Derginin önceki adı: RAED Dergisi / *formerly RAED Journal*

Ulusal ROMATOLOJİ Dergisi

Journal of Turkish Society for Rheumatology

ISSN: 2651-2653

www.romatolojidergisi.org

Cilt / Volume: **15** • **Sayı /** Issue: **2** • **Temmuz /** July **2023**

Türkiye Romatoloji Derneği'nin (TRD) bilimsel yayın organıdır.
Official Publication of Turkish Society for Rheumatology

S. Özbek, 2023

galenos yayınevi

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Web: www.galenos.com.tr **Yayıncı Sertifika No:** 14521
Basım Yeri/Printing at: Son Sürat Daktilo Dijital Baskı Merkezi Sanayi ve Ticaret Ltd. Şti.
Gayrettepe Mahallesi, Yıldızposta Caddesi, Evren Sitesi A Blok
No: 32 D: 1 - D: 3 34349 Beşiktaş, İstanbul, Türkiye
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E-posta: info@sonsuratdaktilo.com
Basım Tarihi/Printing Date: Temmuz 2023/July 2023
ISSN: 2651-2653 **E-ISSN:** 2651-2661
Yılda üç kez yayımlanan süreli yayındır.
International periodical journal published three times in a year.

Ulusal
ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology
www.romatolojidergisi.org

Amaç ve Kapsam / Aims and Scope

Türkiye Romatoloji Derneği'nin (TRD) yayın organı olan Ulusal Romatoloji Dergisi (önceki adı: RAED Dergisi) yılda üç kez, Türkçe ve İngilizce yayımlanan hakemli bir bilimsel dergidir (p-ISSN: 2651-2653; e-ISSN: 2651-2661). Dergi, romatoloji biliminin bütün konularında orijinal deneysel ve klinik araştırmaları, olgu sunumlarını, derlemeleri, tanıtım ve haberleri, yazarlara ve editöre mektupların yanı sıra romatoloji camiasını ilgilendiren duyuruları yayımlar. Bunun dışında romatoloji alanındaki yenilik ve gelişmelere yönelik toplantıların konuşma metinlerini ya da bu gelişmeleri içeren yazıları ek vererek yayımlayabilir. Derleme yazılar genellikle davetli yazı konumunda olduğundan dergiye gönderilmeden önce editör ile iletişime geçilmesi gerekmektedir. Dergi, doğrudan gönderilen derleme türü yazıları kabul etmemektedir.

Ulusal Romatoloji Dergisi **EBSCO, Gale, J-Gate, Türk Medline ve TÜBITAK ULAKBIM TR Dizin** veritabanında İndekslenmektedir.

Ulusal Romatoloji Dergisi'nin amacı ülkemizde romatoloji ile ilgilenen diğer disiplinlerin de katılımıyla romatoloji alanında güncel bir bilimsel tartışma zemini ve arşiv oluşturmaktır. Dergi bu birikimini, saygın bir biyomedikal periyodik olarak uluslararası bilimsel paylaşıma sunmayı ve böylece romatoloji biliminin gelişmesine akademik katkı sağlamayı hedeflemektedir.

Dergide makale yükleme, işlem veya yayınlanma ücreti uygulanmamaktadır. Değerlendirme ve yayın süreci boyunca hiçbir şekilde yazarlardan herhangi bir ücret talep edilmez.Tüm yazılar dergi web sitesinde yer alan online makale sistemi aracılığıyla sisteme yüklenmelidir.

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Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

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Journal of Turkish Society for Rheumatology is indexed in **EBSCO, Gale, J-Gate, Turkish MEDLINE and Tübitak Ulakbim TR Index.**

Journal of Turkish Society for Rheumatology aims to constitute a current scientific discussion platform and archive in rheumatology with the contribution of the disciplines related to rheumatology together. The journal intends to share its experiences with the international scientific community in a prestigious way and to provide academic contribution to the development of rheumatology science.

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Phone: +90 212 621 99 25 Fax: +90 212 621 99 27

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The journal is printed on acid-free paper.

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Dergide yer alan bölümler aşağıda aşağıdaki gibi sınıflandırılmaktadır:

- Klinik Araştırma
- Deneysel Çalışma
- Olgu Sunumu
- Derleme
- Editöre Mektup
- Öneri
- Yazara Mektup
- Kitap Tanıtımı
- Haberler
- Özetler

ETİK VE HAKEM DEĞERLENDİRMESİ

Ulusal Romatoloji Dergisi bağımsız, önyargısız ve çift-kör hakemlik ilkeleri çerçevesinde yayın yapan süreli bir yayın organıdır. Makale baş editöre ulaşınca bilimsel kalitesi değerlendirilir ve ön değerlendirmeyi geçen yazılar yardımcı editöre gönderilir. Bölüm editörü makaleyi 2 hakeme gönderir. Hakemler 21 gün içinde kararlarını belirtmelidirler. Yardımcı editör hakem kararlarına kendi değerlendirme ve önerisini ekleyerek baş editöre gönderir ve son kararı baş editör verir. Hakemlerin kararları çatışıyorsa dergi editörü yeni hakem atayabilir.

Derginin alıntı kontrolü "Crossref Similarity Check" tarafından geliştirilen "iThenticate" programı kullanılarak yapılmaktadır. İntihal raporuna göre makale yazara geri gönderilebilir ya da reddedilebilir.

Yayınlanmak üzere dergiye gönderilen yazılar daha önce başka bir dergide yayınlanmamış veya yayınlanmak üzere eş zamanlı olarak herhangi bir dergiye gönderilmemiş olmalıdır. Bilimsel toplantılarda sunulmuş bildirilerden hazırlanan yazılar, tamamı yayınlanmamış olmak koşuluyla dergiye gönderilebilir. Gelen yazılar Yayın Kurulu tarafından ön incelemeden geçirilir. Derginin yayın amacına uygun olmayan yazılar doğrudan reddedilebilir ya da hakem değerlendirmesine alınmadan yayın amacına ve yayın kurallarına uygun hale getirilmesi amacıyla yazara geri gönderilir. Dergi kapsamına uygun görülen yazılardan klinik araştırma, deneysel çalışma, derleme ve olgu sunumu sınıfı yazılar hakem değerlendirme (eş değerlendirme/*peer review*) sürecine girerler. Yayın Kurulu, hakem yorum ve önerileri doğrultusunda dergiye gönderilen yazıların yayına hazırlanması aşamalarında gerekli gördüğü düzeltme ve değişiklikleri önermeye yetkilidir. Dil birliğini sağlamak amacıyla cümlenin bilimsel anlamını değiştirmeyen kelime değişikliklerini yapabilir. Eş değerlendirme sürecinde gerekli düzelti aşamalarını geçtikten sonra sayfa düzeni yapılıp yayına hazır hale getirilen yazıların provası, son baskı onayı için ilgili (yazışmaların yapıldığı) yazara göndeilir.

Araştırma Etiği

Yazar(lar), insanlar üzerinde yapılan çalışmalarda katılımcı bireylerden Bilgilendirilmiş Olur alındığını yazılarında belirtmeli ve çalışmanın yapıldığı kurumun Etik Kurulu veya eşdeğeri bir kuruldan alınan onay belgesini yazıyla birlikte göndermelidir(ler). Olgu sunumlarında, her olgunun kendisine ait bilgilerin yayın amacıyla kullanılacağına dair bilgilendirildiğini gösterir bir belgenin sunulması gerekir. Tüm çalışmalar Helsinki Deklarasyonu'nun son değişiklikleri işlenmiş şekline uygun yapılmış olmalıdır. Hasta bilgileri 01.08.1998 tarih ve 23420 sayılı Resmi Gazete'de yayımlanan Hasta Hakları Yönetmeliği'ne uygun olarak alınmış olmalıdır. Hayvanlar üzerindeki sonuçları bildiren deneysel çalışmaların, Hayvan Hakları Evrensel Bildirgesi, Deneysel ve Diğer Bilimsel Amaçlarla Kullanılacak Omurgalı Hayvanların Korunması Hakkındaki Avrupa Konvansiyonu (European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purpose), T.C. Tarım ve Köy İşleri Bakanlığı'nın Deneysel ve Diğer Bilimsel Amaçlar İçin Kullanılan Deney Hayvanlarının Üretim Yerleri ile Deney Yapacak Olan Laboratuvarın Kuruluş Çalışma Denetleme Usul ve Esaslarına Dair Yönetmelik, Laboratuvar Hayvanları Biliminin Temel İlkeleri (Principles of Laboratory Animal Science), laboratuvar hayvanlarının bakım ve kullanılmasıyla ilgili el kitaplarında yer alan kural ve ilkelere uygun olarak ve çalışmanın yapıldığı kurumda mevcut ise, Deney Hayvanları Etik Kurulu'ndan alacakları onay sonrasında yapılmış olması gerekir. Etik Kurul onayı yazı ile birlikte sunulmalıdır. Yazılarda, insan ve hayvanlarda yapılan çalışmalarda kullanılan ameliyat sonrası ağrı giderici tedavi yöntemleri hakkında da bilgi verilmelidir.

Yayın Etiği ve Kötüye Kullanım Bildirgesi

Ulusal Romatoloji Dergisi yayın etiğini en yüksek standartlarda uygulamayı ve Yayın Etiği ve Kötüye Kullanım Bildirgesinin aşağıdaki ilkelerine uymayı taahhüt eder. Bu bildirge Committee on Publication Ethics (COPE), Council of Science Editors (CSE), World Association of Medical Editors (WAME) ve International Committee of Medical Journal Editors (ICMJE) adlı birlik ve inisiyatiflerin, dergi editörleri için geliştirdikleri öneri ve kılavuzlar temel alınarak hazırlanmıştır. Yayımlanmak üzere dergiye gönderilen yazılar daha önce başka bir dergide yayımlanmamış (bilimsel toplantılarda sunulmuş ve tam metin yayımlanmış bildiriler dahil) veya yayımlanmak üzere eşzamanlı olarak herhangi bir dergiye gönderilmemiş olmalıdır. Dergiye gönderilen yazılar, bir editör ve en az iki danışman (hakem) tarafından incelenmek suretiyle tek-kör eş değerlendirme *(peer review)* sürecine alınır. Dergimiz gönderilen yazıların herhangi bir aşamada, amaca yönelik bir yazılım aracılığıyla intihal açısından incelenebileceği hakkını saklı tutar. Bu amaçla intihale yönelik izinsiz alıntı ya da düzmece veriler, sahtecilik (tablo şekil ya da araştırma verilerinin uydurma ya da manipüle edilmiş olması) ve araştırmada uygunsuz insan ya da hayvan denekler kullanımına yönelik incelemeler söz konusu

olabilir. Bu standartlara uygun olmayan yazılar dergide yayımlanmaz. Bu standartlara uygun olmayan yazılar dergide yayımlanmaz. Bu kural, yayımlanma sonrası aşamada saptanabilecek bu standartlarla ilgili herhangi bir uyumsuzluk durumunda da geçerlidir ve yazının yayımdan geri çekilmesini gerektirir. Yayın etiği gereği dergimiz intihal ya da duplike yayın şüphesi durumlarını rapor edecektir. Dergimiz, yayın etiğinin kötüye kullanımı ya da ihlali ile ilgili olası durumlarda COPE tarafından geliştirilen Yayın Etiği Akış Şemalarını temel alır.

Yazar Sorumluluğu

Yazarlar gönderdikleri yazıların özgünlüğünü teminat altına almalıdır. Yazının daha önce herhangi bir yerde, herhangi bir dilde yayımlanmadığı ya da yayımlanmak üzere değerlendirmeye alınmış olmadığını beyan etmelidirler. Geçerli telif hakkı sözleşme ve yasalarına uymalıdırlar. Dergimizde tablo, şekil ya da diğer katkı sunan alıntılar gibi telifli materyal ancak geçerli izin ve telif onayı ile yayımlanır. Yazarlar; başka yazarlar, katkı sağlayıcılar ya da kaynaklara uygun bir biçimde atıf yapmalı ve ilgili kaynakları belirtmelidir. Araştırma türü yazıların (kısa raporlar dahil) yazar(lar)ı "çalışmayı tasarlama", "verileri toplama", "verileri inceleme", "yazıyı yazma" ve "verilerin ve analizlerin doğruluğunu onaylama" aşamalarından en az 3 tanesine katılmış olmak ve bu durumu beyan etmek zorundadır. Yazarlar, çalışma ile ilgili bilinmesi gereken ve çalışmanın bulgularını ya da bilimsel sonucunu potansiyel olarak etkileyebilecek bir mali ilişkiyi ya da çıkar çakışması (conflict of interest) veya rekabet (competing interest) alanlarını açıklamakla yükümlüdür. Çalışmaya yapılan tüm mali katkıları, sponsorlukları ya da proje desteklerini açıklıkla bildirmelidirler. Derginin Çıkar Çakışması Politikası ile ilgili ayrıntılı bilgiyi de içeren ve olası çıkar çakışması durumunda kullanılabilecek "Çıkar Çakışması Beyan Formu"na PDF dokümanı olarak erişilebilir. Yazar yayımlanmış yazısında anlamlı bir bilimsel hata ya da uygunsuzluk saptadığında, yazıyı geri çekme ya da hatayı düzeltme amacıyla olabildiğince hızlı bir şekilde editör ile temasa geçme yükümlülüğünü taşır.

Hakem Sorumlulukları

Hakemler gelen yazıları, yazarlarının etnik köken, cinsiyet, cinsiyet tercihi, tabiyet, dini inanış ya da politik felsefelerini dikkate almaksızın bilimsel içerik açısından değerlendirir. Hakemler açısından; araştırma, yazarları ya da destekleyiciler ile ilgili bir çıkar veya rekabet çakışması bulunmamalıdır. Hakem kararları nesnel olmalıdır. Hakemler yazar tarafından atıf yapılmamış yayımlanmış ilintili yayınları belirtmelidir. Gönderilen yazı ile ilgili tüm bilgilerin gizli tutulması ve yazar tarafından yapılan telif hakkı ihlali ve intihal durumlarının farkına vardığında Editöre bildirilmesi ile yükümlüdürler. Hakem, gönderilen bir yazının içeriğinin kendi bilimsel alanı ya da birikimi ile uyumsuz olduğunu düşündüğünde ya da hızlı bir değerlendirme yapamayacağı durumlarda Editörü bilgilendirmeli ve değerlendirme sürecinden affını istemelidir.

Editör Sorumlulukları

Editörler gelen yazıları, yazarlarının etnik köken, cinsiyet, cinsiyet tercihi, tabiyet, dini inanış ya da politik felsefelerini dikkate almaksızın bilimsel içerik açısından değerlendirmelidir. Gönderilen yazıların yayımlanması için adil bir eş değerlendirme süreci sağlamalıdırlar. Gönderilen yazı ile ilgili tüm bilgilerin yayımlanana kadar gizli tutulmasını garanti altına almalıdırlar. Editörler yayının içeriği ve toplam kalitesinden sorumludur. Erratum sayfaları yoluyla gerektiğinde düzeltme yayımlamalıdırlar. Editör; yazarlar, editörler ve hakemler arasında olabilecek herhangi bir çıkar veya rekabet çakışmasına olanak vermemelidir. Ulusal Romatoloji Dergisinde hakem atamasında sadece Editör tam yetkiye sahip olup yazıların yayımlanması ile ilgili sonuç kararından da kendisi sorumludur.

YAYIN POLİTİKASI

Tüm makaleler bilimsel katkıları, özgünlük ve içerikleri açısından bilimsel komite tarafından değerlendirilecektir. Yazarlar verilerinin doğruluğundan sorumludurlar. Dergi gerekli gördüğü yerlerde dil ve uygun değişiklik yapma hakkını saklı tutar. Gereğinde makale revizyon için yazara gönderilir. Daha önce herhangi bir dilde yayınlanmış makaleler dergide yayınlanmak üzere kabul edilmeyecektir. Yazarlar bir başka dergide yayınlanmak üzere olan makaleyi teslim edemez. Tüm değişiklikler, yazar ve yayıncının yazılı izin alındıktan sonra yapılacaktır. Tüm makalelerin tam metinleri derginin www.manuscriptmodule.com/raed web sitesinden indirilebilir.

Yayın Politikası ve Makale Yazım Kuralları aşağıda belirtilen maddeler "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" (2013, http://www.icmje.org/) temel alınarak hazırlanmıştır.

Araştırma makalelerinin hazırlığı, sistematik derleme, meta-analizleri ve sunumu ise uluslararası kılavuzlara uygun olmalıdır:

Randomize çalışmalar için; CONSORT (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285:1987-91) (http://www.consort-statement.org/).

Sistematik derleme ve meta-analizlerin raporlamaları için; PRISMA (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097) (http://www.prisma-statement.org/).

Tanısal değerli çalışmalar için; STARD (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4) (http://www.stard-statement.org/).

Gözlemsel çalışmalar için; STROBE (http://www.strobe-statement.org/).

Meta-analizleri ve gözlemsel çalışmaların sistematik derlemeleri için; MOOSE (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting "Meta-analysis of observational Studies in Epidemiology" (MOOSE) group. JAMA 2000; 283: 2008-12).

GENEL KURALLAR

Aşağıda belirtilen özelliklerin dışında yazılarla ilgili ilkeler açısından "International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts" dokümanları (www.icmje.org) esas alınmalıdır.

Dergiye gönderilecek yazılarda bulunması gereken bölümler sırası ile şunlardır ve her biri ayrı sayfada başlayacak şekilde sunulmalıdır:

Sayfa 1: Başlık sayfası

Sayfa 2: Türkçe Başlık, Özet ve Anahtar Sözcükler

Sayfa 3: İngilizce Başlık (Title), Özet (Abstract) ve Anahtar Sözcükler (Key words)

Sayfa 4 ve sonrası: Temel Metin

Sonraki sayfa: Kaynaklar

Sonraki sayfa: Tablo Açıklama Yazısı ve Tablo (her tablo ayrı sayfada belirtilmelidir)

Sonraki sayfa: Şekil ve Resim Alt Yazıları ve Resim/Şekiller (her şekil ayrı sayfada belirtilmelidir)

Başlık Sayfası

Başlık sayfasında aşağıdaki sıralama gözetilmelidir:

1- Yazının gönderildiği kategori (klinik araştırma, deneysel çalışma, derleme, olgu sunumu vb)

2- Yazının başlığı (başlık 80 karakteri geçmemeli ve standart dışı kısaltmalar içermemelidir)

3- Yazarların ad, soyad, iletişim adresleri ve araştırmanın yapıldığı sırada çalıştıkları kurum

4- Yazının, dergide yayınlandığında devam sayfalarının üst tarafında görünmesi arzu edilen ve 40 karakteri geçmeyen kısaltılmış başlığı

5- Varsa destekleyen kurum ve kuruluşlar

6- Yazı daha önce sunulmuşsa, sunulduğu toplantının ayrıntıları

7- İletişim kurulacak yazarın haberleşme bilgileri

8- Eğer varsa yazının içeriğiyle ilgili maddi desteğin belirtilmesi

Türkçe Özet

Araştırma yazılarında Amaç, Yöntem, Bulgular ve Sonuç bölümlerinden oluşmalı ve 250 kelimeyi geçmemelidir. Derleme ve olgu bildirilerinde yapılandırılmamış özet verilmelidir. Olgu sunumlarının özeti 100 kelimeyi geçmemelidir. Türkçe özet sayfasında en az 3 en fazla 6 anahtar kelime belirtilmelidir.

İngilizce Özet

Araştırma yazılarında "Objectives", "Methods", "Results", and "Conclusions" bölümlerinden oluşmalıdır ve 250 kelimeyi geçmemelidir. İngilizce Özet sayfasında en az 3 en fazla 6 İngilizce anahtar sözcük belirlenmeli, yazının İngilizce başlığı eklenmelidir.

Temel Metin

Giriş, Hastalar/Gereç ve Yöntem, Bulgular, Tartışma ve Kaynaklar bölümlerinden oluşmalıdır. Kısaltmalar standart olmalı ve ilk kullanıldığında parantez içinde açıklanmalıdır. Ölçümlerde uluslararası kabul edilmiş birimler kullanılmalıdır.

Tablo, Şekil ve Resimler

Metinde kullanılış sırasına göre numaralandırılmalı ve gereksiz kullanımdan kaçınılmalıdır. Olgularda kullanılan fotoğraflarda izin alınmalı ve tanınmayı önlemek için gerekli tedbirler uygulanmalıdır. Fotoğraf ve varsa çizim kalitesine özen gösterilmelidir. Yayın Kurulu yeterli kalitede olmadığı gerekçesiyle tablo, şekil ve resimlerde düzeltme veya yenileme isteğinde bulunabilir. Şekil ve resimlerin orijinal olmaları gerekir. Başka bir yayın içinde kullanılmış bulunan resim, şekil ve grafiklerin dergimizde yayımlanabilmesi için, gerekli izinler yazarlar tarafından ve makale başvurusu yapılmadan önce alınmalıdır. İznin alındığını gösterir belgenin kopyası yazıyla birlikte dergiye gönderilmelidir.

Kaynaklar

Kaynaklar güncel ve yazı için gerekli olanlardan seçilmelidir. Yazı metninde kaynaklar parantez içinde gösterilmeli ve kullanılış sırasına göre numaralandırılmalıdır. Süreli yayın adları PubMed kurallarına uygun olarak kısaltılmalı, burada yer almayan dergilerin adlarında kısaltma kullanılmamalıdır. Bildiri özetlerinin kaynak gösterilmesinden kaçınılmalıdır. Bir dergi tarafından kabul edilmiş fakat henüz yayımlanmamış olan yazılar gerektiği şekilde belgelendirilerek kaynak olarak kullanılabilir. Kabul edilmemiş yazılar da dahil olmak üzere bunun dışındaki bilgi, yazı içinde "yayınlanmamış gözlem" olduğu belirtilerek kullanılabilir. Kaynaklar aşağıdaki örneklere göre yazılmalı ve 6 yazara kadar olan kaynaklarda yazarların tamamı sunulmalı, daha fazla yazarı olan kaynak künyeleri, ilk 3 yazar ve sonuna ve ark. (yabancı dildeki kaynakların künyelerinde et al.) kısaltması gelecek şekilde düzenlenmelidir. Kaynakların doğruluğu açısından sorumluluk yazarlara aittir.

Örnekler

Türkçe süreli yayın örneği:

Göksedef D, Ömeroğlu NÖ, Denli Ş, Üreyen C, Sayılgan C, İpek G. Sistemik lupus eritematozuslu bir olguda aort yetmezliği nedeniyle aort kapak replasmanı. Cerrahpaşa Tıp Dergisi 2008;39:73-5.

Yabancı dilde süreli yayın örneği:

Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting antirheumatic therapy in rheumatoid arhritis: a 14-year prospective evaluatin of 1017 consecutive starts. J Rheumatol 1990;17:994-1002.

Elektronik dergide yayımlanan süreli yayın örneği:

Yurdakul S. Is there really a higher risk for infection with anti TNF-alpha agents or is there a selection bias? Lett Ed Rheumatol 1(1):e110006. doi:10.2399/ler.11.0006

Kitap bölümü örneği:

Buchanan WW, Dequeker J. History of rheumatic diseases. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. Edinburgh: Mosby; 2003:3-8.

Hazırlanan yazıların dergiye gönderilmeden önce aşağıdaki kontrol listesine göre gözden geçirilmesi önerilir:

1- Başlık sayfası

2- Özetler (Türkçe ve İngilizce; olgu sunumlarında en fazla 100 sözcük, diğerlerinde en fazla 250 sözcük; araştırma yazılarında yapılandırılmış)

3- Anahtar sözcükler (en az 3'er adet)

4- Temel metin (alt başlıklar)

5- Kaynaklar (ICMJE kurallarına uygunluk)

6- Şekil, tablo ve resimler (numaralandırma; alt yazılar; özgünlük/izin yazısı)

7- Başvuru mektubu

8- Telif Hakkı Devir Formu (tüm yazarlar tarafından imzalanmış)

9- Çıkar Çakışması Beyan Formu (gereğinde)

Journal of Turkish Society for Rheumatology (formerly RAED Journal), the official organ of Turkish Society for Rheumatology, is a peer-reviewed scientific journal published three times in a year in Turkish or English (p-ISSN: 2651- 2653). The journal publishes original contributions in the form of experimental and clinical research articles, case reports, reviews, news, letters to the editor and authors as well as announcements related to all topics of rheumatology. Also, abstracts or full texts of scientific meetings in rheumatology can be published as supplements of the journal. The reviews are usually invited; therefore it is necessary to contact the editor before sending them to the journal. The journal does not accept reviews which are directly submitted.

The article types in the journal are classified as below:

- Clinical Research Article
- Experimental Study
- Case Report
- Review
- Letter to the Editor
- Recommendation
- Letter to the Author
- Book Review
- News
- Abstracts

ETHICS & PEER-REVIEW

Journal of Turkish Society for Rheumatology is an independent journal based on double-blind peer-review principles. The manuscript is assigned to the Editor-in-Chief, who reviews the manuscript and makes an initial decision based on manuscript quality and editorial priorities. Manuscripts that pass initial evaluation are sent to an Associate Editor. The Associate Editor assigns the manuscript to two reviewers (internal and/or external reviewers). The reviewers must review the manuscript within 21 days. The Associate Editor recommends a decision based on the reviewers' recommendations and sends the manuscript to the Editor-in-Chief. The Editor-in-Chief makes a final decision based on editorial priorities, manuscript quality, and Associate Editor's and reviewers' recommendations. If there are any conflicting recommendations from reviewers, the Editor-in-Chief can assign a new reviewer.

All manuscripts submitted are screened for plagiarism using Crossref Similarity Check powered by "iThenticate" software. Results indicating plagiarism may cause manuscripts being returned or rejected.

Manuscripts sent to the journal for publication should not have been previously published in another journal or sent to any journal simultaneously to be published. Manuscripts prepared from papers presented at scientific meetings can be sent to the journal, provided that they are not fully published. Incoming articles are pre-examined by Editorial Board. Manuscripts that are not suitable for publication purposes may be rejected directly or sent back to the author for publication and publication rules without being evaluated by the reviewer. Among the articles deemed appropriate for the scope of the journal, clinical research, experimental study, review and case report class articles enter the peer-review process. The Editorial Board is empowered to propose the corrections and changes it deems necessary during the preparation of the articles sent to the journal in line with the comments and suggestions of the reviewers. In order to ensure language unity, he/she can make word changes that do not change the scientific meaning of the sentence. After the necessary correction steps have passed in the peer evaluation process, the proof of the articles that are made ready for publication and the page layout is sent to the relevant author (for whom correspondence is made) for the final print approval.

Research Ethics

The author(s) should indicate in their articles that Informed Consent was received from the participating individuals in the studies conducted on people and send the approval document(s) received from the Ethics Committee or equivalent board of the institution where the study was conducted. In case reports, a document must be presented, indicating that each case is informed that their information will be used for publication. All work must have been done in accordance with the final amendments to the Helsinki Declaration. Patient information should be obtained in accordance with the Patient Rights Regulation published in the Official Gazette dated 01.08.1998 and numbered 23420. The European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purpose, by the Universal Declaration of Animal Rights, which reports results on animals, for the Protection of Vertebrates to be Used for Experimental and Other Scientific Purposes, T.C. The Regulation of the Ministry of Agriculture and Rural Affairs on the Production Areas of the Experimental Animals Used for Experimental and Other Scientific Purposes and the Regulation on the Establishment Operation Control Procedures and Principles of the Laboratory to Experiment, the Principles of Laboratory Animal Science, by the care and use of laboratory animals. If it is available in accordance with the rules and principles contained in the relevant manuals and in the institution where the study is carried out, it should be made after approval from the Experimental Animals Ethics Committee. Ethics Committee approval must be submitted with the letter. In the articles, the information should be given about post-operative pain-relieving treatment methods used in human and animal studies.

Publication Ethics and Malpractice Statement

Journal of Turkish Society for Rheumatology undertakes to apply the publication ethics to the highest standards and to comply with the following principles of the Publication Ethics and Abuse Declaration. This declaration is prepared based on the suggestions and guidelines developed by the journal on editors of the Committee on Publication Ethics (COPE), Council of Science Editors (CSE), World Association of Medical Editors (WAME) and International Committee of Medical Journal Editors (ICMJE). Manuscripts sent to the journal for publication should not have been previously published in another journal (including papers presented at scientific meetings and published in full text) or simultaneously not sent to any journal for

publication. Manuscripts sent to the journal are taken into the peer review process by an Editor and at least two consultants (reviewers). Our journal reserves the right to examine the submitted articles at any stage in terms of plagiarism through a purposeful software. For this purpose, unauthorized quotations or fraudulent data regarding plagiarism, fraudulence (made up or manipulated in the form or research data of the table) and investigations may be subject to inappropriate human or animal subjects. Manuscripts that do not comply with these standards are not published in the journal. This rule also applies in case of any incompatibility with these standards which can be determined at the post-publishing stage and requires the withdrawal of the article from the publication. Due to publication ethics, our journal will report cases of plagiarism or duplicate publication. Our journal is based on Publication Ethics Flowcharts developed by COPE in possible situations related to malpractice or violation of publication ethics.

