)	p-value
Age (years)	33.63 ± 5.09	32.89 ± 4.04	0.464*
BMI (kg/m^2)	23.67 (20.00-33.00)	23.80 (19.45-30.05)	0.476**
AFC (n)	5.00 (2.00-12.00)	11.00 (8.00-13.00)	0.001**
AMH (ng/mL)	0.92 ± 0.36	3.04 ± 0.96	0.001*
FSH (U/L)	13.11 ± 2.63	6.55 ± 2.18	0.012*
LH (U/L)	8.00 (2.82-13.00)	5.99 (3.89-13.59)	0.066**
E2 (ng/L)	40.80 ± 13.48	39.23 ± 11.41	0.574*
Progesterone (µg/L)	0.84 ± 0.26	1.00 ± 0.22	0.004*

AMH: anti-müllerian hormon *independent t test(mean+SD), **Mann Whitney U test[Median(Min-Max)]. DOR: diminished ovarian reserve, BMI: body mass index, AFC: antral follicle count, FSH: follicle stimulating hormone, LH: luteinizing hormone, E2: estradiol, n: number

Table 2. Comparison of IVF cycle parameters and laboratory outcomes between DOR and control groups

Variables	DOR (n=27)	Control Group (n=63)	p-value
Total FSH Dose (IU)	2834.26 ± 606.07	1826.19 ± 338.15	0.001*
E2 on hCG Day (ng/L)	1079.37 ± 251.01	2578.62 ± 527.10	0.001*
Endometrial Thickness on hCG Day (mm)	10.42 ± 2.23	12.10 ± 1.74	0.001*
Stimulation Duration (days)	10.00 (8.00-12.00)	10.00 (9.00-11.00)	0.756**
Oocytes Retrieved (n)	4.89 ± 1.87	10.43 ± 2.80	0.001*
MII Oocytes (n)	3.30 ± 1.46	7.08 ± 2.16	0.001*
Total Embryos (n)	2.19 ± 0.96	4.90 ± 1.49	0.001*
Number of Embr. Transferred	1.57± 0.62	2.09 ± 0.70	<0.001
Blastocyst Transfer (n)	0	12(19.04)	0.002
Endometrial Thickness on Transfer Day (mm)	11.45 ± 2.15	12.71 ± 1.73	0.004*

IVF: In Vitro Fertilization FSH:follicle stimulating hormone E2: estradiol DOR: diminished ovarian reserve*independent t test(mean+SD), **Mann Whitney U test[Median(Min-Max)]. HCG: human chorionic gonadothropin, mm: milimeter

Table 3. Comparison of obstetric and neonatal outcomes between DOR and control groups

Variables	DOR (n=27)	Control Group (n=63)	p-value
Birth weight(gr)	2300.0 (900.0 – 4000.0)	3150.0 (900.0 – 4100.0)	0.011*
Birth week	38.0 (26.0 – 40.0)	38.0 (28.0 – 40.0)	0.172*
Preterm birth<34 week(n)	8 (29.6%)	7 (11.1%)	0.031**
Preterm birth<37 week(n)	13 (48.1%)	19 (30.2%)	0.102**
GDM(n)	2 (7.4 %)	4 (6.3 %)	0.854**
HDP(n)	4 (14.8 %)	8 (12.7 %)	0.787**
PPROM (n)	7 (25.9 %)	5 (7.9 %)	0.021**
Abruptio placenta(n)	1 (3.7 %)	2 (3.2 %)	0.898**
Intrahepatic cholestasis(n)	1 (3.7 %)	1 (1.6 %)	0.533**
C-Section Rate(n)	19 (70.4 %)	40 (63.5 %)	0.529**
Congenital Anomaly(n)	1 (3.7 %)	3 (4.8 %)	0.823**

DOR: diminished ovarian reserve *Mann Whitney U test[Median(Min-Max)], ** Chi Square test(n%). GDM: gestational diabetes mellitus, PTB: preterm birth, LBW: low birth weight, PPROM: preterm premature rupture of membranes, HDP: hypertensive disorders of pregnancy,gr: grams, c-section: cesarean

Table 4. Logistic regression analysis of factors associated with PPROM in IVF patients

Variable	Coefficient	Std. Error	Wald	p-value	Odds Ratio	95% CI
Constant	-2.812	5.547	0.257	0.612		
BMI	-0.075	0.122	0.378	0.538	0.92	0.72 - 1.17
Age	0.041	0.077	0.292	0.588	1.04	0.89 - 1.21
DOR group	2.025	0.766	6.979	0.008	7.57	1.68 - 34.05
ET on Tx Day	0.004	0.184	0.006	0.979	1.00	0.69 - 1.44
ET on hCG Day	0.306	0.200	2.346	0.125	1.35	0.91 - 2.01
Stimulation Duration	-0.320	0.300	1.135	0.286	0.72	0.40 - 1.30

DOR: diminished ovarian reserve BMI: body mass index Et: endometrial thickness,tx: transfer

markedly lower in the DOR group (1079.37 ± 251.01 ng/L vs. 2578.62 ± 527.10 ng/L, p = 0.001). A significant difference was observed in the number of oocytes retrieved between the two groups (4.89 ± 1.87 vs. 10.43 ± 2.80, p = 0.001). Furthermore, a lower proportion of M2 oocytes was observed in the poor responder group (3.30 ± 1. 46 vs. 7.08 ± 2.16, p = 0.001), and total embryos formed (2.19 ± 0.96 vs. 4.90 ± 1.49, p = 0.001) (Table 2).

