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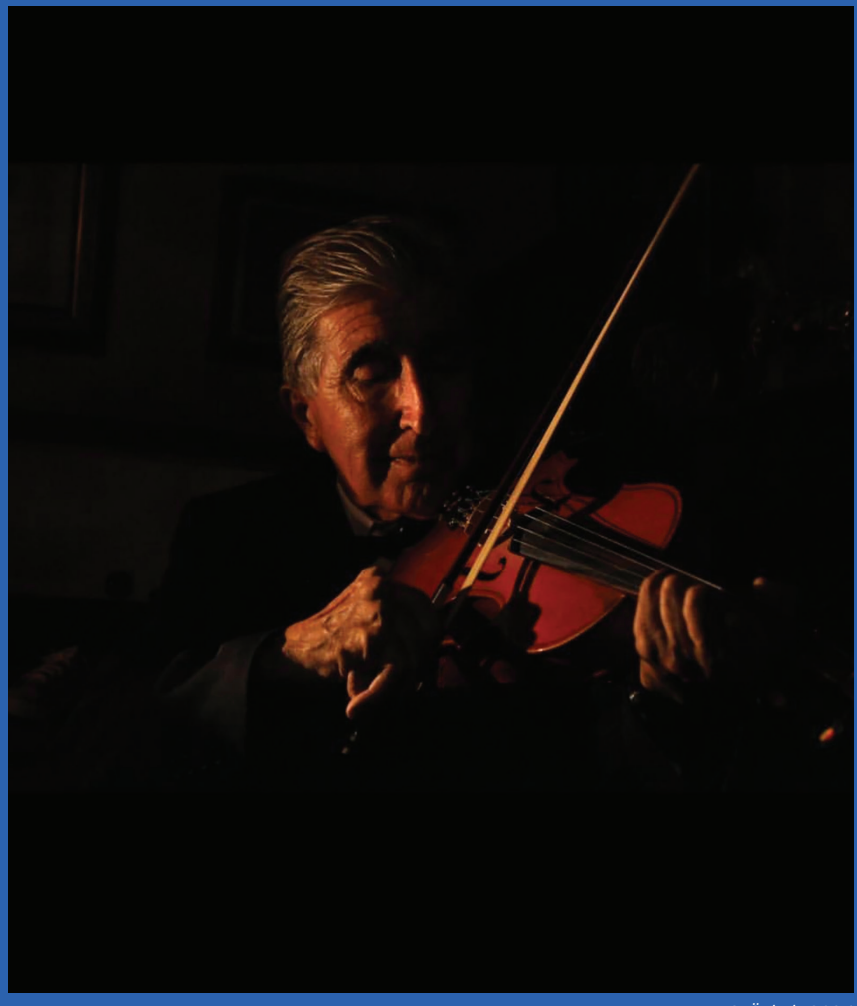

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Ankilozan spondilit hastalarında serum irisin düzeyi ile hastalık aktivitesi arasındaki ilişkinin değerlendirilmesi

Evaluation of the relationship between serum irisin levels and disease activity in ankylosing spondylitis patients

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Öz

Amaç: Aksiyal spondiloartrit başlıca aksiyal iskeleti ve sakroiliyak eklemleri tutan kronik enflamatuvar bir hastalıktır. Bu çalışmada, ankilozan spondilitli (AS) hastalarda irisin düzeyini değerlendirmek, sağlıklı bireylerle karşılaştırmak ve bu adipomiyokin ile AS arasındaki aktivite, fonksiyon ve yapısal hasar arasındaki ilişkiyi test etmeyi amaçladık.

Yöntem: Modifiye New York kriterlerine göre AS olarak sınıflandırılan 97 hasta ve 48 sağlıklı kontrol çalışmaya ardışık olarak dahil edildi. ELISA yöntemiyle serum irisin, interlökin (IL) 6, yüksek duyarlıklı C-reaktif protein (hs-CRP) ölçümleri yapıldı. Hastalık aktivite ve fonksiyonel değerlendirmeleri, spinal radyografik skorlamaları yapıldı. Laboratuvar tetkikler ile hastalık aktivasyon ve radyolojik parametreleri arasındaki ilişki Spearman korelasyon testi ile değerlendirildi.

Bulgular: AS ve kontrollerin yaş ve cinsiyet dağılımları benzer bulundu. Sigara kullanımı AS grubunda anlamlı olarak yüksekti (p=0,004). Serum irisin düzeyleri arasında AS ve kontroller arasında anlamlı farklılık saptanmadı [100,0'a (65,9) karşılık 103,0 (45,5) p=0,997]. Bununla birlikte serum IL-6, hs-CRP, eritrosit sedimentasyon hızı ortalamaları; hasta grubunda anlamlı olarak yüksekti. AS grubunda serum irisin düzeyleri ile enflamatuvar belirteçler, Bath Ankilozan Spondilit Fonksiyonel indeksi, Bath Ankilozan Spondilit Hastalık Aktivite indeksi, Ankilozan Spondilit Hastalığı Aktivite skoru CRP skorları arasında anlamlı korelasyon görülmedi, mSASS skoru ile irisin düzeyi arasında düşük-orta seviyede korelasyon bulundu (r: 0,362, p=0,005).

Sonuç: Bu çalışmada sağlıklı kontrollerle AS hastalarının serum irisin düzeyleri arasında fark ve irisin düzeyi ile hastalık aktivitesi arasında anlamlı bağlantı saptamadık.

Anahtar Kelimeler: Ankilozan spondilit, irisin, miyokin

Abstract

Objective: Axial spondyloarthritis is a chronic inflammatory disease primarily affecting the axial skeleton and the sacroiliac joints. In this study, we aimed to assess irisin levels in patients with ankylosing spondylitis (AS), compare them with healthy individuals, and explore the relationship between this adipomiyokine and activity, function, and structural damage in AS.

Methods: Ninety-seven patients classified as AS according to the modified New York criteria and 48 healthy controls were consecutively enrolled in the study. Serum irisin, interleukin (IL) 6, and high-sensitivity C-reactive protein (hs-CRP) measurements were performed using the ELISA method. Disease activity, functional assessments, and spinal radiographic scoring were conducted. The relationship between laboratory parameters, disease activation, and radiological parameters was evaluated using the Spearman correlation test.

Results: The age and gender distributions of AS and controls were found to be similar. Smoking was significantly higher in the AS group (p=0.004). No significant difference in serum irisin levels was observed between AS and controls [100.0 (65.9) versus 103.0 (45.5), p=0.997]. However, serum IL-6, hs-CRP, and erythrocyte sedimentation rate averages were significantly higher in the patient group. There was no significant correlation between serum irisin levels in the AS group and inflammatory markers, Bath Ankylosing Spondylitis Functional index, Bath Ankylosing Spondylitis Disease Activity index, and Ankylosing Spondylitis Disease Activity score CRP scores, while a low to moderate correlation was found with the mSASS score (r: 0.362, p=0.005).

Conclusion: In this study, we did not find a significant difference in serum irisin levels between healthy controls and AS patients, nor did we observe a significant connection between irisin levels and disease activity.

Keywords: Ankylosing spondylitis, irisin, myokine

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Giriş

Aksiyal spondiloartrit (axSpA) başlıca aksiyal iskeleti ve sakroiliyak eklemleri tutan kronik enflamatuvar bir hastalıktır.[1] Yeni sınıflamaya göre hastalık radyografik axSpA (r-axSpA) diğer adıyla ankilozan spondilit (AS) ve non-radyografik-axSpA (nr-axSpA) olmak üzere iki gruba ayrılmaktadır.[2] Hastalık gelişiminde en önemli genetik risk faktörü HLA-B27'dir, ek olarak ERAP ve interlökin (IL)-23 reseptör polimorfizmleri de hastalık ile ilişkilendirilmiştir.[3,4] AxSpA'da enflamasyon gelişiminde ve sürmesinde rolü olan ana proenflamatuvar sitokin yolakları tümör nekrosis faktör (TNF) ve IL-23/IL-17'dir.[5,6] Bu kronik enflamatuvar süreç içerisinde gözlenen sistemik enflamasyon ek olarak artmış kardiyovasküler (KVS) risk ile karşımıza gelmektedir.[7,8]

İrisin, adipositler ve kas hücreleri tarafından salgılanan bir adipomiyokindir ve enerji metabolizmasını düzenleme potansiyeline sahiptir. Miyokinlerin otokrin/parakrin yolla lokal ve endokrin yolla uzak dokularda etkinlik göstererek, hücreler arasında iletişimde görevli oldukları gösterilmiştir.[9] İrisin peroxisome proliferative activated receptor gamma koaktivator 1 alpha (PGC-1α) aktivasyonuna yanıt olarak beyaz yağ dokusundan da sekrete edilir ve kahverengi yağ dokusunun enerji harcama fenotipi kazanmasına yardımcı olur.[10] İrisinin total enerji tüketimini ve yaşam beklentisini artırdığı, vücut ağırlığını ve bu şekilde obezite ve insülin rezistansını azalttığı düşünülmektedir.[10] İnsan çalışmalarında serum irisin düzeylerinin vücut kitle indeksi (VKİ) ve HbA1c düzeyleri ile negatif korele olduğu ve tip II diyabetik bireylerde daha düşük olduğu da bildirilmiştir.[11,12]

Yapılan çalışmalarda irisin molekülünün; enflamasyon, anjiyogenez, oksidatif stres, endotel hücre disfonksiyonu, lipid ve kemik metabolizması gibi çeşitli süreçlerde yararlı rol oynadığı bildirilmiştir.[13-17] 2022'de Rafaat Ibrahim ve ark.[18] tarafından yapılan hayvan deneyinde 30 sıçanda deneysel olarak romatoid artrit (RA) indüklenmiş ve izlemde 14. günde, artrit kronik faza geçtikten sonra 4 hafta süresinde günlük irisin subkütan enjeksiyon tedavisi uygulandığında tedavi sonrası eklem dokusunda RIPK-3, MLKL, HMGB1, MCP1, IL-6, CHIT1, PN ve TNF-α seviyelerinde belirgin düşüş saptanmıştır. Sonuç olarak irisinin; deneysel olarak indüklenen RA'da immüno-enflamatuvar, nekroptotik moleküler ve biyokimyasal sinyal yollarını modüle ederek terapötik anti-enflamatuvar ve antioksidan etkiler sergilediği çıkarımı yapılmıştır.[18] Yine yapılan çalışmalarda irisinin, enflamatuvar hücrelerin aterosklerotik lezyonlara alınmasını inhibe ederek ve ayrıca makrofajların proenflamatuvar (M1) fenotipinden anti-enflamatuvar (M2) fenotipine geçişi uyararak vasküler enflamasyona karşı anahtar rol oynadığı açıklanmıştır.[19,20]

İrisinin axSpA'daki durumunu değerlendiren sınırlı sayıda çalışma bulunmaktadır. AxSpA'lı hastalarda yapılan iki çalışmada; azalmış serum irisin düzeyinin yüksek hastalık aktivitesi, artmış subklinik ateroskleroz varlığı ve yüksek KVS hastalık riski ile ilişkisi gösterilmiştir.[21,22]

Bu çalışmada, AS kohortumuzdaki hastalarda serum irisin düzeyini sağlıklı kontrollerle karşılaştırarak değerlendirmeyi ve serum irisin düzeyi ile aktivite, fonksiyon ve yapısal hasar arasındaki ilişkiyi test etmeyi amaçladık. Ayrıca iki grup arasındaki irisin düzeyini karşılaştırarak KVS hastalıklar üzerine irisinin etkisi olup olmadığını yorumlamayı planladık.

Gereç ve Yöntem

Çalışma Popülasyonu

Çalışmaya bir üniversite hastanesi romatoloji polikliniğinde takip edilen modifiye New York kriterlerine[2] göre AS olarak sınıflandırılan 97 hasta ve 48 yaş, cinsiyet ve VKİ uyumlu kişi kontrol grubu olarak alındı. Örneklem büyüklüğü tip 1 hata 0,05 ve tip 2 hata %80 kabul edilerek hesaplandı. Örneklem büyüklüğü hesabı MedCalc hazır programında "sampling comprasion of two means" yöntemi ile daha önce kronik böbrek yetmezliğinde irisin düzeylerini araştıran çalışmanın[23] verileri kullanılarak yapıldı. Bu şekilde AS ve sağlıklı kontrol olarak belirlenen gruplara en az 45 kişinin alınmasının yeterli olduğu bulundu. Artmış KVS riskin radyografik axSpA grubunda daha fazla çalışma ile tanımlanmış olması nedeni ile çalışmaya radyografik axSpA hastaları dahil edildi.[24] İrisin düzeylerini etkileyebilecek diabetes mellitus, ciddi hiperlipidemi (total kolesterol >300 mg/dL; trigliserid >400 mg/dL), koroner arter hastalığı veya kalp yetmezliği, serebro vasküler hastalık öyküsü olan veya lipid düşürücü ilaç kullanan, ileri derece obez (VKİ >35) hastalar ile, karaciğer fonksiyon testi bozukluğu, gebelik, kontrolsüz hipertansiyon, böbrek yetmezliği (glomerular filtrasyon hızı 60 mL/dk altı), bilinen malignite olan hastalar ve AS için anti-TNF ilaç kullananlar çalışmaya alınmadı. İzmir Katip Çelebi Üniversitesi Tıp Fakültesi İlaç Dışı Klinik Çalışmalar Etik Kurulu'ndan onay alınmıştır (147/2013).

Yapılandırılmış bir anket formu kullanılarak demografik, klinik, radyografik ve laboratuvar parametreleri elde olundu. Tüm hasta ve kontrollerin sistemik muayeneleri ve AS'li hastalarda spinal mobilite ölçümleri yapıldı. Muayene sonrası tüm hastalardan Bath Ankilozan Spondilit Hastalık Aktivite indeksi (BASDAI),[25,26] Bath Ankilozan Spondilit Fonksiyonel indeksi (BASFI)[27] formları doldurduldu. Ek olarak aktivite için Ankilozan Spondilit Hastalığı Aktivite (ASDAS)-C-reaktif protein (CRP)[28] hesaplandı. Varsa hastaların direkt grafileri modifiye stoke AS spine score

(mSASSS)[29] sistemine göre skorlandı, grafilerde spinal sindesmofit olup olmadığı da kaydedildi. Tüm hastalardan sabah açlığı ile 08.00 ve 10.00 saatleri arasında ön koldan venöz kan örnekleri alınıp santrifüj edilerek analiz zamanına kadar -80 °C'de muhafaza edildi. Serum irisin, yüksek duyarlıklı CRP (hs-CRP) ve IL-6 düzeyleri ticari olarak bulunabilecek araştırma amaçlı sandviç ELISA Kiti (PeloBiotech, Planegg - Germany) kullanılarak çalışıldı. Ek olarak hastaların eritrosit sedimentasyon hızı (ESH), kreatinin, ürik asit, total kolesterol ve trigliserid değerleri de çalışıldı.

İstatistiksel Analiz

İstatistiksel analizler Statistical Package for the Social Sciences (SPSS) 18.0 (IBM, Chicago, IL, USA) hazır paket programı yardımıyla yapıldı. Sürekli değişkenler ortalama ± standart sapma veya ortanca [çeyrekler arası aralık (IQR)], kategorik değişkenler yüzde şeklinde özetlendi. Gruplar arasında sürekli değişkenlerin karşılaştırılmasında normal dağılım değerlendirildikten sonra t-testi veya Mann-Whitney U testi ile yapılırken kategorik değişkenlerin karşılaştırılmasında ise çapraz tablo analiz yöntemleri (ki-kare) kullanıldı. Korelasyon analizi için ise Spearman korelasyon testi uygulandı.

Bulgular

AS ve kontroller arasında yaş, cinsiyet, eğitim seviyesi ve VKİ açısından bir fark saptanmadı, sigara kullanımı AS grubunda anlamlı olarak yüksekti (p=0,004) (Tablo 1). Hasta grubunun ortanca (IQR) semptom başlama yaşı 27 (13), ortalama tanı yaşı 32 (13) idi. Hasta ve kontrol gruplarının demografik, klinik, ve radyolojik bulguları Tablo 1'de özetlenmiştir.

Hasta grubunda altı hastanın kontrollü hipertansiyonu, bir hastanın oral antidiyabetik ile kontrollü diyabeti, bir hastanın antihiperlipidemik kullanımı ve bir hastanın koroner arter hastalığı vardı. Kontrol grubunda komorbiditesi olan hasta yoktu.