Author Responsibility

Authors should ensure the authenticity of the articles they send. They must declare that the manuscript has not been published in any language, or has been evaluated for publication. They must comply with applicable copyright contracts and laws. In our journal, copyrighted material such as tables, figures or other contributory citations is published only with valid permission and copyright approval. Authors; other authors, contributors or sources should cite appropriately and indicate relevant sources. Participating in at least three stages of research type articles (including short reports) "designing the study", "collecting data", "reviewing data", "writing the article" and "confirming the accuracy of data and analysis" must declare. The authors are responsible for disclosing a financial relationship or areas of conflict of interest or competing for interest that should be known about the study and potentially affect the findings or scientific outcome of the study. They must explicitly report all financial contributions, sponsorships or project supports to the study. The "Conflict of Interest Conflict Declaration Form", which contains detailed information about the journal's Conflict of Interest Policy and can be used in case of potential conflict of interest, is available as a PDF document. When the author detects a meaningful scientific error or incompliance in his published article, he has an obligation to contact the Editor as quickly as possible for the purpose of withdrawing or correcting the article.

Reviewer Responsibilities

Reviewers evaluate incoming articles in terms of scientific content, regardless of their authors' ethnicity, gender, gender preference, nationality, religious belief, or political philosophy. For the reviewers; there should be no conflict of interest or competition regarding research, authors or promoters. Reviewer decisions must be objective. The Reviewers should indicate the related publications that have not been cited by the author. They are obliged to keep all information regarding the submitted article confidential and inform the Editor when they become aware of copyright infringement and plagiarism by the author. The reviewer should inform the Editor and ask for forgiveness from the evaluation process when he considers that the content of a sent article is incompatible with his or her scientific field or knowledge, or when he cannot make a quick evaluation.

Editor Responsibilities

Editors should evaluate incoming articles in terms of scientific content, regardless of their authors' ethnicity, gender, gender preference, nationality, religious belief, or political philosophy. They must provide a fair peer-review process for the publication of the submitted articles. They must ensure that all information regarding the submitted letter is kept confidential until it is published. Editors are responsible for the content and overall quality of the publication. If necessary, they should publish a correction through the Erratum pages. The Editor should not allow any conflicts of interest or competition between authors, editors and reviewers. Only the Editor has full authority in the assignment of the reviewers in the Journal of Turkish Society for Rheumatology and is also responsible for the final decision on the publication of the articles.

PUBLICATION POLICY

All articles will be evaluated by the scientific committee in terms of their scientific contributions, originality and content. Authors are responsible for the accuracy of their data. The journal reserves the right to change the language and appropriate changes where it deems necessary. If necessary, the article is sent to the author for revision. Articles previously published in any language will not be accepted for publication in the journal. Authors cannot submit an article that is about to be published in another journal. All changes will be made after the written permission of the author and publisher. The full text of all articles can be downloaded from the journal's website, www.manuscriptmodule.com/raed.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2013, archived at http://www.icmje.org/).

Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

GENERAL RULES

Apart from the features mentioned below, "International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts" documents (www.icmje.org) should be taken as a basis.

The sections that should be included in the articles to be sent to the journal are as follows and should be presented in a way that each starts on a separate page:

Page 1: Title page

Page 2: Turkish Title, Abstract and Keywords

Page 3: Title, Abstract and Key Words in English

Page 4 and afterwards: Main Text

Next page: Resources

Next page: Table Explanation and Table (each table should be specified on a separate page)

Next page: Figure and Image Subtitles and Image / Shapes (each shape must be specified on a separate page)

Title Page

The title page should be considered in the following order:

1- The category in which the article was sent (clinical research, experimental study, review, case report, etc.)

2- Title of the article (the title should not exceed 80 characters and should not contain non-standard abbreviations)

3- Name, surname, contact addresses of the authors and the institution they work at the time of the research

4- The abbreviated title of the article, which is desired to appear at the top of the continuation pages when published in the journal and does not exceed 40 characters.

5- Supporting institutions and organizations, if any

6- If the article has been submitted before, details of the meeting it was presented

7- Communication information of the author to be contacted

8- Indicating the financial support regarding the content of the article, if any

Turkish Abstract

The research articles should consist of the "Objectives", "Methods", "Results", and "Conclusions" sections and should not exceed 250 words. An unstructured abstract should be provided in reviews and case reports. The abstract of case reports should not exceed 100 words. A minimum of 3 and a maximum of 6 keywords should be specified in the Turkish abstract page.

English Abstract

The research articles should consist of "Objectives", "Methods", "Results", and "Conclusions" sections and should not exceed 250 words. At least 3, maximum of 6 English keywords should be determined in the English Abstract page, and English title of the article should be added.

Main Text

The introduction should consist of the Patients / Materials and Methods, Results, Discussion and References sections. Abbreviations should be standard and should be explained in parentheses when they are used first. Internationally accepted units should be used in the measurements.

Tables, Figures and Images

It should be numbered in the order of use in the text, and unnecessary use should be avoided. In the photographs used in the cases, permission should be obtained, and necessary measures should be applied to prevent recognition. Attention should be paid to the quality of photographs and drawings if any. Editorial Board may request correction or renewal in tables, figures and pictures on the grounds that it is not of sufficient quality. Figures and pictures must be original. In order for the pictures, figures and graphics used in another publication to be published in our journal, the necessary permissions must be obtained by the authors and before applying for an article. A copy of the document indicating that the permit has been obtained must be sent to the journal with the article.

References

References should be selected from the ones that are up to date and necessary for the article. References in the text should be indicated in parentheses and numbered according to the order of use. Name of the journals should be abbreviated in accordance with PubMed rules, and abbreviations should not be used in the names of journals which are not included here. Citation of proceedings should be avoided. Manuscripts accepted by a journal but not yet published can be documented as required and used as a source. Information other than this, including unaccepted articles, can be used by stating that there is "unpublished observation" in the article. References should be written according to the examples below, and all the authors should be presented in references up to 6 authors, references which have more authors should be arranged in a way that ''et al.'' abbreviation will be placed at the end of the first three authors. The responsibility for the accuracy of the references belongs to the authors.

Examples

Periodical publication example in Turkish:

Göksedef D, Ömeroğlu NÖ, Denli Ş, Üreyen C, Sayılgan C, İpek G. Sistemik lupus eritematozuslu bir olguda aort yetmezliği nedeniyle aort kapak replasmanı. Cerrahpaşa Tıp Dergisi 2008;39:73-5.

Periodical publication example in a foreign language:

Wolfe F, Hawley DJ, Cathey MA. Termination of slow-acting antirheumatic therapy in rheumatoid arhritis: a 14-year prospective evaluatin of 1017 consecutive starts. J Rheumatol 1990;17:994-1002.

Example of periodical publication published in an online journal:

Yurdakul S. Is there really a higher risk for infection with anti TNF-alpha agents or is there a selection bias? Lett Ed Rheumatol 1(1):e110006. doi:10.2399/ler.11.0006

Example of book section:

Buchanan WW, Dequeker J. History of rheumatic diseases. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. Edinburgh: Mosby; 2003:3-8.

It is recommended that the prepared articles are reviewed according to the following checklist before being sent to the journal:

1- Title page

2- Abstracts (Turkish and English; maximum 100 words in case reports, maximum 250 words in others; structured in research papers)

3- Keywords (at least three each)

4- Main text (subheadings)

5- Resources (Compliance with ICMJE rules)

6- Figures, tables and pictures (numbering; subtitles; originality/ permission letter)

7- Application letter

8- Copyright Transfer Form (signed by all authors)

9- Conflict of Interest Declaration Form (if required)

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Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2023.59244
Ulus Romatol Derg 2023;15(2):53-59

Rituximab use may indicate impaired quality of life in granulomatosis with polyangiitis

Granülomatöz polianjit hastalarında rituksimab tedavisi bozulmuş yaşam kalitesi göstergesi olabilir

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Abstract

Objective: Granulomatosis with polyangiitis (GPA) is an autoimmune disease among the small vessel vasculitides group. It is characterized by the presence of anti-neutrophil cytoplasmic antibodies and can lead to substantial morbidity and mortality if left untreated. In this study, we aimed to evaluate the deterioration in health-related quality of life (HRQoL) of GPA patients and to identify potential factors that may affect HRQoL.

Methods: Forty patients who met the American College of Rheumatology 1990 criteria for GPA classification were included in the study. A control group with similar age and gender characteristics consisted of healthy volunteers. Demographic information, disease characteristics and treatments of the patients were recorded. To evaluate HRQoL, the Turkish version of the Medical Outcomes Study Short-Form 36 (SF-36) was used. Irreversible organ damage attributable to GPA and/or its treatment was assessed using the vasculitis damage index (VDI).

Results: Compared with the control group, SF-36 was significantly impaired for all SF-36 domains except mental health, which is one of the 8 sub-scale components in GPA patients. There was no significant relationship between different SF-36 scores and total VDI score, affected organ system, disease duration, or total steroid dose. Only one negative correlation was observed between the total dose of rituximab and the overall health and emotional role.

Conclusion: Regardless of the disease activity, significantly decreased HRQoL is observed in patients followed up with GPA. Despite advances in management of GPA, our results suggest impairment of HRQoL is still an issue. Furthermore, rituximab treatment may be indicative of altered HRQoL.

Keywords: Granulomatosis with polyangiitis, quality of life, short-form 36, vasculitis damage index, rituximab

Öz

Amaç: Granülomatozis polianjit (GPA), anti-nötrofil sitoplazmik antikor ile ilişkili küçük damar vaskülitleri grubunda yer alan otoimmün bir hastalıktır ve tedavi edilmediği takdirde önemli morbidite ve mortalite ile ilişkilidir. Bu çalışmada, GPA hastalarının sağlıkla ilişkili yaşam kalitesindeki (HRQoL) bozulmayı değerlendirmeyi ve HRQoL'yi etkileyebilecek olası faktörleri belirlemeyi amaçladık.

Yöntem: American College of Rheumatology 1990 GPA sınıflandırması kriterlerini karşılayan kırk hasta çalışmaya dahil edildi. Sağlıklı gönüllülerden benzer yaş ve cinsiyet özelliklerine sahip kontrol grubu oluşturuldu. Hastaların demografik bilgileri, hastalık özellikleri ve tedavileri kaydedildi. HRQoL'yi değerlendirmek için Medical Outcomes Study Short-Form 36 (SF-36) Türkçe versiyonu kullanıldı. GPA'ya ve/veya tedavisine atfedilebilen geri dönüşümsüz organ hasarı, vaskülit hasar indeksi (VDI) kullanılarak değerlendirildi.

Bulgular: Kontrol grubu ile karşılaştırıldığında, GPA hastalarında SF-36 8 alt ölçek bileşeninden biri olan ruh sağlığı dışındaki tüm SF-36 alanları anlamlı olarak bozulmuştu. Farklı SF-36 puanları ile toplam VDI skoru, etkilenen organ sistemi, hastalık süresi veya total steroid dozu arasında anlamlı bir ilişki yoktu. Toplam rituksimab dozu ile yalnızca genel sağlık ve duygusal rol arasında negatif bir korelasyon gözlendi.

Sonuç: Hastalık aktivitesinden bağımsız olarak, GPA ile izlenen hastalarda HRQoL'de anlamlı azalma gözlenmektedir. GPA yönetimindeki ilerlemelere rağmen, sonuçlarımız HRQoL'deki bozulmanın hala bir sorun olduğunu göstermektedir. Ayrıca, rituksimab tedavisi bozulmuş HRQoL'nin göstergesi olabilir.

Anahtar Kelimeler: Granulomatöz polianjit, yaşam kalitesi, kısa-form 36, vaskülit hasar indeksi, rituksimab

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Received / Geliş Tarihi: 22.12.2022 **Accepted / Kabul Tarihi:** 11.04.2023

Cite this article as / Atıf: Akyüz Dağlı P, Güven SC, Erden A, Eksin MA, Armağan B, Küçükşahin O, Omma A. Rituximab use may indicate impaired quality of life in granulomatosis with polyangiitis. Ulus Romatol Derg 2023;15(2):53-59

Introduction

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis) is an anti-neutrophil cytoplasmic antibody associated vasculitis (AAV) which affects various organ systems including upper air ways, lungs, kidneys, peripheral nervous system, gastrointestinal system, joints, eyes and skin, which may lead to mortality and varying degrees of morbidity.[1-3] Mortality can be avoided with early recognition and effective use of immunosuppressants, therefore, assessment of quality of life (QoL) and disease related damage came forth as important aspects well-being in GPA patients.[4-6]

QoL can be defined as an individual's perception of their status in daily life regarding the individual's expectations, aims and standards shaped by own cultural, moral, and social values.[7,8] Several self-reported questionnaires had been developed to quantify health-related quality of life (HRQoL), which is rather subjective and can vary significantly according to the individual's perspective on life. Short-form 36 (SF-36)[9] is a well-established tool to evaluate HRQoL in various patient populations with different conditions and compare with healthy subjects.[1,10-12] Furthermore, SF-36 can also be used to investigate effects of several aspects related to a disease in long-term, such as complications caused by disease itself, treatment agents used for the disease, accompanying comorbidities, patient's demographics and habitual activities.[8,13] SF-36 comprises 36 questions providing composite scores in 8 domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health, with lower scores indicating impaired HRQoL. Accordingly, SF-36 has also been used widespread to evaluate HRQoL in vasculitides patients.[4,14]

The term "disease related organ damage" expresses irreversible deteriorations in functioning of organ systems in varying degrees, caused by any disease related aspect including disease activity and treatment complications, and persists even after the disease is in remission. Irreversible organ damage in vasculitides can be quantified with vasculitis damage index (VDI), which comprises sixty-four domains in eleven organ system-based groups and developed solely for evaluating vasculitis related organ damage.[15,16] Permanent alterations of organ functioning may further hamper HRQoL in GPA patients via complications due to disease activity such as visual and auditory loss, renal and respiratory failure and via treatment associated complications such as malignancies, avascular necrosis and osteoporosis.

Several studies investigated HRQoL in GPA patients; however, there is limited data with contradictory results regarding effects of irreversible organ damage on HRQoL so it is yet to be fully clarified the true impact of hampered organ functions on patient perceived HRQoL.[1,15] Furthermore, earlier studies may not truly reflect effects of recent developments in medical care of GPA patients, therefore, it is intriguing whether impaired HRQoL is still an issue for GPA patients and any new indicators for worse HRQoL emerged. In this study, we aimed to evaluate deteriorations in HRQoL of GPA patients and further investigate potential factors which may impact HRQoL.

Materials and Methods

A cohort was formed from adult patients who had been followed-up in our clinic with a diagnosis of GPA for at least three months. Patients of this cohort were either evaluated during follow-ups or reached via telephone and a visit was arranged. Patients who did not meet the American College of Rheumatology 1990 Classification Criteria for Wegener's Granulomatosis,[17] patients who considered to have active disease at the time of evaluation and patients who did not want to participate were excluded. Patients who had active disease during the evaluation were re-evaluated later when remission achieved. Active disease was decided according to the Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS/WG).[18] Demographics, clinical and laboratory data were recorded.

HRQoL was evaluated with Turkish version of SF-36[19] and disease related permanent damage with VDI. Five factor scale (FFS) scores[20] were calculated to evaluate the disease prognosis at the time of diagnosis. Treatment characteristics and cumulative doses of steroid, cyclophosphamide (CTX) and rituximab (RTX) therapies were recorded. A control group with similar characteristics regarding age and gender were formed from healthy volunteers. Written consent was obtained from all participants.

Demographics and SF-36 scores were compared between GPA patients and healthy controls. Possible correlations between SF-36 scores and demographics, symptom duration, VDI and FFV scores, total doses of steroids, RTX, CTX were investigated in GPA group.

Statistical Analysis

Data was analysed using Statistical Package for the Social Sciences (SPSS) v22.0. Normality of continuous variables was evaluated with Kolmogorov-Smirnov test in addition to visual analyses with plots and histograms. Continuous variables were presented either with median [interquartile range (IQR) or minimum-maximum (min-max)] or mean ± standard deviation (SD) and compared by Mann-Whitney U or Student t-tests according to normality. Categorical

variables are presented with numbers and percentages and compared by x^2 test. Correlations between continuous and ordinal variables were investigated by Spearman's Rho. P values ≤0.05 were considered statistically significant for all comparative analyses. Correlations with a coefficient ≥0.5 and a p-value ≤0.05 considered significant [correlation coefficient (r) between 0.5-0.7 considered moderate, ≤0.7 considered strong and <0.5 considered no correlation].

Ethics approval (E2-21-792) was obtained by Ankara City Hospital Ethics Committee and the study was therefore performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Results

The GPA cohort was consisted of total 81 patients. Twenty-nine patients were either lost to follow-up or could not be reached, 9 were not alive and 3 were not fulfilling American College of Rheumatology 1990 Classification Criteria for Wegener's Granulomatosis.[17] A total of 40 patients were included in the study. Characteristics of the patients were presented in Table 1. Mean ± SD age was 50.4±13.2 years and 42.5% of the patients were male. Seventy percent of the patients had at least one comorbid condition and the most common comorbidities were hypertension (35%), chronic kidney disease (CKD) (15%), osteoporosis (15%) and diabetes mellitus (10%). Median (min-max) FFS score at the time of diagnosis was 0 (0.0-2.0). Median (min-max) VDI score at the time of evaluation was 1.0 (0.0-4.0). When organ system-based subgroups of VDI were investigated, ear nose throat (ENT) damage was the most common (47.5%) followed by renal (25.0%), neuropsychiatric (12.5%) and musculoskeletal (10.0%) damage.

Seventy-two percent of the patients had ever received CTX, 32.5% RTX, 55.0% azathioprine, 20.0% mycophenolate mofetil and 20.0% methotrexate. All patients had been administered glucocorticoids with a median (IQR) total dose of 10120.0 (9460.0) mg. Data regarding treatment agents were presented in Table 1.

Control group comprised 40 healthy volunteers. Age and gender characteristics were similar between patients and controls. All domains of SF-36 were significantly impaired in GPA patients except for mental health (Table 2).

Correlations between the 8 domains of SF-36 and age, body mass index, symptom duration, VDI and FFS scores, total dose of steroids, RTX and CTX treatments were presented in Table 3. Significant correlations were observed only between total RTX dose and general health (r=-0.549, p=0.034) and role emotional (r=-0.513, p=0.050) indicating a moderate negative correlation between total RTX dose and these two SF-36 domains (Table 3).

Table 1. Demographics and clinical characteristics of granulomatosis with polyangiitis patients

	n=40
Age, years, mean ± SD	50.4±13.2
Gender, male, number (%)	17 (42.5)
BMI, mean ± SD	26.7±5.4
Patients with ≥1 comorbidities, number (%)	28 (70.0)
Comorbidities, number (%)	
Hypertension	14 (35.0)
Chronic kidney disease	6 (15.0)
Osteoporosis	6 (15.0)
Diabetes	4 (10.0)
Cataract	3 (7.5)
Avascular necrosis	2 (5.0)
Malignancies	2 (5.0)
Coronary artery disease	1 (2.5)
Congestive heart failure	1 (2.5)
Other	13 (32.5)
Active smokers, number (%)	5 (12.5)
Time from symptom onset, months, median (min-max)	48.0 (4.0-157.0)
Time from diagnosis, months, median (min-max)	42.0 (3.0-156.0)
cANCA positivity in IFA, number (%)	29 (72.5)
PR3 positivity in ELISA, number (%)*	29 (74.4)
VDI score, median (min-max)	1.0 (0.0-4.0)
Patients with involvement in VDI domains, number (%)	
Musculoskeletal	4 (10.0)
Skin/mucous membranes	1 (2.5)
Ocular	1 (2.5)
ENT	19 (47.5)
Pulmonary	0 (0.0)
Cardiovascular	2 (5.0)
Peripheral vascular disease	1 (2.5)
Gastrointestinal	0 (0.0)
Renal	10 (25.0)
Neuropsychiatric	5 (12.5)
Other	4 (10.0)
FFS at baseline, median (min-max)	0 (0.0-2.0)
Treatments	
CTX ever users, number (%)	29 (72.5)
RTX ever users, number (%)	13 (32.5)
Mycophenolate mofetil ever users, number (%)	6 (15.0)
Azathioprine ever users, number (%)	22 (55.0)
Methotrexate ever users, number (%)	8 (20.0)
Cumulative steroid dose, mg, median (IQR)	10120.0 (9460.0)
Cumulative CTX dose, mg, median (IQR)	6000.0 (5000.0)
Number of RTX cycles, median (IQR)	2.0 (4.0)

**Evaluated over 39 patients in whom PR3ELISA had been worked-up, ANCA: Anti-neutrophil cytoplasmic antibody, BMI: Body mass index, CTX: Cyclophosphamide, ELISA: Enzyme linked immunosorbent assay, ENT: Ear nose throat, FFS: Five factor scale, PR3: Proteinase 3, IFA: Immunofluorescent assay, IQR: Interquartile range, RTX: Rituximab, SD: Standard deviation, VDI: Vasculitis damage index*

Table 2. Demographics and SF-36 scores in GPA patients and healthy controls

	GPA patients n=40	Healthy controls n=40	p
Age, years, mean ± SD	50.4±13.2	48.4±12.3	0.246
Gender, male, number (%)	17 (42.5)	17 (42.5)	1.000
SF-36 scores, median (IQR)			
Physical functioning	85.0 (25.0)	95.0 (10.0)	**<0.001**
Role physical	50.0 (100.0)	100.0 (50.0)	**<0.001**
Bodily pain	57.5 (22.5)	85.0 (30.0)	**<0.001**
General health	45.0 (25)	70.0 (35.0)	**<0.001**
Vitality	50.0 (30)	65.0 (25.0)	**0.001**
Social functioning	62.5 (25)	100.0 (37.5)	**<0.001**
Role emotional	33.3 (100.0)	100.0 (66.7)	**0.007**
Mental health	68.0 (24.0)	72.0 (16.0)	0.114

GPA: Granulomatosis with polyangiitis, IQR: Interquartile range, SD: Standard deviation, SF-36: Short-form 36

Table 3. Correlations between SF-36 scores and demographics, symptom duration, total dose of treatment agents, VDI scores, baseline FFS scores

SF-36 domains		Age	BMI	Symptom duration	VDI	FFS	Total CTX dose	Total RTX dose	Total steroid dose
Physical functioning	r	-0.077	0.214	0.008	0.075	-0.099	0.000	-0.339	-0.275
	p	0.643	0.197	0.961	0.652	0.547	0.999	0.217	0.090
Role physical	r	0.198	0.147	-0.052	0.218	0.144	-0.026	-0.388	-0.097
	p	0.227	0.379	0.753	0.182	0.383	0.903	0.152	0.558
Bodily pain	r	-0.032	0.003	0.073	0.039	-0.185	-0.125	-0.248	0.034
	p	0.846	0.986	0.660	0.812	0.259	0.553	0.373	0.837
General health	r	0.016	-0.005	0.022	0.222	-0.082	-0.089	**-0.549**	-0.178
	p	0.925	0.975	0.892	0.175	0.619	0.671	**0.034**	0.278
Vitality	r	-0.117	-0.014	-0.060	0.333	0.203	-0.172	0.205	0.055
	p	0.478	0.933	0.716	0.038	0.214	0.411	0.464	0.738
Social functioning	r	0.208	0.173	0.159	0.251	0.020	-0.043	-0.274	0.045
	p	0.203	0.299	0.335	0.124	0.902	0.840	0.323	0.785
Role emotional	r	0.243	0.147	-0.233	0.104	0.166	-0.083	**-0.513**	-0.232
	p	0.136	0.380	0.154	0.528	0.314	0.695	**0.050**	0.155
Mental health	cc	-0.006	0.102	-0.110	0.111	-0,032	-0.180	0.075	-0.090
	p	0.972	0.544	0.505	0.502	0.844	0.390	0.790	0.584

BMI: Body mass index, CTX: Cyclophosphamide, FFS: Five factor scale, r: Correlation coefficent, RTX: Rituximab, SF-36: Short form 36, VDI: Vasculitis damage index

Discussion

Our results demonstrated impaired HRQoL measured by SF-36 in GPA patients, even in remission defined by BVAS/WG, with deteriorations in all domains of SF-36 except for mental health. We did not observe any significant correlations between SF-36 domains and age, symptom duration, body mass index, irreversible organ damage quantified by VDI and FFS scores at the time of diagnosis. Total dose RTX dose significantly correlated with worse general health and emotional role scores. Such relation was not observed with total CTX and steroid doses.

GPA is a one of the most debilitating rheumatic conditions with frequent organ/life threatening manifestations, long disease duration and recurrent flares, leading to devastating effects of an individual's overall well-being. With intensive monitoring and immunosuppressive treatment, mortality can be evaded in most cases, yet irreversible organ damage caused by the disease and complications due to intensive immunosuppressive treatment comprising steroids and various immunosuppressants may lead to morbidity and impaired HRQoL. Several studies indicated impaired HRQoL in vasculitides.[1,4,14,21-23]

In a cross-sectional study evaluating employment, work disability and QoL in patients with AAV, 189 patients with AAV were evaluated.[24] Specific and non-specific questionnaires, including SF-36, were sent to the patients, and clinical-biological data and determinants that could affect QoL were analyzed.[24] In this study, it was shown

that the QoL was significantly impaired in AAV patients compared to the general population.[24]

A systematic literature review reviewed relevant articles on HRQoL and fatigue, as well as on AAV-related comorbidities.[25] A significant decrease in HRQoL and an increase in fatigue and anxiety were reported in the AAV in this review. Also, in this review, decreased physical component score and mental component score were associated with fatigue, mood disorders, sleep disturbance, and/or unemployment. A cross-sectional comparative study which was conducted to describe aspects of HRQoL in Mexican patients with AAV evaluated patients with AAV and compared them to groups of patients with rheumatoid arthritis, CKD, and healthy volunteers. In this study, significant differences were shown only in the section of bodily pain of SF-36.[26] In a study evaluating the effect of sinonasal morbidity on QoL in AAVs, patients with and without ENT involvement were compared, and it was shown that the QoL, especially in the presence of ENT involvement, was significantly reduced.[27] Studies evaluating HRQoL according to specific involvement patterns are not sufficient.

There have been a few studies specifically evaluating HRQoL of patients with GPA. Faurschou et al.[1] demonstrated worse scores in all domains of SF-36 in GPA patients with inactive disease. Walsh et al.[4] reported altered physical domains of SF-36 even at the time of diagnosis in AAV (58.5% of the patients with GPA), particularly with older age and neurologic involvement. Tomasson et al.[15] reported improvements in SF-36 scores with effective treatment in GPA patients in comparison to baseline SF-36 values and significant correlation with disease activity. We observed marked alterations in HRQoL in GPA patients under remission similar to the results of Faurshcou et al.[1] Remarkably, our results demonstrated sparing of mental health.

Disease related permanent organ damage should presumably be a major aspect regarding HRQoL in GPA. However, previous reports have been contradictory. Furthermore, impact of different organ systems on HRQoL may vary. Faurschou et al.[1] did not report any significant relationship between VDI scores and HRQoL except for a weak correlation with pulmonary domain. Tomasson et al.[15] evaluated patients from two different cohorts and demonstrated an inverse relationship with physical component summary score of VDI only in patients from one cohort. In our study we did not find out a significant inverse correlation between any domain of SF-36 and VDI.

Effects of several other factors on HQoL in GPA had also been evaluated. Walsh et al.[4] reported older age as a factor related with impaired SF-36 scores. Faurschou et al.[1] revealed number of GPA flares and disease duration do not affect SF-36 scores. Our results demonstrated no significant relationship between age, body mass index, symptom duration and SF-36 scores. In addition, we also did not observe any effect of FFS score at the onset of diagnosis, a major prognostic parameter for vasculitides, on SF-36 scores.

Effective immunosuppressive treatment is the cornerstone in management of GPA. Patients with severe manifestations and refractory/recurrent disease usually receive potent treatment agents such as CTX and high dose steroids, including pulse administrations, which increase overall disease burden with addition of treatment related complications. In addition to these conventional agents, RTX, a CD20 B lymphocyte inhibitor, emerged as a highly effective treatment agent in GPA. Although RTX has initially been used for patients who do not respond to conventional agents or could not adhere to other treatments, lately RTX has been considered as principal induction agent particularly in severe disease.[28] Faurschou et al.[1] reported in 2010 that adhering to maintenance therapy with conventional agents was related with impaired physical component summary scores when compared to patients who were off treatment. In our study, we evaluated correlations between total dose of ever administered RTX, CTX, steroids and SF-36 domains, and observed that total RTX dose had significant inverse correlation with general health and role emotional. As aforementioned, RTX was traditionally used in refractory and resistant patients, which was also valid for our cohort. Therefore, increased RTX use may imply refractory and recurrent disease which may be related to the alterations in SF-36 domains.