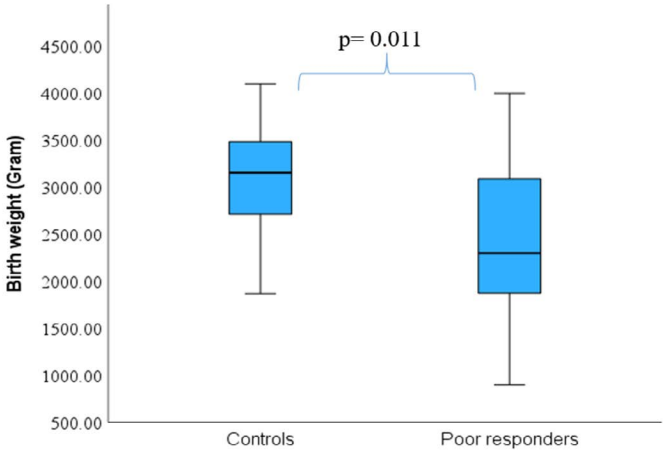


Figure 1. Box Plot Graph Comparing Birth Weight Between DOR and Control Groups in IVF Patients

Birth weight was significantly lower in the DOR group [2300.0 (900.0–4000.0) g vs. 3150.0 (900.0–4100.0) g, p = 0.011] (Figure 1). However, no significant difference was observed in gestational age at birth [38.0 (26.0–40.0) weeks vs. 38.0 (28.0–40.0) weeks, p = 0.172]. Preterm birth (PTB) rates of less than 34 weeks were 29.6% in the DOR group and 11.1% in the control group (p = 0.031). The odds ratio for PTB before 34 weeks was 3.36 (95% CI: 1.07–10.53), indicating a significantly increased risk in the DOR group. Similarly, the incidence of PPROM was significantly higher in the DOR group (25.9% vs. 7.9%, p = 0.021), with an associated odds ratio of 7.57 (95% CI: 1.68–34.05), suggesting a strong association between DOR and PPROM. The rates of GDM and HDP were similar between the groups (7.4% vs. 6.3%, p = 0.854; and 14.8% vs. 12.7%, p = 0.787, respectively). No significant differences were found in placental abruption (3.7% vs. 3.2%, p = 0.898), intrahepatic cholestasis (3.7% vs. 1.6%, p = 0.533), or congenital anomalies (3.7% vs. 4.8%, p = 0.823). Cesarean section rates were higher in the DOR group (70.4% vs. 63.5%), but the difference did not reach statistical significance (p = 0.529) (Table 3).

Logistic regression analysis was performed to assess factors associated with PPROM risk. The analysis revealed that DOR were significantly associated with an increased risk of PPROM in IVF patients compared to controls (Odds Ratio [OR] = 7.57, 95% CI: 1.68-34.05, p = 0.008). BMI (OR = 0.92, 95% CI: 0.72-1.17, p = 0.538), age (OR = 1.04, 95% CI: 0.89-1.21, p = 0.588), endometrial thickness on the day of transfer (OR = 1.00, 95% CI:

0.69-1.44, p = 0. 979), endometrial thickness on hCG day (OR = 1.35, 95% CI: 0.91-2.01, p = 0.125) and duration of stimulation (OR = 0.72, 95% CI: 0.40-1.30, p = 0.286) were not significantly associated with PPROM (Table 4).

DISCUSSION

Having DOR is associated with increased implantation failure , reduced rates of live births (11) and higher miscarriage rates (12). In this article, we investigate whether DOR is also linked to poor obstetric outcomes. We compared the perinatal outcomes of patients with DOR who underwent IVF and had live births with a control group who underwent IVF due to male factors and also had live births. We found that the group with DOR had statistically higher risks of LBW (2.300 gr vs. 3500 gr, p=0.011), PPROM (7 vs 5, p=0.020) and PTB rates of less than 34 weeks (p = 0.031) than the control group.

An expanding body of research endorses the developmental origins of health and disease (DOHaD) hypothesis, suggesting that the foundational elements for chronic conditions are set during early life, particularly through the intrauterine environment (13). For example, compared to infants of normal birth weight, those born with lower weights are at a higher risk of encountering hypertension, diabetes, and other metabolic disorders during both childhood and adulthood (14). Therefore, investigating exposures during the intrauterine period is crucial for researching the etiologies of diseases. Some publications have found that high gonadotropin doses used in patients with low ovarian reserve are associated with aneuploidy and low blastocyst formation (15), while other research fails to observe this correlation (16, 17). LoraK.Shahine et al., found that the number of blasts developing in patients with low ovarian reserve was low and the aneuploidy rate was high (18). In our own study, we found a statistically lower rate of blast transfer in the DOR group.

A study investigates maternal and neonatal complications in women with DOR undergoing IVF or ICS) cycles. Conducted with 193 in the DOR group and 386 in the control group. The results indicated a significantly higher incidence of HDP in the DOR group (5.7%) compared to the control group (2.1%, p= 0.021). Although the incidences of PTB (10.9% vs. 7.5%, p= 0.174) and LBW (6.2% vs. 5.4%, p= 0.704) were higher in the DOR group, these differences were not statistically significant (19). However, in our study, we did not find a significant difference in HDP between the DOR and control groups. With a reduced number of oocytes, DOR is a prevalent condition linked to ovarian aging. Per the advisory statement from the American Society for Reproductive Medicine, the aging of ovaries is linked to irregularities in luteal phase function (20). The production of progesterone and estradiol metabolites during the luteal phase is significantly reduced in women of advanced age. Additionally, it has been documented that vascular issues and hypertensive pregnancy disorders are associated with dysfunction in the luteal phase (21). In our study, the lack of a higher incidence of HDP compared to the control group might be due to the control group not consisting of women of advanced maternal age. A study, which supports our research, also shows that women with a history of HDP do not necessarily exhibit DOR, as measured by AMH levels, compared to women with uncomplicated pregnancies (22).

Zhu et al. (23), examined the effects of DOR on the outcomes of IVF/ICSI among young women aged ≤35 years. The study found that women with DOR had significantly lower rates of blastocyst formation, embryo implantation, clinical pregnancy, and live birth compared to their non-DOR counterparts. However, there were no significant differences in high-quality embryo rates, miscarriage rates, or LBW incidences between the two groups. The study concludes that while DOR reduces clinical pregnancy and live birth rates, it does not increase the risk of perinatal complications or affect the LBW incidence in infants. These findings align with a major study showing no significant differences in low birth weight rates between women with fewer than four oocytes and those with normal ovarian reserve after adjusting for confounders (24). Additionally, a previous study found that infants from IVF patients with low ovarian responsiveness had similar birth weights to those with normal responsiveness, with no significant differences in low birth weight or size for gestational age (25). This may be due to the fact that patients over 35 years of age were also included in the study group and the number of participants was low.