Hasta ve kontrol grupları arasında irisin seviyeleri açısından anlamlı farklılık bulunmamıştır (p>0,05). Bununla birlikte serum IL-6, hs-CRP, ESH ortalamaları; beklenildiği gibi hasta grubunda anlamlı olarak yüksek bulundu. Diğer metabolik testlerin kontrol grubunda yüksek olduğu gözlendi (Tablo 2).

AS grubunda serum irisin düzeyleri ile enflamatuvar belirteçler, BASFI, BASDAI, ASDAS CRP skorları arasında anlamlı korelasyon görülmedi, mSASS skoru ile irisin düzeyi arasında düşük-orta seviyede korelasyon bulundu (r: 0,362, p=0,005) (Tablo 3).

Serum irisin düzeyleri aktiviye (BASDAI <4 vs BASDAI ≥4) ve sindesmofit varlığına göre değerlendirildiğinde fark olmadığı görüldü (Şekil 1).

Tartışma

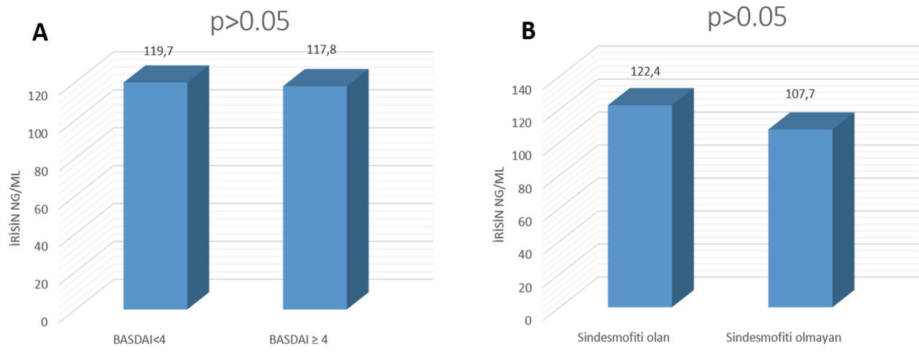
Bizim popülasyonumuzda irisin düzeyleri kontrollerle benzer şekilde bulunmuştur. Literatürde AxSpA ve RA hastalarında kontrollere göre daha düşük düzeyler bildirilmiştir.[21,22,30,31]

Özellikle AxSpA grubunun değerlendirildiği iki çalışmada hasta grubunun özelliklerine bakıldığında dışlama krtierleri açısından belirgin farklılıklar mevcuttur. Yüz on dokuz hasta

Tablo 1. Hasta ve kontrol gruplarının demografik, hastalık ilişkili klinik, ve radyolojik bulguları

	AS hastaları (n=97)	Kontrol (n=48)	p
Yaş, ortanca (IQR)	37 (15,5)	41 (5,2)	0,61
Erkek cinsiyet n (%)	76 (78,4)	36 (75,0)	0,65
Tanı süre, ortanca (IQR)	8,5 (10)		
Eğitim süresi, ortanca (IQR)	11 (3)	11 (7)	0,41
Herhangi bir dönemde sigara kullanımı n; %	70; 76,1	24; 52,2	0,004
Sigara hiç kullanmamış n; %	22; 23,9	22; 47,8	
Sigara halen kullanıyor n; %	48; 52,2	20; 43,5	
Sigarayı bırakmış n; %	22; 23,9	4; 8,7	
VKİ, ortanca (IQR)	26,8 (3,1)	27,3 (2,6)	0,50
BASDAI, ortanca (IQR)	4,7 (3,4)		
BASFI, ortanca (IQR)	2,9 (5,1)		
BASMI, ortanca (IQR)	3,4 (2,6)		
ASDAS-CRP, ortanca (IQR)	2,9 (1,4)		
mSASSS (n=58) , ortanca (IQR)	2 (20)		

AS: Ankilozan spondilit, ASDAS: Ankilozan spondilit hastalık aktivite skoru, BASDAI: Bath ankilozan spondilit hastalık aktivite indeksi, BASFI: Bath ankilozan spondilit hastalık fonksiyonel indeksi, BASMI: Bath ankilozan spondilit hastalık metrolojik indeksi, CRP: C-reaktif protein, IQR: çeyrekler arası aralık, mSASSS: Modifiye stok ankilozan spondilit omurga skoru, VKİ: Vücut kitle indeksi,



Şekil 1. A. Hastalık aktivitesine göre serum irisin değerleri, B. Sindesmofit varlığına göre serum irisin düzeyleri
BASDAI: Bath ankilozan spondilit hastalık aktivite indeksi

Tablo 2. Hasta ve kontrol gruplarının bazı laboratuvar verileri serum miyokin düzeyleri

	AS hastaları (n=97)	Kontrol (n=48)	p
İrısin, ortanca (IQR) (ng/mL)	100,0 (65,9)	103,5 (45,5)	0,997
IL-6, ortanca (IQR) (pg/mL)	4,3 (1,9)	2,1 (0,5)	<0,001
Hs-CRP (<1,0 mg/L), ortanca (IQR) (µg/mL)	2,0 (3,7)	0,3 (0,5)	<0,001
ESH, ortanca (IQR) (mm/h)	15,5 (16)	8,5 (13)	<0,001
Trigliserid (<150 mg/dL), ortanca (IQR) (mg/dL)	102,5 (66,2)	145 (106,5)	0,011
Total kolesterol (<200 mg/dL), ortanca (IQR) (mg/dL)	183 (51)	205,5 (35)	0,017
Kreatinin (0,6-1,3 mg/dL), ortanca (IQR) (mg/dL)	0,7 (0,2)	0,8 (0,2)	0,017
Ürik asit, ortanca (IQR) (mg/dL)	4,6 (1,8)	5,1 (1,9)	0,016

AS: Ankilozan spondilit, hs-CRP: yüksek duyarlıklı C-reaktif protein, IL: İnterlökin, ESH: Eritrosit sedimentasyon hızı

Tablo 3. İrisin ve diğer hasta ve hastalık ilişkili parametrelerin korelasyonu

İrisin		
	R	P
Hs-CRP	0,092	0,16
CRP	0,130	0,67
ESH	0,063	0,25
IL-6	0,047	0,67
Vücut ağırlığı	-0,041	0,62
VKİ	0,055	0,51
BASDAI	0,008	0,50
BASFI	0,095	0,86
ASDAS-CRP	0,084	0,77
mSASSS	0,362	0,005

ASDAS: Ankilozan spondilit hastalık aktivite skoru, CRP: C-reaktif protein, BASDAI: Bath ankilozan spondilit hastalık aktivite indeksi, BASFI: Bath ankilozan spondilit hastalık fonksiyonel indeksi, ESH: Eritrosit sedimentasyon hızı, Hs-CRP: Yüksek duyarlıklı C-reaktif protein, IL: İnterlökin, mSASSS: Modifiye stok ankilozan spondilit omurga skoru, VKİ: Vücut kitle indeksi

ve 30 kontrolün dahil edildiği birinci çalışmada dışlama kriteri belirtilmeyip sadece hastaların kontrollerle VKİ ve yaş açısından benzer olduğu belirtilmiş.[21] Yedi yüz yirmi beş axSpA hastasının dahil edildiği diğer çalışmada ise kontrol grubu bulunmamaktadır ve dışlama kriteri olarak diabetes mellitus ve kronik böbrek yetmezliği varlığı kabul edilmiş.[22] Bizim çalışmamızın ise kronik hastalık varlığı, metabolik durum ve biyolojik tedavi kullanma yönünden sıkı dışlama kriterleri mevcuttu. AxSpA varlığı dışında kontrol grubu ile oldukça benzer grup elde edilmişti ve irisin düzeyine etki edecek obezite, hiperlipidemi, biyolojik ilaç kullanımı gibi durumlar ortadan kaldırılarak irisinin hastalıkla değişiminin daha iyi değerlendirilmesi sağlandı.

2020 yılında Nam ve ark.'nın[21] yaş ve VKİ açısından benzer; 119 AS'li ve 30 sağlıklı kontrol üzerinde yaptığı çalışmada hastaların irisin düzeyinin kontrollerden anlamlı olarak düşük olduğu (p=0,013) bildirilmiştir.[21] Aynı yazarlar ayrıca hastalık aktivitesinin irisin ile direkt korelasyonu gösterememekle birlikte, BASDAI ≥4 olan hastalarda serum irisin düzeylerinin BASDAI <4 olan hastalara göre anlamlı olarak daha düşük olduğunu bildirmişlerdir (p=0,011).[21] 2022 yılında yayınlanan çalışmada, Remuzgo-Martínez ve ark.[22] 725 AS hastasını içeren İspanyol kohortunda serum irisin düzeyleri yanında genetik polimorfizleri de gözden geçirmişlerdir. Bu çalışmada HLA-B27 negatif, sakroiliiti olan, non-steroid anti-enflamatuvar ilaç (NSAID) ve konvansiyonel olarak hastalığı modifiye eden anti-romatizmal ilaçlarla (DMARD) tedavi edilen (biyolojik ajanlara göre) hastalarda irisin düzeyi anlamlı olarak daha düşük saptanmış; Bath AS hastalık metrolojik indeksi, vizüel analog skala global hasta ve hekim skorları

ile de irisin arasında negatif ilişki görülmüştür. Ayrıca düşük irisin seviyesinin karotiste plak varlığı ve aterojenik indeksin yüksek olması ile ilişkili bulunması nedeniyle serum irisin düzeylerinin axSpA hastalarında subklinik ateroskleroz, yüksek KVS risk ve daha şiddetli hastalık varlığına işaret edebileceği ileri sürülmüştür.[22] Remuzgo-Martínez ve ark.[22] irisin ile ESH ve CRP arasında ilişki bulamamıştır ve enflamasyonun diğer göstergeleri olan IL-6 ve TNF-α ile ilişkisine bakılmamasını kısıtlılık olarak belirtmişlerdir.

Bu hasta gruplarına biyolojik tedavi alan hastalar da dahil edilmiştir. Gelişmiş tedavilerin etkileri axSpA ve RA grubunda detaylı olarak verilmiştir. Silva ve ark.[30] biyolojik ajan kullanan RA hastalarında irisin düzeyinin konvansiyonel DMARD'la tedavi edilenlere göre daha yüksek olduğunu bildirmişlerdir. Remuzgo-Martínez ve ark.[22] çalışmasında da IL-17 tedavi alan grupta anti-TNF alan gruba göre anlamlı olarak irisin düzeyi yüksek bulunmuş (sırasıyla 2,76±0,74'e karşın 2,23±0,98, p=0,05) ve tüm tedaviler değerlendirildiğinde de konvansiyonel DMARD ve NSAID alan grupta irisin düzeyinin anlamlı olarak düşük olduğu görülmüş.[22] On yedi hidradenitis supurativa tanılı hasta üzerinde yapılan irisin düzeyinin tedavi klinik yanıtı ile korelasyonunu ve anti-TNF kullanımının irisin düzeyi üzerine etkisini inceleyen çalışmada ise hastaların bazal ve 16 haftalık adalimumab tedavisi sonrası irisin düzeyleri değerlendirildiğinde tedavi sonrası irisin düzeyinin istatistiksel olarak anlamlı olacak şekilde yükseldiği klinik yanıt ile irisin düzeyinin uyumlu olduğu görülmüş.[32]

Yine çalışmamızda irisin ile enflamasyonun ana göstergelerinden birisi ve aynı zamanda bir miyokin olan IL-6 arasındaki ilişki araştırılmış ancak irisin ile arasında anlamlı ilişki gösterilememiştir. Ancak çalışmamızda hastaları yapısal hasar yönünden değerlendirdiğimizde sindesmofit varlığı ile serum irisin düzeyleri arasında ilişki saptamazken, mSASSS skoru ile arasında düşük seviyede bir pozitif korelasyon saptanmıştır. Tanımlayıcı olarak yapılan bu değerlendirmede yapısal hasar ilişkisini değerlendirmek uygun olmayacaktır. Progresyon ile ilişkinin değerlendirilmesi için takip verileri ile izlem sonuçları faydalı olabilecektir.

Çalışmanın Kısıtlılıkları

Çalışmanın önemli kısıtlılıklarından biri egzersiz düzeylerinin ve beslenme alışkanlıklarının analiz edilen değişkenler arasında olmamasıdır. Ayrıca hastalarımızın hastalık sürelerinin ve kısıtlılık düzeylerinin de homojen olmaması; yaşam alışkanlıklarını ve dolayısıyla irisin düzeylerini etkilemiş olabilir.

Sonuç

Bu çalışmada sağlıklı kontrollerle AS hastalarının serum irisin düzeyleri arasında fark ve serum irisin düzeyi ile hastalık aktivitesi arasında anlamlı bağlantı saptamadık. Bu durumdan irisinin bir enflamatuvar marker olarak AS'de kullanılamayacağı sonucu çıkartılabilir. Ayrıca bu durum AS'li hastalarda ek risk faktörleri ve gelişmiş tedavi durumu kontrol edildiğinde artmış KVS riskten adipo-miyokin olarak irisin sorumlu olmadığı şeklinde yorumlanabilir. Yapısal hasar ile olan çelişkili bulgularının gözden geçirilmesi gerekmektedir.

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Hasta Onayı: Hasta ve kontrollerden aydınlatılmış onam formu alınmıştır.

Yazarlık Katkıları

Konsept: D.S., L.D.K., N.K., E.E., S.A., Dizayn: D.S., H.B., N.K., E.E., S.A., Veri Toplama veya İşleme: D.S., H.B., L.D.K., E.E., S.A., Analiz veya Yorumlama: D.S., L.D.K., N.K., E.E., S.A., Literatür Arama: D.S., H.B., L.D.K., E.E., S.A., Yazan: D.S., H.B., L.D.K., N.K., E.E., S.A.

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The evaluation of dynamic and static balance in Familial Mediterranean fever patients

Ailevi Akdeniz ateşi hastalarında statik ve dinamik denge bozukluklarının değerlendirilmesi

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Abstract

Objective: Familial Mediterranean fever (FMF) presents with arthritis attacks, enthesitis, and synovitis in the lower extremities which suggests that balance disorders may develop. The purpose of this study is to evaluate the dynamic and static balance in FMF patients.

Methods: This study was a prospective case-control study. The study included FMF patients who met the modified Tel Hashomer criteria as well as healthy participants. FMF patients' demographics, clinical features, International Severity Scoring System and Maastricht Ankylosing Spondylitis Enthesitis score were assessed. The Berg Balance scale (BBS), Functional Reach test (FRT), timed up and go (TUG), and single leg stance (SLS) tests were used to assess balance performance.

Results: The patient group consisted of 94 FMF patients (62.8% females), and the control group consisted of 90 healthy individuals (52.7% females). When the FRT, BBS, TUG, and SLS scores of the patient and control groups were compared, the patient group performed statistically worse in all scores. High risk of fall was found to be associated with longer disease duration and older age ($p<0.001$ and $p<0.001$). Visual analog scale scores during the attack were higher in patients at risk of falling, and arthralgia and amyloidosis were also more common. ($p=0.032$, $p=0.002$, and $p=0.001$, respectively).

Conclusion: The study found that compared to healthy individuals, FMF patients exhibited worse dynamic and static balance. The existence of amyloidosis and enthesitis, together with a longer and more severe illness, could all be factors in balance loss.

Keywords: Dynamic balance, Familial Mediterranean fever, static balance

Öz

Amaç: Ailevi Akdeniz ateşinin (AAA) yaşam boyu süren enflamasyonun yanı sıra alt ekstremitelerde artrit, sinovit ve entezit atakları ile seyretmesi hastalarda denge bozukluğu gelişebileceğini düşündürmektedir. Bu çalışmanın amacı AAA hastalarında statik ve dinamik denge bozukluğunu değerlendirmektir.

Yöntem: Çalışma prospektif olarak dizayn edilen bir çalışmadır. Modifiye Tel Hashomer kriterlerini karşılayan AAA hastaları ve sağlıklı gönüllüler çalışmaya dahil edildi. AAA hastalarının demografik verileri, klinik özellikleri, Maastricht Ankilozan Spondilit Entezit Skoru ve Uluslararası Şiddet Skorlama Sistemi değerlendirildi. Denge performansı Berg Denge ölçeği (BBS), fonksiyonel uzanma testi (FRT), zamanlı kalk ve yürü (TUG) ve tek ayak duruşu (SLS) testleri ile değerlendirildi.

Bulgular: Hasta grubuna 94 AAA hastası (%62,8 kadın), kontrol grubuna ise 90 sağlıklı birey (%52,7 kadın) dahil edildi. Hasta ve kontrol grupları BBS, FRT, TUG ve SLS testleri açısından karşılaştırıldığında hasta grubundaki puanların tüm değerlendirmelerde istatistiksel olarak daha kötü olduğu görüldü. Düşme riski taşıyan AAA hastaları ileri yaşta ve hastalık süresi daha uzundu (sırasıyla $p<0,001$ ve $p<0,001$). Düşme riski olan hastalarda atak sırasındaki görsel analog ölçeği skorları, artralji varlığı ve amiloidoz varlığı daha yüksekti (sırasıyla $p=0,032$, $p=0,002$, $p<0,001$).