To our best knowledge, for the first time such relation with RTX is demonstrated. The small sample size was the major limitation for our study which avoided advanced statistical analyses to be executed to better demonstrate possible effectors of HRQoL. Secondly, cross-sectional nature of the study avoided detection of temporal changes. Furthermore, due to the small sample size we could not evaluate whether subdomains of VDI had any effect on SF-36 scores. Lastly, since this is a single-center study, general assumptions should be made carefully based on our results.

Conclusion

GPA has multiple aspects, aside from disease related manifestations alone, which may impact the overall well-being. HRQoL provides a perspective to patients

regarding their condition, therefore, assessment of HRQoL may act as an extract to evaluate overall success of the clinicians medical approach contributing to other outcome measures. Despite advances in management of GPA, our results suggest impairment of HRQoL is still an issue. Furthermore, RTX treatment may be indicative of altered HRQoL. Larger studies evaluating GPA patients comprehensively may further clarify the major confounders affecting HRQoL.

Ethics

Ethics Committee Approval: Ethics approval (E2-21-792) was obtained by Ankara City Hospital Ethics Committee and the study was therefore performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Informed Consent: Written consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.E., O.K., A.O., Design: S.C.G., A.E., B.A., O.K., A.O., Data Collection or Processing: P.A.D., M.A.E., Analysis or Interpretation: P.A.D., S.C.G., A.E., B.A., O.K., A.O., Literature Search: P.A.D., S.C.G., A.E., M.A.E., Writing: P.A.D.

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: The author declare that they have no relevant financial disclosures.

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Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2023.99609
Ulus Romatol Derg 2023;15(2):60-66

The relationship between scleral thickness, corneal parameters, and interstitial lung disease in patients with rheumatoid arthritis

Romatoid artritli hastalarda sklera kalınlığı, kornea parametreleri ve interstisyel akciğer hastalığı arasındaki ilişki

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Abstract

Objective: This study aimed to examine scleral thickness (ST) and corneal parameters in patients with rheumatoid arthritis (RA) and healthy individuals and to investigate the association of these parameters with rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Methods: The study recruited 59 patients with RA and 31 healthy individuals of similar age and gender. Patient records were reviewed for serological findings, disease activity score-28, disease duration, and medical treatment. The RA patients were divided into two groups: Those with RA-ILD and those without ILD (RA-noILD). The study measured ST at 1000, 2000, and 3000 μm from the scleral spur, corneal volume as well as central corneal thickness for all participants. Patients with RA-ILD were also assessed with delta high-resolution computed tomography (Δ HRCT) and pulmonary function tests (PFT) to determine the severity of ILD.

Results: The clinical and laboratory characteristics of the RA groups were similar. There were statistically significant differences in ST1000, ST2000, and ST3000 measurements between patients with RA and healthy controls (p=0.007; p<0.001; p=0.001, respectively). However, there was no correlation between ocular parameters and PFT or Δ HRCT.

Conclusion: The study found that patients with RA-ILD had scleral thinning, although there was no scleral involvement. However, this difference was not statistically significant when compared to RA-noILD patients.

Keywords: Scleral thickness, corneal parameters, RA, ILD

Öz

Amaç: Bu çalışmada, romatoid artritli (RA) hastalarda ve sağlıklı kontrollerde kornea parametrelerinin ve sklera kalınlığının (ST) değerlendirilmesi ve bunların romatoid artrit ile ilişkili interstisyel akciğer hastalığı (RA-ILD) ile ilişkisinin belirlenmesi amaçlandı.

Yöntemler: Çalışmaya yaş ve cinsiyet açısından eşleştirilmiş 59 RA'lı hasta ve 31 sağlıklı kontrol dahil edildi. Serolojik bulgular, hastalık aktivite skoru-28, hastalık süresi ve medikal tedavi gibi parametreler kayıt edildi. RA'lı hastalar RA-ILD'si olanlar ve RA'sı olan ancak ILD'si olmayanlar (RA-noILD) olmak üzere iki gruba ayrıldı. Her katılımcının kornea hacmi, kornea kalınlığı ve ST 1000, 2000 ve 3000 μm mesafelerde ölçüldü. RA-ILD'li hastalarda, akciğer tutulum şiddetini belirlemek için delta yüksek çözünürlüklü bilgisayarlı tomografi (Δ HRCT) ve solunum fonksiyon testi (SFT) yapıldı.

Bulgular: RA'lı hastalar ile sağlıklı kontroller arasında karşılaştırıldığında ST1000, ST2000 ve ST3000 seviyelerindeki ölçümleri istatistiksel olarak farklı bulundu (sırasıyla p=0,007; p<0,001; p=0,001). Oküler parametreler ile SFT veya Δ HRCT arasında korelasyon yoktu.

Sonuç: RA-ILD hastalarında skleral tutulum olmamasına rağmen, skleral incelme vardır, ancak RA-noILD hastalarına kıyasla istatistiksel olarak anlamlı bir farklılık göstermezler.

Anahtar Kelimeler: Skleral kalınlık, korneal parametreler, RA, ILD

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Received / Geliş Tarihi: 08.02.2023 **Accepted / Kabul Tarihi:** 20.04.2023

Cite this article as / Atıf: Kaymaz S, Savurmuş N, Karasu U, Kaya H, Ufuk F, Ütebey AR, Çobankara V, Yiğit M. The relationship between scleral thickness, corneal parameters, and interstitial lung disease in patients with rheumatoid arthritis. Ulus Romatol Derg 2023;15(2):60-66

Introduction

Rheumatoid arthritis (RA) is a disease that causes inflammation in the body and primarily affects the joints but can also cause symptoms in other parts of the body.[1] Ocular manifestations occur in 25% of RA patients and may lead to complications like scleritis, keratitis, retinal detachment, episcleritis, keratoconjunctivitis sicca, peripheral corneal ulceration, and choroiditis, which can negatively impact a patient's quality of life.[2,3] Studies have suggested that ocular pathologies in RA are linked to serum levels of tumor necrosis factor-alpha (TNF-α), IL-6, IL-23, TGF-β2, and MMPs.[4-8] Interstitial lung disease (ILD) is another extra-articular manifestation (EAM) of RA that can lead to poor prognosis and increased morbidity and mortality.[9] Therefore, all RA patients should be assessed for ILD, as it can cause irreversible lung damage. Various factors like TNF-α, TNF-β, interleukin (IL)-1, IL-4, IL-5, IL-13, vascular endothelial growth factor, and platelet-derived growth factor have been implicated in the development of ILD.[10]

There are few studies in the medical literature that investigate corneal parameters and scleral thickness (ST) in patients with RA. The prevalence of scleral inflammation in RA is reported to be between 0.63% to 0.67%.[11] RA can cause mild episcleritis or full-thickness scleritis, which may lead to scleral melting in rare cases.[12] Scleral tissue destruction and immune complex deposition have been linked to scleral melting.[11] A published study reported no significant difference between RA patients and healthy controls in terms of ST.

To date, no study has explored the relationship between ILD and ocular parameters in patients with RA. This study aimed to assess corneal parameters and ST in patients with RA and healthy controls, as well as determine their association with ILD.

Materials and Methods

This study was conducted as a cross-sectional study by including RA patients who were monitored by the rheumatology clinic and healthy individuals who underwent routine ophthalmology examinations at the same hospital. The diagnosis of RA was established by a rheumatologist using the American College of Rheumatology diagnostic criteria for RA.[13]

Prior to participating, all individuals were informed about the study's purpose and provided written consent. The study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the Local Ethics Committee of Pamukkale University (approval number: 60116787-020-110161).

This study aimed to collect various data from participants, including age, sex, body mass index (BMI), weight, height, disease duration, serological findings, and disease activity score-28 (DAS-28). Medical treatment of patients was also documented, and all patients underwent a thorough physical examination. Additionally, hematological parameters such as C-reactive protein, erythrocyte sedimentation rate, anti-citrullinated protein antibody (ACPA), and rheumatoid factor (RF) were studied.

Patients were subdivided into two groups based on their clinical features, high-resolution computed tomography (HRCT) results, and pulmonary function tests (PFT).[14-18] The groups included patients with RA-ILD and patients with RA-noILD. The clinical, radiological, histological, and PFT results of the RA-ILD group are presented in Table 1.

To assess the extent and severity of ILD, the delta HRCT scoring system was used,[16] and all HRCT scans were evaluated and scored by two board-certified radiologists. The radiologists were blinded to the characteristics of the patients and had seven and three years of experience in thoracic imaging, respectively. The mean scoring system of A HRCT in patients with RA-ILD is shown in Table 2.

Evaluation of Ocular Parameters

All participants underwent a comprehensive ophthalmological examination, which included visual acuity testing, measurement of intraocular pressure, evaluation of the fundus, assessment of refractive error, biomicroscopy, and measurements of ST and

Table 1. Description of incident RA-ILD cases (n=22)

Clinical, radiological, and PFT parameters	n (%) or mean ± SD
-Dyspnea	12 (54.5)
-Dry cough	14 (63.6)
-Fatigue	18 (81.8)
-Weakness	11 (50)
RA-ILD subtype	
-Cellular NSIP	6 (27.2)
-Fibrotic NSIP	7 (31.8)
-UIP/AIP/DAD	9 (40.9)
Pulmonary function test results	
-Percent predicted FEV1	83.2±15.4
-Percent predicted FVC	78.9±17.7
-FEV1/FVC	82.4±4.8
-DLCO	63.4±21.4

RA-ILD: Rheumatoid arthritis-associated interstitial lung disease, NSIP: Non-specific interstitial pneumonia, UIP: Usual interstitial pneumonia, AIP: Acute interstitial pneumonia, DAD: Diffuse alveolar damage, PFT: Pulmonary function test, FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, SD: Standard deviation

corneal parameters. Individuals who had active ocular inflammation, glaucoma, corneal or lenticular opacity, an active ocular surface disorder such as dry eye, refractive errors greater than ±2 diopters, current or recent use of topical eye drops, a history of ocular surgery or trauma, or who failed to cooperate during any of the measurements were excluded from the study. To eliminate the potential effects of diurnal variations, all measurements were performed between 9:00 am and 11:00 am.

Measurement Techniques

To ensure fairness, one eye of each participant was randomly selected for analysis using a random number generator. An independent expert, who was not aware of the participants' characteristics, evaluated the ST and corneal parameters.

ST

ST was assessed using a spectralis anterior segment module optical coherence tomography (AS-OCT) device manufactured by Heidelberg Engineering GmbH, Germany. Participants were instructed to fixate on a target while the measurement was taken at a nasal gaze angle of 45 degrees, which was repeated three times for optimal image quality. Only high-quality images were deemed suitable for ST measurement, and patients who were uncooperative or had poor-quality images were excluded from the analysis. On each image, SS and ST were manually located. To minimize measurement errors, ST was assessed at three distances from SS, specifically 1000, 2000, and 3000 µm. The outer border of the sclera was identified using the deep episcleral vascular plexus, a narrow hypo-reflective region located outside the solid scleral tissue.

Corneal Parameters

The corneal parameters were measured using an Oculus Pentacam HR device from Oculus, Wetzlar, Germany. The device automatically measured the central corneal thickness (CCT) and corneal volume (CV) and the corneal density was calculated from an optimal quality image obtained after multiple measurements. Images were obtained from 90° to 270° for each participant.

Statistical Analysis

The sample size for the study was determined using G*power 3.1 software, which indicated that at least 72 participants were needed to detect a large effect size (f=0.40) between the RA-ILD and RA-noILD groups, with a type 1 error rate (a) of 0.05 and a study power of 0.85.[19]

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 22.0 for Windows (Chicago, IL, USA). Descriptive statistics were used to summarize demographic characteristics. Continuous variables were presented as mean ± standard deviation or median (minimum and maximum values), while categorical variables were presented as numbers and percentages. The normality assumption of the data was tested using the Kolmogorov-Smirnov test. Non-parametric tests were used to evaluate non-normally distributed data. Spearman's correlation analysis was used to evaluate the correlation between non-parametric variables, with a correlation coefficient (r) of 0.8 considered excellent agreement. Intergroup comparisons were conducted using the post-hoc Bonferroni correction (Mann-Whitney U test) and the Kruskal-Wallis variance analysis, with a significance level of $p<0.05$.

Inter-observer variability was assessed by having two different radiologists evaluate participants' HRCT scans on the same day (A and B same day). The mean values evaluated by each observer were compared to assess inter-observer variation. The average standard deviation was calculated for each probe, and the intra-class correlation coefficient (ICC) was computed using a two-way random model, along with corresponding 95% confidence intervals (CI). An ICC of 0.75-0.9 indicates good reliability, while values greater than 0.90 indicate excellent reliability.[20]

Results

In this cross-sectional study, 62 patients with RA and 31 healthy controls were initially recruited. Three patients were excluded due to comorbidities. Thus, 59 patients with RA (12 males, 47 females; mean age: 54.4±9.3 years; range, 45.1 to 63.7 years) were included. Disease duration was 4.5±4.21 years and DAS-28 was 2.9±0.4. Based on detailed

Table 2. Δ HRCT scoring system of patients with RA-ILD

Components mean ± SD	RUL	RML	RLL	LUL	LLL
Ground glass opacity	0.9±0.6	0.9±0.9	1.0±1.25	0.8±0.70	1.2±1
Fibrosis	1.1±0.5	1.1±1.0	1.2±1.15	0.9±0.70	1.0±1.3
Bronchiectasis	0.7±0.7	0.1±1.1	1.4±1.0	0.2±0.2	1.2±1.2
Honeycombing	0.1±0.25	0	0.4±0.1	0.1±0.20	0.4±0.1
Total HRCT score			18±11.0		

Δ *HRCT: Delta high-resolution computed tomography, ILD: Interstitial lung disease, LUL: Left upper lobe, LLL: Left lower lobe, SD: Standard deviation, RUL: Right upper lobe, RML: Right medial lobe, RLL: Right lower lobe*

examinations, 22 patients with RA-ILD were assigned to group 1, 37 patients with RA-noILD were assigned to group 2, and 31 healthy controls were assigned to group 3. These groups had similar age and gender distribution, and BMI (p=0.312, p=0.752, p=0.789). Additionally, patients with RA-ILD and RA-noILD had comparable disease duration, DAS-28 scores, serum RF and/or ACPA levels, laboratory results, and medical treatment (p>0.05) (Table 3).

ST measurements were obtained at three distances and the corneal parameters were evaluated in all groups. ST measurements were significantly different between patients with RA and healthy controls (p<0.05). However, patients with RA-ILD and RA-noILD had similar ST measurements at all distances, as well as corneal parameters (p>0.05). There was no correlation between ST measurements at three distances, corneal parameters, and AHRCT scores. Inter-observer agreement for AHRCT scores was excellent (ICC=0.955; 95% CI, 0.969-0.995). Additionally, there was no significant correlation between ocular parameters and PFT (p>0.05) (Table 4).

Discussion

RA can cause lung involvement in up to 60% of patients, making it the most common EAM associated with the condition.[21] Additionally, RA can cause eye problems in 39% of patients, which can result in varying degrees of

Table 3. Comparison of clinical and demographic characteristics and measurements of ocular parameters

	Group 1 (n=22) RA with ILD	Group 2 (n=37) RA without ILD	Group 3 (n=31) healthy controls	p-value	Mann-Whitney U test with Bonferroni correction
Demographic and clinical parameters					
Male n (%)	5 (23)	7 (19)	6±19	0.752	
Age (year), mean ± SD	56.1±8.5	54.2±9.8	52.3±7.6	0.312	
BMI, kg/m^2, mean ± SD	25.0±2.8	22±3	25.1±2.5	0.789	
Disease duration (years), mean ± SD	5.9±3.2	7.4±5.2	-	0.323	
DAS-28, mean ± SD	2.8±0.5	3.0±0.6	-	0.724	
-RF, IU/mL, mean ± SD	67±75	74±66	-	0.135	
-ACPA, mean ± SD	151±216	107±104	-	0.296	
-CRP, mg/dL, mean ± SD	7±10.1	5±6.5	-	0.282	
-ESR, mm/hour, mean ± SD	24±22	26.0±19	-	0.411	
Medical treatment					
- Glucocorticoid use n (%)	10 (45)	20 (54)	-	0.116	
- cDMARDS use n (%)	8 (36)	24 (64.8)	-	0.247	
-Biologic DMARD use n (%)	12 (54.5)	15 (40.5)			
Scleral thickness, μm					
- ST1000, mean ± SD	611.5±81.7	618.0±114.8	559.8±40.8	**0.007***	Group 1= Group 2, p=0.338 Group 3 < Group 2, p=0.006* Group 3 < Group 1, p=0.015*
-ST2000, mean ± SD	606.2±78.2	639.62±104	531.9±46.3	**<0.001***	Group 1= Group 2, p=0,222 Group 3 < Group 2, p<0.001* Group 3 < Group 1, p<0.001*
-ST3000, mean ± SD	605.8±76.7	645.7±109	557.1±39.7	**0.001***	Group 1= Group 2, p=0.152 Group 3 < Group 2, p<0.001* Group 3 < Group 1, p=0.015*
Corneal parameters					
--CV, mm^3, mean ± SD	58.2±2.5	57.2±5.9	59.7±2.6	0.092	
--CCT, ✂m, mean ± SD	526.6±28.6	535.4±31.9	545.3±26.7	0.095	

*Kruskal-Wallis test was used. *****p<0.05: statistically significant, RA: Rheumatoid arthritis, ILD: Interstitial lung disease, cDMARDS: Conventional disease-modifying antirheumatic drugs, bDMARDS: Biologic disease-modifying antirheumatic drugs, RF: Rheumatoid factor, ACPA: Anti-citrullinated protein antibody, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ST1000: Scleral thickness at a distance of 1000 μm from scleral spur (SS). ST2000: Scleral thickness at a distance of 2000 μm from SS, ST3000: Scleral thickness at a distance of 3000 μm from SS, D: Diopter, CCT: Central corneal thickness, CV: Corneal volume, SD: Standard deviation, BMI: Body mass index*

Table 4. Spearman's rank correlation coefficients of ▲ HRCT scores and clinical variables with ocular parameters

	HRCT score		FVC		FEV1/FVC		FEV1	
	p	r	p	r	p	r	p	r
Ocular parameters								
ST1000, ✂m	0.515	0.155	0.387	0.205	0.300	-0.244	0.106	0.44
ST2000, ✂m	0.925	0.23	0.215	0.290	0.096	-0.382	0.853	0.110
ST3000, ✂m	0.680	0.98	0.169	0.320	0.068	-0.416	0.644	0.148
CV, mm^3	0.979	0.06	0.848	0.46	0.607	-0.122	0.619	0.119
CCT, ✂m	0.689	0.95	0.749	0.76	0.158	-0.328	0.812	0.57

** p<0.05, statistically significant, ST: Scleral thickness, ST1000: Scleral thickness at a distance of 1000 μm from scleral spur (SS). ST2000: Scleral thickness at a distance of 2000 μm from SS, ST3000: Scleral thickness at a distance of 3000 μm from SS, D: Diopter, CCT: Central corneal thickness, CV: Corneal volume, HRCT: High-resolution computed tomography, FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1 second*

morbidity.[22] The development of extra-articular findings in RA is linked to cytokines such as TNF, IL-1, and IL-6, which are thought to cause inflammation due to an imbalance between pro- and anti-inflammatory cytokines.[23] RA is believed to be caused by a microenvironment that promotes the breakdown of collagen, which can lead to keratitis starting from the perilimbal cornea and spreading toward the central cornea, causing perforations and corneal melting.[24,25]

Unfortunately, there are limited studies evaluating corneal parameters and ST in RA and other connective tissue diseases. A study by Gökmen et al.[11] found that RA patients had a statistically thinner ST than healthy controls due to reasons such as the destruction of scleral tissue and subclinical immune deposition. However, the same study reported that the corneal parameters of RA patients were not different from those of healthy controls, likely because of the suppression of systemic inflammation secondary to the use of immunosuppressive drugs.[6] On the other hand, Kaya et al.[26] found that systemic lupus erythematosus patients had a thicker ST than healthy controls, possibly due to subclinical inflammation and connective tissue involvement. Another study had similar results in patients with systemic sclerosis.[19] Our study showed that RA patients had statistically thicker ST but thinner corneal parameters compared to healthy controls, possibly due to subclinical inflammation and the use of immunosuppressive drugs. However, more research is needed to confirm this relationship.

According to the literature, several biomarkers have been linked to RA-ILD, including MMP-1, IL-18, and IL-13.[27] These biomarkers are associated with collagenous pathologies, which are relevant because the sclera has a dense collagenous structure made up of primarily collagen I fibers (90%), collagen III fibers (5%), and proteoglycans.[28] A published study suggests that MMP-1 is the primary enzyme responsible for breaking down interstitial collagen types I and III.[29] Additionally, Firszt et al.[30] reported that IL-13 induces collagen type-1 expression through matrix metalloproteinase-2 and transforming growth factor-01, while Kim et al.[31] found that IL-18 directly downregulates collagen production via Ets-1 and the ERK pathway in human dermal fibroblasts, indicating antifibrotic properties. These findings suggest that the sclera, with its collagenous structure, may be particularly susceptible to the effects of RA-ILD. However, further research is needed to establish a definitive relationship.

The measurement of CCT is crucial for the diagnosis and management of glaucoma since it affects intraocular pressure (IOP) readings.[32] Previous studies have shown that thicker corneas result in falsely high IOP readings, while thinner corneas produce falsely low readings.[32] Despite RA primarily affecting the cornea and ocular surface, little information is available on the relationship between CCT and CV in RA patients. Prata et al.[33] reported that CCT was slightly thinner in RA patients compared to healthy individuals, although the difference was not significant. Villani et al.[34] reported a significant difference in CCT between RA patients and healthy controls. Nevertheless, a published study found no significant differences in CCTs between RA and control eyes, and CCT was not associated with RA activity.[35] In our study, we compared CCT and CV in RA patients with and without RA-ILD and found no significant differences between these groups and healthy controls. This may be due to the immunosuppressive treatments used by RA patients, which may suppress inflammatory and catabolic cytokines that cause corneal thinning.[36]

RA can affect various anatomic structures such as parenchyma, pleura, upper and lower airways, and vascular structures,[10] leading to a wide range of HRCT findings. In our study, we used HRCT scoring to assess the severity of lung involvement, but we should note that this scoring system does not account for nodules, mosaic perfusion, or pleural effusion in RA-ILD patients. Therefore, this limitation might have affected the relationship or correlation between ocular parameters and the HRCT score. To obtain

more accurate data, we could have used a scoring system that includes all HRCT findings.

Study Limitations

Our study has three potential limitations. First, the correlation between ocular parameters and diffusing capacity of the lungs for carbon monoxide (DLCO) could not be evaluated due to patient unwillingness and non-compliance with the test. Second, since the study was cross-sectional, we could not determine if ocular involvement or pathology developed in subsequent follow-ups. However, RA patients included in the study did not have any ocular involvement symptoms or physical examination findings. Third, the Coronavirus disease-2019 pandemic resulted in some RA-ILD patients being lost to regular outpatient follow-up due to intensive care and mortality anxiety, leading to a smaller sample size of RA-ILD patients in our study.

Conclusion

The ST of RA-ILD patients was found to be slightly thinner compared to RA-noILD patients, but this difference was not statistically significant, even though there were no signs of inflammatory vasculitis, scleromalacia, or active scleritis, and patients were receiving active immunomodulatory treatment. The observed lack of significant difference in ST could be related to the biomarkers associated with RA-ILD. It is therefore recommended that patients with RA-ILD undergo regular follow-up with AS-OCT for scleral evaluation.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the Local Ethics Committee of Pamukkale University (approval number: 60116787-020-110161).

Informed Consent: Prior to participating, all individuals were informed about the study's purpose and provided written consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y., Concept: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y., Design: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y., Data Collection or Processing: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y., Analysis or Interpretation: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y., Literature Search: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y., Writing: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y.

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

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

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Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2023.79663
Ulus Romatol Derg 2023;15(2):67-72

Serum triggering receptor expressed on myeloid cells-1 (TREM-1) levels may be associated with disease activity in patients with familial Mediterranean fever

Ailevi Akdeniz ateşi tanılı hastalarda serum triggering receptor expressed on myeloid cells-1 (TREM-1) düzeyleri hastalık aktivitesi ile ilişkili olabilir

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Abstract

Objective: Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease, which is characterized by self-limited attacks of serositis, fever, and arthritis. Triggering receptor expressed on myeloid cells-1 (TREM-1), a member of the inflammatory immunoglobulin superfamily member, is expressed by neutrophils, monocyte, and macrophages and has a role in promoting inflammatory cascade. The study aimed to evaluate serum soluble TREM-1 (sTREM-1) levels in patients with FMF and compare them according to clinical status.

Methods: A total of 65 FMF patients diagnosed with Eurofever criteria, and 21 healthy controls were enrolled in the study. Patients who were followed in Gazi University Rheumatology Outpatient Clinic were included prospectively and separated into three groups; 1. attack period, 2. remission period, and 3. in remission and have amyloidosis. sTREM-1 levels were assessed from peripheral blood.

Results: Age, sex, duration of disease, and genetic mutations were similar between groups. Patients during the attack period have a significantly higher rate of fever and peritonitis attacks compared to other groups. There was also no significant correlation between the level of sTREM-1 and ongoing inflammation, but have a positive correlation with body mass index and age; also, a negative correlation with Autoinflammatory Disease Activity index score ($p<0.05$).

Conclusion: Serum sTREM-1 levels may have a predictive role in the clinical activity of FMF patients.

Keywords: Familial Mediterranean fever, clinical activity, sTREM-1

Öz

Amaç: Ailevi Akdeniz ateşi (FMF) serosit, ateş ve artrit atakları ile karakterize olan en yaygın monojenik otoenflamatuvar hastalıktır. Enflamatuvar immünoglobulin süper aile üyesinin bir üyesi olan myeloid hücreler-1 (TREM-1) nötrofiller, monosit ve makrofajlar tarafından üretilir ve enflamatuvar kaskadın alevlenmesinde rol oynar. Çalışmada, FMF'li hastalarda serum çözünür TREM-1 (sTREM-1) seviyelerinin değerlendirilmesi ve klinik durum ile karşılaştırılması amaçlanmıştır.

Yöntem: Eurofever kriterleriyle tanı konulmuş olan toplam 65 FMF hastası ve 21 sağlıklı kontrol çalışmaya dahil edilmiştir. Gazi Üniversitesi Romatoloji Kliniği'ni izlenen hastalar prospektif olarak çalışmaya alınmış ve üç gruba ayrılmıştır; 1. atak dönemi, 2. interatak dönem, 3. amiloidoz pozitif hastalarda interatak dönemidir. STREM-1 seviyeleri çalışma grubu üyelerinden alınan periferik kandan alınan serum örneklerinde değerlendirilmiştir.

Bulgular: Yaş, cinsiyet, hastalık süresi ve genetik mutasyonlar gruplar arasında benzerdi. Ayrıca sTREM-1 seviyesi ile devam eden enflamasyon arasında önemli bir korelasyon yoktu, ancak vücut kütle indeksi ve yaşla pozitif bir korelasyon mevcuttu. Ayrıca Otoenflamatuvar Hastalık Aktivite indeksi puanıyla negatif bir korelasyon saptandı ($p<0,05$).

Sonuç: Serum sTREM-1 seviyelerinin FMF hastalarının klinik aktivitesinde öngörücü bir rolü olabilir.

Anahtar Kelimeler: Ailevi Akdeniz ateşi, sTREM-1, klinik aktivite

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Received / Geliş Tarihi: 15.02.2023 **Accepted / Kabul Tarihi:** 22.05.2023

Cite this article as / Atıf: Yıldırım D, Avcu A, Erdoğan E, Erden A, Küçük H. Serum triggering receptor expressed on myeloid cells-1 (Trem-1) levels may be associated with disease activity in patients with Familial Mediterranean Fever. Ulus Romatol Derg 2023;15(2):67-72

Introduction

Familial Mediterranean fever (FMF) is the common hereditary autoinflammatory disease that primarily affects East Mediterranean populations like Turks, Jews, Arabs, and Armenians. Disease is caused by the *MEFV* gene mutations, which encode a protein called pyrin, which has regulatory functions on the innate immune system.[1] Because of the pathophysiological pathway is associated with innate immune system, mechanisms underlying FMF pathogenesis have many immune pathways including intracellular danger sensors, inflammasomes, pyroptosis and NETosis.[1]

Colchicine is an ancient and effective treatment for suppressing clinical activity and ongoing inflammation and decreasing risk of damage.[2] IL-1 antagonists are also effective options for patients who have colchicine resistance and/or intolerance.[3] Disease activity is assessed with frequency, severity, and duration attacks as well as with C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A (SAA) levels at attack-free period. AIDAI score was conducted for numeric evaluation of clinical activity of disease and included all clinical parameters listed in the description of activity and ranges between 0-9.[4]

Soluble TREM-1 (sTREM-1) is a member of the immunoglobulin superfamily and is measured in human studies in two forms: soluble and membrane-bound.[5] When a membrane-bound form of sTREM-1 is activated, toll-like receptor-induced cytokines like TNF, IL-1b, IL-6, and IL-8 increase. So sTREM-1 levels propagate the severity of inflammation.[6] As a result, plasma sTREM-1 levels increased in serum and affected regions like pleural fluid, bronchoalveolar lavage, and cerebrospinal fluid.[6,7]

Many studies described the relationship between sTREM-1 levels and the activity of autoimmune diseases. Synovial fluids of patients with RA showed higher sTREM-1 compared to gouty and osteoarthritis.[8] In a murine model of collagen-induced arthritis, decreasing sTREM-1 levels suppressed inflammation of synovial fluid and treated arthritis.[9] Also, in patients with systemic lupus erythematosus, serum sTREM-1 levels were significantly increased and positively correlated with disease activity score and predictive for neuropsychiatric involvement.[10]

sTREM-1 levels were studied at Adult-onset Still disease (AOSD) and FMF from autoinflammatory diseases. sTREM-1 levels were increased in patients with AOSD and were predictive of the chronic course.[11] Also, patients with FMF levels of sTREM-1 were associated with the presence of amyloidosis in two distinct studies.[12,13] The originality of our study originated from that we compared sTREM-1 levels with the clinical activity scores of patients. We hypothesized that serum levels of sTREM-1 may be associated with the clinical activity of FMF.