There are also reports in the literature that PTB is increased in IVF pregnancies (26). There is a meta-analysis evaluating the association between IVF or ICSI and the risk of spontaneous PTB in singleton pregnancies compared to natural conception. Based on data from 15 cohort studies comprising over 61,000 pregnancies, the analysis reveals that sPTB (<37 weeks) occurs more frequently in IVF/ICSI pregnancies (10.1%) than in naturally conceived ones (5.5%), with an odds ratio of 1.75. The study highlights a significant increase in PTB risk for IVF/ICSI pregnancies but calls for caution in interpretation due to the low quality of evidence (27). A study investigates the impact of infertility causes on perinatal outcomes, specifically PTB and LBW, in singleton pregnancies achieved via IVF or ICSI. Using data from the Human Fertilization and Embryology Authority (HFEA), the study found that ovulatory and tubal disorders significantly increase the risk of PTB and LBW compared to unexplained infertility, while male factor infertility showed no significant impact. The findings suggest that the underlying cause of infertility plays a crucial role in perinatal risks (28). In our study, we found that the rate of PTB below 34 weeks of gestation was statistically significantly higher in patients who underwent IVF due to DOR than in patients who underwent IVF due to male factor.

Limitation of this paper is that it is retrospective and includes very few patients. Due to the retrospective design of our study, no prior power analysis was performed. However, a post hoc power analysis based on birth weight difference yielded 82% statistical power (Cohen's d = 0.73, α = 0.05). Another weakness is the lack of a control group of non-IVF patients. In addition, other potential confounders (such as smoking, socioeconomic status, chronic diseases) could not be evaluated because they were not included in the recorded data. On the other hand the control group was selected only

from patients with male factor-related infertility, which may lead to differences in hormonal environment and may lead to selection bias. In future studies, comparisons with groups with different causes of infertility are recommended.

CONCLUSION

In summary, this study highlights the significant impact of DOR on perinatal outcomes in women undergoing ICSI. While DOR was associated with an increased risk of adverse outcomes such as LBW, PTB before 34 weeks, and PPROM, it did not appear to exacerbate HDP or GDM compared to controls. These findings emphasize the need for personalized management strategies in patients with DOR to mitigate risks and optimize both maternal and neonatal outcomes. Further research with larger cohorts and diverse populations is warranted to deepen our understanding and improve clinical care for this unique patient group.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

Address correspondence to: *Dilay Gok Korucu, University of Health Sciences, Konya City Hospital, Department of Obstetrics and Gynecology, IVF unit, Konya, Türkiye*
e-mail: *dilaygok@yahoo.com*

REFERENCES

1. Abdullah RK, Liu N, Zhao Y, et al. Cumulative live-birth, perinatal and obstetric outcomes for POSEIDON groups after IVF/ICSI cycles: a single-center retrospective study. Sci Rep. 2020;10(1):11822:https://doi.org/10.1038/s41598-020-68896-1
2. Triantafyllidou O, Sigalos G, Vlahos N. Dehydroepiandrosterone (DHEA) supplementation and IVF outcome in poor responders. Hum Fertil (Camb). 2017;20(2):80-7: https://doi.org/10.1080/14647273.2016.1262065
3. Grisendi V, Mastellari E, La Marca A. Ovarian Reserve Markers to Identify Poor Responders in the Context of Poseidon Classification. Front Endocrinol (Lausanne). 2019;10:281: https://doi.org/10.3389/fendo.2019.00281
4. Cromi A, Candeloro I, Marconi N, et al. Risk of peripartum hysterectomy in births after assisted reproductive technology. Fertil Steril. 2016;106(3):623-8: https://doi.org/10.1016/j.fertnstert.2016.05.005
5. Bahadur G, Homburg R, Bosmans JE, et al. Observational retrospective study of UK national success, risks and costs for 319,105 IVF/ICSI and 30,669 IUI treatment cycles. BMJ Open. 2020;10(3):e034566: https://doi.org/10.1136/bmjopen-2019-034566
6. Li S, Tan H, Fu H, et al. Maternal and neonatal complications after IVF/ICSI-fresh embryo transfer in low-prognosis women under the POSEIDON criteria: A retrospective cohort study. BMC Pregnancy Childbirth. 2023;23(1):855: https://doi.org/10.1186/s12884-023-06176-2
7. Jin H, Yan E, Chen D, et al. Diminished ovarian reserve may not be associated with a poorer fresh cycle outcome in women < 38 years. J Ovarian Res. 2023;16(1):77: https://doi.org/10.1186/s13048-023-01158-6
8. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy Hypertens. 2014;4(2):97-104: https://doi.org/10.1016/j.preghy.2014.02.001
9. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. Diabetes Res Clin Pract. 2014;103(3):341-63: https://doi.org/10.1016/j.diabres.2013.10.012
10. Clinical Updates in Women's Health Care Summary: Liver Disease: Reproductive Considerations. Obstet Gynecol. 2017;129(1):236: https://doi.org/10.1097/aog.0000000000001858
11. Leijdekkers JA, Eijkemans MJC, van Tilborg TC, et al. Cumulative live birth rates in low-prognosis women. Hum Reprod. 2019;34(6):1030-41: https://doi.org/10.1093/humrep/dez051
12. Sunkara SK, Khalaf Y, Maheshwari A, et al. Association between response to ovarian stimulation and miscarriage following IVF: An analysis of 124 351 IVF pregnancies. Hum Reprod. 2014;29(6):1218-24: https://doi.org/10.1093/humrep/deu053
13. Barker DJ. The fetal and infant origins of adult disease. Bmj. 1990;301(6761):1111: https://doi.org/10.1136/bmj.301.6761.1111
14. Pelkonen S, Koivunen R, Gissler M, et al. Perinatal outcome of children born after frozen and fresh embryo transfer: The Finnish cohort study 1995–2006. Human Reproduction. 2010;25(4):914-23: https://doi.org/10.1093/humrep/dep477
15. Braga DP, Setti AS, Figueira Rde C, et al. Contributing factors for the incidence of aneuploidy in older patients undergoing intracytoplasmic sperm injection cycles. J Assist Reprod Genet. 2012;29(9):911-6: https://doi.org/10.1007/s10815-012-9795-x
16. Baart EB, Martini E, Eijkemans MJ, et al. Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: A randomized controlled trial. Hum Reprod. 2007;22(4):980-8: https://doi.org/10.1093/humrep/del484
17. Massie JA, Shahine LK, Milki AA, et al. Ovarian stimulation and the risk of aneuploid conceptions. Fertil Steril. 2011;95(3):970-2: https://doi.org/10.1016/j.fertnstert.2010.07.1088
18. Shahine LK, Marshall L, Lamb JD, et al. Higher rates of aneuploidy in blastocysts and higher risk of no embryo transfer in recurrent pregnancy loss patients with diminished ovarian reserve undergoing in vitro fertilization. Fertility and sterility. 2016;106(5):1124-8: https://doi.org/10.1016/j.fertnstert.2016.06.016
19. Han S, Zhai Y, Guo Q, et al. Maternal and Neonatal Complications in Patients With Diminished Ovarian Reserve in In-Vitro Fertilization/Intracytoplasmic Sperm Injection Cycles. Front Endocrinol (Lausanne). 2021;12:648287: https://doi.org/10.3389/fendo.2021.648287
20. Diagnosis and treatment of luteal phase deficiency: a committee opinion. Fertil Steril. 2021;115(6):1416-23: https://doi.org/10.1016/j.fertnstert.2021.02.010
21. von Versen-Höynck F, Narasimhan P, Selamet Tierney ES,et al. Absent or Excessive Corpus Luteum Number Is Associated With Altered Maternal Vascular Health in Early Pregnancy. Hypertension. 2019;73(3):680-90: https://doi.org/10.1161/hypertensionaha.118.12046
22. van Bree BE, Jorissen LM, Pattinaja D, et al. No evidence for a diminished ovarian reserve among patients with hypertensive disorders of pregnancy: a case control study. J Ovarian Res. 2024;17(1):5: https://doi.org/10.1186/s13048-023-01333-9
23. Zhu S, Jiang W, Liao X, et al. Effect of diminished ovarian reserve