Sonuç: Sonuç olarak AAA hastalarında dinamik ve statik dengenin sağlıklı bireylere göre daha kötü olduğu saptandı. Hastalığın daha uzun süreli ve daha şiddetli olması, entezit ve amiloidozun varlığı dengenin bozulmasına katkıda bulunabilmektedir.

Anahtar Kelimeler: Dinamik denge, Ailevi Akdeniz ateşi, statik denge

Introduction

Familial Mediterranean fever (FMF) is distinguished by repeated attacks of arthritis, serositis, self-limiting fever and erysipelas-like erythema.[1] Musculoskeletal symptoms that include lower extremity synovitis, enthesitis, myalgia, arthralgia, and exertional leg pain are also frequently observed in patients with FMF.[2] Symptoms initiate usually before the age of 20, and the attacks last about 12 to 72 hours.[3]

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Although, patients are usually asymptomatic between attacks, in 30% of cases, subclinical inflammation persists during the attack-free period.[4] Subclinical, persistent inflammation is an insidious feature of FMF. This chronic inflammation can lead to a variety of systemic complications, including fatigue, weight loss, growth retardation, amyloidosis, anemia, and decreased bone mineral density.[5-9]

Postural balance is a complex mechanism that requires the interaction of the vestibular, visual, musculoskeletal, and somatosensorial systems. Any disruption in at least one of these systems alters the control of postural balance by causing disturbances in integration between sensory information and motor responses.[10,11] Proprioceptive feedback from joints is an important aspect to maintain balance, accordingly, in rheumatic diseases, balance may be disrupted due to swollen and tender joints. Furthermore, increased pain perception, drug side effects, decreased lower extremity muscle strength, fatigue, sleep disturbance, and decreased mobility may contribute to balance disorder. The association between balance and rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic sclerosis (SSc), and psoriatic arthritis (PsA) has been studied before.[12-15] In the literature, there are studies examining balance disorders in pediatric FMF patients and children with other rheumatic diseases.[16,17] However, balance changes in adult FMF patients have not been investigated yet. It is possible that patients with FMF will experience balance changes due to the disease progression with fatigue, comorbidities, osteopenia, synovitis, enthesitis, arthritis attacks, reduced proprioception in the lower extremities, muscle weakness and older age. The purpose of the study is to evaluate the dynamic and static balance in FMF patients.

Materials and Methods

Study Design and Participants

This study was a prospective case-control study. Patients with FMF who applied to hospital rheumatology clinic between September 2021 and September 2022 and met the modified Tel Hashomer criteria[18] were included in the study. Healthy controls were consecutively selected among volunteers without chronic diseases with similar age, gender, weight, and body mass index properties compared to patient group. Participants over the age of 18 were included in the study. Patients with neurological deficits that could lead to balance problems, lower extremity motor paresis, a history of surgical intervention in the lower extremities or vertebral problems, lower extremity arthritis or contracture, acute trauma or psychiatric disorders affecting communication, visual and vestibular disorders that could lead to balance problems, and pregnancy were all excluded from the study. Informed consent form was obtained from all participants in the study. The study was conducted in accordance with the Declaration of Helsinki and with the approval of the Ankara City Hospital Ethics Committee (IRB no: E1-21-1959, date: 25.08.2021).

Data Collection

The demographic data and comorbidities (hypertension, hypothyroidism, coronary artery diseases, chronic kidney disease, chronic obstructive pulmonary disease/asthma, diabetes mellitus) of all participants and age at diagnosis, attack characteristics (fever, pleuritic pain, erysipelas-like erythema, abdominal pain), visual analog scale (VAS) during attacks, annual number of attacks, presence of amyloidosis, *MEFV* gene mutations and medical treatments of patients with FMF were recorded. In the evaluation of the musculoskeletal system, the patients' history of arthritis, sacroiliitis, and enthesitis in the heel were investigated. The presence of sacroiliitis and enthesitis in the heel was evaluated radiographically by 2 rheumatologists with at least 5 years of radiological evaluation experience. The presence of enthesitis was determined by standard palpation methods. Enthesitis was defined as tenderness at the site of the enthesis applied with a pressure of ~4 kg/cm^2 (enough to whiten the tip of the inspector's nail) by the standard palpation approach.[19] It was noted as present or absent according to their responses to standard palpation over the entheseal regions. Enthesitis sites were evaluated over 13 sites defined with reference to the Maastricht Ankylosing Spondylitis Enthesitis score (MASES). The patients were scored between 0 and 13 points, according to MASES.[20] Disease severity was evaluated using the International Severity Scoring System (ISSF) developed by Demirkaya et al.[21] The ISSF total score ranged from 0 to 10, with a total score of ≥6 for severe disease, 3-5 for moderate disease, and ≤2 for mild disease.

Data Collection Tools

Balance Tests

The functional and dynamic balance performance of the patient group consisting of FMF patients and the control group consisting of healthy volunteers was determined by the Berg Balance scale (BBS), timed up and go (TUG) test and Functional Reach test (FRT), and their static balance was determined by right and left single leg stance (SLS) (eyes open and closed) tests.

The BBS consists of 14 parameters that assess the patient's ability to maintain balance while performing movements statically or dynamically. Each item is scored from 0 to 4,

and the maximum score of the test is 56.[22] A score of <40 is associated with an almost 100% risk of falling.[23]

The TUG test is a method used to evaluate dynamic balance and functionality. The patients were asked to get up from the chair, to return after walking 3 meters without touching anything, to walk back to the chair and return to the sitting position, and the time spent during this activity was recorded as TUG. Average time score recorded after 3 trials. Shumway Cook et al.[23] reported that individuals who completed the TUG test for 13.5 seconds or longer had a risk of falling.[24]

In the FRT test, each subject is asked to stand upright with their feet shoulder-width apart, position the arm closer to the wall at 90 degrees of shoulder flexion, and reach forward as far as possible without taking a step. The distance between the starting position of the third fingertip and the position it extends was measured and recorded in centimeters (cm). This test was repeated 3 times and average values were obtained.[25] In frail elderly patients, a reach of <18.5 cm indicates the risk of falling.[26]

For the SLS test, the patients were asked to lift one foot so that it did not touch the supporting leg. They were told to hold it in this way, and the test was terminated when the foot touched the ground again. The time elapsed during this activity was recorded as the SLS score in seconds. The test was performed in two positions for the right and left legs and with eyes open and closed. Each test was performed in triplicate, and the mean value was considered for statistical analysis in the study.[27] SLS values of <5 seconds are associated with an increased risk of falling.[28]

The FMF patients were separated into two groups based on the cut-off values in the balance tests: Those with and without the risk of falling in any of the tests.

Statistical Analysis

SPSS 22 (IBM Corp. Armonk, NY) was used for statistical analysis. Normality of continuous variables were tested with Shapiro-Wilk's test, and with plots and histograms additionally. Normally distributed variables were presented as mean ± standard deviation, and as median (interquartile range) otherwise. Categorical variables were presented as number and percentages. Continuous variables were compared between groups by Mann-Whitney U or Student t-tests according to normality. X^2 test was used to compare categorical variables. P values <0.05 were considered statistically significant.

Results

The patient group consisted of 94 FMF patients (59 females and 35 males), and the control group consisted of 90 healthy individuals (51 females and 39 males). Demographic and anthropometric characteristics were similar between groups (Table 1). Disease characteristics, genetic mutations, medical treatments, MASES and ISSFS scores of the FMF patients were shown in Table 1.

Table 1. Demographic and anthropometric features of the patient and the control groups

	Patients (n=94)	Controls (n=90)	p
Age, years, mean ± SD	37.61±10.96	37.08±10.32	0.459
Sex, female, n (%)	59 (62.8)	51 (56.7)	0.399
BMI, mean ± SD	25.02±3.94	22.96±2.99	0.083
Active smokers, n (%)	25 (26.6)	20 (22.2)	0.490
Comorbidities, n (%)			
Hypertension	15 (16)		
Chronic kidney disease	17 (18.1)		
Coronary artery disease	5 (5.3)		
COPD/asthma	2 (2.1)		
Hypothyroidism	8 (8.5)		
Age of diagnosis, years, mean ± SD	27.3±12.31		
Disease duration, years, median (IQR)	9 (11)		
Attacks per year, median (IQR)	3 (6.5)		
FMF attack characteristics, n (%)			
Fever	70 (74.5)		
Abdominal pain	91 (96.8)		
Pleuritic pain	22 (23.4)		
Arthralgia	61 (64.9)		
Erysipelas-like erythema	5 (5.3)		
VAS-pain, median (IQR)	8 (1)		
Sacroiliitis, n (%)	10 (10.6)		
Arthritis, n (%)	25 (26.6)		
Heel enthesitis, n (%)	19 (20.2)		
Amyloidosis, n (%)	17 (18.1)		
MEFV mutations, n (%)*			
M694V heterozygous	25 (26.6)		
M694V homozygous	15 (16)		
M694V/M680I heterozygous	7 (7.4)		
M694V/V726A heterozygous	8 (8.5)		
M694V/E148Q heterozygous	6 (6.4)		
E148Q heterozygous	6 (6.4)		
M680I homozygous	2 (2.1)		
V726A heterozygous	7 (7.4)		
No mutation	2 (2.1)		
Treatment agents, n (%)			
Colchicine	92 (97.9)		
Anakinra	24 (25.5)		
Canakinumab	15 (16)		
TNF-α inhibitors	6 (6.4)		
ISSF, median (IQR)	3 (3)		
MASES, median (IQR)	0.5 (3)		

**: MEFV mutation of 78 patients is known, BMI: Body mass index, , SD: Standard deviation, IQR: Interquartile range,ç COPD: Chronic obstructive pulmonary disease, FMF: Familial Mediterranean fever, ISSF: International Severity Scoring System, MASES: Maastricht Ankylosing Spondylitis Enthesitis score, TNFα: Tumor necrosis factor alpha, VAS: Visual analog scale*

Balance Test Outcomes

Static and dynamic balance test results in the groups were shown in Table 2. In all evaluations, the difference between the patient and control groups' scores on the BBS, TUG, FRT and SLS (right and left, eyes open and closed for each side) tests was statistically significant. The patient group's scores were lower. Number of patients with a score indicating risk fall according to cut-off values in any of the tests were higher in FMF group (28.7% vs. 5.5%, p<0.001).

The FMF patients were divided into two groups based on the cut-off values from the balance tests: Those who had a risk of falling in any test and those who did not. Demographic, clinical and balance parameters of the patients are shown in Table 3. FMF patients with a higher risk of falling had longer disease duration and were older (p<0.001 and p<0.001, respectively). Comorbidities such as hypertension, chronic kidney disease, coronary artery disease, and hypothyroidism were more common in patients at risk of falling (p<0.001, p<0.001, p=0.009, p=0.027, respectively). Patients who were at risk of falling had higher VAS scores during the attack, as well as higher levels of arthralgia and amyloidosis. (p=0.032, p=0.002, p<0.001, respectively). Patients at risk of falling had considerably higher ISSF and MASES scores than those who were not. (p>0.001 and p=0.001, respectively). Anakinra and canakinumab were more commonly used to treat patients at risk of falling.

Table 2. Comparison of dynamic and static balance in patient and control groups and patients at risk of falling

	Patients (n=94)	Controls (n=90)	p
BBS, score, median (IQR)	56 (3)	56 (0)	<0.0001
FRT, cm, median (IQR)	29 (9)	31 (5)	0.002
TUG, sec, median (IQR)	7.44 (1.21)	7.3 (0.46)	0.007
SLS, sec, median (IQR)			
Eyes open, (R)	34 (19.5)	39 (8.5)	0.003
Eyes closed, (R)	11 (5.93)	12 (4.03)	0.009
Eyes open, (L)	33 (20.48)	38.5 (9.25)	0.003
Eyes closed, (L)	11.2 (6)	11.45 (4.05)	0.020
Patients with fall risk, n (%)	27 (28.7)	5 (5.6)	<0.0001

BBS: Berg balance scale, cm: Centimeter, FRT: Functional reach test, L: Left, R: Right, sec: Second, SLS: Single leg stance test, TUG: Timed up and go test , SD: Standard deviation

Discussion

In our study, dynamic balance performances were evaluated with BBS, FRT, and TUG and static balance performances were evaluated with SLS. The scores were worse in FMF patients than those in healthy controls. Patients at higher risk of falling due to the cut-off value of any test were older and had the disease for longer periods of time, and amyloidosis was observed more frequently in these patients. The ISSF score, which measures disease severity, and the MASES score, which assesses the presence of enthesitis, were higher in patients with increased risk of falling.

Postural control or balance is a complex process requiring an intact network between the musculoskeletal, sensory, and cognitive systems.[29] A decrease in balance performance is observed in case of an alteration in any of these systems. Balance disorder in rheumatic diseases such as RA,[12] AS,[13] PsA,[14] SSc[15] had been investigated, however to the best of our knowledge, there is no study examining the static and dynamic balance in FMF, which may cause musculoskeletal manifestations and other complications such as amyloidosis,

Table 3. Comparison characteristics of FMF patients with and without fall risk

	FMF patients with fall risk (n=27)	FMF patients without fall risk (n=67)	p
Age, years, mean ± SD	44.18±10.83	34.97±9.92	<0.0001
Sex, female, n (%)	18 (66.7)	41 (61.2)	0.619
Age of diagnosis, years, mean ± SD	28.85±14.14	26.68±11.54	0.443
Disease duration, years, median (IQR)	14 (10)	7 (10)	0.000
Attacks per year, median (IQR)	3 (11)	3 (4)	0.596
FMF attack characteristics, n (%)			
Fever	21 (77.8)	49 (73.1)	0.640
Abdominal pain	27 (100)	64 (95.5)	0.264
Pleuritic pain	8 (29.6)	14 (20.9)	0.365
Arthralgia	24 (88.9)	37 (55.2)	0.002
Erysipelas-like erythema	2 (7.4)	3 (4.5)	0.567
Comorbidities, n (%)			
Hypertension	12 (44.4)	3 (4.5)	<0.001
Chronic kidney disease	14 (51.9)	3 (4.5)	<0.001
Coronary artery disease	4 (14.8)	1 (1.5)	0.009
Hypothyroidism	3 (4.5)	5 (18.5)	0.027
COPD/Asthma	1 (1.5)	1 (3.7)	0.501

Table 3. Continued

	FMF patients with fall risk (n=27)	FMF patients without fall risk (n=67)	p
VAS-pain, median (IQR)	8 (2)	7 (2)	0.032
Sacroiliitis, n (%)	4 (14.8)	6 (9)	0.404
Heel enthesitis, n (%)	8 (29.6)	11 (16.4)	0.149
Arthritis, n (%)	8 (29.6)	17 (25.4)	0.673
Amyloidosis, n (%)	14 (51.9)	3 (4.5)	<0.001
MEFV mutations, n (%)*			
M694V heterozygous	5 (18.5)	20 (29.9)	
M694V homozygous	10 (37)	5 (7.5)	
M694V/M680I heterozygous	1 (3.7)	6 (9)	
M694V/V726A heterozygous	1 (3.7)	7 (10.4)	
M694V/E148Q heterozygous	2 (7.4)	4 (6)	0.081
E148Q heterozygous	1 (3.7)	5 (7.5)	
M680I homozygous	0 (0)	2 (3)	
V726A heterozygous	2 (7.4)	5 (7.5)	
No mutation	0 (0)	2 (3)	
Treatment agents, n (%)			
Colchicine	26 (96.3)	66 (98.5)	0.501
Anakinra	19 (70.4)	5 (7.5)	<0.001
Canakinumab	9 (33.3)	6 (9)	0.003
TNF-α inhibitors	3 (11)	3 (4.5)	0.234
ISSF, median (IQR)	6 (3)	2 (2)	<0.001
MASES, median (IQR)	2 (5)	0 (2)	0.001

**: MEFV mutation of 78 patients is known, COPD: Chronic obstructive pulmonary disease, FMF: Familial Mediterranean fever, ISSF: International Severity Scoring System, MASES: Maastricht Ankylosing Spondylitis Enthesitis score, TNFα: Tumor necrosis factor alpha, VAS: Visual analog scale, SD: Standard deviation, IQR: Interquartile range*

all of which have potential to deteriorate balance. BBS, FRT, and TUG tests are reliable and easily applicable tests to evaluate balance in the outpatient setting.[30] In our study, when the BBS, FRT, and TUG tests were compared with age and gender-matched healthy volunteers, it was observed that the dynamic balance was worse in FMF patients. Likewise, the SLS test scores, in which static balance was evaluated in two ways (eyes open and closed), were found to be lower in FMF patients than in healthy volunteers. There may be several reasons for this postural instability observed in FMF patients. In FMF arthralgia, arthritis, and tenosynovitis, especially in the lower extremities, sacroiliitis, entheses in the lower extremities, and exertional leg pain may occur.[30] This may cause a loss of static and dynamic balance by disrupting the lower extremity proprioception of the patients. Furthermore, subclinical inflammation observed even in the attack-free period disrupts endothelial function and causes atherothrombosis, anemia, heart disease, osteoporosis, and secondary amyloidosis.[31,32] This persistent chronic inflammation associated with FMF had been shown to be an important risk factor for the development of low body mass index.[33] Studies had revealed that local or systemic inflammatory cytokines released from arthritic joints of FMF patients may play a role in bone loss and that systemic and local effects on cartilage growth in long bones may lead to osteopenia and osteoporosis.[34-36] It is a known fact that both posture disorders and balance disorders due to myopathy are seen in osteoporotic individuals.[37] In addition, the presence of slowly progressive secondary amyloid-related polyneuropathy in FMF patients with a long disease duration may also cause deterioration in balance performance.