Materials and Methods

Study Design

The study was a cross-sectional study conducted in the outpatient clinic between March and September 2022. Patients who have been diagnosed with FMF according to Eurofever criteria and above 18 years old were included in the study.[14] Patients who were younger than 18 years old and have other autoinflammatory diseases were excluded. Clinical demographic features, genetic mutations, median levels of serum CRP and ESR levels at attack-free period, and spot urinary excretion of protein/creatinine ratio were recorded. Severity, duration, frequency of attacks, current medications, and colchicine resistance/intolerance were also entered into registry records. The dominant attack type is determined based on the type of attack that the patient experienced most frequently during the entire duration of the disease. All study protocol was compatible with the Declaration of Helsinki. Informed consent was obtained from all participants and kept in study documents. The Local Ethical Committee of Gazi University approved the study (approval number: 622, date: 25.12.2017).

Definition of Clinical Status

Auto-Inflammatory Diseases Activity index (AIDAI) was calculated for all patients to obtain a clinical score.[4] Colchicine resistance is defined as typical attacks of disease which have a frequency of once-a-month and/or high levels of acute phase proteins at an attack-free period for a minimum of 3 months.[15] Damage was assessed with parameters of the Autoinflammatory Disease Damage index like amenorrhea, infertility, joint diseases, chronic renal disease, and insufficiency which are not explained with other reasons.[16]

Laboratory Examinations

Serum venous blood samples were taken from all participants and centrifugated at 3000 rpm for 10 minutes and stored at -80 °C. Blood samples from the attack period were taken within first 6 hours of the attack. Blood sTREM-1 levels were studied by ELISA method via Elabscience- Human Strem-1 (E-EL-H1596) kit and results were expressed as pg/mL.

Statistical Analysis

Results were analyzed with SPSS statistical program 21.0 version. The distribution of all numeric variables was

assessed with one sample Kolmogorov-Smirnov test and all of them showed irregular distribution. Kruskal-Wallis and Mann-Whitney U tests were used according to the number of compared groups. Nominal parameters were compared with chi-square test. Correlations of numeric variables were performed with Pearson's test. P values under 0.05 were accepted as statistically significant.

Results

Table 1 shows all demographic features of the participants. The mean age of the study group was 35.6±11.6 and patients with amyloidosis have a significantly higher mean age (39.7±9.6 years) when compared to other groups (p=0.038). Dominant attack types were peritonitis and fever for patients during the attack period; peritonitis for those at attack-free period and arthritis for patients with amyloidosis. The percentage of fever and peritonitis were significantly different between FMF groups (p=0.025 and p=0.046, in order). Twenty-five patients were treated with only colchicine with maximal tolerable dose (38%), 7 patients were treated with only IL-1 antagonists because of colchicine intolerance (10.7%) and 32 patients were treated with colchicine and IL-1 antagonists because of colchicine resistance (51.3%). Patients treated with IL-1 antagonists were significantly higher in patients with amyloidosis and colchicine dose was lower when compared to patients without amyloidosis because of the restriction of glomerular filtration rate (p=0.002). Most of the patients were in remission respecting to AIDAI score [median: 4 (interquartile range: 3.75)], patients with attack periods were also in remission but have occasional attacks when triggering factors were increased. Ten (15%) patients have high AIDAI score and the distribution between groups was similar.

Plasma sTREM-1 levels were similar between all study groups (p>0.05, Table 2, Figure 1). Patients at attack period and amyloidosis did not show higher levels of sTREM-1 when compared to other groups. Correlation analysis showed a positive correlation of sTREM-1 levels with age (r=0.384, p<0.001) and body mass index (r=0.331, p=0.003); controversially a negative correlation with AIDAI score (r=-0.307, p=0.014). As expected, patients in the attack period had significantly higher levels of CRP and ESR and patients

Table 1. Demographic and clinical properties of the study group

	Patient at attack period (n=16)	Patients at attack-free period (n=30)	Patients with amyloidosis (n=19)	Healthy control (n=21)	p
Age [years, median (IQR)][a]	35 (17)	**28 (15)**	**42 (11.5)**	29.5 (18.8)	**0.038**
Sex (number of patients, female/male)	8/8	15/15	5/14	9/12	0.38
Smoking (number)	7 (43.75)	14 (46.6)	8 (42.1)	6 (28.5)	0.27
Education (number)[b]					
Primary school	2	2	3	1	0.13
Middle school	1	2	3	4	
High school	7	11	5	4	
University	4	15	6	11	
Body mass index [kg/m^2 median (IQR)]	26.6 (9.14)	22.09 (6.65)	21.22 (6.51)	23.25 (4.52)	0.22
Duration of disease [years, median (IQR)]	14 (12.3)	16 (10.5)	20 (14)	-	0.19
Type of attacks [number (%)][d,e]					
Fever	12 (75)	19 (63.3)	6 (31.5)		**0.025**
Peritonitis	12 (75)	24 (80)	9 (47.3)		**0.046**
Pleuritis	6 (37.5)	11 (36.6)	3 (15.7)		0.24
Arthritis	12 (75)	21 (70)	11 (57.8)		0.52
Erysipeal-like erythema	3 (16.7)	5 (16.6)	0	-	0.14
Mutations [number (%)][e]					
M694V	17	28	25		0.92
M680I	4	8	4		
R761H	2	0	0	-	
V726A	1	2	1		
R202Q	1	1	0		
F479L	0	0	1		
E148Q	0	7	1		

[a]Statistical difference is caused between attack-free and amyloidosis groups, [b]Data is available for 72% of the study group, [c]Participants at the control and attack-free period have a similar duration of education; but higher compared to other groups, [d]Differences were caused from amyloidosis group, [e]Other types of attack like myalgia and orchitis were not available in the study population, [e]Number of single gene mutations was counted to result, some data is missing. IQR: Interquartile range

with amyloidosis had higher levels of median proteinuria when compared to other FMF groups (p=0.036,0.001 and <0.001 in order, Table 2). But when CRP and ESR levels at attack-free were compared, all patient groups had similar CRP and sedimentation levels (p=0.942).

Discussion

In this study, we observed for the first time, plasma sTREM-1 levels were negatively correlated with the clinical activity score of FMF patients. Mean levels were not correlated with markers of ongoing inflammation. Meanwhile, sTREM-1 levels were not found elevated in FMF patients when compared to healthy controls.

Soluble TREM-1 levels were first studied in patients with FMF in 2019 by Gorlier et al.[12]. They enrolled 56 FMF patients and 6 of them had amyloidosis. Similar to our results, no significant difference was observed between patients at the attack and attack-free periods, and also correlation was not observed with CRP and ESR levels. But they showed higher levels of sTREM-1 in patients with amyloidosis even though SAA levels (SAA) were normal.[12] In another study, patients with FMF (42 with amyloidosis) and for control, 5 patients with AA amyloidosis secondary to other inflammatory diseases, and 20 healthy individuals were enrolled. Soluble TREM-1 levels were significantly higher in the FMF amyloidosis group compared to FMF without amyloidosis and healthy controls whereas levels were similar between FMF patients and healthy controls.[13] Our results were not showed any difference between patients with/without amyloidosis. Compatible with Ugurlu and Egeli[13] results, we did not show any difference between patients and healthy controls. These studies showed a significant relationship between serum levels of sTREM-1 and amyloidosis whereas our results did not align with these results. The first report in 2019, compared 6 amyloidosis patients with 50 FMF patients, and the other 42 amyloid-positive FMF patients with 20 patients without amyloidosis. Study population may affect results and there is more uniform distribution in the number of groups in our study.

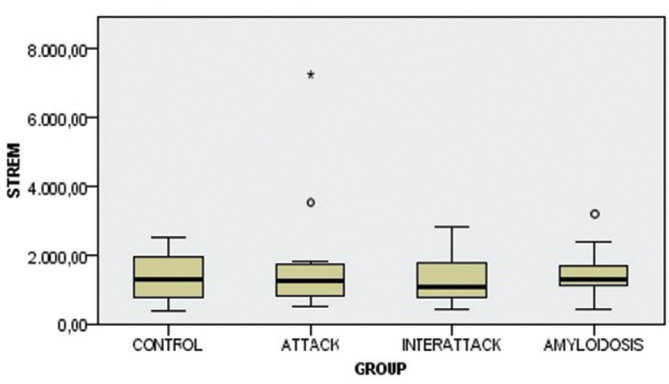

Figure 1. Independent Samples Kruskal-Wallis test

We also did not observe a significant correlation between sTREM-1, CRP, and ESR levels. In our study majority of patients were in remission and median levels of CRP and ESR were similar during the attack-free period. We suggest that fewer patients with active disease as part of our study may have an impact on this outcome. sTREM-1 levels did not increase in patients during the attack period in our study, compatible with previous results.[13] So, we can conclude that

Table 2. Clinical and laboratory features of patients

	Patient at attack period (n=16)	Patients at attack-free period (n=30)	Patients with amyloidosis (n=19)	p
Colchicine dose [mg/day, (median (IQR)]	1 (1.38)	1.25 (1)	1 (1)	0.92
Treatment				
Only colchicine	6	18	1	NA
Colchicine+IL-1 antagonists	7	10	16	
Only IL-1 antagonits	3	2	2	
AIDAI score [median (IQR)][a]	3.5 (5.25)	4 (4.5)	0 (4)	0.036
Corresponding inflammatory disease[b]				
Spondylitis [number (%)]	3	5	3	0.9
Psoriasis [number (%)]	0	0	2	
Vasculitis [number (%)]	1	1	1	
CRP [mg/L, median (IQR)][c]	10.5 (11.25)	3 (4,8)	4 (7)	**0.036**
ESR [mm/hour median (IQR)][c]	19.5 (17.5)	13 (9)	18.5 (18.25)	**0.001**
Urinary protein/creatinine excretion [mg/day median (IQR)][d]	87.5 (94)	74 (81)	1542 (1791)	**<0.001**
sTREM(pg/mL median(IQR))	1256 (940)	1076 (855)	1296 (772)	0.67

[a]Difference is caused by the attack group, [b]There were no any patients with corresponding Behcet's or Inflammatory bowel disease, [c]Difference is caused by attack group, [d]Difference is caused from amyloidosis group. AIDAI: Autoinflammatory diseases activity score, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IL-1: Interleukin 1, IQR: Interquartile range, sTREM: Serum triggering receptor expressed on myeloid cells-1

sTREM-1 levels are not a useful tool for predicting FMF attacks.

In our study age and body mass index, had a positive correlation with serum TREM-1 levels. Macrophages located in adipose tissue contribute to low-grade inflammation that causes metabolic dysfunction in obese patients. TREM-1 is also secreted by myeloid cells in adipose tissue and recently, this marker had studied in obese and normal-weight patients.[17] They showed a positive correlation between sTREM-1 levels and BMI, but not with CRP levels. Considering that data, BMI affects serum levels of sTREM-1. The relationship between age and sTREM-1 levels is controversial in previous studies. Some studies showed a correlation between age and sTREM-1 levels.[12,18,19] Minimal increased inflammatory activity is described for people at increasing ages.[20-22] So, this relationship may be related to physiological changes.

Also, we found a negative correlation between clinical activity score and sTREM-1 levels in patients with FMF. Despite the growing information about FMF pathogenesis, pyrin's mechanisms of immune system regulation remain unclear and often contradictory. IFN-γ, TNF-α, IL-6, IL-12, and IL-17 are increased in FMF even in the attack-free period, IL-4,17,22 were found to be normal in patients with FMF when compared to healthy controls.[23] In the same study, they have shown that IL-1 levels were also similar between patients and healthy controls despite the important effect of this interleukin in the pathogenesis. A negative correlation between clinical activity and sTREM-1 levels may be associated with Th1/Th2/Th17 pathway disturbances related to the predominance of innate immune system response. More studies are needed to elucidate this topic. However, the presence of markers associated with the clinical activity may be useful in clinical practice, especially for patients who are not competent to describe attack history.

sTREM-1 levels were proven to have a relation with higher disease activity in many autoimmune conditions like scleroderma, systemic lupus erythematosus, and rheumatoid arthritis. Also, it is involved with systemic manifestations of these conditions like SLE- thrombosis, neuropsychiatric SLE, and scleroderma-pulmonary involvement.[10,24,25] Also, in autoinflammatory conditions, a recent study showed higher sTREM-1 levels in AOSD patients with higher disease activity. They also showed that sTREM-1 levels are an independent risk factor for the chronic course of AOSD.[11] The clinical course of AOSD is highly diverse and has different cytokine pathways. The systemic pattern favors the IL-1b, IL-18, and IFN-c, whereas IL-6, TNF-a, and IL-8 predominate in the chronic articular pattern.[26] Systemic involvement of AOSD mostly has an implication of autoinflammatory disease more than chronic course. The relationship between sTREM-1 and other autoinflammatory conditions has not been documented yet.

Study Limitations

This study has some limitations. Firstly, we were unable to collect SAA due to technical deficiencies in our laboratory. There is a strong relationship between SAA levels and the risk of amyloidosis.[27] Also, our study population is mostly composed of patients without ongoing inflammation and in remission period. The inclusion of inadequately treated patients can increase the reliability of the data.

Conclusion

Higher levels of sTREM-1 are associated with the clinical activity but are not predictive of attack period and amyloidosis in patients with FMF. sTREM-1 is not superior to non-specific acute phase reactants in FMF especially when patients are in an attack period.

Ethics

Ethics Committee Approval: The Local Ethical Committee of Gazi University approved the study (approval number: 622, date: 25.12.2017).

Informed Consent: Informed consent was obtained from all participants and kept in study documents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.Y., H.K., Design: D.Y., H.K., Data Collection or Processing: A.A., E.E., Analysis or Interpretation: A.E., Literature Search: H.K., Writing: D.Y.

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: The author declare that they have no relevant financial disclosures.

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Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2023.38258
Ulus Romatol Derg 2023;15(2):73-81

Sonoelastography and S100 proteins in the differential diagnosis of IgG4-related disease (IgG4-RD)

IgG4 ilişkili hastalığın (IgG4-RD) ayırıcı tanısında sonoelastografi ve S100 proteinleri

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Abstract

Objective: In the present study, we wanted the investigate the reliability and validity of S100 biomarkers in the differential diagnosis of IgG4-related disease (IgG4-RD) and to examine the relationship between two-dimensional shear wave elastography (2D-SWE) scores of parotid/lacrimal glands, which is used as an effective auxiliary tool in disease prognosis.

Methods: Twenty-seven amyloidosis, 17 sarcoidosis, 13 IgG4-RD, and 21 healthy controls (HCs) presenting to rheumatology outpatient clinic were included in this cross-sectional study. S100A8, S100A9, S100A12, and S100A8/A9 (calprotectin) protein levels were detected with the ELISA test. Evaluation of all groups of the parotid and lacrimal glands were performed using 2D-SWE.

Results: There was no significant difference between patient and healthy control groups with respect to age, sex, and body mass index. The mean levels of S100A9 and S100A12 proteins were significantly higher in amyloidosis (S100A9; 25.09±7.92 vs. 12.91±8.74, S100A12; 627.87±643.83 vs. 344.03±118.02, p=0.001) and sarcoidosis groups (S100A9; 23.67±12.34 vs. 12.91±8.74, S100A12; 600.4±381.26 vs. 344.03±118.02 p=0.001) compared to HCs. The calprotectin levels were significantly higher in amyloidosis than IgG-RD and HCs. For the parotid and lacrimal glands, the mean shear wave elasticity mode values were significantly higher in the IgG4-RD patient compared with HCs, amyloidosis, and sarcoidosis groups (all p=0.001), respectively. 2D SWE scores in parotid glands, reflecting loss of elasticity, had a positive correlation with S100A9 level in IgG4-RD (r=0.948, p=0.014).

Conclusion: Results of this study suggest that S100A9, S100A12, and calprotectin are promising biomarkers and might facilitate differential diagnosis of IgG4-RD, sarcoidosis, and amyloidosis. S100A9 and parotid elasticity could be novel biomarker and tool for the assessment of activity status in patients with IgG4-RD.

Keywords: S100A8, S100A9, S100A12, calprotectin, sonoelastography

Öz

Amaç: Bu çalışmada, IgG4-RD hastalığının ayırıcı tanısında S100 biyobelirteçlerinin güvenilirliğini ve geçerliliğini araştırmak ve hastalık prognozunda etkili bir yardımcı araç olarak kullanılan parotis/lakrimal bezlerin iki boyutlu shear wave elastografi (2D-SWE) skorları ile arasındaki ilişkiyi incelemek istedik.

Yöntem: Bu kesitsel çalışmaya romatoloji polikliniğine başvuran 27 amiloidoz, 17 sarkoidoz, 13 IgG4-RD ve 21 sağlıklı kontrol (SK) dahil edildi. ELISA testi ile S100A8, S100A9, S100A12 ve S100A8/A9 (kalprotektin) protein seviyeleri tespit edildi. Parotis ve lakrimal bezlerin elastisite değerlendirilmesi 2D-SWE kullanılarak yapıldı.

Bulgular: Hasta ve sağlıklı kontrol grupları arasında yaş, cinsiyet ve vücut kitle indeksi açısından anlamlı fark yoktu. S100A9 ve S100A12 proteinlerinin ortalama düzeyleri amiloidoz (S100A9; 25,09±7,92 vs. 12,91±8,74, S100A12; 627,87±643,83 vs. 344,03±118,02, p=0,001) ve sarkoidoz (S100A9; 23,67±12,34 vs. 12,91±8,74, S100A12; 600,4±381,26 vs. 344,03±118,02 p=0,001) gruplarında sağlıklı kontrollere göre anlamlı olarak daha yüksek saptandı (p<0,05). Kalprotektin seviyeleri, amiloidoz grubunda IgG-RD ve kontrol grubuna göre önemli ölçüde daha yüksekti. Parotis ve lakrimal bezler için ortalama 2D-SWE skorları IgG4-RD grubunda kontrol, amiloidoz ve sarkoidoz gruplarına göre anlamlı derecede yüksekti (p<0,01). Elastikiyet kaybını yansıtan parotis bezlerindeki 2D- SWE skorları, IgG4-RD grubunda S100A9 düzeyi ile pozitif korelasyona sahipti (r=0,948, p=0,014).

Sonuç: Bu çalışmanın sonuçları, S100A9, S100A12 ve kalprotektinin umut verici biyobelirteçler olduğunu ve IgG4-RD, sarkoidoz ve amiloidozun ayırıcı tanısını kolaylaştırabileceğini düşündürmektedir. S100A9 ve parotis elastisitesi, IgG4-RD'li hastalarda hastalık aktivite durumunun değerlendirilmesi için yeni bir biyobelirteç ve araç olabilirler.

Anahtar Kelimeler: S100A8, S100A9, S100A12, kalprotektin, sonoelastografi

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Received / Geliş Tarihi: 20.04.2023 **Accepted / Kabul Tarihi:** 18.06.2023

Cite this article as / Atıf: Karadeniz H, Yılmaz Demirci N, Cerit MN, Allahverdiyeva S, Paşaoğlu H, Karaoğlan A, Erden A, Küçük H, Öztürk MA. Sonoelastography and S100 proteins in the differential diagnosis of IgG4-related disease (IgG4-RD). Ulus Romatol Derg 2023;15(2):73-81

Introduction

Amyloidosis, sarcoidosis, and IgG4-related disease (IgG4-RD) are systemic fibroinflammatory diseases, in which innate immunity and adaptive immunity play a prominent role. They may affect exocrine glands (such as salivary and lacrimal glands) causing dryness symptoms.[1] Diagnosis is based on a combination of clinical, laboratory, and radiographic findings with the exclusion of other disease entities.[2,3] Due to the heterogeneity in the location and size of organs which they involve, their clinical presentation is insidious, and the severity of the disease displays larger variation than other rheumatological diseases.

At the initial stage, pathologies associated with cellular infiltration are detected in the regions they involve, while in time they lead to fibrosis, resulting in irreversible organ defects.[4,5] Unfortunately, at early stages, diagnosis can not be made based upon clinical and laboratory findings, and diagnosis is established usually at later stages when organ damage presents with symptoms. Even though important advances have been made in the diagnosis of these diseases, there is an unmet need for specific early diagnosis, biomarkers for monitorization and prediction, and for diagnostic tools in routine clinical practice. Most diagnostic tests have limitations such as invasiveness, higher cost, or limited accessibility.[6,7]

The S100A protein family represents a large calcium-binding sub-family playing a regulative role in many cellular functions.[8] In physiological conditions, S100 proteins are present in low amounts in the body. However, they increase markedly under conditions of heat, trauma, infection, and in many inflammatory processes. S100 proteins, released by neutrophils and monocytes, activate innate immune pathways, mediated by cytokine-activated toll-like receptor for advanced glycation end (RAGE) products. RAGE-products, lead to an increase in the levels of tumor necrosis factor, interleukin-1β, and interleukin-6 cytokines.[9] Increased levels of inflammatory cytokines further stimulate neutrophils and macrophages, creating an inflammatory vicious circle. Hence, as activity and damage increase via positive feedback, serum S100 protein levels are further upregulated. Differential diagnosis of IgG4-RD includes amyloidosis and sarcoidosis, and diagnosis of these conditions can be challenging requiring novel biomarkers. To the best of our knowledge, there is no reported association between S100 proteins and sonoelastography of IgG4-RD.

Two-dimensional shear wave elastography (2D-SWE) is a newly emerged ultrasonography (US) imaging technique that can assess the elastic properties of tissues and help diagnose certain diseases by identifying local or diffuse alterations in the stiffness of tissues. We measure quantitative assessment of tissue elasticity in meters and kilopascals per second with this technique.[10,11] The utility of parotid and lacrimal sonoelastography has been shown both for supporting diagnosis and differentiating primary Sjögren's syndrome from tumoral lesions.[12]

Hence, in this study, we investigated the utility of measuring serum S100 proteins in a cohort of IgG4-RD patients. We wanted to study simple tests and tools, which may help in the determination of diagnosis and estimation of prognosis, such as S100A8, S100A9, S100A12, S100A8/A9 (calprotectin), and 2D-SWE in IgG4-RD, amyloidosis, sarcoidosis and if possible, to find a cut-off value for diseases.

Materials and Methods

This cross-sectional study included 27 amyloidosis, 17 sarcoidosis, and 13 IgG4-RD patients and 21 healthy controls (HC) which were followed in the rheumatology outpatient clinic. We included patients whether newly diagnosed or relapsing, who fulfilled the 2019 American College Rheumatology for IgG4-RD, the 1999 American Thoracic Society classification criteria for sarcoidosis, and the Tel Hashomer criteria for familial Mediterranean fever (FMF). The etiology of all amyloidosis patients was due to FMF. Individuals were examined and evaluated by an experienced rheumatologist. Healthy controls, who had no signs or symptoms participated to the study. Exclusion criteria were being a minor, lack of consent and having sialolithiasis, gland operation, parasympatholytic or antidepressant use, history of radiotherapy on the neck region, hepatitis B and C, osteoarthritis, cardiomyopathy, central nervous system diseases, malignancy, bacterial and viral infections, pregnancy, and Coronavirus disease-2019. Demographic data included age, gender, body mass index (BMI), and history of smoking. Laboratory tests included complete blood count (CBC), creatinine, uric acid, lipid profile, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

Enzyme-linked Immunosorbent Assay (ELISA) for Serum S100 Proteins

The blood samples of all the participants were drawn into pro-coagulation tubes. The serum was collected immediately after centrifugation at 3000g for 15 minutes at 4 °C. Washing processes were done with a BIOTEK brand washing device (ELx50 Bioelisa Washer, Bio-Tec. Instruments, Inc.), and absorbance readings were carried out with a BIOTEK brand reader (ELx800 UV Universal Microplate Reader, Bio-Tec. Instruments, Inc.). Then the serum samples were stored at -80 °C until tested. Serum

S100A8, S100A9, S100A12, and calprotectin levels were analyzed using a commercial ELISA kit according to the manufacturer's instructions (Elabscience). All serum samples were diluted by 1:100. Results of S100A8, S100A9, S100A12, and calprotectin levels are expressed in nanograms per milliliter. Human S100A8, S100A9, S100A12, and calprotectin were studied with a commercially available ELISA kit (Boster Immunoleader En Rage PicoKineTMCA, USA). For S100A8 analytic measurement range was 0.63-40 ng/mL LoD: 0.38 ng/mL, for S100A9 it was 0.78-50 ng/mL, LoD: 0.47 ng/mL, S100A12 0.16-10 ng/mL LoD: 0.1 ng/mL and for calprotectin 1.56-100 ng/mL LoD: 0.94 ng/mL. absorbances for standards and samples were measured at 450 nm wavelength. Concentrations obtained from standard curves were expressed in ng/mL.

Ultrasound Examination

Ultrasonographic assessments (UA) of the lacrimal and salivary glands were conducted by two radiologists, using a LOGIQ S8 (GE Healthcare Systems, Waukesha, WI, USA) US device with a 9 MHz linear transducer. The radiologists did not have access to the medical records of the patients. Patients were NPO for 60 minutes prior to the examination. The examination continued with two-dimensional shear wave elastography. Elastography of the lacrimal and salivary glands were performed while both groups were in a supine location with the head turned to the across and the neck hyperextended. The participants were advised to breathe normally with their eyes closed. During the evaluation of the parotid glands with elastography, the patients were advised to breathe calmly and not to swallow. While the evaluation of the glands was made in both planes, their measurements were conducted only in the transverse plane (at the mandibular angle level for the parotid gland, at the middle of the gland level for the lacrimal gland). The 2D-SWE examinations were performed using a similar methodology described for liver evaluation.[13] The elasticity was defined with Young's modulus (elasticity modulus/estimated tissue stiffness), measured in kiloPascals (kPa). For conducting 2D-SWE evaluation, an adequate quantity of ultrasound gel was used, and no pressure was applied on the examined tissue. During the 2D-SWE evaluation, a sufficient proportion of ultrasound gel was used to show the tissue, and no pressure was applied to the any of groups. For the evaluation of the lacrimal gland, a 2-mm diameter region of interest (ROI) was placed in the middle of the lacrimal gland. For the parotid gland elastography evaluation, the probe was placed at a distance of 1.5 cm from the glandular capsule and a 3-mm ROI was placed in the superficial parenchyma in a homogeneous area. For both the lacrimal and parotid glands, three serial measurements were made in a similar procedure, at equal depth and localization. The average of the right and left gland elasticity measurements was used in the analyses (Figure 1A-D). Intraclass correlation levels between parotid and lacrimal gland elasticity values were evaluated for intra-rater and inter-rater reproducibility. (Supplementary Table 1).

The study was conducted after the ethical approval of the Ethics Committee of Gazi University complied with the Declaration of Helsinki (approval no: 2023.549). Informed consent was obtained from all patients and controls before the initiation of the study.

Statistical Analysis

For statistical analyses, NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used. In the evaluation of data, descriptive statistical methods [mean, standard deviation (SD), median, frequency, percentage, minimum, maximum] were utilized. Whether quantitative data were distributed normally was evaluated with the Shapiro-Wilk test and graphics. In the comparison of more than two groups between normally distributed quantitative parameters, One-Way ANOVA analysis, and was. When quantitative parameters were not normally distributed, in the comparisons between more than two groups, the Kruskal-Wallis tests and Dunn's test were used. Chi-square or Fisher's Exact tests were used to compare categorical variables. In the evaluation of the relationship between quantitative variables, Pearson's and Spearman's correlation tests were utilized for correlation analyses. In order to determine predictive values for parameters, diagnostic screening tests (sensitivity, specificity, PPV, NPV) and ROC analyses were used distinguishing IgG4-RD patients from healthy subjects. The optimal cut-off values for the sensitivity and specificity of S100A8, S100A9, S100A12 and S100A8/A9 in predicting IgG4-RD were calculated by using Youden's index. The p-value of <0.05 was considered statistically significant.