on the outcome of fresh embryo transfer in IVF/ICSI cycles among young women: A retrospective cohort study. BMC Womens Health. 2024;24(1):230:https://doi.org/10.1186/s12905-024-03039-6
24. Yang X, Zhang J, Wu J, et al. Association between the number of oocytes retrieved and neonatal outcomes after freeze-all IVF cycles. Human Reproduction. 2019;34(10):1937-47: https://doi.org/10.1093/humrep/dez137
25. Huang J, Lu X, Lin J, et al. Association between peak serum estradiol level during controlled ovarian stimulation and neonatal birthweight in freeze-all cycles: A retrospective study of 8501 singleton live births. Human Reproduction. 2020;35(2):424-33: https://doi.org/10.1093/humrep/dez262
26. Salmeri N, Alteri A, Farina A, et al. Preterm birth in singleton pregnancies conceived by in vitro fertilization or intracytoplasmic sperm injection: an overview of systematic reviews. Am J Obstet Gynecol. 2024;231(5):501-15.e9: https://doi.org/10.1016/j.ajog.2024.05.037
27. Cavoretto P, Candiani M, Giorgione V, et al. Risk of spontaneous preterm birth in singleton pregnancies conceived after IVF/ICSI treatment: Meta-analysis of cohort studies. Ultrasound Obstet Gynecol. 2018;51(1):43-53: https://doi.org/10.1002/uog.18930
28. Sunkara SK, Antonisamy B, Redla AC, et al. Female causes of infertility are associated with higher risk of preterm birth and low birth weight: Analysis of 117 401 singleton live births following IVF. Human reproduction. 2021;36(3):676-82: https://doi.org/10.1093/humrep/deaa283

NEU PRESS

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2025.01829
Selcuk Med J 2025;41(3): 165-170

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

The Role of Demodex in Patients with Facial Dermatosis

Fasiyal Dermatozlu Hastalarda Demodeks' in Rolü

Gunseli Kekec[1], Hatice Meral Eksioglu[2], Emine Yalcin Edguer[2]

[1]University of Health Sciences, Konya City Hospital, Konya, Turkiye
[2]University of Health Sciences, Ankara Training and Research Hospital, Ankara, Turkiye

ÖZET

Amaç: Bu çalışmada yüz dermatozu nedeniyle takip edilen hastalarda ve sağlıklı bireylerde yüzeyel deri biyopsisi yöntemi kullanılarak Demodex spp. sıklığının araştırılması ve bu patojenin yüz dermatozu, hijyen alışkanlıkları ve deri tipi ile ilişkisinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmamıza klinik ve / veya histopatolojik olarak rozasea, steroide bağlı perioral dermatit, perioral dermatit, seboreik dermatit, akne vulgaris tanısı alan her yaş grubundan 103 yüz dermatozuna sahip hasta, kontrol grubu olarak ise Ankara Eğitim Araştırma Hastanesi Deri ve Zührevi Hastalıklar Polikliniği' ne başvuran, yüz dermatozu olmayan, aynı yaş ve cinsiyet dağılımında 104 gönüllü hasta dahil edildi. Demodex spp. yoğunluğunu tespit etmek için en uygun yöntemlerden biri olan non - invaziv standart yüzeyel deri biyopsisi (SYDB) seçildi. Hastalar ve dermatozların alt grupları, kontrol grubundaki gönüllülerle; yaş, cinsiyet, demodeks pozitifliği, cilt tipi, hijyen alışkanlıkları gibi değişkenler bakımından istatistiksel olarak karşılaştırıldı.

Bulgular: Hasta grubunun yaş dağılımı 8 - 81 arasında değişmekte olup yaş ortalaması 37.37, kontrol grubunun yaş dağılımı 10 - 76 arasında değişmekte olup yaş ortalaması 35.42 idi. Hasta ve kontrol gruplarında Demodex varlığı arasında yaş, cinsiyet ve hijyen alışkanlıkları açısından istatistiksel olarak anlamlı bir korelasyon saptanmadı (p>0.05). Yüz dermatozu olan hastaların alt grupları karşılaştırıldığında, seboreik dermatitli hastaların %60,7'sinde Demodex tespit edildi (p=0,015). Yağlı cilde sahip hastalarda da anlamlı Demodex pozitifliği tespit edilmiştir. (p=0.010).

Sonuç: Yağlı cilt tipi ve yüz dermatozlarından seboreik dermatit Demodex ile pozitif yönlü anlamlı bir ilişki gösterse de yaş, cinsiyet, hijyen alışkanlıkları gibi faktörler bakımından Demodex varlığı ile ilişkili bulunmamıştır.

Anahtar Kelimeler: Demodeks, fasiyal dermatoz, seboreik dermatit, yağlı cilt

ABSTRACT

Objective: In this study, we aimed to investigate the frequency of Demodex spp. using the superficial skin biopsy method in patients with facial dermatosis and healthy individuals and to determine the relationship between this pathogen and facial dermatosis, hygiene habits, and skin type.