In individuals with chronic diseases, the presence of pain, fatigue, and related sleep disorders and depression negatively affect balance performance. As with other rheumatic diseases, the presence of pain, fatigue, and sleep disorders that impair the quality of life in FMF patients had been reported in previous studies.[38,39] In a study conducted with pediatric FMF patients, it was shown that sleep quality was negatively affected as the number of attacks increased.[40] Also, Kucuksahin et al.[39] found that poor sleep quality was associated with attack frequency, fatigue, and levels of inflammatory markers during the attack. These psychological factors may be the reason for these balance disorders seen in FMF patients in our study.

The majority of the first attacks of FMF occur at the end of the teenage years.[3] Clinical episodes are accompanied by an increase in acute phase reactants such as erythrocyte sedimentation rate, C-reactive protein, serum amyloid A (SAA), and fibrinogen. All these laboratory parameters

usually return to normal levels during attack-free periods. However, it has been reported that subclinical inflammation may continue in some patients during attack-free periods and may lead to the development of amyloidosis, which can be complicated by end-stage renal disease.[31,41] High and prolonged SAA levels and prolonged disease duration are risk factors for the development of amyloidosis.[42] So far, 22 different forms of localized amyloidosis have been described.[43] Amyloid deposition can affect the central nervous system as well as peripheral motor, sensory, and autonomic nerves.[44] In addition, myopathy has been reported in patients with amyloidotic kidneys with FMF.[45] Accordingly, our results demonstrated worse postural stability and an increased risk of falling in FMF patients with a longer disease duration and presence of amyloidosis. Considering that more than one-third of adults aged 65 and over fall at least once a year, increasing age, comorbidities, gait impairment, muscle weakness, and decreased balance contribute to an increased risk of falls. Therefore, it is inevitable that increasing age and long-term disease risk will affect the risk of falling in FMF patients.

Symptoms of the disease are caused by mutations in the *MEFV* gene, which encodes the pyrin protein, which has a critical role in the regulation of inflammatory pathways. Mutant pyrin causes clinical manifestations of the disease, mostly due to overproduction of IL-1b.[46,47] ISSF score is a disease severity measurement tool related to organ dysfunction, chronic sequelae, attack frequency, attack characteristics, and acute phase reactants. In our study, the ISSF scores were found to be higher in patients with increased risk of falling, suggesting that as the disease progresses, it also affects balance performance due to chronic inflammation.

Enthesis is seen in more than 2 out of 3 patients with FMF. Irregular local auto-inflammation is the main pathogenic feature in FMF. The primary target of the disease is the serous organs, but innate immune system elements in the entheseal regions can be activated by uncontrolled minor traumatic forces. Thus, unregulated auto-inflammation driven by the innate immune system induces inflammation in these regions.[48-50] In a study, more severe disease, prolonged attacks, and high acute phase reactants were found to be related with presence of enthesitis in FMF. In addition, the frequency of arthritis, exertional leg pain, and myalgia were higher in these patients.[50] In the study of Eshed et al.[48], enthesis, arthritis, myalgia, and exertional leg pain were found to be associated with each other. In our study, the MASES enthesis score was found to be higher in patients with a high risk of falling, which may be due to this association of enthesis with other musculoskeletal symptoms.

Study Limitations

There were limitations in our study. First, due to its cross-sectional study design, effects of treatment initiation on balance were not evaluated. Second, majority of our patients were under treatment, therefore, to the best of our knowledge regarding treatment naïve patients could not be obtained. In addition, electrophysiologic evaluations were not studied as a part of the study protocol. Lastly, the relationship between the psychological and socioeconomic status and balance disorder, a factor which may play a role in balance patient perception-wise, was not assessed.

Conclusion

In conclusion, to the best of our knowledge, this study is the first to examine balance in FMF patients. Our findings showed that FMF patients had worse dynamic, functional, and static balance than healthy controls. Increased disease severity and duration, as well as the existence of enthesitis, amyloidosis, and other comorbidities, may all lead to a worsened balance. Studies with higher power would better elucidate and confirm the relationship between FMF and balance.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and with the approval of the Ankara City Hospital Ethics Committee (IRB no: E1-21-1959, date: 25.08.2021).

Informed Consent: Informed consent form was obtained from all participants in the study.

Authorship Contributions

Concept: O.K., Design: Ş.E., Data Collection or Processing: E.A., Analysis or Interpretation: S.C.G., Literature Search: K.O., Writing: H.E.K.

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

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Infection frequency may not increase in Familial Mediterranean fever

Ailevi Akdeniz ateşinde enfeksiyon sıklığı artmayabilir

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Abstract

Objective: To the best of our knowledge, there is no study evaluating the infectious features of Familial Mediterranean fever (FMF) in the literature. Here, we tested two hypotheses: infection is more common in FMF and FMF severity and infection may be linked.

Methods: We included three groups: FMF (363 patients), spondyloarthropathy (SpA-patients) (112 patients) and control (121 patients). We screened participants for infection characteristics in the last year with a pre-approved and validated questionnaire. Firstly, we compared infection rates, frequency of infection types, and infection severity within groups. We then evaluated the factors associated with infection in FMF.

Results: We found that infection rates were similar in FMF, SpA-patients and controls. However, admission to the infection outpatient clinic was more common in FMF (p=0.001) and the duration of workforce loss due to infection was longer in FMF than controls (p=0.002). Furthermore, FMF-patients with infection had higher disease severity (p=0.004), high acute phase reactants between attacks (p=0.006) and more site involvement during attacks (p<0.001). In multivariate analyses, the latter was found to be significant (p=0.003).

Conclusion: We discovered no increase in the infection rate of FMF patients. Patients with infections, on the other hand, may have more severe FMF.

Keywords: Auto-inflammatory diseases, disease activity, Familial Mediterranean fever, infection

Öz

Amaç: Literatürde Ailevi Akdeniz ateşi (AAA) enfeksiyon özelliklerini değerlendiren bir çalışma bulunmamaktadır. Bu çalışmada, iki hipotezi test ettik: enfeksiyon AAA'da daha yaygın olabilir ve AAA şiddeti ile enfeksiyon arasında bir ilişki olabilir.

Yöntem: Çalışmaya üç ayrı grup dahil ettik: AAA (363 hasta), spondiloartropati (SpA) (112 hasta) ve kontrol (121 hasta). Katılımcıları son bir yıl içindeki enfeksiyon özellikleri açısından önceden onaylanmış ve geçerli bir anketle taradık. İlk olarak, gruplar içinde enfeksiyon oranlarını, enfeksiyon türlerinin sıklığını ve enfeksiyonun şiddetini karşılaştırdık. Daha sonra AAA'da enfeksiyonla ilişkilendirilen faktörleri değerlendirdik.

Bulgular: AAA, SpA-hastaları ve kontroller arasında enfeksiyon oranlarının benzer olduğunu bulduk. Ancak, enfeksiyon polikliniğine başvuru AAA'da daha yaygındı (p=0,001) ve enfeksiyon nedeniyle iş gücü kaybının süresi AAA'da kontrollere göre daha uzundu (p=0,002). Ayrıca, enfeksiyonlu AAA hastalarının daha yüksek hastalık şiddeti (p=0,004), ataklar arası yüksek akut faz reaktanları (p=0,006) ve ataklar sırasında daha fazla bölge tutulumu (p<0,001) vardı. Çoklu değişken analizlerinde, sonuncusunun önemli olduğu bulundu (p=0,003).

Sonuç: Çalışmamızda AAA hastalarının enfeksiyon oranında artış gözlenmemiştir. Bununla birlikte, enfeksiyonlu hastaların daha şiddetli AAA'ya sahip olabileceği görülmüştür.

Anahtar Kelimeler: Oto-enflamatuvar hastalıklar, hastalık aktivitesi, Ailevi Akdeniz ateşi, enfeksiyon

Introduction

Infection is a leading cause of morbidity and mortality in rheumatic diseases. Infections could be triggered by both the diseases themselves and the treatments for these auto-inflammatory and auto-immune diseases. Infections in Familial Mediterranean fever (FMF) can, however, cause serious illness.[1] The main factors that increase the risk of infection in systemic lupus erythematosus (SLE) are impaired cellular and humoral immune functions.[2] Furthermore, even before the use of biologic

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disease-modifying rheumatologic drugs, the rate of infection in rheumatoid arthritis (RA) patients was higher than in the general population.[3] On the other hand, disease activities may be linked to increased infection frequency. In the RADIUS-1 cohort, RA patients were found to be at higher risk of infection correlating with increased disease activity.[4] Additionally, hospitalization for infection in SLE patients was linked to disease activity, regardless of corticosteroid dose.[5] However, majority of infection risk is attributed to treatment in rheumatological diseases. Regardless of disease, immunosuppressive therapies, including corticosteroids, alkylating agents, all conventional synthetic, biologic, and targeted synthetic disease-modifying drugs, pose serious infection risks.[6-8]

FMF is an auto-inflammatory disease characterized by recurrent episodes of fever and polyserositis.[9] The majority of the mutations associated with auto-inflammatory diseases are directly linked to the innate immune system.[10] Pyrin is an inflammasome sensor that is often activated in response to infective pathogens.[11] During an infection, it increases both local and systemic inflammation while decreasing bacterial load.[12] In FMF and cryopyrinopathies, pyrin and cryopyrin mutations, respectively, are the main changes associated with the auto-inflammatory clinical spectrum.[13] Pyrin mutations may limit the immune system's first line of defence against pathogens in the above setting. In addition, infectious insults can cause uncontrolled inflammation, which can lead to attacks. As far as we know, although pyrin is mutated in FMF, there is no study in the literature that evaluates the propensity for infection in patients with FMF. Also, recurrent infections in FMF patients are risk factors for the development of amyloidosis and can cause progression as seen in amyloid storm during amyloidosis.[14] Infection, which is one of the environmental factors, can also influence the disease progression.[1]

In this study, we tested the validity of our two hypotheses. Our first hypothesis is that FMF patients, like other rheumatic diseases, have a higher risk of infection than the general population due to mutation in pyrin. Our second hypothesises that severe FMF and infection are linked.

Material and Methods

Study Participants' Characteristics and Selection Methods

The study group included 363 FMF patients who met the Tel-Hashomer Criteria.[15] The study included all consecutive FMF patients who presented within a one-year period and met the inclusion criteria. All FMF patients who had taken conventional synthetic, biologic, and targeted disease-modifying drugs, corticosteroids, and immunosuppressive drugs including interleukin (IL)-1 blockers for at least 18 months were excluded from the study. Here, thirty patients were excluded because they were taking an IL-1 blocker, and four were excluded because they were taking other anti-inflammatory disease-modifying drugs, corticosteroids, or immunosuppressive drugs. Additionally, we included two different control groups. The first included 112 spondylarthritis (SpA) patients who met the classification criteria of Assessment of Spondylarthritis International Society for SpA as the diseased control.[16] The study included all consecutive SpA patients who presented to the rheumatology outpatient clinic within three months and had not used conventional synthetic, biological, or targeted disease-modifying drugs, corticosteroids, or immunosuppressive drugs for at least 18 months. This was our disease control group. One of the reasons for including this group was to assess our performance on the task and the test's validity. The other group consisted of healthy controls who were matched with FMF patients in a 3:1 ratio for age (mean age ± standard deviation) and gender. Healthy controls were selected among those who applied to occupational health outpatient clinics for routine care. The healthy control group excluded people who had known inflammatory diseases or were taking immunosuppressive drugs. Participants in the three groups were excluded form study if they were under the age of 18 or over the age of 65, those with malignancy, pregnancy, had a diagnosis of primary or secondary immunodeficiency, or were breastfeeding. All participants were literate and perceptive. In total, 596 patients were participated in the trial, which was separated into three distinct groups.

Research Variables and Methods

We used a pre-approved and validated questionnaire to screen all participants' infectious disease characteristics, outcomes, and overall infection risk factor in the previous 12 months.[17] We used this questionnaire to assess the frequency and types of infection by asking, "How often have you had specific infections in the last 12 months?" [upper respiratory tract infections (URTI); urinary tract infection (UTI); gastro-intestinal tract infection, invasive mucosal infections, pneumonia, mucosal herpes infections and other unclassified infections], the frequency of antibiotic prescription by asking "How often did a physician prescribe antibiotics (drugs against infections; but no ointments for external use) in the past 12 months?", the characteristics of vaccination by questioning" Have you ever been vaccinated against specific disease?" (fully vaccination for pneumococcus and vaccinated for influenza in the past year), the need for hospitalization for infectious diseases by inquiring "How

often did you receive inpatient care in the past 12 months due to an infectious disease?" (stay in hospital wards at least overnight for infection diagnosis or treatment), frequency and number of applications to infectious diseases outpatient clinics by asking "How often did you receive outpatient care (medical practice or clinic) in the past 12 months due to an infectious disease?" (not hospitalized overnight, but a visits clinic for infection diagnosis or treatment) and the number of days lost in workforce due to infection in the past 12 months by asking "How many working days were you on sick leave in the past 12 months due to an infectious disease?" In addition, the risk factors for infectious diseases in the past 12 months such as hospitalization for non-infectious diseases and length of stay, surgery in the past year, removal surgeries for lymphoid tissues (appendectomy, splenectomy, tonsillectomy, thymectomy, nasal polyp excision) at any time and organ/systemic specific infections at any time (sexually transmitted diseases, osteomyelitis, septic arthritis, endocarditis, infective nephritis, human immunodeficiency virus, zoster infection) were evaluated.

Demographic characteristics including age, gender, smoking history, and comorbidities (hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, diabetes mellitus) were collected from all study participants. Additionally, in both FMF and SpA groups, disease duration and disease activity were recorded. Here, the International Severity Scoring System for FMF (ISSF) was used to evaluate the severity of the disease which ranges from 0 to 10, where 10 is the most severe.[18] Furthermore, patients were classified as severe disease (≥6), intermediate disease (3-5) and mild disease (≤2) based upon ISSF scores. Also, ASAS-endorsed disease activity score (ASDAS) was used to assess the disease activity of patients with SpA.[19]

We obtained additional information from the FMF patients. Age of onset of symptoms, FMF related symptoms, MEFV mutations, if available, frequency, severity and duration of attacks, acute phase reactant levels over the previous year, presence of amyloidosis and FMF treatment were all recorded.

We also collected information from patients who had been infected with Coronavirus disease-2019 (COVID-19) infection. However, our hypothesis did not include assessing the outcome or severity of COVID-19 in FMF patients. We assigned COVID-19 to infection types in terms of disease involvement. We also highlight the COVID-19 data separately.

First, we compared the three groups in terms of the infectious disease frequency, infection types, and outcomes. Then, for only FMF-related parameters and infection risk factors, we compare FMF patients with and without infection. Finally, we looked at the relationship between disease severity and infectious disease features in FMF patients. We divided disease severity into two categories: Mild disease (ISSF ≤2) and moderate-severe disease (ISSF ≥3).

This study was approved by the Local Research Ethics Committee and carried out in compliance with the Helsinki Declaration (date: 09.03.2022, approval number: 2022/514/221/4 - University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee). All the patients gave written informed consent.