Results

Twenty-seven amyloidosis (12 female, 15 male; mean age 42.96±11.21 years), 17 sarcoidosis (14 female, 3 male; mean age 50.64±8.22 years), and 13 IgG4-RD (6 female, 7 male, mean age 51.58±10.74 years) patients presenting to the rheumatology outpatient clinic, and 21 HCs (12 female, 9 male; mean age 40.47±7.87 years) were included in the present study. There was no significant difference between patient and healthy control groups with respect to age, sex, and BMI. Patient groups were comparable in demographic characteristics, the prevalence of comorbidities,

involvements, and frequency of mucocutaneous symptoms (Table 1). Kidney (77.8%), lacrimal/salivary glands (37%), and gastrointestinal (GI) involvement (37%) were the most common region in amyloidosis, respectively, while lung (88.2%) and kidney (46.2%) involvement were most common in sarcoidosis and IgG4-RD, respectively.

While no significant difference was found between groups in terms of S100A8 protein values (p=0.221), S100A9 protein values were found to be significantly higher in amyloidosis (mean ± SD 25.09±7.92 ng/mL) and sarcoidosis (mean ± SD 23.67±12.34 ng/mL) groups than those in the control group (mean ± SD 12.91±8.74 ng/mL) (p=0.001). Likewise, S100A12 values were also found to be significantly higher in amyloidosis and sarcoidosis groups than in HCs [mean ± SD 627.87±643.83 ng/mL vs. 344.03±118.02 ng/mL, 600.4±381.26 ng/mL vs. 344.03±118.02 ng/mL, (p=0.001)] respectively. While calprotectin levels were found to be higher in the amyloidosis group than those in the IgG4-RD group (mean ± SD 810.76±772.58 ng/mL vs. 470.97±279.82 ng/mL, p=0.025) the difference did not reach statistical significance in sarcoidosis group (Table 2) (Figure 2A, 2B). In the statistical comparison, each disease was given a letter; a. control ; b. amyloidosis; c. IgG4-RD; d. sarcoidosis. (Table 2).

B-mode US evaluation revealed that all patients have increased echogenicity in parotid glands compared to HCs (p=0.001). Echogenicity did not differ significantly in lacrimal glands between groups. However, there was significant difference in the heterogeneous texture of lacrimal glands between groups (p=0.001). For the parotid glands, the mean shear wave elasticity mode values were significantly higher in the IgG4-RD patients compared with HCs, amyloidosis, and sarcoidosis groups (mean ± SD 16.27±3.48 vs. 9.89±2.60 kPa, 16.27±3.48 vs. 12.95±4.03 kPa, 16.27±3.48 vs. 12.84±3.25 kPa, all p=0.001), respectively (Table 3). For lacrimal glands, the mean shear wave elasticity mode values were significantly higher in the IgG4-RD patients compared with healthy subjects (mean ± SD 7.88±2.09 vs. 5.18±1.49 kPa, p=0.001), respectively.

In correlation analysis, 2D-SWE scores in parotid glands, reflecting loss of elasticity, had a positive correlation with S100A9 level in IgG4-RD (r=0.806; p=0.001) and amyloidosis (r=0.467; p=0.014) groups. In correlation analysis, in the amyloidosis group, a significant positive correlation was found between S100A12, (r=0.682; p=0.001) and calprotectin (r=0.847; p=0.001) values and S100A8. In both amyloidosis (r=0.644; p=0.001) and IgG4-RD (r=0.654; p=0.015) groups, a positive correlation was found between S100A12 and calprotectin values. In all groups, no significant relation was found between S100 values and traditional activity markers (ESR, CRP) (p>0.05) (Supplementary Table 2).

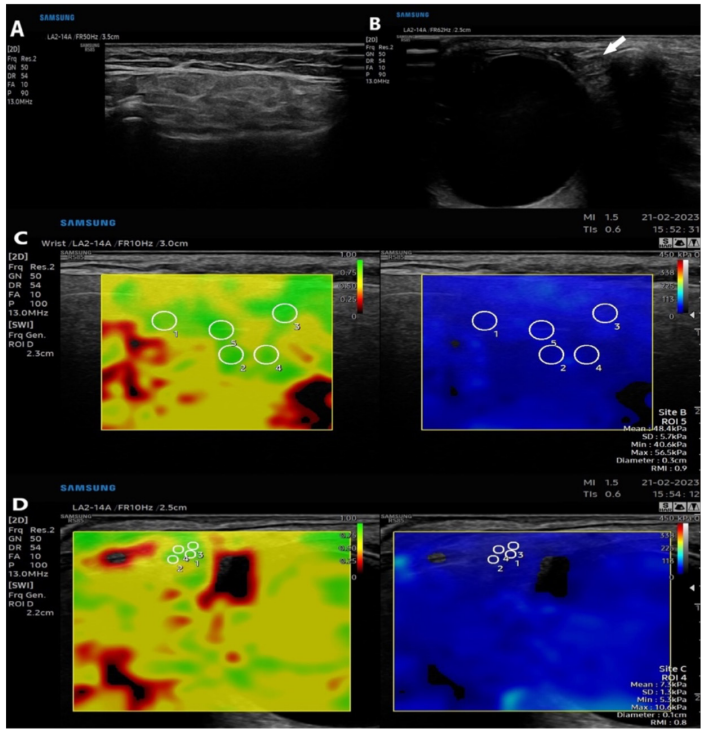

Figure 1. (A), Increased echogenicity and heterogeneous texture of parotid gland in the amyloidosis patient. (B) Heterogeneous texture of lacrimal gland in the IgG4-RD patient (white arrow), (C, D), Examples of the increased parotid and lacrimal elastography measurements performed in an IgG4-RD patient, respectively
IgG4-RD: IgG4-related disease

In amyloidosis patients, the cut-off value for S100A9 was determined as ≥12.7 ng/mL (sensitivity 96.3%, specificity 57.14%). Similarly, cut-off values for S100A12 and calprotectin were established to be ≥355.46 ng/mL (sensitivity 81.48%, specificity 71.43%) and ≥437.61 ng/mL (sensitivity 81.48%, specificity 47.62%), respectively (Table 4) (Figure 2C).

The mean shear wave elasticity cut-off scores that best discriminate IgG4-RD patients' parotid and lacrimal glands from HCs were 12.55 kPa and 5.5 kPa, respectively. A parotid gland 2D-SWE score of 12.55 kPa had a sensitivity and specificity of 92.3% and 80.95%, respectively. In the parotid elasticity ROC curve for IgG4-RD patients, the area under the curve was found to be 91.6% with a 5.5% standard error. The corresponding values were 86.3% and 6.2% respectively for lacrimal elasticity (Figure 2D).

Discussion

The present study is the first to evaluate the S100A8, S100A9, S100A12, and calprotectin of IgG4-RD, sarcoidosis, or amyloidosis patients as potential novel biomarkers. Our results suggest that S100A9, S100A12, and calprotectin proteins may be reliable, non-invasive biomarkers that can be used in the differential diagnosis of patients with suspected disease. Among investigated S100 proteins, S100A9 protein displayed the highest level of discriminatory power between amyloidosis cases and healthy controls. We demonstrated that S100A9 and S100A12 may have discriminatory power for not only amyloidosis but also sarcoidosis from healthy controls. And we evaluated the parotid/lacrimal gland involvement in these patients with 2D-SWE. Our results suggest that parotid/lacrimal US elastography could be a reliable, non-invasive auxiliary tool that can be used in the diagnosis of patients suspected of IgG4-RD. Furthermore, S100A9 biomarkers provided a prognostic value that was correlated well with the parotid elastography.

IgG4-RD, amyloidosis, and sarcoidosis are different multisystemic autoimmune diseases of unknown etiology in which immune dysregulation, genetic, and other unknown factors are in the pathogenesis.[1] Early diagnosis can be

Table 1. Demographic and clinical features of groups

	Amyloidosis (n=27)	Sarcoidosis (n=17)	IgG4-RD (n=13)	Control (n=21)	p
Age, years (mean ± SD)	43.11±11.19	46.94±5.89	48.85±8.93	43.81±6.93	0.100
Sex, female n (%)	12 (44.4)	14 (82.4)	6 (46.2)	12 (57.1)	0.073
BMI, kg/cm² (mean ± SD)	25.32±3.73	27.22±3.88	25.67±4.71	25.47±4.04	0.263
Smoking[1], n (%)	10 (37)	3 (17.6)	9 (69.2)	7 (33.3)	**0.041**
Disease duration, years	8 (2-20)	3 (1-17)	2 (1-6)	-	**0.001**
Involvements, n (%)					
-Lung	2 (7.4)	15 (88.2)	1 (7.7)	-	**0.001**
-Kidney	21 (77.8)	0 (0)	6 (46.2)	-	**0.001**
-Orbital	1 (3.7)	2 (11.8)	3 (23.1)	-	0.173
-Lacrimal/salivary glands	10 (37.0)	1 (5.9)	3 (23.1)	-	0.065
-GI	10 (37.0)	2 (15.4)	2 (11.8)	-	**0.003**
-Skin	4 (14.8)	5 (29.4)	0 (0)	-	0.093
-Lymph node	2 (7.4)	5 (29.4)	4 (30.8)	-	0.080
-Arthritis/arthralgia	20 (74.1)	6 (75.0)	2 (15.4)		**0.002**
Xerostomia, n (%)	8 (29.6)	9 (52.9)	4 (30.8)	-	0.178
Xerophthalmia, n (%)	6 (22.2)	9 (52.9)	3 (23.1)	-	**0.044**
Comorbidity, n (%)					
-Hypertension	17 (63.0)	5 (29.4)	4 (30.8)	2 (9.5)	
-Diabetes mellitus	2 (7.4)	4 (23.5)	0 (0)	0 (0)	**0.001**
-Coronary artery disease	3 (11.1)	1 (5.9)	4 (30.8)	0 (0)	
Treatment[2], n (%)					
-Corticosteroids[3]	1 (3.7)	14 (82.4)	11 (84.6)	-	**0.001**
-Colchicine	23 (85.2)	0 (0)	0 (0)	-	**0.001**
-Methotrexate	0 (0)	4 (23.5)	9 (69.2)	-	**0.001**
-Immunsupressants[4]	0 (0)	1 (5.9)	1 (7.7)	-	0.055
-Biologics[5]	20 (74.0)	0 (0)	2 (15.4)	-	**0.001**

GI: Gastrointestinal, [1]Active smoking, [2]Current treatment, BMI: Body mass index, [3]Current corticosteroid treatment, [5]Cyclophosphamide, azathioprine or mycophenolate, [5]Anakinra, canakinumab, rituximab, SD: Standard deviation, IgG4-RD: IgG4-related disease

Table 2. Evaluation of S100A8, S100A9, S100A12, calprotectin values, parotid/lacrimal gland shear wave elastography scores and laboratory measurements by groups

	Amyloidosis (n=27)	Sarcoidosis (n=17)	IgG4-RD (n=13)	Control (n=21)	p
S100A8, ng/mL	112.53±94.12	96.73±63.19	89.94±42.34	91.71±48.16	0.221
S100A9, ng/mL	25.09±7.92[a,b]	23.67±12.34[a,d]	21.12±13.82	12.91±8.74	**0.001**
S100A12, ng/mL	627.87±643.83[a,b]	600.4±381.26[a,d]	376.20±108.36	344.03±118.02	**0.001**
Calprotectin, ng/mL	810.76±772.58[b,c]	570.63±350.48	470.97±279.82	443.93±281[a,b]	**0.025**
Parotid elasticity, kPa	12.95±4.03[(a,b) (b,c)]	12.84±3.25[(c,d)]	16.27±3.48[a,c]	9.89±2.60	**0.001**
Lacrimal elasticity, kPa	6.55±1.71	6.18±2.15	7.88±2.09[(a,c)]	5.18±1.49	**0.001**
ESR (mm/h)	32.00±25.81[a,b]	17.69±14.55[c,d]	43.08±26.32[a,c]	14.05±12.7	**0.001**
CRP (mg/L)	12.78±23.67	11.93±8.98	20.62±38.79[a,c]	4.20±1.81	**0.047**
Platelet (x10³/uL)	239.67±63.6	306.53±101.4[b,d]	305.92±88.7[c,d]	244.9±41.4	**0.006**
Hemoglobin (g/dL)	12.73±2.07	13.33±1.45	12.79±1.85	13.72±1.84	0.197
Creatinine, mg/dL	2.20±2.41[a,b]	0.71±0.12[b,d]	0.83±0.26	0.70±0.13	**0.001**
Uric acid, mg/dL	6.13±1.69[a,b]	4.94±1.06	5.34±2.11	4.86±0.94	**0.021**
Total cholesterol, mg/dL	190.4±54.78	205.4±38.76	198.0±57.54	176.9±58.42	0.156
Triglyceride, mg/dL	196.6±127.9[a,b]	154.2±67.52	165.2±81.73	115.5±51.47	**0.019**
LDL, mg/dL	113.8±34.26	122.7±29.9	126.7±40.12	107.6±48.63	0.142
HDL, mg/dL	47.06±13.46	54.74±13.67	40.98±11.96	45.99±10.09	0.061

Values are presented as number (%), mean ± standard deviation or median [Q1-Q3]. CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, [a]Control, [b]Amyloidosis, [c]IgG4-RD, [d]Sarcoidosis, IgG4-RD: IgG4-related disease, kPa: KiloPascals

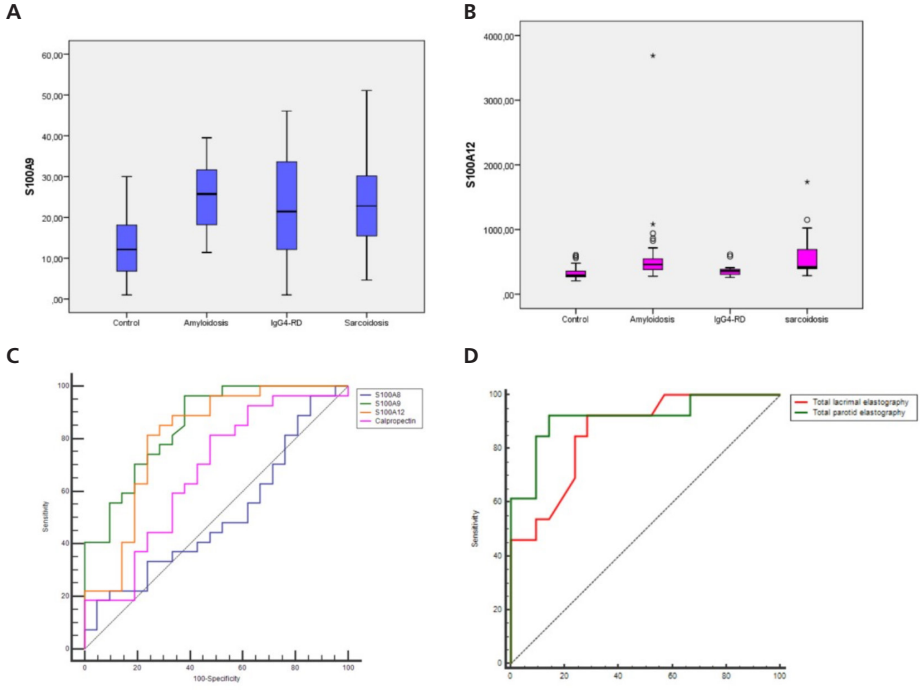

Figure 2. (A, B) Comparison of plasma S100A9 and S100A12 levels in amyloidosis, IgG4-RD, sarcoidosis patients and healthy groups, **(C)** Receiver operating characteristic curve analysis of S100A8, S100A9, S100A12 and calprotectin in amyloidosis. **(D)** Receiver operating characteristic curve analysis of parotid and lacrimal gland elasticity score in IgG4-RD. The area under the curve discriminates between IgG4-RD patients and healthy control subjects
IgG4-RD: IgG4-related disease

challenging. For definitive diagnosis gland and organ biopsies are required. However, both due to the invasiveness of the procedures and inadequate sampling may lead to a delay in diagnosis.[14] Biopsy can be challenging depending on the localization. Various studies have demonstrated that these diseases actually account for 25 to 50% of pseudoinflammatory diseases.[15] Unfortunately, we do not have adequate information on which patients will have a

Table 3. Comparison of elasticity (kPa) of parotid and lacrimal glands using two-dimentional shear wave elastography and B-mode ultrasonography

	Amyloidosis (n=27)	Sarcoidosis (n=17)	IgG4-RD (n=13)	Control (n=21)	p
Parotid gland elasticity (kPa)	12.95±4.03[b,c]	12.84±3.25[d,c]	16.27±3.48	9.89±2.60[a,c]	0.001
Lacrimal gland elasticity (kPa)	6.55±1.71	6.18±2.15	7.88±2.09	5.18±1.49[a,c]	0.001
P.G echogenicity, n (%)					
-Normal	14 (51.9)	9 (52.9)	6 (46.2)	21 (100)	0.001
-Increased	13 (48.1) [a,b]	8 (47.1) [a,d]	7 (53.8) [a,c]	0 (0)	
P.G texture, n (%)					
-Homogeneous	20 (74.1)	11 (64.7)	7 (53.8)	17 (81.0)	0.359
-Heterogeneous	7 (25.9)	6 (35.3)	6 (46.2)	4 (19.0)	
P.G posterior border, n (%)					
-Visible	18 (66.7)	10 (58.8)	7 (53.8)	15 (71.4)	0.724
-Invisible	9 (33.3)	7 (41.2)	6 (46.2)	6 (28.6)	
L.G echogenicity, n (%)					
-Normal	23 (85.2)	16 (94.1)	11 (84.6)	20 (95.2)	0.606
-Increased	4 (14.8)	1 (5.90)	2 (15.4)	1 (4.80)	
L.G texture, n (%)					
-Homogeneous	14 (51.9)	9 (52.9)	10 (76.9)	20 (95.2)	0.002
-Heterogeneous	13 (48.1)[a,b]	8 (47.1)[a,d]	3 (23.1)	1 (4.80)	

P.G: Parotid gland, L.G: Lacrimal gland, [a]Control, [b]Amyloidosis, [c]IgG4-RD, [d]Sarcoidosis, kPa: KiloPascals, IgG4-RD: IgG4-related disease

Table 4. ROC curve analysis of S100 proteins and elastography

	Cut-off value	Sensitivity	Specificity	AUC	Std. error	95% confidence interval	p
IgG4-RD							
Parotid elasticity	≥12.55	92.31	80.95	0.916	0.055	0.808-1000	0.001
Lacrimal elasticity	≥5.5	92.31	66.67	0.863	0.062	0.740-0.985	0.001
Amyloidosis							
S100A9	≥12.7	96.3	57.14	0.853	0.054	0.746-0.959	0.001
S100A12	≥355.46	81.48	71.43	0.804	0.068	0.671-0.938	0.001
Calprotectin	≥437.61	81.48	47.62	0.668	0.081	0.510-0.826	0.047

IgG4-RD: IgG4-related disease, AUC: Area under the curve, ROC: Receiver operating characteristic

more aggressive course of disease, and inadequate diagnosis and monitorization result in irreversible organ damage in clinical practice. Irreversible organ damage decreases the rate of response to current treatment as well as causing higher rate of morbidity and financial burden. Hence, it is important to establish the diagnosis, differential diagnosis, activity, and recurrence in these diseases at an early stage.

S100 proteins are small (10-12 kDA) cytosolic proteins which undergo conformational changes by binding calcium. They have basic functions in the body such as cell proliferation, cellular differentiation, energy metabolism, calcium homeostasis, recovery of cardiac tissue after cellular injury, and DNA repair. They regulate immunocomplex balance by playing a role both in pro-inflammatory pathways and anti-inflammatory pathways.[16] Previous studies have shown that S100 proteins were related to disease activity in several inflammatory diseases, such as juvenile rheumatoid arthritis, reactive arthritis, acute gout arthritis, psoriatic arthritis, and systemic lupus erythematosus.[17] In the present study, S100A9 and S10012 proteins were found to be significantly higher in amyloidosis and sarcoidosis patients than in healthy controls, whilst calprotectin was found to be higher only in amyloidosis patients than in the IgG4-RD group. In previous studies, it was reported that transthyretin amyloid (ATTR) amyloidosis patients with GI symptoms had high fecal calprotectin levels. In the present study, the highest calprotectin levels were found in amyloidosis patients with GI involvement. Therefore, if high serum calprotectin levels are detected in amyloidosis patients without GI involvement, these patients may undergo colonoscopy with biopsy in the early period, preventing GI pathologies from developing.

All new generation US devices are equipped with elastography features. Sonoelastography is a non-invasive

imaging method that can quantitatively evaluate tissue stiffness. 2D-SWE reduces operator-dependent limitations by providing a ROI box on top of the color-coded images and reveals a numerical value reflecting tissue stiffness. [18] Elastography has broad applications in liver and thyroid diseases for the assessment of tumor/nodular lesions and parenchymal fibrosis. In addition, its utility has been previously demonstrated in skin and tendon involvement of various rheumatic diseases.[19] In our study, parotid elastography scores were significantly higher in IgG4-RD than in the control group. For the cut-off value of 12.55 kPa, sensitivity, and specificity were found as 92.3% and 80.95%, respectively. In addition, S100A9 strongly correlated with lacrimal gland SWE values, reflecting the severity of the disease.

Study Limitations

A small sample size was a major limitation of our study. Another limitation was the absence of serial S100 proteins and sonoelastography measurements; therefore, we could not determine whether its levels changed with treatment or whether it may predict relapse.

Conclusion

S100A9, S100A12, and calprotectin might be promising biomarkers in IgG4-RD, amyloidosis, or sarcoidosis for diagnostic purposes. And this study suggests that the parotid gland lose elasticity in patients with IgG4-RD and amyloidosis. In addition, 2D-SWE, and especially the S100A9 biomarker, can be used as helpful tools that can facilitate prognosis in the early stages of the disease.

Ethics

Ethics Committee Approval: The study was conducted after the ethical approval of the Ethics Committee of Gazi University complied with the Declaration of Helsinki (approval no: 2023.549).

Informed Consent: Informed consent was obtained from all patients and controls before the initiation of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.K., Concept: H.K., A.K., A.E., H.Kü., M.A.Ö., Design: H.K., N.Y.D., M.N.C., S.A., H.P., A.K., A.E., H.Kü., M.A.Ö., Data Collection or Processing: H.K., N.Y.D., M.N.C., S.A., H.P., A.K., A.E., H.Kü., M.A.Ö., Analysis or Interpretation: H.K., N.Y.D., Literature Search: H.K., A.E., H.Kü., Writing: H.K.

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

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

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Supplementary Table 1. ICC scores for intra- observer and interobserver measurements in the sonoelastography findings

	Intraobserver (ICC)	p	Interobserver (ICC)	p
Parotid gland elasticity	0.983	**0.001****	0.864	**0.001****
Lacrimal gland elasticity	0.996	**0.001****	0.949	**0.001****
P.G echogenicity	0.989	**0.001****	0.991	**0.001****
P.G texture	0.987	**0.001****	0.864	**0.001****
P.G posterior border	0.944	**0.001****	0.880	**0.001****
L.G echogenicity	0.899	**0.001****	0.881	**0.001****
L.G texture	0.961	**0.001****	0.940	**0.001****

ICC: Intraclass correlation coefficient, P.G: Parotid gland, L.G: Lacrimal gland

Supplementary Table 2. Correlation of S100 proteins with parotid/lacrimal elastography scores, ESR and CRP in amyloidosis, sarcoidosis and IgG4-RD

	Amyloidosis (n=27)				Sarcoidosis (n=17)				IgG4-RD (n=13)			
	S100A9		S100A12		S100A9		S100A12		S100A9		S100A12	
	r	p	r	p	r	p	r	p	r	p	r	p
S100A8, ng/mL	-0.083	0.682	0.445	0.128	0.275	0.286	0.389	0.123	0.311	0.301	0.159	0.603
S100A9, ng/mL	1.000				1.000				1.000			
S100A12, ng/mL	-0.188	0.348	1.000		0.206	0.428	1.000				1.000	
S100A8/A9, ng/mL	-0.098	0.628	0,644	**0.001**	0.184	0.480	0.309	0.155	0.094	0.761	0.454	0.287
Parotid elasticity, kPa	0.948	**0.014**	0.970	0.08	0.213	0.411	0.213	0.411	0.806	**0.001**	0.374	0.209
Lacrimal elasticity, kPa	0.227	0.255	0.263	0.185	0.325	0.203	-0.028	0.914	-0.176	0.564	-0.465	0.109
ESR, mm/h	0.163	0.417	0.222	0.265	0.205	0.447	0.118	0.664	0.492	0.087	0.000	1.000
CRP, mg/dL	-0.029	0.887	0.063	0.759	0.080	0.761	0.321	0.209	0.366	0.219	0.088	0.775

CRP: C-reactive protein, ESR: Erythrocte sedimentation rate, IgG4-RD: IgG4-related disease, kPa: KiloPascals

Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2023.03511
Ulus Romatol Derg 2023;15(2):82-88

The assessment of hyposalivation and its impact on mouth disability in systemic sclerosis patients

Sistemik skleroz hastalarında hiposalivasyon ve hiposalivasyonun oral yetersizliğe olan etkisinin değerlendirilmesi

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Abstract

Objective: This study aimed to evaluate the reduction in salivary flow rate (SFR) and the effect of hyposalivation on mouth disability of SSc patients and to the relationship between Sjogren's syndrome (SS) related, SSc-related autoantibodies and hyposalivation in SSc patients

Methods: SSc patients who fulfilled American College of Rheumatology/European Alliance of Associations for Rheumatology 2013 criteria of SSc, were included in this cross-sectional study. Unstimulated whole SFR (UWSFR) was performed for the sialometric assessment. The mouth handicap in SSc (MHISS) scale was used for the evaluation of mouth disability.

Results: Seventy-two SSc patients (91.7% female) were included in the study. The mean age of patients was 52.2±13 years with 65.3% limited cutaneous SSc (lcSSc). Subjective xerostomia was presented in 44% of patients and reduced UWSFR (≤0.1 mL/min) was detected in 39% of patients. A significant difference was not displayed in terms of the presence of xerostomia and hyposalivation between lcSSc and diffuse cutaneous SSc (dcSSc) patients. Patients with hyposalivation had significantly higher MHISS total and subscale 2 scores compared to patients with normal SFR (p=0.04 and p=0.01, respectively). Decreased saliva production was related to the presence of dysphagia [odds ratio (OR): 2.86, 95% confidence interval (CI): 1.01-8.13; p=0.045], anti-Ro60/SSA autoantibody (OR: 3.7, 95% CI: 1.08-12.55; p=0.036), xerophthalmia symptom (OR: 4.3, 95% CI: 1.56-11.77; p=0.005), positive Schirmer's test (OR: 20.7, 95% CI: 6.02-71.08; p<0.001), higher MHISS total (OR: 1.05, 95% CI: 1.00-1.09; p=0.043), and higher MHISS domain 2 scores (OR: 1.13, 95% CI: 1.02-1.24; p=0.02).

Conclusion: Hyposalivation and xerostomia are commonly observed in SSc. Patients with hyposalivation had significantly higher mouth disability. The risk factors for hyposalivation in SSc were the presence of anti-Ro60/SSA autoantibody, dysphagia, subjective and objective xerophthalmia, higher MHISS total, and higher MHISS domain 2 scores.

Keywords: Disability, mouth, salivary flow rate, systemic sclerosis, xerostomia

Öz

Amaç: Bu çalışmanın amacı sistemik skleroz (SSc) hastalarında uyarılmamış tüm tükürük akış hızının (UWSFR) değerlendirilmesi, hiposalivasyonun ağız yetersizliği üzerine etkisini ve Sjögren sendromu (SS) ve SSc ilişkili antikorlar ile azalmış tükürük miktarı arasındaki ilişkiyi değerlendirmektir.

Yöntem: Bu kesitsel çalışmaya Amerikan Romatoloji Cemiyeti/Avrupa Romatizma Birliği 2013 SSc kriterlerini karşılayan hastalar dahil edildi. Sialometrik değerlendirmede UWSFR kullanıldı. Hastalığın ağız ilişkili etkilerini değerlendirmek için SSc ağız engeli (MHISS) skalası kullanıldı.

Bulgular: Çalışmaya yetmiş iki SSc hastası (%91,7'si kadın) dahil edildi. Hastaların ortalama yaşı 52,2±13 yıldı ve %65,3'ü sınırlı kutanöz SSc (lcSSc) hastasıydı. Hastaların %44'ünde kserostomi semptomu mevcutken; azalmış UWSFR (≤0,1 mL/dk) hastaların %39'unda saptandı. Hastalık alt tiplerine göre hastalar karşılaştırıldığında, kserostomi ve hiposalivasyon görülme sıklığı açısından anlamlı bir fark saptanmadı. Hiposalivasyonu olan ve olmayan hastalar karşılaştırıldığında, SSc ilişkili klinik özellikler, hastalık ciddiyeti ve sağlık yetersizlikleri benzerdi. Tükürük akım hızı azalmış hastalarda normal tükürük akış hızı olan hastalara göre anlamlı derecede MHISS toplam ve MHISS alt ölçek 2'nin puanları yüksekti (p=0,04 ve p=0,01, sırasıyla). SSc hastalarında düşük tükürük üretimi ile disfaji, [risk oranı (RO): 2,86, %95 güven aralığı (GA): 1,01-8,13; p=0,045)], anti-Ro60/SSA antikoru (RO: 3,7, %95 GA: 1,08-12,55; p=0,036), kseroftalmi (RO: 4,3, %95 GA: 1,56-11,77; p=0,005), Schirmer's testi pozitifliği (RO: 20,7, %95 GA: 6,02-71,08; p<0,001), MHISS toplam ölçek puanında (RO: 1,05, %95 GA: 1,00-1,09; p=0,043), ve MHISS alt ölçek 2 puanında artış (RO: 1,13, %95 GA: 1,02-1,24; p=0,02) arasında ilişki saptanmıştır.