Materials and Methods: A total of 103 patients of all age groups who were clinically and/or histopathologically diagnosed with rosacea, steroid-induced perioral dermatitis, perioral dermatitis, seborrheic dermatitis, or acne vulgaris were included in the study. As a control group, 104 volunteer patients of the same age distribution who were admitted to the Skin and Venereal Diseases Polyclinic and did not have facial dermatosis were included in the study. A non-invasive standard superficial skin biopsy (SSSB), the most appropriate method for detecting Demodex spp. density, was performed. The patients and dermatose subgroups were statistically compared with the volunteers in the control group in terms of variables such as age, sex, Demodex positivity, skin type, and hygiene habits.

Results: The age distribution of the patient group ranged between 8-81 years with a mean age of 37.37±17.15 years. The age distribution of the control group ranged between 10-76 years and the mean age was 35.42±15.76 years. There was no statistically significant relationship between the presence of Demodex in the patient and control groups in terms of age, sex, and hygiene habits (p>0.05). When the subgroups of patients with facial dermatosis were compared, Demodex was detected in 60.7% of patients with seborrheic dermatitis (p=0.015). Significant Demodex positivity was also detected in patients with oily skin. (p=0.010).

Conclusion: Oily skin type and seborrheic dermatitis, one of the facial dermatoses, has a significant association with Demodex, while factors such as age, sex, hygiene habits were not found to be associated with the presence of Demodex.

Keywords: Demodex, facial dermatosis, seborrheic dermatitis, oily skin

INTRODUCTION

Demodex mites are members of the family Demodicidae, order Prostigmata, and class Arachnida, and are commonly found in humans, especially on the face (1). Only two mite species, Demodex folliculorum (DF) and Demodex brevis (DB), have been identified in humans (2). While Demodex folliculorum settles mostly in the infundibular part of hair follicles, DB settles in the deeper sebaceous glands and ducts (2, 3). Although these parasites can be found in any part of the skin, they are most commonly seen on the face. They are found more on the forehead, cheek, nose, nasolabial fold, chin, and eyelid, where sebum production is higher than in other areas of the face (4).

Demodex mites may play a role in the etiopathogenesis of rosacea, acne vulgaris, blepharitis, perioral dermatitis, seborrheic

Geliş Tarihi/Received: 8 February/Şubat 2025 **Kabul Tarihi/Accepted:** 4 September/Eylül **Yayın Tarihi/Published Online:** 28 September/Eylül 2025

Sorumlu Yazar/Corresponding Author: Gunseli Kekec, University of Health Sciences, Konya City Hospital, Konya, Turkiye **e-mail:** gunseli-07@hotmail.com

Atıf yapmak için/ Cite this article as: Kekec G, Eksioglu HM, Yalcin Edguder E. The Role of Demodex in Patients with Facial Dermatosis. Selcuk Med J 2025;41(3): 165-170

Disclosure: *Author has no a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

dermatitis, pustular folliculitis, papulopustular lesions of the scalp, and pustular lesions in acquired immunodeficiency syndrome (AIDS) (5). It has been reported that pathogenicity against these mites may increase in conditions such as lack of attention to skin hygiene, intensive use of cosmetic products, increased sebum production with sweating, oily skin, advanced age, and immunodeficiency (6).

In this study, we aimed to investigate the frequency of Demodex spp. using the superficial skin biopsy method in patients with facial dermatosis and healthy individuals and to determine the relationship between this pathogen and facial dermatosis, hygiene habits, and skin type.

MATERIAL METHOD

This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ankara Training and Research Hospital Clinical Research Ethics Committee, and written informed consent was obtained from all patients. 103 patients of all age groups who were clinically and/or histopathologically diagnosed with rosacea, steroid-induced perioral dermatitis, perioral dermatitis, seborrheic dermatitis, acne vulgaris and who agreed to be investigated for Demodex and who were admitted to the Ankara Training and Research Hospital Skin and Venereal Diseases Outpatient Clinic were included in the study. As a control group, 104 volunteer patients with the same age distribution who were admitted to the same outpatient clinic, did not have facial dermatosis, and accepted the study conditions were included in the study.

Data on hygiene habits (common towel, number of face washes, use and type of facial cleanser, and use of cosmetic products) and skin types were collected from the patients upon their first admission to the study. The patients and control group were examined one hour after washing and drying their faces with white soap. If the change in the napkin was in the form of a slight moistening when we gently pressed the entire face, it was classified as a neutral skin type. If the napkin appeared almost dry and not moist at all, it was classified as a dry skin type. If the napkin was dry when you did the napkin test on the cheek area, but oily around the nose and forehead, it was classified as a mixed skin type. If the napkin appeared quite oily and moist when applied to the entire face, it was classified as oily skin type

Non-invasive standard superficial skin biopsy (SSSB), which is the most appropriate method for the detection of Demodex spp. density, was performed. A drop of cyanoacrylic adhesive was placed on the clean slide. It was pressed on the lesioned skin area of the patient, held for one minute, and then withdrawn. Immersion oil was dripped onto the sample and covered with a coverslip. The preparations were examined under a light microscope at x10 and x40 magnifications to determine the density of Demodex spp. per cm2. The presence of five or more Demodex spp. per cm2 was considered positive for diagnosis.

Statistics

Data analysis was performed with SPSS (Statistical Package for Social Science (SPSS) 15.0 program, and a 95% confidence

Table 1. Demographic data of patients with facial dermatosis and control patients

Variables		Patient (n=103)	Control (n=104)	p
Age (Mean)		37,37±17,15	35,42±15,76	
Age Subgroup				0,443
	≤25 years	36 (%34,9)	36 (%34,6)	
	26-35 years	16 (%15,5)	23 (%22,1)	
	≥36 years	51 (%49,5)	45 (%43,2)	
Gender				0,027*
	Female	57 (%55,3)	73 (%70,1)	
	Male	46 (%44,6)	31 (%29,8)	

Table 2. Presence of Demodex in patient and control groups.

		Patient Group (n=103)	Control Group (n=104)	p
Demodex	Negative	59 (%57,3)	69 (%67)	0,179
	Positive	44 (%42,7)	35 (%34)	

Table 3. Distribution of Demodex in patient and control groups according to age.

		Demodex (-)	Demodex (+)	p
Patient Group	≤25 years	26 (%72,2)	10 (%27,7)	0,075
	26-35 years	8 (%50)	8 (%50)	
	≥36 years	25(%49)	26 (%51)	
Control Group	≤25 years	25 (%69,4)	11 (%30,6)	0,886
	26-35 years	15 (%65,2)	8 (%34,7)	
	≥36 years	19 (%54,2)	16 (%45,7)	

level was used. The chi-square test of independence was used to analyze the relationship between categorical variables. The p-value calculated as a result of the analysis was less than the significance coefficient of 0.05, indicating a relationship between the variables.