Statistical Analyses

Statistical analyses were carried out using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA). To determine if the data were normally distributed, the Kolmogorov-Smirnov test was performed. None of the parameters distributed normally. Therefore, firstly, comparisons of continuous variables were made by Kruskal-Wallis or Mann-Whitney U according to the number of groups. In addition, chi-square test was used to compare categorical variables. We then performed post-hoc analysis with Bonferonni adjusted Mann-Whitney U or chi-square tests if necessary. We also performed multivariate analyses with logistic regression analyses to assess FMF related parameters and infection risk factors associated with infection in FMF patients. We included age, gender, colchicine dose (mg/day) and significantly different variables found in univariate analyses except individual attack sites into the model. We think that number of different attack sites represents all these variables. We calculated the sample size of the study with G*Power (Universität Kiel, Germany). At 95% power, α error level 0.05, and effect size 0.5, the total number of participants needed was 280 (210 cases/70 controls). P-value lower than 0.05 was considered as statistically significant. The categorial parameters were presented as numbers and percentages consecutively and continuous variables were shown as median (interquartile range). Infection frequencies, number of outpatient visits, length of stay and number of days lost in work were calculated in only positive cases.

Results

Demographic Characteristics of the Participants

The prevalence of male patients in the SpA group was observed to be higher compared to both FMF patients

and the control group (p=0.01). Furthermore, the median age in the SpA group was the highest among the studied groups, and SpA patients were significantly older than those with FMF (p<0.001). Notably, comorbidities were more frequently identified in SpA patients in comparison to the other groups (p<0.001).

It is noteworthy that none of the patients in the SpA cohort exhibited reactive arthritis. Among the 363 FMF patients, nine (4.1%) were diagnosed with amyloidosis. Importantly, none of these amyloidosis patients required dialysis, and none had a glomerular filtration rate below 30 mL/min. Conversely, none of the SpA patients were found to have amyloidosis in this study.

Infection Characteristics of Study Groups

Our first hypothesis is that FMF patients, like other rheumatologic disorders, have an elevated infection risk.

While the infection frequency in the previous year was statistically similar in all three groups, both the FMF group and the control group experienced a higher total number of infection attacks compared to patients with SpA in the last year (p=0.001). Furthermore, the number of different types of infections in FMF patients and the control group was higher than in SpA patients (p=0.001).

The frequency of specific infection types in FMF patients and the control group was generally similar, except for URTI, which were significantly higher in the control group (p=0.003). Although SpA patients had a higher frequency of comorbidities than the other groups, the frequency of infection types was either similar or lower than the other two groups. URTI and UTI were identified as the most common types of infections in FMF patients.

Notably, the prevalence of COVID-19 in the past year was similar across all groups. Only one patient in each group experienced COVID-19-related pneumonia, while the remaining cases were characterized by upper respiratory tract infections. The only risk factor for infections that differed significantly between FMF patients, and the control group was surgical removal of lymphoid tissues at any time (p=0.04). In this study, FMF patients had a higher rate of appendectomy than the control group. Vaccination characteristics were similar between the FMF and control groups. In addition, none of the study participants had been admitted to the intensive care unit in the previous year for infectious or non-infectious conditions.

In individuals with FMF, there was a notable increase in both the frequency of visits to the infectious disease outpatient clinic (p=0.002) and the duration of work absenteeism due to infection (p=0.003) when compared to the control group. Conversely, in patients with SpA, these factors were found to be comparable to those in the control group.

Demographic and infection disease characteristic of the participants were shown in Table 1.

FMF Characteristics of Patients with or without Infection in the Past Year

Our second hypothesis is that FMF severity is related to infection. First, we assessed disease features such as disease severity as a risk factor for infection.

Demographic characteristics were similar between the patients with or without infection in the past year.

Pleuritis, fever, arthritis, exertional leg pain and myalgia were more common in FMF patients who had an infection in the last year. However, none of the FMF patients in our cohort met the International Society for Spondylarthritis Assessment of Spondylarthritis classification criteria. Furthermore, the infected FMF group had higher ISSF scores, a higher frequency of increased acute phase reactants between attacks, and a higher number of different sites involved in FMF episodes.

The infected group received influenza vaccine at a higher rate than the uninfected group (p=0.03). Furthermore, the frequency of hospitalization for non-infectious conditions was higher in the infected group (p=0.01). All other infection risk factors were similar between groups.

Disease and infection characteristics of infected and non-infected FMF patients in the past year was shown in Table 2.

In multivariate analyses, the only variable associated with infection in FMF patients was number of different sites involved during attack (odds ratio: 1.48, 95% confidence interval: 1.12-1.75, p=0.003) (Table 3).

Demographic and Infectious Characteristics of FMF Patient Classified in Terms of Disease Severity

As part of our second hypothesis, we examined the infectious characteristics of FMF patients with severe disease to determine the significance of disease severity in infection.

Patients with FMF who had moderate-to-severe disease were prescribed a higher median colchicine dose compared to those with mild disease (p=0.005). In the previous year, both groups showed similar frequencies and total numbers of infection attacks. However, there was a tendency towards an increased infection frequency in the last year among patients with moderate-to-severe FMF compared to those with mild disease. Additionally, individuals with more severe disease experienced a higher frequency of both URTI (p=0.008) and COVID-19 (p=0.03).

Table 1. Demographic and infection disease characteristic of the participants

	FMF n=363	SpA n=112	Control n=121	p	Post-hoc analyses
Gender (M/F)	123/240*	55/57*+	41/80+	0.01	0.004*
					0.001+
Age (years)	33.0 (25.0-43.0)*	38.0 (31.0-46.7)*	34.0 (24.0-42.0)	<0.001	<0.001*
Disease duration (years)	8.0 (4.0-14.0)	6.0 (3.0-12.0)	N/A	0.03	
Smoking, n (%)	94 (25.9)	38 (33.9)	38 (31.4)	0.16	
Comorbidity, n (%)[1]	57 (15.7)*^	29 (25.9)*+	7 (5.8)^+	<0.001	0.01*^
					<0.001+
ISSF score	1.0 (1.0-3.0)	N/A	N/A		
ASDAS	N/A	2.5 (2.5-2.5)	N/A		
Infection characteristics[2]					
Infection in the past year, n (%)	241 (66.4)	61 (54.5)	75 (62.0)	0.06	
Total number of infections in the past year (n)	2.0 (1.0-3.0)*	1.0 (1.0-2.0) *+	2.0 (1.0-3.0) +	0.001	<0.001*+
URTI, n (%)	143 (39.4)^	43 (38.4) +	68 (56.2) ^+	0.003	0.001^
					0.007+
Frequency of URTI (n)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.43	
Pneumonia, n (%)	18 (5.0)	5 (4.5)	9 (7.4)	0.51	
Frequency of pneumonia (n/year)	1.0 (1.0-1.0)	1.0 (1.0-1.5)	1.0 (1.0-1.0)	0.89	
UTI, n (%)	113 (31.1)*	16 (14.3)*	28 (23.1)	0.009	<0.001*
Frequency of UTI (n/year)	1.0 (1.0-2.0)^	1.0 (1.0-1.0)	1.0 (1.0-1.0)^	0.009	0.004^
GTI, n (%)	47 (12.9)*	3 (2.7)*+	16 (13.2) +	0.007	0.002*
					0.003+
Frequency of GTI (n/year)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.43	
Invasive mucosal infections, n (%)	20 (5.5)	1 (0.9)	6 (5.0)	0.77	
Frequency of invasive mucosal infections (n/year)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	1.0 (1.0-2.5)	0.77	
Mucosal herpes infection, n (%)	46 (12.7)*	2 (1.8)*+	11 (9.1)+	0.003	0.001*
					+0.01+
Frequency of herpes infection (n/year)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.21	
Other infections, n (%)	15 (4.2)	7 (6.3)	1 (0.8)	0.28	
COVID-19*, n (%)	20 (5.5)	8 (7.1)	2 (1.7)	0.12	
Number of different types of infection (n)	2.0 (1.0-2.0)*	1.0 (1.0-2.0)*+	2.0 (1.0-3.0)+	0.001	0.004*
					<0.001+
Prescript antibiotics in the past year, n (%)	187 (51.5)	47 (42.0)	50 (41.3)	0.09	
1-3 times	152 (41.9)	43 (38.4)	46 (38.0)		
4-6 times	25 (6.9)	3 (2.7)	3 (2.5)		
>6 times	10 (2.8)	1 (0.9)	1 (0.8)		
Application to infection disease outpatient clinic, n (%)	105 (28.9)^	31 (27.7)+	16 (13.2)^+	0.002	0.001^
					0.006+
Number of applications to infection disease outpatient clinic (n)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	1.0 (1.0-2.0)	0.07	
Hospitalization due to infection in the past year, n (%)	19 (5.2)	2 (1.8)	0 (0)	0.12	
Duration of hospitalization due to infection (day)	2.0 (1.0-5.0)	1.0 (1.0-1.0)	N/A	0.19	
Loss of workforce due to infection in the past year, n (%)	45 (12.4)	9 (8.0)	7 (5.8)	0.08	
Loss of workforce due to infection (days)	10.0 (5.0-12.0)^	10.0 (7.5-20.0)+	4.0 (2.0-5.0)^+	0.003	0.002^
					0.001+
Infection risk factors/precautions					
Surgery in the past year, n (%)	16 (4.4)	2 (1.8)	0 (0.0)	0.20	
Hospitalization due to noninfection diseases in the past year, n (%)	16 (4.4)	8 (7.1)	1 (0.8)	0.05	
Removal surgeries of lymphoid tissues at any time, n (%)[3]	60 (16.5)^	9 (8.0)	8 (6.6)^	0.04	0.007^

Table 1. Continued

	FMF n=363	SpA n=112	Control n=121	p	Post-hoc analyses
Pet ownership, n (%)	22 (6.1)	12 (10.7)	5 (4.1)	0.10	
Full vaccinated for pneumococcus, n (%)	8 (2.2)	5 (4.5)	3 (2.5)	0.42	
Vaccinated for influenza in the past year, n (%)	18 (5.0)	2 (1.8)$^{+}$	13 (10.7)$^{+}$	0.009	0.005^{+}
Organ/system specific infections at any time, n (%)[4]	2 (0.9)	2 (1.8)	1 (0.8)	0.45	

ASDAS: ASAS-endorsed disease activity score, COVID-19: Coronavirus disease-19, F: Female, GTI: Gastro-intestinal tract infection, ICU: Intensive care unit, ISSF: The International Severity Scoring System for FMF, M: Male, URI: Urinary tract infection, URTI: Upper respiratory tract infections

[1]Comorbidities: Hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, diabetes mellitus.

[2]Infection frequencies, number of outpatient visits, length of stay and number of days lost in work were calculated in only positive cases.

[3]Organ/system specific infections: Sexually transmitted diseases, osteomyelitis, septic arthritis, endocarditis, infective nephritis, human immunodeficiency virus, zoster infection,

[4]Removal surgeries: Appendectomy, splenectomy, tonsillectomy, thymectomy, nasal polyp excision.

**: The difference between FMF and SpA patients in post-hoc analyses*

+: The difference between SpA patients and controls in post-hoc analyses

^: The difference between FMF patients and controls in post-hoc analyses

COVID-19 patients were also classified according to the type of involvement. P<0.05 was significant. P<0.016 was significant in post-hoc analyses

Moreover, patients with moderate-to-severe FMF exhibited a higher frequency of admissions to the infectious disease outpatient clinic (p=0.03) and experienced greater work loss due to infection (p=0.04) than those with mild FMF.

It is noteworthy that all infection risk factors and precautions were similar between the two groups. Demographic and infectious characteristics of FMF patient classified in terms of disease severity was shown in Table 4.

Discussion

In the study evaluating the validity of our two hypotheses about the relationship between FMF and infection, we found that FMF patients had same infection frequency as healthy controls and disease controls. However, FMF patients had a higher rate of admission to an infectious outpatient clinic and a longer duration of workforce loss in the previous year than the control group. Furthermore, even though the only independent factor related to infection in FMF patients was the number of locations involved during the attack, FMF patients who had infection in the previous year had more severe disease than patients who did not have infection. As a result, our initial hypothesis that FMF, like other rheumatic diseases, raises the risk of infection is not fully supported. However, the severity of FMF was higher in patients infected in the previous year, and these patients can be considered to have more severe infections based on the hospitalization frequency and loss of workforce due to infection.

To our knowledge, this is the first study to assess the infectious characteristics of FMF patients. The most common types of infections in our FMF patients were URTI and UTI. Bacterial etiologies are the most common cause of infection in SLE, followed by viral and fungal infections. The most common types of infection in SLE are respiratory tract, urinary tract, and skin infections.[2] In addition, the most common sites of infection in SpA patients were the respiratory tract, followed by the skin, genitourinary system, upper respiratory tract, sinuses, and gastrointestinal tract.[20] Furthermore, respiratory tract infections are the most common in RA patients, followed by skin and genitourinary system infections.[21]

In our study, the most common sites of infection in FMF patients were similar to other inflammatory diseases, such as the respiratory tract and genitourinary system. Infections in rheumatological conditions may be caused by defects in both the adaptive and innate immune systems.[22] In the innate immune system, neutrophil dysfunction, and deficiencies in their numbers due to pathological immune complex or antibodies can impair the first line of defense against pathogens.[23] Similarly, in many rheumatological diseases, adaptive immune system disorders caused by partial T-cell dysfunction may increase the frequency of infection.[24] As we mentioned before, the relationship between infection and disease severity can be bidirectional. Infection can cause severe attacks and amyloidosis, or severe disease can cause infection. According to our findings, infection could be a contributing factor to more severe FMF while triggering attacks. Several infectious pathogens have previously been linked to the onset of juvenile idiopathic arthritis.[25] As a result, while our study cannot establish a causal relationship, future prospective studies may investigate the role of infections in severe FMF. Although infection rates in all FMF patients, regardless of activity, are comparable to control groups, we believe that the uncontrolled, unprovoked, and increased inflammatory environment and dysfunction of pyrin protein in FMF may limit the resistance to pathogens in the mucosal regions such as respiratory and genitourinary tracts or frequent infections in common mucosal sites can cause severe disease.

Table 2. Disease and infection characteristics of infected and non-infected FMF patients in the past year

	FMF patients with infection n=241	FMF patients without infection n=122	p
Gender (M/F)	77/164	46/76	0.27
Age (years)	34.0 (25.0-43.0)	31.0 (25.0-43.0)	0.63
Age at FMF onset (years)	14.0 (8.0-20.0)	15.0 (8.0-23.2)	0.24
Disease duration (years)	8.0 (3.5-14.0)	8.0 (5.0-12.2)	0.93
Smoking, n (%)	65 (27.0)	29 (23.8)	0.51
Comorbidity, n (%)[1]	34 (14.1)	23 (18.9)	0.24
FMF disease characteristics			
Peritonitis, n (%)	217 (90.0)	112 (91.8)	0.66
Pleuritis, n (%)	112 (46.5)	36 (29.5)	0.002
Fever, n (%)	163 (67.6)	57 (46.7)	<0.001
Arthritis, n (%)	90 (37.3)	29 (23.8)	0.008
Erysipeloid erythema n (%)	38 (15.8)	22 (18.0)	0.60
Exertional leg pain, n (%)	66 (27.4)	22 (18.0)	0.04
Myalgia, n (%)	95 (39.4)	28 (23.0)	0.001
Enthesitis, n (%)	21 (8.7)	4 (3.3)	0.05
Amyloidosis, n (%)	8 (3.3)	1 (0.8)	0.15
Attacks per year	2.0 (1.0-6.0)	2.0 (0.0-6.0)	0.08
Attack duration (day)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	0.09
VAS attack score (0-100)	50.0 (30.0-70.0)	50.0 (30.0-70.0)	0.24
Number of sites involved during attack	3.0 (2.0-3.0)	2.0 (1.0-3.0)	<0.001
Colchicine dosage (mg/day)	1.0 (1.0-1.5)	1.0 (1.0-1.5)	0.19
Elevated acute phase reactants, n (%)[2]	101 (41.9)	33 (27.0)	0.006
MEFV exon 10 homozygotes, n (%)	33 (13.7)	12 (9.8)	0.82
ISSF score (0-10)	2.0 (1.0-3.0)	1.0 (1.0-2.0)	0.004
Infection risk factors/precautions			
Surgery in the past year, n (%)	14 (5.8)	2 (1.6)	0.06
Hospitalization due to non-infection diseases in the past year, n (%)	15 (6.2)	1 (0.8)	0.01
Removal surgeries for lymphoid tissues at any time, n (%)[3]	41 (17.0)	19 (15.6)	0.72
Pet ownership, n (%)	17 (7.1)	5 (4.1)	0.26
Full vaccinated for pneumococcus, n (%)	7 (2.9)	1 (0.8)	0.20
Vaccinated for influenza in the past year, n (%)	16 (6.6)	2 (1.6)	0.03
Organ/system specific infections at any time, n (%)[4]	2 (0.8)	0 (0.0)	N/A

F: Female, FMF: Familial Mediterranean fever, ICU: Intensive care unit, ISSF: The International Severity Scoring System, M: Male, MEFV: Mediterranean fever gene, VAS: Visual analogue score.