Sonuç: SSc'de hiposalivasyon ve kserostomi sık rastlanmaktadır. Hiposalivasyonu olan hastalarda artmış ağız yetersizliği mevcuttur. Anti-Ro60/SSA antikoru, disfaji, kseroftalmi (subjektif semptom veya tanısal Schirmer's testi), MHISS toplam ve alt ölçek 2'nin artan puanları SSc hastalarında hiposalivasyon için risk faktörleridir.

Anahtar Kelimeler: Hiposalivasyon, kserostomi, sistemik skleroz, tükürük akış hızı, yetersizlik

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Received / Geliş Tarihi: 05.05.2023 **Accepted / Kabul Tarihi:** 10.07.2023

Cite this article as / Atıf: Avanoglu Guler A, Karadeniz H, Bilici R, Satış H, Babaoğlu H, Ataş N, Küçük H, Göker B, Haznedaroğlu S, Öztürk MA, Tufan A. The assessment of hyposalivation and its impact on mouth disability in systemic sclerosis patients. Ulus Romatol Derg 2023;15(2):82-88

Introduction

Systemic sclerosis (SSc) is a complex autoimmune disease characterized by pathogenic mechanisms including the dysregulated immune system, vasculopathy, and proceeding fibrosis, which mainly affect the skin and internal organs.[1] SSc is related to significant morbidity and mortality.[2,3] Moreover, in SSc, more than half of the death is directly related to disease-specific causes, the most common of which are pulmonary fibrosis, pulmonary arterial hypertension (PAH), and cardiac causes, respectively.[4]

In SSc, frequently observed manifestations such as orofacial involvement might have deleterious effects on the life of patients with social, psychological, and functional aspects; however, these involvements might be underdiagnosed or neglected due to being overshadowed by life-threatening complications and the complex nature of the disease.[5] One of the most common findings among orofacial involvement is sicca syndrome (xerostomia, xerophthalmia) in SSc patients with a high prevalence ranging from 64% to 75%.[6,7] Xerostomia, a sensation of dry mouth, is frequently reported by SSc patients due to decreased saliva production of salivary glands.[8] When considering the etiology of hyposalivation in SSc there have been two actual reasons; the exact known cause is higher concomitance of Sjogren syndrome (SS) marked by lymphocytic sialadenitis with SSc, and, in the light of recent histologic evidence, SSc leads to fibrosis of salivary gland, which might result in impairment of saliva production and excretion.[7,8] Moreover, the multi-center study supporting the latter hypothesis has reported that approximately two-thirds of SSc patients have sicca symptoms and half of patients have fibrotic lesions while only twenty percent of patients fulfilled the criteria for primary SS.[6]

The salivary flow rate (SFR) of patients with SSc is prominently low compared to the general population, and it is demonstrated that the presence of SSc is an independent predictor for saliva production. Besides, SSc patients have markedly impaired oral health-related quality of life (HRQoL).[9] The mouth handicap in Systemic Sclerosis scale (MHISS) is a specific tool developed to evaluate SSc patients on the mouth disability associated with reduced mouth opening, sicca syndrome, and aesthetic concerns and independent predictor of disability and HRQoL.[10,11] The primary aim of this study was to demonstrate reduced saliva production in SSc and its impact on oral disability evaluated by the MHISS scale. The secondary objective was to investigate the association between SS/SSc-related specific autoantibodies and hyposalivation.

Materials and Methods

Study Design and Participants

This cross-sectional, single-center study included patients who fulfilled the American College of Rheumatology/European League Against Rheumatism 2013 criteria of SSc from the Department of Rheumatology in Gazi University Hospital.[12] Exclusion criteria for patients were active smoking, the concomitance of other diseases, which could affect salivary glands (hepatitis C virus infection, lymphoma, sarcoidosis, immunoglobulin-G4 related disorders, adult immune-deficiency syndrome, graft-versus-host disease), and prior radiotherapy of head or neck. Patients who gave informed and written consent in accordance with the Declaration of Helsinki were included in this study, which was approved by the Ethics Committee of Gazi University Hospital (reference number: 456, date: 17.05.2021).

Data Collection

Demographic data, clinical features of SSc, and ongoing treatments were obtained from patients' interviews and medical records. Clinical features were evaluated and recorded as such, the disease duration [time between the onset of first non-Raynaud's Phenomenon (RP) symptoms and the last evaluation], disease subsets [classified as limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) according to the distribution of skin involvement by LeRoy et al.[13], history/active of digital ulcers (DUs), musculoskeletal involvement (presence of arthralgia, arthritis, myositis, or joint contractures), gastroesophageal involvement (presence of gastroesophageal reflux symptoms with evidence of esophageal dysmotility detected by esophageal manometry or barium esophagogram), interstitial lung disease (ILD) (presence of ILD findings on high resolution computed tomography), PAH (suspected findings on echocardiography and confirmed by right heart catheterization), cardiac involvement (presence of diastolic dysfunction, arrhythmias, pericardial effusion, pericarditis or myocarditis), and scleroderma renal crisis.

Laboratory tests were Rheumatoid Factor by nephelometry (positivity >20 IU/mL), presence of hypergammaglobulinemia, anti-nuclear antibody (ANA) by indirect immunofluorescence (positivity was accepted as titers >1/160), anti-Ro 60 and 52 (SS-A), anti-La (SS-B), anti- topoisomerase I, and anti-centromere antibodies by enzyme-linked immunosorbent assay.[13]

Xerophthalmia and xerostomia symptoms were evaluated using American College of Rheumatology/European Alliance of Associations for Rheumatology

inclusion criteria sicca questionnaire in all participants. Objective xerophthalmia was confirmed by Schirmer's test (positivity was the wetness of the paper ≤5 mm after 5 min.) in all participants. An unstimulated whole saliva collection test, an objective indicator of xerostomia, was used for the assessment of the hypofunction of salivary glands in SSc patients. UWSFR is equal to or less than 0.1 mL/min as accepted decreased SFR or hyposalivation.[14] Microstomia was considered less than 40 mm of interincisal distance.[5]

The mouth disability was evaluated by the MHISS scale questionnaire validated in the Turkish language.[15] MHISS contains 12 item questionnaires, each of which is scored ranging from 0 (never) to 4 (always). MHISS is divided into three domains: handicap related to reduced mouth opening (score range: 0-20), mouth dryness (score range: 0-20), and aesthetic concerns (score range: 0-8). Higher scores of MHISS express more handicaps of mouth.[10] HRQoL of patients was assessed by the Health Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ) visual analog scale of overall disease severity, validated in the Turkish version.[16-19] SSc disease severity of participants was examined with the Physician's Global Assessment (PGA) on the numeric rating scale, ranging from 0 to 10 (no severity to extremely severe disease).

Statistical Analysis

All statistical analyses of data were performed using Statistical Package for the Social Sciences software v16.0 (SPSS Inc, Chicago IL). P-values of less than 0.05 were considered statistically significant. Demographic data, clinical features, and assessments of disease severity and disability were compared according to disease subsets (lcSSc and dcSSc) and hyposalivation. Categorical variables were analyzed using the chi-square or Fisher's exact tests. The distributions of numeric variables were examined by visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Based on the distribution of data, analyses were reported using the median with interquartile range (IQR) and mean with standard deviation (SD). The Student's t-test and Mann-Whitney U test were used for the comparison of variables between groups, as appropriate. Univariate regression analyses were performed and calculated odd ratios (ORs) with 95% confidence intervals (95% CI) to determine the risk factors of hyposalivation in SSc patients.

Results

Seventy-two patients (91.7% female) were included in the study. The mean age of patients was 52.2±13 years. The median duration of the disease was 5 years and almost two-thirds of patients (65.3%) had lcSSc. The characteristics of the disease in participants were demonstrated in Table 1.

Sicca symptoms were reported in fifty-seven percent of patients. Thirty-two patients (44%) had subjective xerostomia while hyposalivation was detected in twenty-eight patients (39%). Subjective xerophthalmia was observed in thirty-one patients (43.1%) concordant with the result of positivity of Schirmer's test. Thirty-five percent of the patients were using medications with xerogenic side effects, including calcium-channel blockers, beta-blockers, diuretics, angiotensin-converting enzyme inhibitors, and selective serotonin reuptake inhibitors. The use of xerogenic medications did not have a statistically meaningful effect on hyposalivation in SSc patients (28.6% in patients with reduced UWSFR and 38.6% in patients with normal UWSFR; p=0.53). The evaluation of mouth disability in all patients showed that the median total MHISS score was 14 (minimum-maximum: 0-43) and the median MHISS subscale 2, assessing dry mouth, was 6 (minimum-maximum: 0-19).

The comparison of patients according to the disease subset, subjective xerostomia and the reduction in UWSFR were similar (p=0.35; p=0.52, respectively). MHISS total and subscale 2 scores were significantly higher in patients with dcSSc (p<0.001 and p=0.003, respectively) (Table 2). Likewise, dcSSc patients had markedly higher MHISS subscales 1 and 3 scores than lcSSc patients (p<0.001). Besides, patients with lcSSc presented significantly lower HAQ and SHAQ-disease severity than dcSSc patients (p=0.024 and p=0.04).

The comparison of SSc-related features in terms of hyposalivation displayed that the disease duration and organ involvements were similar in both groups. Similarly, there was no statistically significant difference in disease severity evaluated by PGA and health disability measured by SHAQ and HAQ between the two groups. Furthermore, the frequency of dysphagia was prominently increased in patients with reduced USWFR than in patients with normal USWFR (75% vs 51%; p=0.04); however, the presence of gastroesophageal involvement and gastroesophageal reflux were similar between patients with reduced salivary production and patients with normal salivary production (85.7% vs 86%; p=1.00 and 55.6% vs 65%; p=0.46, respectively). Patients with reduced UWSFR had a statistically higher rate of sicca and xerophthalmia symptoms and positivity of Schirmer's test rather than patients with normal UWSFR (71.4% vs 47.7%; p=0.04, 64.3% vs 29.5%; p=0.007 and 82.1% vs 18.2%; p<0.001, respectively). Notwithstanding, xerostomia symptom was reported in sixteen patients with hyposalivation (57.1%)

and seventeen patients with normal SFR (38.6%) (p=0.15). Regarding serologic evaluation, the only positivity of anti-Ro60/SSA antibody was statistically frequent in patients with hyposalivation (p=0.03) (Table 3). The assessment of health and mouth disability of patients showed that a significant difference was detected in terms of total MHISS and MHISS subscale 2 between patients with reduced UWSFR and patients with normal SFR (p=0.04 and p=0.01, respectively). The risk factors of hyposalivation in SSc patients were determined as the presence of dysphagia (OR: 2.86, 95% CI: 1.01-8.13; p=0.045), anti-Ro60/SSA autoantibody (OR: 3.7, 95% CI: 1.08-12.55; p=0.036), presence of subjective xerophthalmia (OR: 4.3, 95% CI: 1.56-11.77; p=0.005), positive Schirmer's test (OR: 20.7, 95% CI: 6.02-71.08;

Table 1. The baseline characteristics of SSc patients

	SSc (n=72)	lcSSc (n=47)	dcSSc (n=25)	p
Female, n (%)	66 (91.7)	43 (91.5)	23 (92)	1.00
Age, years, mean ± SD	52.24 (13.00)	52.62 (12.62)	51.52 (14.16)	0.75
Smoking, ever, n (%)	19 (26.4)	15 (31.9)	4 (16)	0.14
Disease duration, median (IQR) years	5 (8)	5 (9)	5 (7)	0.59
mRSS, median (IQR)	11 (10)	9 (6)	20 (10)	<0.001
Maximal mouth opening, mean (SD)	3.63 (0.65)	3.78 (0.6)	3.33(0.68)	0.005
Microstomia (interincisal distance <40 mm), n (%)	47 (65.3)	28 (59.6)	19 (76)	0.08
Digital ulcers, n (%)	30 (41.7)	14 (29.8)	16 (64)	0.006
Musculoskeletal involvement, n (%)	42 (58)	23 (48.9)	19 (76)	0.03
Gastrointestinal involvement, n (%)	62 (85.9)	38 (80.9)	24 (96)	0.46
Oesophageal involvement, n (%)	57 (79.2)	37 (78.2)	20 (80)	0.37
Cardiac involvement, n (%)	19 (26.4)	14 (29.8)	5 (20)	0.44
ILD, n (%)	38 (52.8)	19 (40.4)	19 (76)	0.04
PAH, n (%)	7 (10)	4 (8.5)	3 (12)	0.84
Renal crisis, n (%)	6 (8.3)	5 (10.6)	1 (4)	0.63
Autoantibodies, positivity n (%)				
ANA ≥1/160	70 (97.2)	46 (97.9)	24 (96)	1.00
Anti-centromere	16 (22.2)	13 (27.7)	2 (8)	0.46
Anti-Topoisomerase	39 (54.2)	20 (42.6)	19 (76)	0.007
Anti-Ro60/SSA	14 (19.4)	7 (14.9)	7 (28)	0.30
Anti-Ro52/SSA	11(15.3)	8 (17)	3 (12)	0.88
Anti-La/SSB	2 (2.8)	1 (2.1)	1 (4)	1.00
RF	16 (22.2)	11 (23.4)	5 (20)	0.74
Hypergammaglobulinemia, n (%)	15 (20.8)	8 (17)	7 (28)	0.23
Sicca Symptoms, n (%)	41 (56.9)	25 (53.2)	16 (64)	0.38
Xerostomia	32 (44.4)	19 (40.4)	13 (52)	0.35
Xerophthalmia	31 (43.1)	20 (42.7)	11 (44)	0.90
Schirmer's test ≤5 mm/5 min	31 (43.1)	19 (40.4)	12 (48)	0.53
UWSFR ≤ 0.1 mL/min, n (%)	28 (38.9)	17 (36.2)	11 (44)	0.52

ANA: Antinuclear antibody, dcSSc: Diffuse cutaneous systemic sclerosis, ILD: Interstitial lung disease, IQR: Interquartile range, lcSSc: Limited cutaneous systemic sclerosis, mRSS: Modified Rodnan skin score, PAH: Pulmonary arterial hypertension, RF: Rheumatoid factor, SD: Standard deviation, SSc: Systemic sclerosis, UWSFR: Unstimulated whole saliva flow rate

Table 2. The assessment of health and mouth disability in SSc patients

	SSc (n=72)	lcSSc (n=47)	dcSSc (n=25)	p
MHISS total, median (IQR)	14 (19)	9 (15)	27 (18)	<0.001
MHISS subscale 1, median (IQR)	4 (11)	2 (8)	11.5 (11)	<0.001
MHISS subscale 2, median (IQR)	6 (9)	4 (9)	8 (9)	0.003
MHISS subscale 3, median (IQR)	3 (6)	0 (3)	5.5 (4)	<0.001
PGA, mean±SD	4.91 (1.42)	4.27 (1.54)	5.21 (1.14)	0.20
HAQ, median (IQR)	0.62 (1)	0.5 (1.2)	1 (0.87)	0.024
SHAQ-disease severity, median (IQR)	1.4 (2.15)	0.6 (2.2)	1.45 (1.0)	0.040

IQR: Interquartile range, HAQ: Health assessment questionnaire, MHISS: Mouth handicap in Systemic Sclerosis, PGA: Physician's Global Assessment, SD: Standard deviation, SHAQ: Scleroderma HAQ, SSc: Systemic sclerosis

Table 3. The evaluation of disease-related autoantibodies profile, mouth, and health disability of SSc patients in accordance with salivary production

	UWSFR >0.1 mL/min n=44	UWSFR ≤0.1 mL/min n=28	p
Autoantibody positivity, n (%)			
ANA ≥1/160	42 (95.5)	28 (100)	0.52
Anti-centromere antibody	9 (20.9)	6 (21.4)	1.00
Anti-topoisomerase II antibody	23 (52.3)	16 (57)	0.8
Anti-Ro60/SSA antibody	5 (11.4)	9 (32)	0.03
Anti Ro52/SSA	8 (18.6)	3 (10.7)	0.57
Anti-SSB antibody	1 (2.3)	1 (3.6)	1.00
Double positive*	3 (6.8)	5 (17.9)	0.50
RF positivity, n (%)	8 (18.2)	8 (28.6)	0.38
Hypergammaglobulinemia, n (%)	9 (20.9)	6 (21.4)	1.00
MHISS total, median (IQR)	13 (17)	20 (21)	0.04
MHISS subscale 1, median (IQR)	3.5 (10)	7.5 (14)	0.20
MHISS subscale 2, median (IQR)	4 (9)	8 (7)	0.01
MHISS subscale 3, median (IQR)	1 (5)	4 (6)	0.45
PGA, mean ±SD	5 (1.5)	5 (1.3)	0.27
HAQ, median (IQR)	0.5 (1.12)	0.92 (1.1)	0.34
SHAQ-disease severity, median (IQR)	1 (2.1)	1.4 (1.3)	0.24

**Positivity of anti-topoisomerase and anti-SSA/SSB. ANA: Antinuclear antibody, IQR: Interquartile range, HAQ: Health assessment questionnaire, MHISS: Mouth handicap in Systemic Sclerosis, PGA: Physician's Global Assessment, RF: Rheumatoid factor, SD: Standard deviation, SHAQ: Scleroderma HAQ, SSc: Systemic sclerosis, UWSFR: Unstimulated whole saliva flow rate*

p<0.001), higher MHISS total scores (OR: 1.05, 95% CI: 1.00-1.09; p=0.043), and higher MHISS domain 2 scores (OR: 1.13, 95% CI: 1.02-1.24; p=0.02) by using univariate regression analyses.

Discussion

Sicca symptoms are one of the most frequent findings with a higher prevalence in SSc patient.[6,7,20] Our study demonstrated the prevalence of sicca symptoms in 57% of SSc patients and tended to be increased in dcSSc. Besides, subjective xerostomia was observed in 44.4% of patients consistent with the results from previous reports.[21,22]

Xerostomia can lead to numerous complications including dysphagia, mucosal infections, periodontal diseases, and denutrition, and eventually result in a reduction in quality of life.[8,23] Several studies displayed that decreased SFR namely objective xerostomia was frequently observed in SSc patients and indeed, SSc was considered as an independent risk factor of saliva production.[9,24] Recent histopathologic reports suggested that salivary gland involvement in SSc is not only caused by the presence of secondary SS but also progressive fibrosis, which is one of the hallmark mechanisms of SSc, might directly lead to impairment of salivary glands.[6-8] In our study, hyposalivation (UWSFR ≤1 mL/min) was detected in 39% of SSc patients. A study assessing sicca symptoms and prevalence of SS in SSc patients reported 35% of patients with reduced salivary production, congruent with our finding. Furthermore, older age and positive SS-A autoantibody were considered as predictors of SS in SSc patients.[7] In addition, SSc-related clinical manifestations prominently observed in SSc patients with SS, were lcSSc subset and absence of ILD.[6,25,26] According to our results, there were not any significant associations detected between the disease subsets, disease duration, organ involvements, disease severity scores measured with PGA, and decreased salivary production. However, the positivity of anti-SSA antibodies was frequently observed in SSc patients with decreased salivary production and considered as predictor for hyposalivation in SSc patients. Similarly, a recent study revealed the important association between reduced saliva production and the positivity of at least one SS-related antibody and reported that disease severity scores were not related to saliva production.[27] On the other hand, the study with a small number of dcSSc patients without concomitant SS or SS-related antibodies displayed reduced SFR in dcSSc patients and a negative correlation between disease severity and SFR.[24] In addition to the positivity of SS-A antibody, in our cohort, subjective xerophthalmia symptoms and objective xerophthalmia were predictors for decreased saliva production in SS patients as expected.

Dysphagia is one of the most common symptoms in SSc patients. SSc-related various causes are resulting in dysphagia such as esophageal dysmotility, gastroesophageal reflux, myositis, microstomia, or xerostomia.[28] Our study showed that the dysphagia was significantly related to reduced saliva production. However, there was no significant association

observed between decreased saliva production and gastroesophageal involvement, which might be suggested that xerostomia might be one of the main contributors to dysphagia in our study.

Recent evidence has revealed that SSc has a detrimental impact on the oral health of patients, which eventuates in significant oral disabilities. The Canadian SSc oral health study demonstrated that SSc patients had impaired oral HRQoL assessed by the Oral Health Impact Profile which is widely used for the evaluation of oral health disability whereas it is not a specific instrument for SSc.[9] Moreover, another Canadian SSc oral health study reported that oral HRQoL was related to global HRQoL. However, there was not any significant relationship detected between disease subset, disease duration, PGA disease severity, and oral HRQoL.[29] Our study showed that SSc patients with decreased SFR had prominently worse oral HRQoL evaluated with the MHISS scale and MHISS subscale 2 scores reflecting disabilities related to mouth dryness were significantly higher in these patients. Furthermore, an increase in MHISS total and MHISS subscale 2 scores were considered as risk factors for reduction in saliva production in SSc patients.

Study Limitations

This study had a few limitations. First, there was not a control-healthy group to confirm the increased risk of hyposalivation in SSc. Another important limitation was that secondary SS has not been diagnosed due to the requirement of histopathologic evaluation which needs invasive procedure, that is why, the prevalence of secondary SS has been not demonstrated. Despite all limitations, the most important strength of the study was the first report to assess the effect of hyposalivation on oral health and disability with MHISS which is the SSc-specific instrument developed for orofacial involvement of SSc.

Conclusion

In conclusion, our study demonstrated that the prevalence of xerostomia and reduction in salivary production were frequently observed in SSc patients. It was founded that risk factors for the presence of hyposalivation in SSc were the positivity of anti-Ro60/SSA antibody, xerophthalmia, and dysphagia symptom. Besides, SSc patients with hyposalivation had markedly poorer oral HRQoL assessed by MHISS. Moreover, a significant relationship between hyposalivation and higher MHISS scores was thought that MHISS might be more commonly used for follow-up for salivary gland hypofunction or salivary gland involvement of SSc patients.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Gazi University Hospital (reference number: 456, date: 17.05.2021).

Informed Consent: Informed consent was obtained from patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.A.G., Haz.K., M.A.Ö., A.T., Design: A.A.G., R.B.S., H.S., H.B., N.A., H.K., A.T., Data Collection or Processing: A.A.G., Haz.K., R.B.S., H.S., H.B., N.A., Analysis or Interpretation: A.A.G., Haz.K., R.B.S., H.S., H.B., N.A., A.T., Literature Search: A.A.G., Haz.K., R.B.S., H.S., H.B., N.A., H.K., Writing: A.A.G., H.K., B.G., S.H., M.A.Ö., A.T.

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

Financial Disclosure: The authors declare that they have no relevant financial disclosures.

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Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2023.29591
Ulus Romatol Derg 2023;15(2):89-94

Plasma exchange therapy in systemic lupus erythematosus: A single-center retrospective cohort study

Sistemik lupus eritematozusda plazma değişim tedavisi: Tek merkez retrospektif kohort çalışması

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Abstract

Objective: Few randomized controlled studies investigating the role of plasma exchange (PLEX) therapy shown no significant benefit in the management of lupus nephritis. However small case series have suggested potential efficacy in certain types of organ involvement in systemic lupus erythematosus (SLE).

Methods: We conducted a retrospective review of patient records who received PLEX therapy between October 2013 and March 2022 at our apheresis unit. Patients under the age of 18 and those who underwent PLEX therapy for non-rheumatic and rheumatic diseases other than SLE were excluded from the study. We collected comprehensive data including the primary indication for PLEX therapy, procedural details, concurrent immunosuppressive medications, overall survival, outcomes of organ involvement, and any complications associated with PLEX therapy.

Results: Among 58 patients with rheumatic diseases who underwent PLEX therapy we included 17 SLE patients. The main indication for PLEX was catastrophic antiphospholipid syndrome (n=5), diffuse alveolar hemorrhage (DAH) (n=5), neuropsychiatric involvement (n=4), thrombotic microangiopathy (n=2) and renal involvement (n=1). Nine patients experienced severe/opportunistic infections resulting in death only in 1 patient during PLEX. Additionally, 3 patients died due to active disease during PLEX. Among the survived patients PLEX therapy provided remission in 13 patients.

Conclusion: PLEX can be regarded as a supplementary treatment along with immunosuppressives, particularly for a subset of SLE patients experiencing conditions such as DAH and neuropsychiatric involvement. Despite high frequency of severe/opportunistic infections only one patient died.

Keywords: Plasma exchange, plasmapheresis, systemic lupus erythematosus, lupus

Öz

Amaç: Plazma değişimi (PLEX) tedavisinin lupus nefriti yönetiminde anlamlı bir fayda sağlamadığını gösteren az sayıda randomize kontrollü çalışma bulunmaktadır. Bununla birlikte, küçük olgu serileri, sistemik lupus eritematozusun (SLE) bazı organ tutulum tiplerinde plazma değişiminin etkili olabileceğini bildirmiştir.

Yöntem: Ekim 2013 ile Mart 2022 tarihleri arasında PLEX tedavisi alan hastaların kayıtlarını geriye dönük olarak inceledik. On sekiz yaşın altındaki hastalar, SLE dışında romatizmal hastalığı olanlar ve romatizmal hastalık dışı nedenlerle PLEX tedavisi yapılan hastalar dışlandı. PLEX tedavisinin başlıca endikasyonu, işlem detayları, eşzamanlı olarak kullanılan immünosüpresif ilaçlar, genel sağkalım, organ tutulumunun sonuçları ve PLEX tedavisi ilişkili komplikasyonlar gibi bilgiler not edildi.

Bulgular: Romatizmal hastalığı olup PLEX tedavisi uygulanan 58 hastadan 17 SLE hastası çalışmaya dahil edildi. PLEX tedavisinin birincil endikasyonları katastrofik antifosfolipid sendromu (n=5), diffüz alveolar hemoraji (DAH) (n=5), nöropsikiyatrik tutulum (n=4), trombotik mikroanjiyopati (n=2) ve renal tutulum (n=1) idi. PLEX sırasında 9 hastada ciddi/fırsatçı enfeksiyonlar geliştiği görüldü. Bir hasta enfeksiyona bağlı, 3 hasta aktif hastalık nedeniyle PLEX devam ederken kaybedildi. Sağ kalan hastaların 13'ünde PLEX tedavisi ile remisyon sağlandı.

Sonuç: PLEX, DAH ve nöropsikiyatrik tutulum gibi SLE hastalarının belli bir alt grubu için immünosüpresiflerle birlikte ek bir tedavi olarak değerlendirilebilir. Hastalarımızın yaklaşık yarısı ciddi veya fırsatçı enfeksiyonlarla karşılaşsa da, yalnızca bir hastada enfeksiyona bağlı mortalite gözlenmiştir.