RESULTS

Of the 103 patients with facial dermatosis, 57 were female (55.3%) and 46 were male (44.6%). In the control group of 104 patients, 73 were female (70.1%) and 31 were male (29.8%). The demographic data of patients with facial dermatosis and control patients are shown in Table 1. The age distribution of the patient group ranged between 8-81 years with a mean age of 37.37±17.15 years. The age distribution of the control group ranged between 10-76 years and the mean age was 35.42±15.76 years. As indicated in Table 1, the patient and control groups were homogeneous in terms of age distribution. The presence of Demodex in the patient and control groups is presented in Table 2. Demodex was detected in 44 (42.7%) and 59 (57.3%) of 103 patients in the patient group. In the control group, 35 (34%) patients had Demodex, while 69 (67%) did not. There was no statistically significant difference between the patient and control groups in terms of the presence of Demodex (p>0.05)

Demodex was detected in 10 (27.7%) of 36 patients aged 25 years and younger, 8 (50%) of 16 patients aged 26-35 years, and 26 (51%) of 51 patients aged 36 years and older in the patient group. In the control group, Demodex was found in 11 (30.6%) of 36 patients aged ≤ 25 years, 8 (34.7%) of 23 patients aged 26-35 years, and 16 (45.7%) of 35 patients aged ≥ 36 years. There was no statistically significant relationship between the presence of Demodex and age in the patient and control groups (p>0.05) (Table 3). Demodex was found in 26 of 57 female (45.6%) and 18 of 46 male (39.1%) in the patient group. In the control group, Demodex was found in 25 of 73 female (34.2%) and 10 of 31 male (32.2%). There was no statistically significant relationship between the presence of Demodex and sex in the patient and control groups (p>0.05) (Table 4). Among patients with facial dermatosis, 48 (44%) had rosacea, 25 (23%) had acne, 28 (26%) had seborrheic dermatitis, 7 (6%) had perioral dermatitis, and 1 (1%) had contact dermatitis.

When the subgroups of patients with facial dermatosis were compared in terms of the presence of Demodex, Demodex was found in 22 (45.8%) of 48 patients with rosacea, 8 (32.0%) of 25 patients with acne vulgaris, and 1 (14.3%) of patients with perioral dermatitis. There was no statistically significant relationship between the presence of Demodex and rosacea, acne vulgaris, or perioral dermatitis (p=0.281). Demodex was detected in 17 (60.7%) of 28 patients with seborrheic dermatitis and a statistically positive relationship was found between seborrheic dermatitis and the presence of Demodex (p=0.015) (Table 5).

When common towel use, frequency of face washing, use of facial cleanser and cosmetic products were evaluated in the patient and control groups, the higher rate of common towel use in the patient group was statistically significant (p=0.044). In addition, the use of facial cleanser was lower in the patient group than in the control group (p=0.004). When hygiene habits were analyzed under the subheadings of common towel, number of face washes, use and type of facial cleanser, and use of cosmetic products, Demodex was found in 36% of patients who used "common towel" and in 40.6% of those who did not. Demodex was present in 54.5% of those who washed their face once a day or less and in 38.6% of those who washed their face five times or more. Mites were detected in 37.4% of those who did not use facial cleansers and 29.1% of those who did. Demodex was detected in 47.3% of those who used soap as a facial cleanser and in 30% of those who used non-

Table 4. Distribution of Demodex in patient and control groups according to gender.

		Demodex (-)	Demodex (+)	p
Patient Group	Female	31 (%54,3)	26 (%45,6)	0,645
	Male	28 (%60,8)	18 (%39,1)	
Control Group	Female	48 (%65,7)	25 (%34,2)	1,000
	Male	21 (%67,7)	10 (%32,2)	

Table 5. Relationship between Demodex and facial dermatoses.

		Demodex (-)	Demodex (+)	p
Rosacea	-	102 (%64,2)	57 (%35,8)	0,281
	+	26 (%54,2)	22 (%45,8)	
Acne vulgaris	-	111 (%61,0)	71 (%39,0)	0,648
	+	17 (%68,0)	8 (%32,0)	
Seborrheic dermatitis	-	117 (%65,4)	62 (%34,6)	0,015*
	+	11 (%39,3)	17 (%60,7)	
Perioral dermatitis	-	122 (%61,0)	78 (%39,0)	0,179
	+	6 (%85,7)	1 (%14,3)	
Contact dermatitis	-	128 (%62,1)	78 (%37,9)	0,382
	+	0 (%0,0)	1 (%100)	

Table 6. Relationship between facial dermatoses, demodex and skin type.

		Patient (n=103)	Control (n=104)	Demodex (-)	Demodex (+)	p
Skin Type	Neutral	3 (%2,9)	10 (%9,7)	11 (%84,6)	2 (%15,4)	0,010*
	Oily	52 (%50,5)	13(%12,6)	30 (%46,2)	35 (%53,8)	
	Dry	30 (%29,1)	49(%47,6)	54 (%68,4)	25 (%31,6)	
	Mix	18 (%17,5)	32(%31,1)	33 (%66,0)	17 (%34,0)	

soap cleansers. Although Demodex was found to be positive in 33.7% of those who used cosmetic products and 42.3% of those who did not. No statistically significant relationship was observed between hygiene habits and the presence of Demodex (p>0.05).

In the patient group, 2.9% had neutral skin, 50.5% had oily skin, 29.1% had dry skin, and 17.5% had mixed skin types. There was a statistically significant difference in skin structural characteristics between the patient and control groups (p<0.05). Demodex was detected in 15.4% of those with neutral skin, 53.8% of those with oily skin, 31.6% of those with dry skin and 34.0% of those with mixed skin. There was a statistically significant relationship between the presence of Demodex and the skin type(p=0.010). Demodex mites were detected at a higher rate in the group with oily skin than in the group with neutral, dry, and mixed skin type (Table 6).