[1]Comorbidities: Hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, diabetes mellitus.

[2]Erythrocyte sedimentation rate and/or C-reactive protein during attack free period at least two times 1 month apart (at least ≥ 2 weeks after the last attack)

[3]Organ/system specific infections: Sexually transmitted diseases, osteomyelitis, septic arthritis, endocarditis, infective nephritis, human immunodeficiency virus, zoster infection.

[4]Removal surgeries: Appendectomy, splenectomy, tonsillectomy, thymectomy, nasal polyp excision. COVID-19 patients were also classified according to the type of involvement. p<0.05 was significant

Table 3. Multivariate analyses for risk factors for infections in FMF

	OR	95% CI	p
Male gender	1.41	0.86-2.29	0.16
Age	1.00	0.98-1.02	0.54
Number of sites involved during attack	1.48	1.12-1.75	0.003
ISSF score	1.07	0.88-1.29	0.47
Hospitalization due to non-infection diseases in the past year	0.17	0.02-1.38	0.09
Elevated acute phase reactants[1]	0.68	0.41-1.15	0.68
Colchicine dosage (mg/day)	1.16	0.69-1.95	0.56
Vaccinated for influenza in the past year	0.32	0.70-1.15	0.32

[1]Erythrocyte sedimentation rate and/or C-reactive protein during attack free period at least two times 1 month apart (at least ≥2 weeks after the last attack)

p<0.05 was shown bold, CI: Confidence interval, FMF: Familial Mediterranean fever, OR: Odds ratio, ISFF: The International Severity Scoring System

Table 4. Demographic and infection characteristics of FMF patient classified in terms of disease severity

	Mild disease n=257	Moderate-severe disease n=106	p
Gender (M/F)	87/170	36/70	0.98
Age (years)	33.0 (25.0-44.0)	32.5 (24.7-42.0)	0.23
Age at FMF onset (years)	15.0 (8.2-21.0)	11.0 (7.0-20.0)	0.002
Disease duration (years)	8.0 (4.0-14.0)	8.0 (4.0-13.0)	0.69
Smoking, n (%)	57 (22.2)	37 (34.9)	0.12
Comorbidity, n (%)[1]	42 (16.3)	15 (14.2)	0.60
Amyloidosis, n (%)	6 (2.3)	3 (2.8)	0.76
Colchicine dosage (mg/dL)	1.0 (1.0-1.5)	1.5 (1.0-1.5)	0.005
Infection characteristics[2]			
Infection in the past year, n (%)	163 (63.4)	78 (73.6)	0.06
Total number of infections in the past year (n)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.84
URTI, n (%)	90 (35.0)	53 (50.0)	0.008
Frequency of URTI (n)	1.0 (1.0-1.0)	1.0 (1.0-1.5)	0.79
Pneumonia, n (%)	13 (5.1)	5 (4.7)	0.89
Frequency of pneumonia (n/year)	1.0 (1.0-1.5)	1.0 (1.0-1.0)	0.50
UTI, n (%)	79 (30.7)	34 (32.1)	0.80
Frequency of UTI (n/year)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.86
GTI, n (%)	31 (12.1)	16 (15.1)	0.43
Frequency of GTI (n/year)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	0.26
Invasive mucosal infections, n (%)	17 (6.6)	3 (2.8)	0.15
Frequency of mucosal infections (n/year)	1.0 (1.0-2.5)	1.0 (1.0-2.0)	0.30
Mucosal herpes infection, n (%)	35 (13.6)	11 (10.4)	0.39
Frequency of herpes infection (n/year)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.61
Other infections, n (%)	12 (4.7)	3 (2.7)	0.15
COVID-19*, n (%)	10 (3.9)	10 (9.4)	0.03
Number of different types of infection (n)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.31
Prescript antibiotics, n (%)	128 (49.8)	59 (55.7)	0.79
Application to infection disease outpatient clinic, n (%)	66 (25.7)	39 (36.8)	0.03
Number of applications to infection disease outpatient clinic (n)	1.0 (1.0-2.0)	1.0 (1.0-3.0)	0.75
Hospitalization due to infection in the past year, n (%)	12 (4.7)	7 (6.6)	0.45
Duration of hospitalization due to infection (day)	3.0 (1.0-5.0)	1.0 (1.0-3.0)	0.29
Loss of workforce due to infection in the past year, n (%)	26 (10.1)	19 (17.9)	0.04
Loss of workforce due to infection (days)	10.0 (4.75-10.0)	10.0 (7.0-14.0)	0.38
Infection risk factors/precautions			
Surgery in the past year, n (%)	14 (5.4)	2 (1.9)	0.13
Hospitalization due to non-infection diseases in the past year, n (%)	9 (3.5)	7 (6.6)	0.19
Removal surgeries of lymphoid tissues at any time, n (%)[3]	39 (15.2)	21 (19.8)	0.28
Pet ownership, n (%)	16 (6.2)	6 (5.7)	0.83
Full vaccinated for *pneumococcus*, n (%)	4 (1.6)	4 (3.8)	0.19
Vaccinated for influenza in the past year, n (%)	11 (4.3)	7 (6.6)	0.35
Organ/system specific infections at any time, n (%)[4]	0 (0.0)	2 (1.9)	N/A

COVID-19: Coronavirus disease-19, M: Male, F: Female, FMF: Familial Mediterranean fever, GTI: Gastro-intestinal tract infection, ICU: Intensive care unit, ISSF: The International Severity Scoring System, MEFV: Mediterranean fever gene, URI: Urinary tract infection, URTI: Upper respiratory tract infections, VAS: Visual analogue score

[1]Comorbidities: Hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, diabetes mellitus.

[2]Infection frequencies, number of outpatient visits, length of stay and number of days lost in work were calculated in only positive cases.

[3]Organ/system specific infections: Sexually transmitted diseases, osteomyelitis, septic arthritis, endocarditis, infective nephritis, human immunodeficiency virus, zoster infection.

[4]Removal surgeries: Appendectomy, splenectomy, tonsillectomy, thymectomy, nasal polyp excision. COVID-19 patients were also classified according to the type of involvement.

p<0.05 was significant

There are several factors that may be associated with an increased risk of infection in rheumatic diseases.[21] In our study, the main risk factors for infection in FMF patients were disease severity, the number of sites involved during attacks, and elevated acute phase reactants between attacks. Therefore, we think that the severity of FMF and the parameters in the severity scale may be related to the increased risk of infection. Disease activity in RA and SLE is also associated with an increased risk of infection. All immunological dysfunctions associated with these diseases may increase during worse disease activity.[26,27] Likewise, the severity of FMF, which is characterized by high acute phase reactants during attack-free period, combined with widespread attacks may exacerbate the disorders in the immune system. Amyloidosis is more common in more severe FMF disease, particularly when acute phase reactants are high between attacks. Also, infection diseases may exacerbate accumulation of amyloid proteins in FMF patients with stable amyloidosis.[14] Thus, infections in these cases may play a dual role in the development and progression of amyloidosis.

In addition, patients with more severe FMF received a higher median colchicine dose. However, there is no definitive proof in the literature linking colchicine and infections.[28]

Some variables associated with severe infection, such as longer duration of loss of workforce due to infection and admission to the infectious outpatient clinic in the previous year, were found to be more common in FMF patients than in controls, but not in SpA patients. Furthermore, loss of workforce due to infection and admission to the infectious outpatient clinic in the previous year are more common in severe FMF cases than in mild cases. However, hospitalization due to infection, which is one of the serious infection indices,[29] did not change with the presence of FMF and the severity of the disease. However, based on the findings, we can speculate that infection and FMF severity may be linked, as in other rheumatological diseases.

We found that the infection frequency in the last year was similar in FMF patients to controls and SpA. We think that there are two reasons for this similarity. Although it may be controversial[30] receiving anti-tumor necrosis factor therapy is the main risk factor for infection in SpA. To rule out treatment effects, none of the SpA patients in our study had previously received immunosuppressive therapy. Therefore, infection rates in SpA were not higher than controls. Furthermore, SpA and FMF patients may have taken more COVID-19 prevention measures than controls.

Another noteworthy aspect is that episodes of FMF can present symptoms like infectious disease, potentially resulting in misdiagnosis and inappropriate treatment strategies. This underscores the importance of accurate differentiation between FMF and infectious conditions to ensure proper diagnoses and effective therapeutic approaches.

Study Limitations

There are some limitations to the study. To begin with, the information is based on the patent's response to a pre-approved questionnaire. The authors of the questionnaire urged researchers to use it with caution in the original paper. However, it has been demonstrated that it is quite reliable in detecting infection rates. Furthermore, they emphasized that the section on infectious risks should be improved. Finally, it is preferable to conduct a prospective study in which patients and medical databases are checked for infection on a weekly basis to avoid recall errors. Second, we did not confirm incidents of infection during the visits. and we only cross-sectionally looked at last year's infection data. Finally, the diseased control group of the study was SpA patients who were not on immunosuppressive drugs. This group has similar infection rate with general population. We did not include other rheumatological diseases, such as RA, because they cannot be studied without the use of immunosuppressive drugs. However, among rheumatological diseases, the SpA group has a lower infection rate, as expected. Despite the fact that, infectious diseases were clinically heterogeneous, we divided the patients based on having an infectious disease in the previous year and then compared the disease related features in infected and non-infected patients for the first time in the literature to show risk factors for any kind of infection in FMF patients. Finally, it's important to note that the questionnaire utilized in this study lacks validation in Turkish.

Conclusion

In summary, having FMF might not necessarily lead to a higher overall frequency of infections compared to individuals without the condition. However, individuals with severe FMF, as indicated by higher disease severity scores, may encounter more episodes of infectious attacks. Additionally, there appears to be a correlation where individuals who had an infection in the last year may also have increased disease severity.

Ethics

Ethics Committee Approval: This study was approved by the Local Research Ethics Committee and carried out in compliance with the Helsinki Declaration (date:

09.03.2022, approval number: 2022/514/221/4 - University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee).

Informed Consent: All the patients gave written informed consent.

Authorship Contributions

Concept: N.Ş., M.E.T., Design: M.E.T., Data Collection or Processing: R.M., Ö.V., E.B., S.Y.Ö., Analysis or Interpretation: N.Ş., M.E.T., Literature Search: R.M., S.Y.Ö., Writing: N.Ş., M.E.T.

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Safety profile of tofacitinib in rheumatoid arthritis: a single-center experience

Romatoid artrit hastalarında tofasitinibin güvenlik profili: tek merkez deneyimi

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Abstract

Objective: To assess the adverse events (AEs) of tofacitinib in rheumatoid arthritis (RA) patients and to present real-life experiences.

Methods: Data on the demographic characteristics, comorbidities, and the AEs of 71 RA patients using tofacitinib was collected. Coronary artery disease, cerebrovascular disease, pulmonary embolism, malignancy, and mortality were defined as serious AEs. The risk factors for serious AEs were defined.

Results: Infections were the most common drug-related AEs, most of which were upper respiratory and urinary tract infections. Malignancy was detected in 3 patients in follow-up. No significant difference was found in the rates of overall AEs except urinary tract infections, between patients <65 years and those ≥65 years of age. However, serious AEs were observed more frequently in patients aged ≥65 years (p=0.019). Older age, male gender, pre-existing hyperlipidemia, and the initial year of tofacitinib treatment were significantly associated with developing serious AEs. Four patients (median age= 65.9 years) died.

Conclusion: Real-life data on the safety profile of tofacitinib in RA was presented in this study. Male gender was an independent risk factor for serious AEs in subjects receiving tofacitinib. Patients with older age, male gender, those with hyperlipidemia, and those in their first year of treatment should also be closely monitored for serious AEs.

Keywords: Tofacitinib, adverse events, rheumatoid arthritis, older age

Öz

Amaç: Romatoid artrit (RA) hastalarında tofasitinibin yan etkilerini (YE) değerlendirmeyi ve gerçek yaşam verilerini sunmayı amaçladık.

Yöntem: Tofacitinib kullanan 71 RA hastasının demografik özellikleri, komorbiditeleri ve YE'leri değerlendirildi. Koroner arter hastalığı, serebrovasküler hastalık, pulmoner emboli, malignite ve mortalite ciddi YE olarak gruplandırıldı. Ciddi YE'ler için risk faktörleri tanımlandı.

Bulgular: Enfeksiyonlar ilaca bağlı en yaygın YE'ler olup, bunların çoğu üst solunum yolu ve idrar yolu enfeksiyonlarıydı. Takipte 3 hastada malignite tespit edildi. <65 yaş ve ≥65 yaş hastalar arasında idrar yolu enfeksiyonları dışındaki genel YE oranlarında anlamlı bir fark bulunmadı. Ancak 65 yaş ve üzeri hastalarda ciddi YE'ler daha sık görüldü (p=0,019). İleri yaş, erkek cinsiyet, hiperlipidemi varlığı ve tofasitinib tedavisinin ilk yılı ciddi YE'lerin gelişmesiyle anlamlı düzeyde ilişkiliydi. Ortanca yaşları 65,9 olan 4 hasta hayatını kaybetti.

Sonuç: Bu çalışmada tofasitinibin RA'daki güvenlik profiline ilişkin gerçek yaşam verileri sunulmuştur. Erkek cinsiyet, tofacitinib kullanan hastalarda ciddi YE'ler için bağımsız bir risk faktörüydü. İleri yaş, erkek cinsiyet, hiperlipidemisi olan ve tedavinin ilk yılında olan hastalar ciddi YE'ler açısından yakın izlenmelidir.

Anahtar Kelimeler: Tofasitinib, yan etkiler, romatoid artrit, ileri yaş

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease presenting with inflammatory arthritis and joint damage that can cause joint destruction, deformity, and progressive disability. The estimated prevalence is about 0.24-1%.[1,2] It is also associated with a wide variety of extra-articular features and comorbidities which can lead to lower quality of life, increased morbidity, and mortality.[3] Early diagnosis and early initiation of treatment are aimed to prevent irreversible damage to the joints. There are various therapeutic agents used in the management including glucocorticoids, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biologic (b) DMARDs [tumor necrosis factor (TNF) inhibitors and non-TNF biologics], and targeted synthetic(ts) DMARDs [Janus kinase (JAK) inhibitors]. The 2015 American College of Rheumatology (ACR) RA

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treatment guidelines recommended the primary use of TNF inhibitor treatments instead of tofacitinib in early RA patients with moderate to high disease activity despite DMARDs.[4] On the other hand, the European Alliance of Associations for Rheumatology (EULAR) 2019 guidelines and 2021 ACR guideline recommend either bDMARDs or tsDMARDs in combination with methotrexate (MTX) in patients who do not respond to the first csDMARD strategy and have poor prognostic factors.[5,6] Subsequently, the 2022 update of EULAR recommendations for RA patients reported the priority use of bDMARDs in patients with poor prognostic factors and failure to the first csDMARDs. It was stated that JAK inhibitors may be used, taking into account the relevant risk factors.[7]

The EULAR also established recommendations for the management of patients with difficult-to-treat RA in 2021.[8] In patients unresponsive to at least two b/tsDMARDs, especially two TNF inhibitor treatments, the use of b/tsDMARDs with a different target was suggested.[8]

The Janus kinase-signal transducer and activator of transcription signaling pathway has a crucial role in RA pathogenesis. JAK inhibitors inhibit the activity of the JAK family that lead to suppression of the effect of cytokines. Tofacitinib is one of the JAK inhibitors approved in many countries worldwide in the treatment of RA.[9,10]

Tofacitinib is generally well tolerated, although adverse events (AEs) have been reported in some patients. Infections are the most commonly reported AEs. In addition, malignancy, cardiovascular events, thrombosis, laboratory abnormalities (neutropenia, lymphopenia, elevated liver enzymes, increase in serum creatinine concentration, or changes in lipid levels), and gastrointestinal perforations are some of the other reported AEs.[11-13] The malignancies and major adverse cardiovascular events (MACE) risk of tofacitinib were evaluated and compared to TNF inhibitors in a study including patients ≥50 years of age with at least one additional cardiovascular risk factor (ORAL Surveillance study).[14] The risk of MACE and cancers were found to be higher in the tofacitinib group. We aimed to review the AEs in RA patients using tofacitinib and present our single-center real-life experience in this study.