Anahtar Kelimeler: Plazma değişimi, plazmaferez, sistemik lupus eritematozus, lupus

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Received / Geliş Tarihi: 08.06.2023 **Accepted / Kabul Tarihi:** 07.07.2023

Cite this article as / Atıf: Özgüler Y, Ak T, Esatoğlu SN, Elverdi T, Eşkazan AE, Uğurlu S, Hatemi G, Seyahi E, Melikoğlu M, Fresko İ, Ar MC, Hamuryudan V. Plasma exchange therapy in systemic lupus erythematosus: A single-center retrospective cohort study. Ulus Romatol Derg 2023;15(2):89-94

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with a wide range of clinical symptoms and a variable disease course. The prognosis of patients has improved with the introduction of combined immunosuppressive and glucocorticoid (GC) therapy.[1] In general, management of SLE depends on disease severity, disease activity, clinical manifestations, and comorbidities. Cutaneous manifestations, musculoskeletal manifestations, and serositis are typically indicative of less severe disease, and may exhibit fluctuations in accordance with disease activity. Frequently, these conditions can be managed through the administration of nonsteroidal anti-inflammatory drugs or low-potency immunosuppressive agents, in addition to hydroxychloroquine and/or brief regimens of GCs. Organ or life-threatening disease manifestations, such as kidney, lung, and central nervous system involvement require more aggressive immunosuppression. In those patients, immunosuppressives (e.g. mycophenolate mofetil, cyclophosphamide) are mostly combined with high doses of systemic GCs. However, there is still some subgroup of patients who do not respond well to the standard of care (SOC).[2] Despite the lack of high-quality data, therapeutic plasma exchange therapy (PLEX) has been considered as an alternative treatment option in refractory and/or severe SLE patients.[3]

PLEX has been used for almost four decades in a wide variety of autoimmune diseases in which humoral factors play a role in the pathogenesis.[4] The underlying idea of the PLEX is based on the assumption that the reduction or elimination of specific pathological substances (e.g., autoantibodies, immune complexes, cryoglobulins) from the plasma can lead to the prevention of additional damage or even might help reversing the pathological condition.[5] The American Society for Apheresis (ASFA) has categorized the use of PLEX into four distinct groups based on the currently available evidence.[6] Category-I disorders are for which PLEX is the first-line therapy, either alone or with a combination of other therapies. PLEX is accepted as the second-line therapy in category-II disorders. If the benefit of PLEX has not been fully demonstrated, those group of disorders are classified as category-III. If the published evidence indicates or implies that PLEX could potentially be harmful or ineffective, those disorders are classified as category-IV. PLEX has been studied in few randomized controlled trials (RCT) in patients with lupus nephritis (LN) and none of them demonstrated any significant improvement in renal outcome compared to the SOC.[7-11] On the other hand, there are significant number of case reports and series have reported positive outcome especially in refractory and severe SLE patients.[3,12,13] According to ASFA guidelines, SLE patients with severe types of organ involvement, including central nervous system (CNS) involvement, diffuse alveolar hemorrhage (DAH), thrombotic microangiopathy, cryoglobulinemia, cytopenia, hyperviscosity, but not LN, are classified into category-II.[6] Additionally, the ASFA guideline published in 2019 upgraded catastrophic antiphospholipid syndrome (CAPS) from Category II to Category I.[14] In the ASFA guideline published in 2023, CAPS continues to be classified under Category I.[6]

The objective of this real-world study was to retrospectively evaluate the overall survival of patients, identify causes of mortality, assess the incidence of infectious and non-infectious complications, and determine the risks and benefits of PLEX therapy in patients with SLE [with or without antiphospholipid syndrome (APS)] in a real-world clinical setting.

Materials and Methods

A retrospective chart review was conducted on patients who received PLEX therapy between October 2013 and March 2022. We excluded patients who underwent PLEX treatment for conditions other than rheumatic diseases, such as thrombotic thrombocytopenic purpura (TTP), multiple sclerosis, or hyperviscosity syndrome, and who were under 18 years old. Additionally, patients with rheumatic diseases other than SLE, including ANCA-associated vasculitis (AAV) (n=28), cryoglobulinemic vasculitis (n=7), systemic sclerosis (n=2), Goodpasture syndrome (n=2), IgA vasculitis (n=1), and dermatomyositis (n=1), were also excluded. We have previously reported the outcome of PLEX therapy among our 28 AAV patients.[15] We obtained comprehensive data from patient charts, including information on the underlying rheumatic disease, the primary indication for PLEX therapy, specific procedural details (such as the use of albumin and/or, fresh frozen plasma (FFP) peripheral or central venous catheters, and a number of PLEX sessions), concomitant immunosuppressive treatments [such as steroid pulses, cyclophosphamide (CYC), rituximab (RTX), or intravenous immunoglobulin (IVIG)], overall survival rates, outcomes of organ involvement, and any complications associated with PLEX therapy. Mortality, and as well as the impact on organ function, were assessed both during the administration of PLEX and at the 3-month and 12-month post-treatment follow-up. We examined the occurrence of infections during the initial 5-week period since patients treated with PLEX have been shown to continue to exhibit low levels of immunoglobulin G until week 5.[16] We also assessed the mortality until the final follow-up

appointment for patients. The study was planned according to the Declaration of Helsinki, and an independent ethics committee of Cerrahpasa Medical Faculty gave permission to conduct this study (date: 02.06.2022, approval number: 396452).

Statistical Analysis

The demographic, baseline, and follow-up characteristics of the patients were presented with the descriptive statistics. Data are expressed as means and standard deviations (SD), median values with ranges (Q1-Q3) or frequency (%).

Results

Baseline Characteristics of Patients

The retrospective analysis of medical records identified a total of 318 individuals who received PLEX treatment between October 2013 and March 2022 at our apheresis facility. Following the exclusion of 253 patients who underwent PLEX for non-rheumatic conditions, 41 patients with rheumatic diseases other than SLE, and 7 patients who were below the age of 18, a total of 17 patients diagnosed with SLE were subjected to further evaluation (Figure 1).

As expected, the majority of the patients were female (n=15, 88%) and the mean age of the patients was 33.4±9.4. The main indications for PLEX were DAH in 5 patients, CAPS in 5, CNS involvement in 4, TTP in 2 patients, and rapidly progressive glomerulonephritis (RPGN) in 1 patient (Table 1). Hemodialysis was also started concomitant with PLEX therapy in 3 patients. The causes for hemodialysis were CAPS in 1, class IV LN in 1 and RPGN in 1 patient. Due to the patient's thrombocytopenia and the potential risk of hemorrhage associated with PLEX therapy, a renal biopsy could not be performed in the case of RPGN. Immunosuppressive agents (CYC, RTX), high dose intravenous pulse methylprednisolone (1 g/day for 3 days) followed by prednisolone 1 mg/kg/day were initiated in all but two patients in conjunction with PLEX. IVIG was used in combination with immunosuppressives in 11 patients and as a solo treatment in 2 patients. The treatment details of each patient are given in the Table 1.

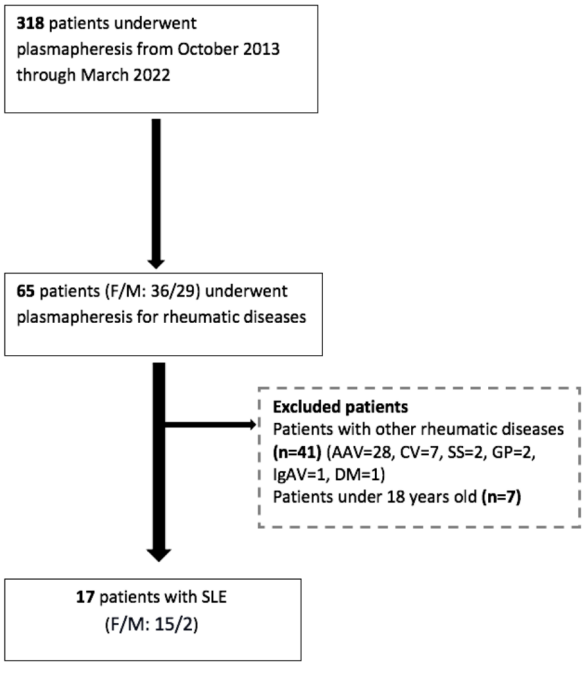

Figure 1. Flow-chart of the included patients
AAV: ANCA-associated vasculitis, CV: Cryoglobulinemic vasculitis, DM: Dermatomyositis, GP: Goodpasture syndrome, IgAV: IgA vasculitis, SLE: Systemic lupus erythematosus, SS: Systemic sclerosis

Ten (59%) out of 17 SLE patients had concomitant APS (Table 1). Three patients had triple positive antiphospholipid (aPL) profile, one had double positivity [lupus anticoagulant (LA) + anticardiolipin (aCL)] and the remaining had only one type of aPL [LA=3, aCL=2, antibeta-2 glycoprotein (anti-β2GPI) =1] antibodies. Anti-double-stranded DNA (anti-dsDNA) was positive in 11 patients, Ro/SSA was positive in 2, anti-Smith (anti-Sm) was positive in 2, and La/SSB was positive in one patient.

Features of Plasma Exchange Therapy

The median number of PLEX was 4 (Q1-Q3=3-5) (Table 2). A Fresenius Comtec 2010 machine (centrifugal technique) was used for the procedure to exchange an average of 1.3 plasma volumes. PLEX was performed using a central venous catheter and peripheral veins in 9 (53%) and 8 (47%) patients, respectively. Plasma was replaced with fresh frozen plasma (FFP) (n=5, 29%), albumin (n=2, 12%), or both (n=10, 59%).

Outcomes

Death and Complications

Four (24%) patients died during PLEX therapy. The cause of mortality in three patients was attributed to the underlying active disease, i.e. CAPS (n=2) and RPGN (n=1). Death in one patient was associated with both infection (CMV infection and pseudomonas aeruginosa pneumonia) and active disease (CNS involvement).

While no additional deaths occurred within the first three months, three more deaths were observed before month 12 related to COVID-19 infection, relapsing disease (DAH), and aspiration-related cardiopulmonary arrest.

Table 1. Clinical characteristics and outcome of 17 SLE patients who underwent PLEX therapy

Age/Sex	Concomitant APS	Main indication for PLEX	Concomitant IS	Infection during PLEX	Outcome
31/F	No	DAH	MP+CYC+IVIG	No	Remission at month 12
23/F	Yes	CAPS	MP+CYC+IVIG	No	Died at month 7 due to cardiopulmonary arrest
25/F	Yes	CAPS	MP+RTX+IVIG	No	Remission at month 12
30/F	No	CNS inv.	MP+RTX+IVIG	No	Remission at month 12
30/M	Yes	DAH	MP+CYC	No	Remission at month 12
28/F	No	RPGN	MP+CYC+IVIG	CMV	Died during PLEX
35/F	No	CNS inv.	MP+IVIG	CMV+ PAP	Died during PLEX
25/M	Yes	DAH	MP+CYC+IVIG	CMV	Died due to active disease at month 4
26/F	No	CNS inv.	MP+CYC	SMP	Remission at month 12
52/F	No	DAH	MP+IVIG	CMV + Lobar pneumonia	Died due to COVID-19 after 4 months of PLEX
47/F	Yes	DAH	MP+CYC+IVIG	PJP	Remission at month 12
49/F	Yes	CAPS	IVIG	Pneumonia	Died during PLEX
26/F	Yes	CAPS	MP+RTX+IVIG	PJP	Remission at month 12
47/F	Yes	CAPS	IVIG	No	Died during PLEX
32/F	Yes	TTP	MP+CYC+IVIG	Pneumonia + Soft tissue infection	Remission at month 12
34/F	Yes	CNS inv.	MP+RTX	No	Remission at month 12
28/F	No	TTP	MP+CYC	No	Remission at month 12

APS: Antiphospholipid syndrome, CAPS: Catastrophic antiphospholipid syndrome, CMV: Cytomegalovirus, CNS: Central nervous system, CYC: Cyclophosphamide, DAH: Diffuse alveolar hemorrhage, F: Female, IS: Immunosuppressives, IVIG: Intravenous immunoglobulin, M: Male, MP: Methylprednisolone, PAP: Pseudomonas aeruginosa pneumonia, PJP: Pneumocystis jirovecii pneumonia, PLEX: Plasma exchange, RPGN: Rapidly progressive glomerulonephritis, RTX: Rituximab, SMP: Stenotrophomonas maltophilia pneumonia, TTP: Thrombotic thrombocytopenic purpura

Table 2. Features of plasma exchange therapy

Median number of PLEX sessions (Q1-Q3)	**4 (3-5)**
PLEX with	
FFP, n (%)	5 (29)
Albumin, n (%)	2 (12)
FFP and albumin, n (%)	10 (59)
Route of venous access	
Peripheral venous, n (%)	8 (47)
Central venous, n (%)	9 (53)

FFP: Fresh frozen plasma, PLEX: Plasma exchange

The median follow-up starting from PLEX day 1 to the last visit was 19.2 months (Q1-Q3=1.7-40.4 months). Two additional deaths occurred after the first year of PLEX treatment. One patient (DAH) died due to COVID-19 at month 21, and the other (CAPS) died due to SLE related severe damage (heart and renal failure) at month 48.

Nine patients (53%) developed severe/opportunistic infections within the first 5 weeks of PLEX. Three of those patients had more than one type of infection. CMV was the most common type of infection and detected in 4 patients. Details on infections are given in the Table 1. Death was associated with infection only in 1 patient who also had concurrent active disease.

Organ Survival

Among the 5 patients with DAH, all recovered after PLEX therapy. Only 1 patient died due to a relapse of DAH at month 4. Among the 4 patients with CNS involvement, 3 recovered and one died due to active disease and infection while on PLEX therapy. Among the 5 patients with CAPS, 2 experienced multiple thrombotic complications such as multifocal cerebral infarcts, Budd-Chiari syndrome, and digital ischemia and died during PLEX therapy. The third patient who presented with extensive lower extremity deep vein thrombosis, Libman-Sacks endocarditis, and severe cutaneous necrosis, died at month 7 due to aspiration-related cardiopulmonary arrest. In the remaining two patients, one

had portal thrombosis and digital necrosis, and the other had Budd-Chiari syndrome and multiple cerebral infarcts. These two patients were still in remission at month 12. Two patients with TTP were also in remission at month 12. One with RPGN died while receiving PLEX therapy.

Discussion

Initially, PLEX therapy was introduced as a treatment for SLE with the assumption that removing pathogenic autoantibodies and immune complexes would help control disease activity. The first RCT conducted in SLE, where patients received six courses of PLEX within a span of two weeks, showed no clinical improvement.[17] However, this was a small study consisting of 10 mild SLE patients in each study arms. Furthermore, the patients included in this study probably did not represent the SLE patients who are most likely to benefit from PLEX therapy. The other RCT with a larger sample size (n=86), comparing PLEX plus prednisone and cyclophosphamide versus prednisone and cyclophosphamide alone in patients with LN also showed no benefit and had to be terminated early.[10] Subsequent controlled studies, which included small number of patients, repeatedly demonstrated no efficacy of PLEX in patients with LN.[8,18-20] The discouraging results of these studies have led to a significant decline in the use of PLEX therapy in lupus setting. However, data from the registries indicate that there are still some SLE patients receiving and benefiting from PLEX therapy.[21-23] Similarly, in our daily practice we prefer using PLEX therapy to treat some severe forms of SLE patients. Our findings, along with those from the registries support that PLEX therapy remains valuable for a carefully selected group of patients with specific indications such as DAH and CNS involvement. However, conducting prospective trials to precisely evaluate the role of PLEX therapy in these patient subgroups poses challenges due to the rarity of such cases.

The present study is a retrospective evaluation of 17 patients diagnosed with SLE who received therapeutic PLEX at our center. Within this cohort of patients, PLEX was primarily administered to five patients as a therapeutic intervention for CAPS, which is classified as Category I in the ASFA guideline. PLEX indications in the remaining 11 patients were DAH (n=5), CNS involvement (n=4) and TTP (n=2) all of which are Category II. Only in one patient PLEX indication was RPGN. Four out of 17 (24%) patients died during PLEX therapy; the cause was CAPS in 2 patients, CNS involvement in 1, and RPGN in 1 patient. Despite the high rate of severe/opportunistic infections (53%) observed within the first five weeks of PLEX therapy, only one patient died. It was difficult to definitively conclude whether the cause of death was due to the infection or the active disease in this patient.

Since the early years of PLEX therapy, concerns have been raised regarding an increased risk of infections due to the associated decrease in immunoglobulin levels.[24] The initial RCT conducted in SLE specifically assessing the infection rate in patients undergoing PLEX did not observe an elevated risk of infection in the PLEX group (68%) compared to SOC group (74%).[10] However, a recent meta-analysis conducted in ANCA-associated vasculitis revealed an increased risk of infection with PLEX therapy.[25] Additionally, non-rheumatic diseases such as TTP and autoimmune encephalitis exhibited a low infection rate.[26,27] These findings suggest that aggressive immunosuppressive therapy, high dose GC therapy and severe organ dysfunction may contribute to an elevated risk of infection in rheumatic diseases.

Study Limitations

Our study has several limitations. Firstly, it had a retrospective design. Secondly, the evaluation was conducted on a small number of SLE patients who received PLEX therapy, as it was based on the experience of a single center. Thirdly, it is difficult to attribute the observed benefits or complications solely to PLEX therapy given that almost all patients concurrently received high-dose GCs and immunosuppressive drugs. Fourthly, except for two patients (one with TTP and the other with RPGN), most of the patients were refractory to immunosuppressives which might be the explanation for the high mortality rate observed in this cohort.

Conclusion

In conclusion, despite the previous discouraging outcomes from RCTs, PLEX therapy continues to be employed at our center to manage severe SLE patients, similar to real-world data from registries. PLEX can be considered as an adjunctive treatment in addition to immunosuppressives, especially in a subgroup of SLE patients with DAH and CNS involvement. Although severe/opportunistic infections occurred in around half of our patients, infection-related mortality was observed in only one patient.

Ethics

Ethics Committee Approval: The study was planned according to the Declaration of Helsinki, and an independent ethics committee of Cerrahpasa Medical Faculty gave permission to conduct this study (date: 02.06.2022, approval number: 396452).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Y.Ö., T.A., S.N.E., T.E., A.E.E., S.U., G.H., E.S., M.M., İ.F., M.C.A., V.H., Design: Y.Ö., T.A., S.N.E., T.E., A.E.E., S.U., G.H., E.S., M.M., İ.F., M.C.A., V.H., Data Collection or Processing: Y.Ö., T.A., S.N.E., T.E., A.E.E., S.U., G.H., E.S., M.M., İ.F., M.C.A., V.H., Analysis or Interpretation: Y.Ö., T.A., S.N.E., T.E., A.E.E., S.U., G.H., E.S., M.M., İ.F., M.C.A., V.H., Literature Search: Y.Ö., T.A., S.N.E., T.E., A.E.E., S.U., G.H., E.S., M.M., İ.F., M.C.A., V.H., Writing: Y.Ö., T.A., S.N.E., T.E., A.E.E., S.U., G.H., E.S., M.M., İ.F., M.C.A., V.H.

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

Financial Disclosure: The authors declare that they have no relevant financial disclosures.

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Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2023.36349
Ulus Romatol Derg 2023;15(2):95-101

Conventional and molecular cytogenetic analyses in Behçet's syndrome patients with gastrointestinal involvement

Gastrointestinal sistem tutulumlu Behçet sendromu hastalarında konvansiyonel ve moleküler sitogenetik analizler

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Abstract

Objective: We aimed to determine the frequency of trisomy 8 and other potential chromosomal abnormalities among Behçet's syndrome (BS) patients with gastrointestinal system (GIBS) involvement and those without myelodysplastic syndrome.

Methods: Between September 2014 and April 2015, 29 GIBS patients and 23 healthy controls were enrolled. Peripheral blood samples were collected from these patients for conventional cytogenetic analysis and fluorescence in situ hybridization (FISH) analysis specifically targeting chromosomes 8 and 9.

Results: Conventional cytogenetic analysis of 29 GIBS patients revealed clonal chromosome losses in 14 patients. One patient had a clonal del(8)(q11q13), and one patient had a constitutional t(5;10)(q33;p13). Polyploid metaphases were observed in 27 of 29 patients. In 7 of 23 control cases clonal aneuploidies were observed, and in two cases structural abnormalities along with numerical ones were detected. No clonal anomaly was observed in 14 cases. Polyploidy was detected in 13 of 23 cases in the control group. While trisomy 8 and 9 were detected in one patient by FISH analysis, only trisomy 9 was detected in one patient. The patient with trisomy 8 was diagnosed with polycythemia vera.

Conclusion: The frequency of chromosomal abnormalities observed in GIBS patients was found to be consistent with the literature. Trisomy 8 does not seem to be a feature of GIBS unless there is a

Öz

Amaç: Bu çalışmada, miyelodisplastik sendromu eşlik etmeyen gastrointestinal sistem tutulumu olan Behçet sendromu (GIBS) hastalarında trizomi 8 ve diğer potansiyel kromozomal anomalilerinin sıklığını araştırmayı amaçladık.

Yöntem: Eylül 2014 ile Nisan 2015 tarihleri arasında, 29 GIBS hastası ve 23 sağlıklı birey kontrol grubu olarak çalışmaya dahil edildi. Bu hastalardan periferik kan örnekleri alınarak konvansiyonel sitogenetik analiz ve kromozom 8 ve 9'u hedefleyen floresan in situ hibridizasyon (FISH) analizi yapıldı.

Bulgular: Yirmi dokuz GIBS hastasında yapılan konvansiyonel sitogenetik analizler sonucunda 14 hastada klonal kromozom kayıpları gözlendi. Bir hastada klonal olarak del(8)(q11q13) gözlenirken, bir hastada konstitüsyonel olarak t(5;10)(q33;p13) saptandı. Yirmi dokuz hastanın 27'sinde poliploid metafazlar gözlendi. Kontrol grubunda yer alan 23 olgunun 7'sinde klonal kromozom kayıp ve artışları, 2'sinde sayı ve yapı anomalileri saptanırken, 14 olguda klonal anomali gözlenmedi. Kontrol grubunu oluşturan 23 olgunun 13'ünde poliploidi tespit edildi.

FISH analizi ile 1 hastada trizomi 8 ve 9 tespit edilirken bir hastada sadece trizomi 9 saptandı. Trizomi 8 olan hastaya polisitemia vera tanısı konuldu.

Sonuç: GIBS hastalarında gözlenen kromozomal anomali sıklığı literatürle uyumlu bulunmuştur. Trizomi 8, GIBS hastalarının bir özelliği gibi görünmemekle beraber varlığı eşlik eden bir hematolojik hastalığı kuvvetle düşündürmektedir.

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Received / Geliş Tarihi: 08.06.2023 **Accepted / Kabul Tarihi:** 12.07.2023

Cite this article as / Atıf: Esatoğlu SN, Yılmaz Ş, Hatemi G, Kuru RD, Çırakoğlu A, Hatemi İ, Erzin YZ, Tarkan Argüden Y, Deviren A, Hacıhanefioğlu S, Salihoğlu A, Çelik AF. Conventional and molecular cytogenetic analyses in Behçet's syndrome patients with gastrointestinal involvement.
Ulus Romatol Derg 2023;15(2):95-101

hematologic condition. However, its presence strongly suggests the possibility of such a condition.

Keywords: Behçet's syndrome, gastrointestinal, cytogenetics, FISH, chromosomal abnormalities

Anahtar Kelimeler: Behçet sendromu, gastrointestinal, sitogenetik, FISH, kromozom anomalileri

Introduction

Behçet's syndrome (BS) is a multisystemic and chronic vasculitis with unknown etiology and associated with chronic inflammation. Besides mucocutaneous symptoms such as oral and genital ulcers and papulopustular lesions, organ involvement can also be observed. Involvement of the ocular, vascular, nervous and gastrointestinal system is responsible for morbidity and mortality.[1]

The association between BS and myelodysplastic syndrome (MDS) is well-established, with several cases reported in the last two decades.[2,3] Previous reviews of these cases have indicated that gastrointestinal system involvement is a frequent characteristic of this association, which can be severe and unresponsive to treatment.[4-9] The frequency of gastrointestinal involvement in BS varies in different geographic regions. It is more commonly reported in BS patients from the Far East, with a prevalence of up to 30%, whereas the prevalence is lower in Europe and the Middle East, ranging from 3-8%.[10] However, gastrointestinal system involvement seems to be closely associated with MDS regardless of geographic location.[2] Possible theories that could explain the relationship between BS and MDS include the altered immune function due to BS or DNA damage caused by immunosuppressive agents that are used in the management of BS.

MDS is overall the most common hematological disorder in BS.[11] The frequency of trisomy 8 in BS is significantly higher than that seen in primary MDS (87% vs 6%).[9,12] Lee et al.[13] compared 61 MDS patients with autoimmune manifestations and 134 MDS patients without it and trisomy 8 was found to be associated with BS. Another study involving 46 MDS patients further demonstrated that intestinal ulcers were more common in patients with trisomy 8 than in those without it (3/8 vs 0/38).[14] Similarly, Ahn et al.[11] reported an association between gastrointestinal system involvement and trisomy 8 in BS associated with MDS. Fever has been identified as an inherent feature in BS patients with MDS and trisomy 8 since a higher frequency of fever observed in these individuals compared to those without trisomy 8 (79.5% vs. 33.3%).[2] Trisomy 8 has also been found to be associated with inflammatory fever in pediatric patients with fever of unknown origin.[15] In addition, BS patients with gastrointestinal system involvement have been observed to be more resistant to immunosuppressive therapies. Alternative treatment approaches directed at MDS were found to be more beneficial in managing gastrointestinal manifestations, even if MDS itself does not require treatment.[3] Lastly, constitutional trisomy 8 has been linked to an increased risk of developing features of BS.[16,17] Taken together, these findings suggest that trisomy 8 may trigger inflammation in BS.

Several retrospective series have suggested the presence of trisomy 8 as a risk factor for gastrointestinal system involvement in BS.[4-6,8,18,19] Trisomy 9 is another chromosomal anomaly that is commonly seen in BS associated with MDS with gastrointestinal system involvement.[8,9,20] In this study, we aimed to determine the presence of trisomy 8 and trisomy 9 and possible chromosomal changes that may play a role in the pathogenesis of gastrointestinal system involvement of BS.

Materials and Methods

Patients

Between September 2014 and April 2015, 29 BS patients with gastrointestinal system involvement were included in the study. Gastrointestinal system involvement had been confirmed with colonoscopy. We did not include our 2 patients with MDS who were already known to have trisomy 8. For control group, 23 healthy individuals were enrolled. After obtaining signed informed consent forms, 5 cc of heparinized peripheral blood was taken from all participants for conventional cytogenetics and fluorescence *in situ* hybridization (FISH) analyses. Patient charts were reviewed for demographic data, BS manifestations, and medications. The study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the ethics committee (2014/83045809-876). The study was funded by Scientific Research Projects Coordination Unit (project no: 40937).

Cytogenetics and FISH Analysis

Conventional cytogenetic analyses were performed using standard 72 h peripheral lymphocyte culture technique. A mitogen mix [phorbol 12-myristate 13-acetate (PMA) + pokeweed mitogen (PWM) +Phytohemagglutinin (PHA)] was used to induce both T and B lymphocytes. Fifty (31-65) GTL-banded metaphases were analyzed whenever possible.

Slides were examined using a Nikon Eclipse E600 W light microscope. Metaphases were evaluated according to International System for Human Cytogenetic Nomenclature 2016[21] and photographed using an automated imaging system (Applied Imaging-Powergene). FISH was performed using liquid alpha satellite probes specific to centromere regions of chromosomes 8 and 9. At least 200 cells were counted under a Nikon Eclipse E600 W fluorescence microscope using a triple filter (DAPI-FITCH-Texas red).

Statistical Analyses

Statistical analyses were performed using SPSS 20.0. We used descriptive statistics to describe variables. Continuous variables were represented as mean and standard deviation. Chi-square test was used for comparison of categorical variables.

Results

We studied 29 BS patients with gastrointestinal system involvement (13 women and mean age: 40.1±9.7 years). All patients fulfilled International Study Group Criteria for BS.[22] The mean age at diagnosis was 27±11 years for BS and 32±11 years for gastrointestinal system involvement. BS preceded the diagnosis of gastrointestinal system involvement of BS in 19 patients. The mean duration from BS diagnosis to the diagnosis of gastrointestinal involvement of BS was 7.3±5 years. Among the remaining 10 patients, BS and gastrointestinal involvement of BS were diagnosed concomitantly in 7 and 3 patients were diagnosed with BS after 2, 3, and 5 years of gastrointestinal system involvement. Apart from gastrointestinal system involvement, 9 patients also had involvement of another major organ/s (eye involvement in 5, vascular involvement in 5, and central nervous system involvement in 2). At the time of sampling, 22 patients were on azathioprine therapy, 6 were on 5-ASA compounds, and the remaining 1 had never used any medication for BS previously (Table 1).

Conventional cytogenetic analysis of 29 BS patients with gastrointestinal system involvement revealed clonal chromosome losses in 14 patients. The most common monosomies were monosomy 20, 19, 21, and 18, respectively. One patient had a clonal del(8)(q11q13) and, one patient had a constitutional t(5;10)(q33;p13). In 13 patients, no clonal chromosomal abnormality was found. Polyploid metaphases were observed in 27 of 29 patients. Trisomy 8 was not detected in any of the patients (Table 2). Among the 23 control cases, 17 had clonal aneuploidies, and 2 had both structural and numerical abnormalities. No clonal anomaly was observed in 14 cases. Polyploidy was detected in 13 of 23 cases in the control group (Table 3). Polyploidy was significantly more frequent in BS patients with gastrointestinal system involvement compared to the control group (p=0.002). However, there was no significant difference in the frequency of structural or numerical abnormalities between the two groups (p=0.25).