DISCUSSION

DF and DB species are accepted as pathogens that settle in the human body. While it has been stated that the settlement of mites in pilosebaceous follicles may be harmless, some authors have stated that they may play a role in the etiopathogenesis of skin diseases localized on the face (2). When the incidence of Demodex according to age was examined in studies, it was reported that there were no mites in children, it was rare in adolescents, and the incidence of mites increased with age (8-10). The incidence of Demodex increases with age, with a rate of 13% between the ages of 3 and 15 years and up to 95% between the ages of 71 and 96 years (11). In our study, the total incidence rate of Demodex was 38.1%. When the distribution according to age groups was evaluated, although not significant, it was found that the rate of Demodex was positively correlated with age in accordance with the literature. This finding may be due to the increase in sebaceous activity with age, which creates a favorable environment for mite proliferation and increases the incidence of mites in older individuals. There are conflicting results in the literature regarding the relationship between sex and Demodex. In their study conducted in 2010 on patients with a diagnosis of rosacea, Taş et al. found that the rate of parasite presence in females was higher than that in males and reported a significant relationship between sex and mite positivity (12). In this study, no significant relationship was found between sex and Demodex positivity in the control and patient groups.

Different results related to the relationship between facial dermatoses and Demodex have been reported in the literature. In skin biopsy samples obtained by Roihu and Kariniemi in 1998 from 80 patients with rosacea, 40 patients with eczematous eruptions, and 40 patients with discoid lupus erythematosus, the prevalence of mites in patients with rosacea (51%) was higher than that in patients with eczema (28%) and discoid lupus erythematosus (31%) (13). Of the 103 patients who participated in our study, 44% had rosacea. Demodex was positive in 45.8% of 48 patients with rosacea. Although not significant, a high rate of Demodex positivity was found on the faces of patients with rosacea, similar to that reported in the literature. Polat et al. detected DF in 12 (15.4%) of 78 patients with acne vulgaris in samples taken from three different facial regions, including the forehead, cheek, and chin, and from pimples using the SSSB method (14). Baysal et al. detected Demodex in 11.8% of 101 patients with acne vulgaris and stated that they could not detect any mites in the control group (15). In this study, 25 (23%) of 103 patients with facial dermatosis were diagnosed with acne vulgaris, and Demodex mites were found to be positive in 32% of them. However, no significant differences were observed when compared with those without acne vulgaris (p>0.05). It was thought that the fact that acne vulgaris is generally seen in the adolescent age group and the incidence of Demodex mites increases with age may be the reason for the low rate of mites seen in this young patient group.

In contrast to the above studies, the lack of a statistically significant relationship between rosacea, acne vulgaris, and perioral dermatitis and Demodex positivity in our study may be due to the small number of patients in these groups, or it may be due to the inability to detect mites located deep in the follicles with the SSSB method.

Seborrheic dermatitis is a chronic and superficial inflammatory skin disorder that typically presents with erythematous, oily, yellow squames on sebaceous gland-rich areas, such as the scalp, face, chest, back, and flexural regions. Although its exact etiology remains unidentified, multiple factors, including increased sebum production, Pityrosporum ovale colonization, medications, immune dysfunction, genetic predisposition, neurological disorders, psychological stress, dietary habits, lifestyle, and environmental factors, have been associated with its development or worsening of its symptoms (16). In a case-control study conducted by Karabay et al. in 2020 with 127 patients, the three most common facial dermatoses, acne vulgaris, rosacea, and seborrheic dermatitis, were investigated in terms of Demodex etiopathogenesis via superficial skin biopsy (17). The findings of this study suggest a significant association between Demodex infestation and the presence of rosacea, acne vulgaris, and seborrheic dermatitis in patients with psoriasis. Immune system activation, inflammatory responses, and follicular alterations induced by Demodex mites may play a role in the pathogenesis of these conditions. In a case-control study conducted by Kilinc et al. in

2023, Demodex mites were investigated in the lesions of patients with seborrheic dermatitis, in their skin without lesions, and in the control group; mite positivity was found to be 50%, 2.6%, and 12.5%, respectively. In light of the statistical data obtained, they thought that Demodex, which is a part of the microbiota, may be a predisposing factor in the development of Seborrheic Dermatitis (18). In a study conducted by Karıncaoğlu et al. in 2009, mites were found to be positive in 50% of patients with seborrheic dermatitis (19). In this study, seborrheic dermatitis was detected in 28 of the 103 patients (26%). 60.7% of the patients with seborrheic dermatitis had Demodex, which was higher than the rate reported by Karıncaoğlu et al. in 2009 and there was a relationship between seborrheic dermatitis and the presence of Demodex ($p<0.05$). This result supports the commonly known theories that increased mite density may stimulate sebaceous follicles and increase sebum secretion, and that cytokines released from keratinocytes by reactivating the immune system or stimulating inflammation with toxic products induce Seborrheic Dermatitis and the possible role of Demodex in the pathogenesis of seborrheic dermatitis.

In a study conducted in 2005, Fabienne et al. reported that washing the face twice a day with a cleanser or soap decreased Demodex density in humans. They stated that this was because the chemical agents in the soap covered the face and controlled and prevented infestation (20). It is thought that sebum ratio increases in those who do not use facial cleanser and wash their face less frequently and creates a suitable environment for mite reproduction. However, Zhao et al. did not find a relationship between daily face washing frequency, hygienic practices such as washing the face with soap or cleanser, and Demodex infestation in their study conducted with the SSSB method in 756 students with or without facial dermatosis. They suggested that although the facial cleanser and soap used clean the skin surface, they cannot clean the sebaceous glands and hair follicles. They also reported that the use of common towels may increase the risk of infestation (21). In this study, no relationship was found between hygiene habits and the presence of Demodex ($p>0.05$). This result is consistent with the study of Zhao et al.

In two different studies conducted in 2009, Demodex mites were found at a higher rate in patients with mixed and oily skin than in patients with dry and neutral skin (22, 23). Zhao et al. reported that mite infestation was more intense in oily and mixed skin than in dry and neutral skin types (21). In this study, Demodex was present in 53.8% of oily, 34% of mixed, 31.6% of dry, and 15.4% of neutral skin types. Zhao et al. claimed that oily and mixed skin types were associated with Demodex density and that the movement of Demodex in the pilosebaceous unit increased sebum secretion by stimulating the sebaceous glands. Consistent with the literature, a statistically significant relationship was found between oily skin and Demodex positivity ($p=0.01$). This suggests that increased sebaceous activity in oily skin may create a favorable environment for mite proliferation.

Our study had some limitations. Firstly, although the SSSB technique chosen to detect mite positivity is the most useful method for this type of study, it cannot detect mites in deep-seated hair follicles. In addition, statistically significant results may not have been obtained in subgroup analyses due to the insufficient number of patients, especially in the perioral and contact dermatitis subgroups. In our prospectively designed study, all data collection, questionnaire, and microscopic evaluation phases were performed by a single physician, and blinding was not performed.