Materials and Methods

Seventy-one RA patients who were on tofacitinib between January 2014 and April 2022 were included in the study. The 2010 ACR/EULAR classification criteria was used to diagnose RA.[15] Gender, age at diagnosis, follow-up time, tofacitinib treatment duration, smoking status, co-morbidities, body mass index, and the laboratory examinations [hemoglobin, leukocyte, platelet, alanine aminotransferase (ALT), creatinine, and aspartate aminotransferase (AST)] at the beginning of the tofacitinib treatment, at the 3rd month, and at the last visit were evaluated retrospectively. The treatment regimen was tofacitinib 5 mg twice a day.

The presence of AEs was reviewed from the medical records of patients. Detailed analysis and severity of AEs were assessed according to symptoms, physical examination findings, and laboratory findings. Serious AEs were described as any AEs that were life-threatening, causing death, need for hospitalization, or causing disability. Coronary artery disease, cerebrovascular disease, pulmonary embolism, malignancy, and mortality were defined as serious AEs. The associated infectious AEs were detailed and suspected AEs such as pretibial edema, tinnitus, and ecchymosis were also noted. The frequency of AEs in patients <65 and ≥65 years of age were also compared. We used age 65 years as a threshold value to compare variables and evaluate risk factors for severe AEs in patients receiving tofacitinib. Age over 65 years was identified as a risk factor for the use of tofacitinib by the European Medicines Agency (EMA) and also stated as a risk factor in the 2022 update of the EULAR recommendations for patients with RA.[7,16]

Statistical Analysis

Descriptive statistics were presented as frequency, median (minimum-maximum), mean and standard deviation. Visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk's test) were used to decide whether a variable had a normal distribution. The chi-square test or Fisher's exact test (if the data did not meet the assumptions of the chi-square test) were used to examine the differences between categorical variables. Friedman test, Wilcoxon test, ANOVA, and paired samples t-test were also used for statistical analyses. Univariate and multivariate logistic regression analyses were used to report risk factors for severe AEs in patients receiving tofacitinib and to define the independent risk factors. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A p-value of less than 0.05 was used as the cutoff for statistical significance. The SPSS (version 20.0) was used in the statistical analyses.

The study was approved by the Aydın Adnan Menderes University Ethics Commission (approval number: 2022/110, date: 10.06.2022) and was conducted according to the guidelines of the Declaration of Helsinki.

Results

There were 71 RA patients (62 female, 9 male) receiving tofacitinib. The median age was 60.0 (29.6-77.4) years while the median age at diagnosis was 47.5 (19.4-72.0) years. The

median duration of tofacitinib treatment was 23 (1-66) months. At the enrollment of the study, tofacitinib treatment was discontinued in 45.1 percent of patients (n=32). Of those, the reasons for medication discontinuation were lack of (or poor) response to drugs (n=8), AEs (n=17), and patient's decision (n=7). The demographics and clinical features were summarized in Table 1.

Infections were the most common drug-related AEs (n=45), most of which were upper respiratory and urinary tract infections. The treatment agents used in the combination treatment were leflunomide (n=22), hydroxychloroquine (n=18), MTX (n=17), sulfasalazine (n=3), and methylprednisolone (n=38, with a median dose of 4 mg). In addition, twenty patients (29%) had a history of coronavirus disease-2019 (COVID-19) infection during tofacitinib. Intensive care unit admission was required for COVID-19 pneumonia in two of them. Malignancy was detected in three patients; one had squamous cell carcinoma of the skin, one had prostate cancer, and the other had lung cancer. They were diagnosed with cancer at 56 months, 8 months, and 21 months, respectively, after starting tofacitinib. Four patients with a median age of 65.9 years, two of whom were male, died. Two of them died from COVID-19 pneumonia, one from lung cancer, and one from acute myocardial infarction. The median time from initiation of tofacitinib to death was 7.5 (3-23) months. Apart from these patients, sudden cardiac death occurred five months after stopping tofacitinib in one patient. Reported AEs during tofacitinib were listed in Table 2.

Serious AEs occurred in 10 patients (14.0%). There was no statistically significant difference in comparison of the observed AEs rates in patients <65 and ≥65 years of age, except for urinary tract infections, which were significantly more common in those <65 years of age. In addition, serious AEs were more frequently encountered in patients 65 years or older (31.6% vs. 7.7%, p=0.019).

The median leukocyte number at treatment initiation was 9.120 (4.880-21.900) which was significantly higher than that at the 3rd month and at the last visit (p=0.01, p=0.001; respectively). Platelet levels showed an increasing tendency at the last visit, from 313.3 (±77.8) 10^3/μL at the initiation of treatment to 333.1 (±93.3) 10^3/μL at the last

Table 1. The demographics and clinical characteristics of the patients with rheumatoid arthritis

	Rheumatoid arthritis (n=71)
Sex, n (%)	
Female	62 (87.3)
Male	9 (22.7)
Age, years, median (min-max)	60.0 (29.6-77.4)
Age at diagnosis, years, median (min-max)	47.5 (19.4-72.0)
Time interval between diagnosis and onset of tofacitinib, years, median (min-max)	6.2 (0.1-39.4)
Median follow-up time, years, median (min-max)	8.7 (0.8-41.6)
Status of tofacitinib treatment, n (%)	
Ongoing	39 (54.9)
Discontinued	32 (45.1)
Duration of tofacitinib treatment, month, median (min-max)	23.0 (1-66)
Body mass index, median (min-max)	28.9 (16.5-47.7)
Overweight, n (%)	25/66 (37.8)
Obesity, n (%)	25/66 (37.8)
Smoking status, n (%)	
Smoker	9/68 (13.2)
Ex-smoker	9/68 (13.2)
Non-smoker	50/68 (73.5)
Pre-existing co-morbidities, n (%)	
Hypertension	24 (33.8)
Diabetes mellitus	15 (21.1)
Hyperlipidemia	11 (15.5)
Coronary artery disease	6 (8.5)
Cerebrovascular disease	2 (2.8)
Pulmonary embolism	2 (2.8)
Deep vein thrombosis	1 (1.4)

Min-max: Minimum-maximum

visit (p=0.013). However, leukopenia or thrombocytopenia was not observed in any patient. There was no statistically significant difference in the levels of hemoglobin, creatinine, ALT, and AST between the beginning of the tofacitinib, at the 3rd month, and at the last visit (Table 3).

Older age (aged ≥65 years), male gender, pre-existing hyperlipidemia, and the initial year of tofacitinib treatment were associated with developing serious AEs (OR: 5.538; 95% CI: 1.358-22.589; p=0.017, OR: 7.467; 95% CI: 1.567-35.577; p=0.012, OR: 1.159; 95% CI: 1.159-22.823;

Table 2. Reported adverse events in patients with rheumatoid arthritis treated with tofacitinib

	Total number of patients, n (%)	Age <65 years, n (%)	Age ≥65 years, n (%)	p value
Hypertension	6 (8.5)	3 (5.8)	3 (15.8)	0.332*
Coronary artery disease	3 (4.2)	1 (1.9)	2 (10.5)	0.173*
Cerebrovascular disease	2 (2.8)	0 (0)	2 (10.5)	0.069*
Pulmonary embolism	1 (1.4)	1 (1.9)	0 (0)	1.000*
Malignity	3 (4.2)	2 (3.8)	1 (5.3)	1.000*
Infection				
COVID-19 infection	20 (29.0)	15 (28.8)	5 (26.3)	0.834
Upper respiratory tract infections	20 (29.0)	15 (28.8)	5 (26.3)	0.834
Urinary tract infections	17 (24.0)	16 (30.8)	1 (5.3)	0.029*
Pneumonia	4 (5.6)	3 (5.8)	1 (5.3)	1.000*
Bronchitis	3 (4.2)	3 (5.8)	0 (0)	0.559*
Herpes zoster infection	2 (2.8)	2 (3.8)	0 (0)	1.000*
Other infections				
Cellulitis	1 (1.4)	0 (0)	1 (5.3)	0.268*
Periodontal abscess	1 (1.4)	1 (1.9)	0 (0)	1.000*
Tinea incognito	1 (1.4)	1 (1.9)	0 (0)	1.000*
Tinea pedis	1 (1.4)	1 (1.9)	0 (0)	1.000*
Gastrointestinal symptoms				
Nausea	3 (4.2)	3 (5.8)	0 (0)	0.559*
Abdominal pain	2 (2.8)	1 (1.9)	1 (5.3)	0.466*
Diarrhea	2 (2.8)	1 (1.9)	1 (1.9)	0.466*
Constipation	1 (1.4)	1 (1.9)	0 (0)	1.000*
Elevated liver function tests	1 (1.4)	1 (1.9)	0 (0)	1.000*
Others				
Skin discoloration	1 (1.4)	0 (0)	1 (5.3)	0.268*
Pretibial edema	1 (1.4)	1 (1.9)	0 (0)	1.000*
Tinnitus	1 (1.4)	0 (0)	1 (5.3)	0.268*
Itching	1 (1.4)	1 (1.9)	0 (0)	1.000*
Bruising, ecchymosis	1 (1.4)	0 (0)	1 (5.3)	0.268*
Erythematous lesion on the leg	1 (1.4)	1 (1.9)	0 (0)	1.000*
Dizziness	1 (1.4)	1 (1.9)	0 (0)	1.000*
Death	4 (5.6)	2 (5.4)	2 (10.5)	0.289*

**: Fisher's exact test, COVID-19: Coronavirus disease-2019*

Table 3. Laboratory characteristics of the patients at the beginning of the tofacitinib, at the 3rd month and at the last visit

	Beginning of tofacitinib	3rd month	Last visit	p value
Hemoglobin (g/dL)	12.1 (9.4-14.7)	12.2 (9.4-15.2)	12.1 (8.8-14.7)	0.263
Leukocyte (10^3/μL)	9.050 (4.880-21.900)[a, b]	7.990 (1.049-21.140)[a]	8.225 (4.530-19.530)[b]	0.002
Platelet (10^3/μL)	313.3±77.8[c]	310.0±74.1[d]	333.1±93.3[c, d]	0.008
Creatinine (mg/dL)	0.7 (0.5-2.7)	0.7 (0.5-2.7)	0.7 (0.5-2.8)	0.119
Alanine aminotransferase (U/L)	17.0 (7.0-45.0)	16.0 (1.0-40.0)	18.0 (7.0-92.0)	0.133
Aspartate aminotransferase (U/L)	16.0 (9.0-81.0)	18.0 (9.0-33.0)	17.0 (9.0-66.0)	0.202

Median (min-max) or mean (± SD); [a, b, c, d]: Significant differences between parameters in the same letters, SD: Standard deviation

p=0.031, and OR: 4.219; 95% CI: 1.053-16.901; p=0.042; respectively). On the other hand, age, obesity, smoking, pre-existing hypertension, pre-existing diabetes mellitus, and pre-existing coronary artery disease were not risk factors. The male gender was also detected as an independent risk factor for serious AEs in patients receiving tofacitinib in multivariate analysis (OR: 6.868; 95% CI: 1.140-41.356; p=0.035) (Table 4).

Discussion

We retrospectively evaluated the safety profile of tofacitinib in RA patients in a tertiary rheumatology center in Turkey and defined the risk factors for serious AEs as male gender, older age, pre-existing hyperlipidemia, and the initial year of the tofacitinib treatment. Tofacitinib safety assessment in RA was investigated in phase II-IV and long-term extension studies previously.[17-22] In line with our findings, the rate of serious AEs was stated to be higher in elderly patients than in younger patients.[23] In the long-term safety analysis, male gender and older age were also reported as risk factors for serious infection events.[24] The presence of traditional risk factors at baseline (eg. older age, higher body mass index, and elevated blood pressure) and higher baseline triglyceride levels were identified as risk factors for MACE. With these caveats kept in mind, the relationship between RA and increased cardiovascular morbidity and mortality should be taken into account.[25] The presence of traditional risk factors also increases the risk of cardiovascular disease in RA patients.[26]

The integrated analysis of trials and long-term safety profile of tofacitinib up to 8.5 years was reported in 2017.[27] Afterward, the long-term analysis results up to 9.5 years was published in 2020.[24] Analysis of 7061 patients' data revealed serious infections in 576 patients, herpes zoster infections in 782 patients, malignancies [excluding non-melanoma skin cancer (NMSC)] in 177 patients, NMSC in 129 patients, MACE in 85 patients, arterial thromboembolism in 84 patients, venous thromboembolism in 59 patients, and deep venous thrombosis in 36 patients.[24] Tofacitinib safety assessment was found to be similar to bDMARDs except for herpes zoster infection. We also reported most of the aforementioned AEs in our cohort and infection was the most common among them. The rate of serious AEs of tofacitinib was reported as 26.3% in a follow-up period of up to 9.5 years.[24] We found it as 14% at a median follow-up of 8.7 years.

EMA recommended using tofacitinib with caution due to possible AEs. One of the recommendations was to use tofacitinib in patients over 65 years of age only if there is no alternative treatment available.[16] However, the comparison of the two treatments (tofacitinib versus biologic DMARDs) for the incidence of infections and serious infections in RA patients aged 65 years or older and less than 65 years revealed a similar risk of serious infection events in patients receiving tofacitinib 5 mg twice daily (BID) and adalimumab. Also, the increased risk with tofacitinib 10 mg BID in older patients was reported.[28] We did not find any difference in the rate of infections or AEs in older patients (aged ≥65) compared with younger patients (<65 years) except for the increased frequency of serious AEs in patients receiving tofacitinib 5 mg BID.

Table 4. Risk factors for serious adverse events in patients receiving tofacitinib

	B	S.E.	Wald	p	OR	95% CI
Risk factors for serious adverse events (univariate logistic regression analysis)						
Age ≥65 years	1.712	0.717	5.696	0.017	5.538	1.358-22.589
Male gender	2.010	0.797	6.370	0.012	7.467	1.567-35.577
Presence of obesity	0.218	0.906	0.058	0.810	1.243	0.211-7.338
Smoking	-1.190	0.770	2.386	0.122	0.304	0.067-1.377
Pre-existing hypertension	0.203	0.741	0.075	0.784	1.225	0.287-5.233
Pre-existing diabetes mellitus	0.080	0.850	0.009	0.925	1.083	0.205-5.733
Pre-existing coronary artery disease	-0.219	1.153	0.036	0.850	0.804	0.084-7.697
Pre-existing hyperlipidemia	1.638	0.760	4.639	0.031	1.159	1.159-22.823
First year of tofacitinib treatment	1.440	0.708	4.133	0.042	4.219	1.053-16.901
Risk factors for serious adverse events (multivariate logistic regression analysis)						
Age ≥65 years	1.264	0.808	2.445	0.118	3.539	0.726-17.254
Male gender	1.927	0.916	4.424	0.035	6.868	1.140-41.356
Pre-existing hyperlipidemia	1.165	0.860	1.833	0.176	3.204	0.594-17.295
First year of tofacitinib treatment	1.374	0.837	2.694	0.101	3.953	0.766-20.400

CI: Confidence interval, OR: Odds ratio, S.E.: Standard error

Pulmonary embolism was observed in one patient (1.4%) in our study group. In 2019, increased rates of pulmonary embolism and all-cause mortality were reported in patients receiving a 10 mg BID of tofacitinib compared to the tofacitinib 5 mg BID or TNF inhibitor regimens.[16] However, a meta-analysis of randomized controlled trials revealed a decreased rate of venous thromboembolism (VTE) in patients receiving both the 5 mg or 10 mg tofacitinib compared to the placebo group. In the subgroup analysis, the increased risk of VTE was reported in patients receiving 10 mg tofacitinib BID than those receiving 5 mg BID.[29]

Three (4.2%) of our patients were diagnosed with malignancy while on tofacitinib treatment. Association between tofacitinib and cancer is unclear. The result of a meta-analysis revealed no increased risk of cancer for tofacitinib compared with csDMARDs or TNF inhibitors.[30] Likewise, in the analysis of 5.671 patients with moderate-to-severe RA receiving tofacitinib, the incidence ratios of malignancies (excluding NMSC) were reported to be within the expected range.[31] On the other hand, the risk of cancer was reported to be higher in RA patients ≥50 years of age with at least one additional cardiovascular risk factor.[14] Tofacitinib should be used with caution in elderly RA patients.

Study Limitations

The main limitation is the retrospective design of the study. Another is that most of the patients were female. It might have affected our results. Besides, we did not assess disease activity and did not correlate it with the presence of AEs. However, we believe that our real-life data will contribute to the literature on the safety profile of tofacitinib. Knowledge and awareness of physicians are essential to monitoring carefully of patients and detecting AEs.