The cut-off values for FISH analyses were set as 5%. The FISH results for centromeres 8 and 9 of the patients are shown in Figure 1. FISH analysis of chromosome 8 revealed that only 1 patient had trisomy 8 in more than 20% of interphase cells while trisomy 8 was detected in fewer than 5% of interphase cells in the remaining 28 patients. In FISH analysis of chromosome 9, trisomy 9 was detected in fewer than 5% of interphase cells in 27 patients. One patient had trisomy 9 in 5-10% of interphase cells. In another patient, who also had trisomy 8 in more than 20% of interphase cells, trisomy 9 was observed in 10-20% of interphase cells. Subsequently, this patient was evaluated by hematology and diagnosed with polycythemia vera. During a 7-year follow-up, no hematological or solid malignancy developed in the remaining patients. In 8 patients, monosomy 8 was observed in 5-10% of the cells and, in 2 patients more than 20% of the cells. Monosomy 9 was shown in 5-10% of the cells in 11 patients and 10-20% in 4 patients. Two of the 11 patients with 5-10% monosomy 9 had that abnormality also in their

Table 1. Demographic and clinical characteristics of patients

Variable	Behçet's syndrome patients with gastrointestinal involvement (n=29)
Women, n (%)	13 (45)
Mean (SD) age at BS diagnosis, years	27±11
Mean (SD) age at GIBS diagnosis, years	32±11
BS manifestations, n (%)	
Oral ulcers	29 (100)
Genital ulcers	25 (86)
Papulopustular lesions	12 (41)
Erythema nodosum	8 (28)
Arthritis	5 (17)
Pathergy positivity	8 (28)
Eye involvement	5 (17)
Vascular involvement	5 (17)
Central nervous system involvement	2
Medications, n (%)	
Azathioprine	20 (69)
Azathioprine and TNFi	2
5-ASA compounds	6 (21)
No treatment	1

BS: Behçet's syndrome, GIBS: Gastrointestinal involvement of Behçet's syndrome, SD: Standard deviation, TNFi: Tumor necrosis factor alpha inhibitors

conventional cytogenetic analysis. None of the control group had aneuploidies of chromosomes 8 and 9 by FISH.

Discussion

In this study, we investigated the presence of trisomy 8, trisomy 9, and other potential chromosomal abnormalities in BS patients with gastrointestinal system involvement. Conventional cytogenetic analysis of 29 BS patients with gastrointestinal system involvement revealed clonal chromosome losses in 14 patients. The most common monosomies were monosomy 20, 19, 21, and 18, respectively. Only one patient exhibited structural abnormalities (del(8)(q11q13) and a marker chromosome). The patient who carried a constitutional balanced translocation (t(5;10)(q33;q13)) did not have any acquired chromosome abnormalities. Furthermore, FISH analysis detected trisomy 8 in one patient that was not observed by conventional cytogenetic analysis. This patient was further diagnosed with polycythemia vera.

Chromosomal abnormalities have been reported among BS patients with accompanying MDS or another hematologic disorder. The most common chromosomal abnormality observed in these patients was trisomy 8 (87%), followed by trisomy 9 (13%) and trisomy 15 (9%).[9] However, there are only a few studies investigating chromosomal abnormalities among BS patients without any hematologic disorder. In a study conducted by Denman et al.[23] in 1980, chromosomal abnormalities were found to be more common in BS patients (16 out of 38, 42%) compared to healthy controls (1 out of 17, 6%). However, the authors did not provide information on the type of chromosomal abnormalities, BS manifestations and medications of these 38 patients.[23] On the other hand, another study reported no numerical or structural abnormalities among 38 BS patients.[24] The authors did not report the BS manifestations, however, none of the patients had received any medications for BS prior to sampling. Interestingly, in our study, all except one patient showed chromosomal abnormalities, and the monosomies observed among the 14 BS patients have not been reported previously. However, we also observed rather more than expected, numerical and structural chromosomal abnormalities, as well as polyploidies in our control group.

Table 2. The types and frequencies of chromosomal abnormalities among the 29 BS patients with gastrointestinal involvement

Number of patients (%)	Numerical chromosomal abnormality	Structural chromosomal abnormality
27 (93)	Polyploidy	
8 (28)	-21	
7 (24)	-19	
6 (21)	-X	
4 (14)	-18, -20	
3 (10)	-16, -22	
2 (7)	-Y, -4, -6, -9, -10, -11, -12	
1 (3)	-3, -7, -8, -13, -14, -17	t(5;10))(q33;p13), del(8)(q11;q13)

**A variable number of polyploid cells ranging from 1 to 7 were detected. The ploidy levels ranged from 3n (69 chromosomes) to 6n (138 chromosomes)*

Table 3. The types and frequencies of chromosomal abnormalities in control group

Number of patients (%)	Numerical chromosomal abnormality	Structural chromosomal abnormality
13 (57)	Polyploidy	
4 (17)	-21	
3 (13)	-22	
2 (9)	-18	
1 (4)	-X, +1, -10, -12, -19, -20	del(1)(q32q42), del(6)(q14q16)

**A variable number of polyploid cells ranging from 1 to 5 were detected. The ploidy levels ranged from 3n (69 chromosomes) to 4n (92 chromosomes)*

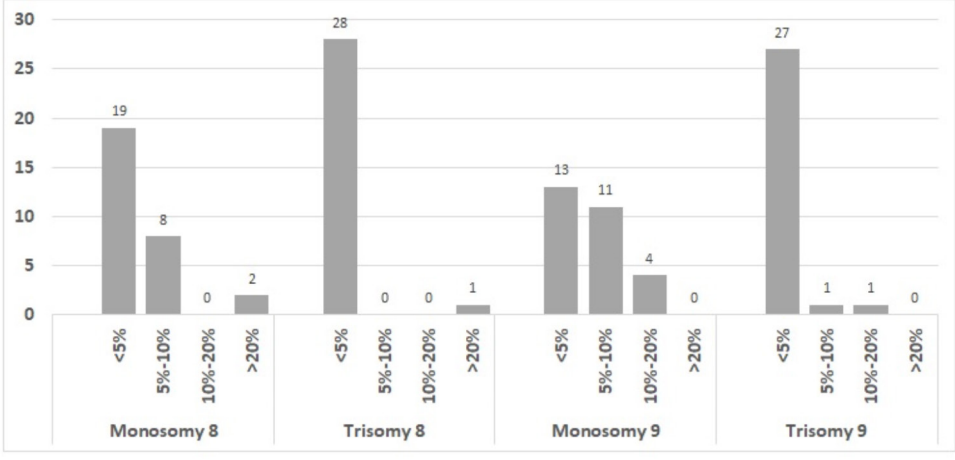

Figure 1. FISH results for centromeres 8 and 9 of 29 BS patients with gastrointestinal involvement
BS: Behçet's syndrome, FISH: Fluorescence in situ hybridization

This could be related to the fact that PMA which is included in our mitogen mix can induce mitotic dysfunction and cause poliploidisation.[25,26] There was no statistical difference between BS and control group regarding numerical and structural chromosome abnormalities. Therefore, in that respect our results may be considered in accordance with the literature. But polyploidy ratio was significantly higher in BS group than controls in our study.

Arimura et al.[27] conducted a study to investigate the presence of morphological myelodysplasia in BS patients. They observed significant trilineage myelodysplasia in bone marrow cells of 8 out of 15 BS patients. However, all these patients did not show any chromosomal abnormalities. The incidence of apoptotic bone marrow cells was lower in BS patients compared to patients with MDS, but higher when compared to normal controls. The authors suggested that this finding may explain the absence of peripheral cytopenia observed among BS patients. Unlike other rheumatologic disorders where lymphoproliferative disorders are the most common type of hematologic malignancy,[28] several studies have consistently reported MDS as the most common type of malignancy among BS patients.[11,29-31] In a meta-analysis, BS patients were found to have an increased risk of developing hematologic malignancies [pooled risk ratio (RR), 2.58; 95% confidence interval (CI): 1.61-3.55].[30] Another study specifically investigating BS patients with gastrointestinal system involvement reported that the risk of hematologic malignancy was significantly higher in both men and women.[32] The standardized incidence ratio (SIR) was 23.90 (95% CI: 2.89-86.32) for men and 34.47 (95% CI: 4.17-124.51) for women. The SIRs observed in BS patients with gastrointestinal system involvement were significantly higher compared to the SIRs observed in all BS patients, regardless of the type of involvement. Furthermore, another study reported a higher prevalence of gastrointestinal system involvement in BS patients with malignancy compared to those without malignancy.[31] Our findings, which show a high prevalence of chromosomal abnormalities among our patients, may provide an explanation for why BS patients with gastrointestinal involvement have a higher risk of developing hematologic malignancies.

We had previously reported that among our 198 BS patients treated with cyclophosphamide 15 (8%) patients developed malignancies, with bladder carcinoma being the most common.[33] Huang et al.[29] investigated the relationship between medications for BS and the risk of malignancy. They found that cyclophosphamide was associated with a 10-fold increase in the risk of developing malignancies.[29] In our patient population, none of them had been exposed to cyclophosphamide previously, but 76% was currently using azathioprine. Thiopurines have been implicated as a risk factor for the development of lymphoma among patients with inflammatory bowel disease,[34] which shares many similar clinical features with gastrointestinal system involvement of BS.[1] Furthermore, current use of thiopurines has also been associated with an increased risk of myeloid clonal disorders, including acute myeloid leukemia and MDS among patients with inflammatory bowel disease.[35] In our study, it should be noted that 22 of the 29 BS patients included in the analysis were taking azathioprine at the time of serum sampling, which could potentially provide an explanation for our findings.

Study Limitations

Our study has some limitations. First, we studied a small number of patients due to the low prevalence of gastrointestinal system involvement of BS in Turkey. Also, it would be preferable to perform conventional cytogenetic analysis on bone marrow samples. However, previous studies have demonstrated that conventional cytogenetic analysis performed on both peripheral blood and bone marrow samples yield similar results.[36] Second, it would be more preferable to study treatment-naive patients in order to minimize confounding factors related to drug-induced chromosomal changes.

Conclusion

In the future, further research with larger cohorts is warranted. Future studies should include appropriate control groups, such as healthy controls, adequate number of BS patients who have been exposed to immunosuppressive drugs and those who have never been exposed, as well as BS patients with different types of involvement. These additional studies will provide a more comprehensive understanding of the relationship between chromosomal abnormalities and BS. Finally, it should be noted that trisomy 8 is not typically considered a characteristic feature of BS with gastrointestinal system involvement, unless there is an associated hematologic condition. Considering that the patient with trisomy 8 in this study was also diagnosed with polycythemia vera, which is another myeloid clonal disorder, the presence of this chromosomal abnormality strongly suggests the possibility of a coexisting hematologic condition.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki.

Approval was obtained from the ethics committee (2014/83045809-876).

Informed Consent: All participants gave their written informed consent.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.N.E., G.H., A.F.Ç., Design: S.N.E., G.H., A.F.Ç., A.S., Data Collection or Processing: Ş.Y., A.Ç, R.H.K., İ.H, Y.Z.E., Y.T.A., A.D., S.H., A.S., Analysis or Interpretation: S.N.E., Ş.Y., A.Ç, R.H.K. Literature Search: S.N.E, Writing: S.N.E., G.H., A.F.Ç., Ş.Y., A.Ç, R.H.K.

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

Financial Disclosure: The study was funded by Scientific Research Projects Coordination Unit (project no: 40937).

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Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Orijinal Araştırma / Original Article

DOI: 10.4274/raed.galenos.2023.80774
Ulus Romatol Derg 2023;15(2):102-105

Romatoid artritli hastalarda düz el grafisi çekimlerinde ters gri tonlama yöntemi: Pilot çalışma

Inverted grayscale in hand X-rays in patients with rheumatoid arthritis: A pilot study

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Öz

Amaç: Bu çalışmanın amacı romatoid artrit (RA) tanısında düz grafi görüntüleri üzerinde yapılan dijital düzenleme yöntemi olan ters gri tonlamanın (TGT) değerlendirilebilirliğini test etmektir.

Yöntem: RA tanısı olan veya enflamatuvar artropati şüphesi ile 2020 Haziran ve 2022 Eylül tarihleri arasında polikliniğimize ardışık olarak başvuran, el ön-arka standart eklem grafisi (X-ray) çekilmiş hastalar arasından rastgele seçilmiş 15 hastaya ait el grafilerinin standart ve TGT görünümleri en az 2 yıl romatoloji tecrübesine sahip 3 romatoloji uzmanı tarafından değerlendirildi. RA ve osteoartrit bulgularının varlığı ve kararlarından ne kadar emin oldukları Likert ölçeği ile sorgulandı. Romatoloji uzmanlarının değerlendirmeleri radyoloji uzmanının değerlendirmesi ile kıyaslanarak değerlendiriciler arası uyum Cohen Kappa (CK) testi ile hesaplandı. CK testi ile elde edilen değişkenlik kat sayısına göre değerlendiriciler arası uyum; <0,20: uyum yok, 0,21-0,40: zayıf uyum, 0,41-0,60: orta uyum, 0,61-0,80: iyi uyum, 0,80-1: çok iyi uyum olarak kabul edildi.

Bulgular: RA'lı hasta görüntülerinin değerlendirmesinde, değerlendirmeciler arasında düşük-orta derecede uyum saptandı. Daha az tecrübeye sahip uzmanların TGT görüntüleri için yaptıkları değerlendirmeler farklılık gösterirken, daha tecrübeli romatoloji uzmanının TGT ve standart görüntü değerlendirme için radyologla uyumu benzer düzeyde saptanmıştır. Değerlendirmecilerin verdikleri kararlarından ne kadar emin olduğunu ifade eden Likert ölçeği skoru tüm araştırmacılar için yüksek saptanmıştır.

Sonuç: TGT romatoloji uzmanları tarafından kolay değerlendirilebilir bir yöntemdir. Ancak, TGT'nin özellikle daha az tecrübeli uzmanların, RA bulgularını tespit etmesinde ek katkısını değerlendirmek için daha büyük ölçekli çalışmaya ihtiyaç bulunmaktadır.

Anahtar Kelimeler: Romatoid artrit, tanısal görüntüleme, dijital radyografi

Abstract

Objective: To test the evaluability of inverted grayscale (IGS), a digital editing method on plain X-ray images, in diagnosing rheumatoid arthritis (RA).

Methods: Standard and IGS views of X-rays of 15 patients who were randomly selected among patients with RA or suspected inflammatory arthropathy who applied to our outpatient clinic consecutively between June 2020 and September 2022, were evaluated by 3 rheumatology specialists with at least 2 years of rheumatology experience. The presence of findings of RA and osteoarthritis (OA) and how confident they were in their decisions were assessed. The evaluations of the rheumatologists were compared with the evaluation of the radiologist, and the inter-rater agreement was calculated with the Cohen Kappa (CK) test. Inter-rater agreement according to the coefficient of variation obtained with the CK test was defined as; <0.20: no agreement, 0.21-0.40: poor agreement, 0.41-0.60: moderate agreement, 0.61-0.80: good agreement, 0.80-1: excellent agreement.

Results: In evaluating images of patients with RA, a low-moderate agreement was found between the raters. While the agreement level of less experienced specialists for IGS and standard view differed, the agreement level of the more experienced rheumatologist was similar for TGT and standard views. The Likert scale score, which expresses how confident the evaluators are in their decisions, was high for all researchers.

Conclusion: IGS is a method that rheumatologists can easily evaluate. However, large-scale studies are needed to evaluate the additional contribution of IGS in detecting RA findings, especially by less experienced specialists.

Keywords: Rheumatoid arthritis, diagnostic imaging, digital radiography

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Geliş Tarihi/Received: 06.07.2023 **Kabul Tarihi/Accepted:** 13.07.2023

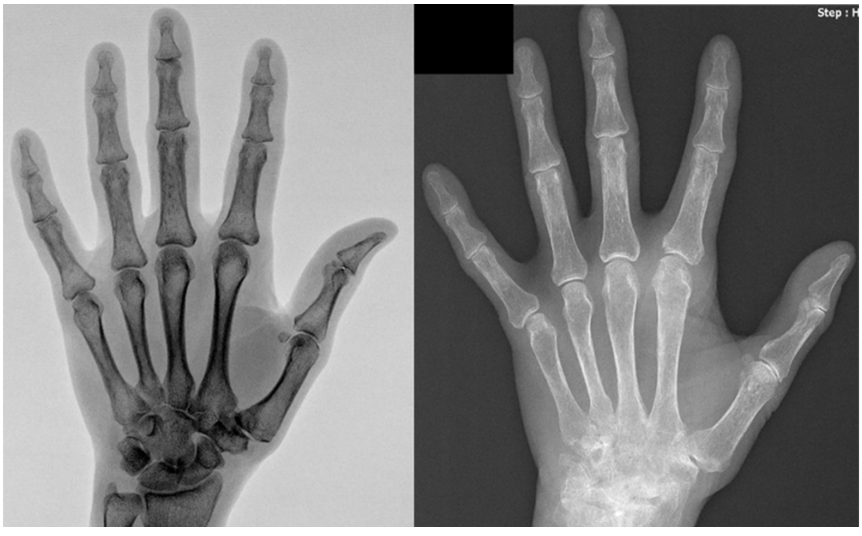
Atıf / Cite this article as: Erdoğan M, Öztürk A, Yurttaş B, İçaçan OC, Bes C. Inverted grayscale in hand X-rays in patients with rheumatoid arthritis: A pilot study. Ulus Romatol Derg 2023;15(2):102-105

GİRİŞ

Romatoid artrit (RA) eklemlerde kalıcı hasarla seyredebilen kronik otoimmün bir hastalıktır. Hastalığın güncel sınıflandırılma kriterleri klinik ve laboratuvar değerlendirmesine dayanmaktadır.[1] Konvansiyonel radyografi, hastalığın hem tanı hem de eklem hasarının tespit ve takibinde en sık kullanılan yöntemdir. Son birkaç dekattır yeni görüntüleme yöntemleri test edilmektedir. Bunlardan manyetik rezonans görüntüleme (MRG), ultrasonografi (USG), multidedektör bilgisayarlı tomografi (BT) gibi, artık günlük pratikte kullanılan yöntemler yanında henüz araştırma amaçlı kullanılmakta olan birden çok seçenek bulunmaktadır.[2,3] Bu yöntemlerin, maliyet, uygulayıcı bağımlı olması, yüksek radyasyon maruziyeti, her merkezde ulaşılabilir olamaması gibi kullanımlarını kısıtlayan sorunları bulunmaktadır. Düz grafi, erken dönem RA'da hassasiyetinin düşük olmasına rağmen, her merkezde ulaşılabilir, valide edilmiş ve düşük radyasyon gibi avantajlara sahip bir görüntüleme yöntemidir. Ters gri tonlama (TGT), Picture Archiving and Communication System; Marosis; Infinitti (PACS) sistemi kullanılarak yapılabilen, standart görüntülerdeki dijital düzenleme metotlarından biridir. TGT, yapıların parlak bir zemin üzerinde koyu renkte gösterilmesini sağlamaktadır (Şekil 1). Akciğer nodüllerinin tespitinde tanısal ek katkı sağladığı gösterilmiş bu yöntemin, enflamatuvar hastalıklarda eklem görüntülenmesinde kullanımı üzerine yapılmış bir çalışma bulunmamaktadır. Merkezimizde RA ve ankilozan spondilit hastalarının tanısında TGT'nin kullanımı ile ilgili el, ayak ve sakroiliak eklem TGT grafilerinin tanıya katkısı üzerine bir çalışma planlanmıştır. Bu çalışma, TGT yönteminin romatoloji hekimlerince değerlendirilebilirliğini ölçmek adına pilot çalışma olarak planlanmıştır.

Gereç ve Yöntem

RA tanısı olan veya enflamatuvar artropati şüphesi ile 2020 Haziran ve 2022 Eylül tarihleri arasında polikliniğimize ardışık olarak başvuran, el ön-arka standart eklem grafisi (X-ray) çekilmiş hastaların kayıtları hastane bilgi yönetim sistemi üzerinden incelendi. ICD-10 (International Classification of Diseases) kodlamasına göre RA ve osteoartrit (OA) tanısı olan hastaların verileri çıkarıldı. Bu hastalar arasından rastgele örnekleme yöntemi ile 60 hasta seçildi. Bu hastaların dosyaları incelenerek seropozitif RA tanılı 8 hasta, OA tanılı 7 hasta radyolojik değerlendirme yapmayan çalışmacı (ME) tarafında seçilerek çalışmaya dahil edildi. Her hastaya ait sağ ve sol el düz grafileri standart ve TGT görüntü olarak PACS sistemi üzerinden elde edildi. Görüntüler, Portable Network Graphic formatında kaydedilerek değerlendirici olmayan araştırmacı tarafından (ME) karışık olarak numaralandırıldı. Görüntüler kas iskelet sistemi radyoloğu ve en az 2 yıl deneyimi olan 3 romatoloji uzmanı tarafından klinik ve laboratuvar verilerine kör olarak değerlendirildi. Değerlendiricilerden her grafi için şu sorulara yanıt vermeleri istendi; 1) RA lehine bulgu var mı? 2) OA lehine bulgu var mı? 3) Kararınızdan ne kadar eminsiniz? (0-10 arası puan). Değerlendiriciler arası değişkenlik Cohen Kappa (CK) testi ile değerlendirildi. CK testi ile elde edilen değişkenlik kat sayısına göre (κ) değerlendiriciler arası uyum; <0,20: uyum yok, 0,21-0,40: zayıf uyum, 0,41-0,60: orta uyum, 0,61-0,80: iyi uyum, 0,80-1: çok iyi uyum olarak kabul edildi. Romatoloji uzmanları değerlendirme yaparken verdikleri kararlarından ne kadar emin oldukları Likert ölçeği ile değerlendirildi (0 en düşük, 10 en yüksek puan). Değerlendiricilerin standart ve TGS görüntüler için verdikleri ortalama Likert ölçeği puanları tek yönlü Anova testi kullanılarak kıyaslandı.



Şekil 1. Düz el grafisinin standart ve ters gri tonlama görüntüleri
Aynı hastaya ait sol el grafisinin, ters gri tonlama (sol) ve standart görüntüleri (sağ)

İstatistiksel Analiz

İstatistiksel analizler için SPSS (Statistical Package for the Social Sciences v.20) kullanıldı. Çalışma, Başakşehir Çam ve Sakura Şehir Hastanesi etik kurulu tarafından onaylandı (onay numarası: KAEK/2022.05.159).

Bulgular

HBYS sisteminden standart düz el grafisi çekilmiş 1.916 hastadan, RA tanısı ile uyumlu 154 hasta tespit edildi. Bu hastalar içinden seropozitif RA tanılı 8 hasta ve OA tanılı 7 hastaya ait 60 görüntü değerlendirildi. RA'lı hasta görüntülerinin değerlendirmesinde, 1 numaralı değerlendirici ile radyolog arasında standart görüntüler için zayıf uyum saptanmış (K: 0,326), TGT görüntüler için ise uyum saptanmamıştır (K: 0,07). İki numaralı değerlendirici ile radyolog arasında standart görüntüler (K: 0,76) için iyi uyum, TGT görüntüler için ise orta uyum (K: 0,583) saptanmıştır. Üç numaralı çalışmacı için ise her iki görüntü biçimi için zayıf uyum saptanmıştır (K: 0,4 vs. 0,39). OA'lı hastalara ait grafi görüntülerinin değerlendirmesinde, 3. çalışmacı ile radyolog arasında standart görüntüler için orta uyum (K: 0,41) ancak diğer görüntüler için zayıf uyum saptanmıştır (Tablo 1). Değerlendiricilerin verdikleri kararlarından ne kadar emin olduğunu ifade eden Likert ölçeği skoru, ikinci değerlendiricide standart görüntü için daha yüksek iken (8,1±1,29 vs. 7,3±1,2) diğer iki değerlendiricide benzer saptandı (Tablo 1).

Tartışma

Çalışmamızda benzer ve daha kısa uzmanlık tecrübesine sahip 2 romatoloji uzmanı (1 ve 2 numaralı değerlendirici) ve daha uzun uzmanlık tecrübesine sahip bir romatoloji uzmanının (3 numaralı değerlendirici) yaptığı, klinik ve laboratuvar bulgularına kör olarak yapılmış değerlendirmeler, radyoloji uzmanının değerlendirmeleri ile genel olarak düşük ve orta uyum göstermiştir. Daha az tecrübeli değerlendiricilerin standart ve TGT görüntüler için uyumları benzer düzeyde değilken daha tecrübeli değerlendiricinin her iki görüntü için uyumu benzer düzeyde saptanmıştır. Her üç değerlendiricinin de değerlendirmelerinden ne kadar emin oldukları sorusuna verdikleri puan hem standart hem de TGT görüntü için benzer ve yüksek bulunmuştur.

Direkt eklem grafisinin, RA tanısında hem tanıda hem de takipte hassasiyeti, BT, MRG, USG gibi daha yeni görüntüleme tekniklerine kıyasla daha düşüktür.[2] Bunun yanında düşük radyasyon maruziyeti ve maliyeti, kolay ulaşılabilirliği gibi avantajları nedeniyle klinik pratikteki yerini kaybetmemiştir.[4] Dijital görüntüleme sistemleri standart görüntülemelere ek olarak görüntünün çözünürlük, renk, parlaklık gibi özelliklerini değiştirerek değerlendiricilere tanısal avantajlar sağlayabilmektedir.[5] TGT'nin, pulmoner nodül tanısında tanısal hassasiyeti artırdığı gözlemlenmiştir.[6] Sun ve ark.[7] ise, standart görüntü karşılaştırıldığında spinoplevik ölçümlerde gözlemci içi ve gözlemciler arası uyumda artış bildirmiştir. Merkezimizde her iki hastalık için de TGT'nin tanıya katkısını değerlendirmek üzere iki çalışma planlamıştır. TGT'nin romatoloji uzmanlarınca değerlendirilebilirliğini test etmek üzere yapılan bu pilot çalışmada, TGT ile standart düz grafi görüntülerini değerlendirirken romatologların verdikleri kararlardan emin olma düzeyleri bir çalışmacıda daha düşük olmakla beraber her üç çalışmacı için de yeterince yüksek saptanmıştır. Radyoloji uzmanı ile uyum düzeyi yönünden, standart görüntü ile TGT arasında, iki çalışmada ters yönde fark saptanmışken, daha deneyimli üçüncü değerlendiricide bu fark saptanmamıştır. Radyolojik değerlendirmelerde değerlendiriciler arası değişkenlik hem düz grafi hem de daha yeni görüntülemeler için bilinen bir özelliktir.[8] Değerlendiricilerin eğitim sonrası tanı hassasiyeti değişkenlik gösterebilir.[9] Dolayısıyla TGT, özellikle daha az tecrübeli romatoloji uzmanlarının ya da uzmanlık eğitimi alan hekimlerin RA tanısını olumlu ya da olumsuz etkileyebilir. Bu çalışmada, değerlendirici içi uyum değerlendirmesi yapılmamıştır. Planlanan büyük ölçekli çalışmamız hem TGT'nin tanıya etkisinin hangi yönde olduğunu aydınlatmada hem de değerlendirici içi uyumu saptamada bilgi sağlayacaktır.

Tablo 1. Romatoloji uzmanlarının standart ve ters gri skala görüntüler için uyum

Değerlendirici	Değerlendirici uzmanlık süresi (Ay)	Standart görüntü			Ters gri skala görüntü		
		RA korelasyon kat sayısı	OA korelasyon kat sayısı	Değerlendirme puanı*	RA korelasyon kat sayısı	OA korelasyon kat sayısı	Değerlendirme puanı*
1	33	0,07	0,254	8,53±0,57	0,326	0,256	8,43±1
2	30	0,76	0,367	8,1±1,29	0,583	0,253	7,3±1,2
3	120	0,4	0,41	8,6±1,65	0,394	0,402	8,79±1,5

RA: Romatoid artrit, OA: Osteoartrit

**Değerlendiricilerin verdikleri kararda ne kadar emin oldukları sorusuna on üzerinden verdikleri puan ortalamasıdır, ortalama ve standart sapma olarak belirtilmiştir.*

Çalışmanın Kısıtlılıkları

Çalışmamız, pilot çalışma olarak az sayıda görüntü ile yapıldığından sonuçların klinik pratiğe etkisi üzerine yorum yapılabilmesi mümkün görünmemektedir. Ayrıca, TGT'nin, BT veya MRG gibi daha hassas yöntemler ile mukayeseli değerlendirmesi tanısal hassasiyet ve özgüllüğü hakkında daha kesin bilgi sağlayabilir. İlk kez değerlendirme yapmalarına rağmen değerlendiriciler, TGT için verdikleri kararlarda standart görüntü ile benzer kararlılık göstermişlerdir.

Sonuç

Sonuç olarak bu çalışma, basit ve kolay ulaşılabilir bir dijital görüntü düzenleme yönteminin romatoloji uzmanları tarafından tutarlı şekilde değerlendirilebilir bir yöntem olduğunu düşündürmektedir. Ancak planlanan daha geniş ölçekli çalışmamızın sonuçları olmadan TGT'nin tanısal rolü hakkında yorum yapmak mümkün değildir.

Etik

Etik Kurul Onayı: Çalışma, Başakşehir Çam ve Sakura Şehir Hastanesi etik kurulu tarafından onaylandı (onay numarası: KAEK/2022.05.159).

Hasta Onayı: Hasta onamı alınmıştır.

Hakem Değerlendirmesi: Editörler kurulunda olan ve editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazarlık Katkıları

Konsept: M.E., C.B., Dizayn: M.E., C.B., Veri Toplama veya İşleme: M.E., Analiz veya Yorumlama: M.E., A.Ö., B.Y., O.C.İ., C.B., Literatür Arama: M.E., Yazan: M.E.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

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