CONCLUSION

Oily skin type and seborrheic dermatitis, one of the facial dermatoses, has a significant association with Demodex, while factors such as age, sex, hygiene habits were not found to be associated with the presence of Demodex. In larger patient groups, more comprehensive studies are needed on the relationship between Demodex mites and demographic characteristics of patients, their role in the pathogenesis of facial dermatoses, especially seborrheic dermatitis, drug use, hygiene and eating habits, and structural features of the skin.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

Address correspondence to: *Gunseli Kekec, University of Health Sciences, Konya City Hospital, Konya, Turkiye*
e-mail: *gunseli-07@hotmail.com*

REFERENCES

1. Aycan ÖM, Otlu GH, Karaman Ü, et al. Çeşitli Hasta ve Yaş Gruplarında Demodex sp. Görülme Sıklığı. Türkiye Parazitoloji Dergisi. 2007;31(2):115-8.
2. Baima B, Sticherling M. Demodicidosis Revisited. Acta Derm Venereol. 2002;82:3-6. DOI: 10.1080/000155502753600795
3. Jansen T, Melnik BC, Schadendorf D. Steroid Induced Periorificial Dermatitis in Children Clinical Features and Response to Azelaic Acid. Pediatr Dermatol. 2010;27(2):137-42. DOI: 10.1111/j.1525-1470.2009.00979.x
4. Karincaoglu Y, Bayram N, Aycan O, Esrefoglu M. The Clinical Importance of Demodex Folliculorum Presenting with Nonspecific Facial Signs and Symptoms. J Dermatol. 2004;31:618-26. DOI: 10.1111/j.1346-8138.2004.tb00567.x
5. Zhao YE, Peng Y, Wang X, et al. Facial Dermatosis Associated with Demodex: A Case-Control Study. J Zhejiang Univ Sci B. 2011;12(12):1008-15. DOI: 10.1631/jzus.B1100179
6. Bonnar E, Eustace P, Powel FC. The Demodex Mite Population in Rosacea. J Am Acad Dermatol. 1993;28:443–8. DOI: 10.1016/0190-9622(93)70065-2
7. Akilov OE, Mumcuoglu KY. Association Between Human Demodicosis and HLA Class I. Clin Exp Dermatol. 2003;28(1):70-3. DOI: 10.1046/j.1365-2230.2003.01173.x
8. Budak S, Yolasığmaz A. Demodicosis Folliculorum. İmmun Yetmezlikte Önemi Artan Parazit Hastalıkları. Türkiye Parazitoloji Derneği Yayınları. 1995;12(I):169–71.
9. Basta-Juzbasic A, Subic JS, Ljubojevic S. Demodex Folliculorum in Development of Dermatitis Rosaceiformis Steroidica and Rosacea Related Diseases. Clin Dermatol. 2002;20:135–140. DOI:

10.1016/s0738-081x(01)00244-9
10. Aycan OM, Otlu GH, Karaman U, et al. Frequency of Demodicosis in Various Patient and Age Groups. Acta Parasitologica Turcica. 2007;31:115–8.
11. Litwin D, Chen W, Dzika E, et al. Human Permanent Ectoparasites; Recent Advances on Biology and Clinical Significance of Demodex Mites: Narrative Review Article. Iran J Parasitol. 2017;12:12-21.
12. Taş CZ, Yılmaz H, Akdeniz N, et al. Association of Demodicosis with Acne Rosacea. Pak J Med Sci. 2010;26(3):640-3.
13. Roihu T, Kariniemi AL. Demodex Mites in Acne Rosacea. J Cutan Pathol. 1998;25:550-2. DOI: 10.1111/j.1600-0560.1998.tb01739.x
14. Polat E, Aygün G, Ergin R, et al. Akne Vulgaris Patogenezinde Demodex Folliculorum ve Propionibacterium Acnes'in Rolü. Türkiye Parazitoloji Dergisi. 2003;27(2):148-51.
15. Baysal V, Aydemir M, Yorgancigil B, et al. The Role of Demodexes on Etiology and Pathogenesis of Acne Vulgaris. Acta Parasitologica Turcica. 1997;21:265–8.
16. Siadat AH, Iraji F, Shahmoradi Z, et al. The efficacy of 1% metronidazole gel in facial seborrheic dermatitis: a double blind study. Indian J Dermatol Venereol Leprol. 2006;72(4):266-9. DOI: 10.4103/0378-6323.26745. PMID: 16880571.
17. Aktaş Karabay E, Aksu Çerman A. Demodex folliculorum infestations in common facial dermatoses: acne vulgaris, rosacea, seborrheic dermatitis. An Bras Dermatol. 2020;95(2):187-93. DOI: 10.1016/j.abd.2019.08.023
18. Kilinç F, Akbaş A, Özkara Duman ZT et al. Presence of Demodex in Seborrheic Dermatitis Lesions and its Relationship with Disease Severity: A Case Control Study. Turkiye Klinikleri Journal of Dermatology. 2023;33.67-72. DOI: 10.5336/dermato.2023-95656
19. Karincaoglu Y, Tepe B, Kalaycı B, et al. Is Demodex Folliculorum an Aetiological Factor in Seborrhoeic Dermatitis? Clin Exp Dermatol. 2009;34(8):516-20. DOI: 10.1111/j.1365-2230.2009.03343.x
20. Fabienne F, Marie Anne G, Thierry B. Demodicosis and Rosacea: Epidemiology and Significance in Daily Dermatologic Practice. J Am Acad Dermatol. 2005;52:74-87. DOI: 10.1016/j.jaad.2004.05.034
21. Zhao YE, Guo N, Xu J, et al. Sociodemographic Characteristics and Risk Factor Analysis of Demodex Infestation (Acari: Demodicidae). J Zhejiang Univ Sci B. 2011;12(12):998-1007. DOI: 10.1631/jzus.B1100079
22. Cao YS, You QX, Wang L, et al. Facial Demodex Infection Among College Students in Tangshan. Chinese Journal of Parasitology. 2009;27(3):271-3.
23. Zhao, Ye., Peng, Y., Wang, Xl. et al. Facial dermatosis associated with Demodex: a case-control study. J. Zhejiang Univ. Sci. 2011;B12, 1008–1015. DOI: 10.1631/jzus.B1100179