Conclusion

Adverse effects such as infections, cardiovascular disease, malignancy, and death may occur in patients using tofacitinib, similar to observations in patients receiving other biological agent treatments. Especially patients with older age, male gender, those with hyperlipidemia, and those in their first year of treatment should be closely monitored for serious AEs. Further multicenter studies with larger numbers of patients and real-life experience might provide additional insight into the safety profile of tofacitinib.

Ethics

Ethics Committee Approval: The study was approved by the Aydın Adnan Menderes University Ethics Commission (approval number: 2022/110, date: 10.06.2022) and was conducted according to the guidelines of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: T.A., C.D., G.S., S.Ç., T.Ş., Design: T.A., C.D., G.S., S.Ç., T.Ş., Data Collection or Processing: T.A., C.D., G.S., S.Ç., T.Ş., Analysis or Interpretation: T.A., G.S., S.Ç., T.Ş., Literature Search: T.A., C.D., G.S., S.Ç., T.Ş., Writing: T.A., C.D., G.S., S.Ç., T.Ş.

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

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The frequency of autoimmune disease in the first degree and other relatives of the breast cancer patients

Meme kanserli hastaların birinci derece ve diğer yakınlarındaki otoimmün hastalık sıklığı

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Abstract

Objective: Autoimmune diseases (ADs) are observed more frequently in patients with breast cancer (BC) compared to healthy population. However, the frequency of ADs in their relatives has not been studied. In the present study, we aimed to compare the frequency of ADs among the first-degree and other relatives of patients with BC with healthy controls.

Methods: We included 100 women aged 18 years and older who were followed up with the diagnosis of BC in our oncology clinic, and randomly selected female employees aged 18 and over in our hospital as the control group. The frequencies of ADs among relatives of the two groups were investigated using a detailed questionnaire.

Results: Frequency of having at least one relative with AD was 76% in the BC group and 36% in the control group (p<0.001). The frequency of ADs in the relatives of the BC group was 5.5 times higher than in the relatives of the control group. In detailed analyzes, when the degree of kinship was considered, it was found that the risk increased to 11.5 times in the first-degree relatives of BC patients; however, no increased risk was found among more distant relatives.

Conclusion: In our study, we found more ADs among the first-degree relatives of patients with BC compared to the control group. This result suggests that common genetic factors may be playing roles in the pathogenesis of BC and ADs.

Keywords: Breast cancer, autoimmune diseases, genetic predisposition

Öz

Amaç: Otoimmün hastalıklar (OİH), meme kanseri (MK) hastalarında sağlıklı popülasyona göre daha sık görülmektedir. Ancak hasta yakınlarında OİH sıklığı çalışılmamıştır. Bu çalışmada, MK'li hastaların birinci derece ve diğer akrabalarında OİH sıklığını sağlıklı kontrollerle karşılaştırmayı amaçladık.

Yöntem: Onkoloji kliniğimizde MK tanısı ile izlenen 18 yaş ve üstü ardışık 100 kadını ve kontrol grubu olarak hastanemizin rastgele seçilmiş 18 yaş ve üzeri kadın çalışanlarını dahil ettik. İki grubun akrabaları arasındaki OİH sıklıkları ayrıntılı bir anket kullanılarak araştırıldı.

Bulgular: Çalışma gruplarının akrabaları arasında en az bir OİH varlığı, MK grubunun akrabalarında %76 iken, kontrol grubunun akrabalarında %36 idi (p<0,001). MK grubu akrabalarındaki OİH sıklığı, kontrol grubu akrabalarına kıyasla 5,5 kat daha fazlaydı. Akrabalık derecesi dikkate alınarak yapılan detaylı analizlerde, MK hastalarının birinci derece akrabalarında riskin 11,5 kat arttığını; ancak, daha uzak akrabalar arasında risk artışı olmadığı tespit edildi.

Sonuç: Çalışmamızda, MK hastalarının birinci akrabaları arasında, kontrol grubuna kıyasla daha fazla OİH saptadık. Bu sonuç, MK ile OİH'nin patogenezinde ortak genetik faktörlerin rol oynayabileceğini düşündürmektedir.

Anahtar Kelimeler: Meme kanseri, otoimmün hastalıklar, genetik yatkınlık

*This study was prepared based on the internal medicine specialty thesis titled "Frequency of autoimmune disease in first-degree and other relatives of breast cancer patients", which we completed in September 2017 under the supervision of Prof. Dr. Berna Göker (Internal medicine specialty thesis, Gazi University Faculty of Medicine, Ankara, Turkey, 2017).

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Introduction

Autoimmune diseases (ADs) are a frequent cause of morbidity, affecting about 7-10% of individuals living in Western countries.[1] Malignant disorders may contribute to the risk of ADs by leading to a predisposition to the development of autoantibodies.[2] The previous studies demonstrated a positive epidemiological correlation between breast cancer (BC) and ulcerative colitis, psoriasis, Graves' disease, and multiple sclerosis. [3-6]

ADs are observed more frequently among patients with cancer than in the healthy population.[7] Environmental factors, occupational status, drug exposures and genetic predisposition could be involved in the pathogenesis of both cancers and AD. However, the frequency of ADs among the first-degree relatives of cancer patients has not been studied. If found to increase, this might suggest the possibility of common genetic predisposition of these two conditions. Thus, we aimed to compare the frequency of ADs in first-degree and other relatives of BC patients with that of healthy controls.

Materials and Methods

We included 100 consecutive female patients; aged 18 years and over; who were followed up with the diagnosis of BC in the oncology clinic in our hospital in March 2017. The control group comprises 100 randomly selected women aged 18 years and over from our hospital's staff. After the patient and control groups were informed about the study and their consent was obtained, data were collected with a questionnaire, through face-to-face interviews.

First, we collected data, including past medical history, age at diagnosis, smoking status, and presence of ADs in first-degree and other relatives of patients in the BC group and individuals in the control group. We specifically questioned the presence of type 1 diabetes mellitus (DM), Hashimoto's thyroiditis, Graves' disease, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), autoimmune hepatitis, myasthenia gravis (MG), primary biliary cirrhosis (PBS), autoimmune hemolytic anemia, connective tissue disorders, Sjögren's syndrome, and scleroderma. Data on other parameters, such as pathological diagnosis, hormone receptor test results, and body mass index (BMI), were obtained from medical records.

Statistical Analysis

While categorical variables are shown as frequencies and percentages, we reported continuous variables as means and standard deviations. Regarding statistical analysis, we compared the continuous variables between the groups using an Independent Samples t-test. For categorical variables, on the other hand, we utilized a chi-square test when the number of observations less than 5 was less than 25% and Exact and Likelihood Ratio tests when it was more than 25%. Then, we compared the ratios for the values with a significant association. Finally, we calculated odds ratios (ORs) with confidence intervals (CIs) using logistic regression analysis to determine how many times more type 1 DM, Hashimoto's thyroiditis, Graves' disease, and RA were encountered in first-degree and other relatives in the patient group compared to the control group. The One-Way ANOVA method was used to simultaneously compare the means of three or more independent conditions. SPSS 21 was used for statistical analyses (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

Ethical Considerations

The Research Ethics Committee of Gazi University granted ethical approval to our study (no: 2017-114 dated: 03.07.2017).

Results

The median [interquartile range (IQR)] ages of the BC and control groups were 54 (32-76) years and 36 (20-55) years, respectively ($p<0.00001$). The med (IQR) BMIs of the study groups were 27.9 (17.9-46.5) in the patient group and 24.3 (16.4-34.6) in the control group ($p<0.001$). There was no significant difference between the groups by smoking status ($p=1.00$). The pathological diagnosis, stage of disease at the time of diagnosis, and hormone receptor test results in patients with BC are given in Table 1.

We found a significant difference in the presence of at least one AD between the relatives of BC patients and the relatives of those in the control group (76% vs. 36%, $p<0.001$). This difference was more marked when only the first-degree relatives were analyzed (65% vs. 14%, $p<0.00001$). The incidence of ADs in the relatives of the BC patients was higher than in the relatives of the control group (OR: 5.5). In detailed analyses, when the degree of kinship was considered, it was found that the risk increased more in the first-degree relatives of BC patients (OR: 11.5); however, no increased risk was found among distant relatives. The distribution of ADs among the first-degree and other relatives of the groups is shown in Table 2.

Regarding ADs, type 1 DM was detected in 16% of the first-degree relatives of the patient group, 5% of the first-degree relatives of the control group; 8% of the other relatives of the patient group, and 9% of the other relatives of the control group. Graves' disease was detected in 20%

of the first-degree relatives of the patient group, 1% of the first-degree relatives of the control group; 4% of the other relatives of the patient group, and 3% of the other relatives of the control group. Hashimoto's thyroiditis was detected in 33% of the first-degree relatives of the patient group, 8% of the first-degree relatives of the control group; 7% of the other relatives of the patient group, and 5% of the other relatives of the control group. While 29% of the first-degree relatives and 10% of the other relatives of the BC patients had RA, this was 5% and 12% in the control

Table 1. Patient distribution by pathological diagnosis, disease stage at the time of diagnosis, and hormone receptor test results

		Frequency (n=100)
Pathological diagnosis, n (%)	Invasive ductal carcinoma	86 (86)
	Invasive lobular carcinoma	6 (6)
	Mixed tumor	7 (7)
	Medullary carcinoma	1 (1)
Diagnostic stage, n (%)	Early stage	47 (47)
	Locally advanced	44 (44)
	Metastatic	9 (9)
Hormone receptor test results, n (%)	ER +	9 (9)
	PR +	2 (2)
	ER +, PR +	50 (50)
	c-ERB B2	9 (9)
	ER +, PR +, c-ERB B2 +	19 (19)
	ER -, PR -, c- ERB B2 -	8 (8)
	ER +, c-ERB B2 +	2 (2)
	PR +, c- ERB B2 +	1 (1)

Results are expressed as frequency (%). ER: Estragen receptor, PR: Progesterone receptor

Table 2. Autoimmune diseases distribution among the relatives of the groups

		Patient (n=100)	Control (n=100)	p1	OR (95% CI)	p2
Autoimmune disorders, n (%)	Yes	76 (76)	36 (36)	<0.001	5.54 (2.96-10.25)	<0.001
	No	24 (24)	64 (64)			
Type 1 diabetes mellitus, n (%)	Yes	24 (24)	14 (14)	0.071	-	-
	No	76 (76)	86 (86)			
Graves' disease, n (%)	Yes	24 (24)	4 (4)	<0.001	7.58 (2.52-22.78)	<0.001
	No	76 (76)	96 (96)			
Hashimoto's thyroiditis, n (%)	Yes	40 (40)	13 (13)	<0.001	4.46 (2.20-9.05)	<0.001
	No	60 (60)	87 (87)			
Rheumatoid arthritis, n (%)	Yes	39 (39)	17 (17)	<0.001	3.12 (1.62-6.3)	<0.001
	No	61 (61)	83 (83)			

Results are expressed as frequency (%). CI: Confidence interval, OR: Odds ratio, p1: Chi-square test, p2: Logistic regression

Table 3. Autoimmune diseases distribution among the first-degree relatives of the groups

		Patient (n=100)	Control (n=100)	p1	OR (95% CI)	p2
Autoimmune disorders, n (%)	Yes	67 (67)	15 (15)	<0.001	11.51 (5.78-22.92)	<0.001
	No	33 (33)	85 (85)			
Type 1 diabetes mellitus, n (%)	Yes	16 (16)	5 (5)	0.011	3.62 (1.27-10.30)	0.016
	No	84 (84)	95 (95)			
Graves' disease, n (%)	Yes	20 (20)	1 (1)	<0.001	24.75 (3.25-188.42)	0.002
	No	80 (80)	99 (99)			
Hashimoto's thyroiditis, n (%)	Yes	33 (33)	8 (8)	<0.001	5.66 (2.46-13.04)	<0.001
	No	67 (67)	92 (92)			
Rheumatoid arthritis, n (%)	Yes	29 (29)	5 (5)	<0.001	7.61 (2.86-21.05)	<0.001
	No	71 (71)	95 (95)			

Results are expressed as frequency (%). CI: Confidence interval, OR: Odds ratio, p1: Chi-square test, p2: Logistic regression

Table 4. Autoimmune diseases distribution among the other relatives of the groups

		Patient (n=100)	Control (n=100)	p1	OR (95% CI)	p2
Autoimmune disorders, n (%)	Yes	25 (25)	33 (33)	0.741	-	-
	No	75 (75)	67 (67)			
Type 1 diabetes mellitus, n (%)	Yes	8 (8)	9 (9)	0.800	-	-
	No	92 (92)	91 (91)			
Graves' disease, n (%)	Yes	4 (4)	3 (3)	0.552	-	-
	No	96 (96)	97 (97)			
Hashimoto's thyroiditis, n (%)	Yes	7 (7)	5 (5)	0.700	-	-
	No	93 (93)	95 (95)			
Rheumatoid arthritis, n (%)	Yes	10 (10)	12 (12)	0.651	-	-
	No	90 (90)	88 (88)			

Results are expressed as frequency (%). CI: Confidence interval, OR: Odds ratio, p1: Chi-square test, p2: Logistic regression

Table 5. Hormone receptor distribution in first-degree relatives have any autoimmune disease of patients with breast cancer

Hormone receptor status	Patient (n=100)	First-degree relatives with the autoimmune disease in the patient group (n=65)	First-degree relatives without the autoimmune disease in the patient group (n=35)	p1 value
ER+, n (%)	9 (9)	7 (11)	2 (6)	0.399
PR+, n (%)	2 (2)	2 (3)	0 (0)	-
ER+/PR +, n (%)	50 (50)	33 (51)	17 (49)	0.833
c-ERB B2 +, n (%)	9 (9)	5 (8)	4 (11)	0.533
ER+/PR+/c-ERB B2 +, n (%)	19 (19)	13 (20)	6 (17)	0.728
ER-/PR-/c-ERB B2 -, n (%)	8 (8)	4 (6)	4 (11)	0.353
ER+/PR-/c-ERB B2+, n (%)	2 (2)	0 (0)	2 (6)	-
ER-/PR+/c- ERB B2+, n (%)	1 (1)	1 (1)	0 (0)	-
p2 value		0.763	0.00001	

Results are expressed as frequency (%).ER: Estragen receptor, PR: Progesterone receptor, p1: Chi-square test, p2: One-Way ANOVA analysis

group, respectively. Accordingly, we concluded that type 1 DM (OR: 3.6), Graves' disease (OR: 24.7), Hashimoto's thyroiditis (OR: 5.7), and RA (OR: 7.6) were more common in the first-degree relatives of the patient group compared to the first-degree relatives of the control group (Table 3). The findings revealed that the groups did not significantly differ by the presence of at least one AD among their other relatives (Table 4).

In the groups, only one relative had autoimmune hepatitis, MG, or autoimmune hemolytic anemia, while none of the relatives of the study populations had SLE, PBS, connective tissue disorder, Sjögren's disease, or scleroderma.

The comparison of hormone receptor test results with the frequency of at least one AD in first-degree relatives was evaluated in Table 5, and no statistical difference was found between the groups (p=0.763). On the contrary, comparing the hormone receptor test results of patients whose first-degree relatives did not have AD, a statistically significant difference was detected between the patient group with estrogen and progesterone receptor positivity and with estrogen-only or c-ERB B2 or triple-negative or both estrogen and c-ERB B2 positivity ($p<0.05$). No statistically significant difference was detected when the hormone receptor test results were compared individually between groups with and without first-degree relatives with any AD.

Discussion

We found a significantly increased frequency of ADs among the first-degree relatives of the patients with BC, but not among distant relatives compared to the control group. The disease stage at the time of diagnosis and pathological diagnosis were evaluated. We found that 47% of the patients were early stage, 44% were locally advanced, and 9% were metastatic. Yet, the literature does not offer sufficient findings pertinent to the disease stage at diagnosis. In this study, we could not conclude a significant difference between ADs between the groups' relatives by the disease stage at the time of diagnosis and pathological diagnosis.

In a previous study, it was reported that autoimmune thyroiditis is more common in patients with estrogen-positive compared to other thyroid diseases.[8] However, relationship between hormone receptor test results and other ADs has not been studied previously. In our study, we did not find a significant difference between the hormone receptor test

results of patients with BC and the frequency of ADs in their first-degree relatives. However, more comprehensive studies are needed to evaluate the relationships between hormone receptors status and ADs.

We found that the frequency of ADs in the first-degree relatives of the patient group was significantly higher than in the first-degree relatives of the control group and that there was no significant difference in other relatives, supporting the hypothesis of the role of common genetic pathogenesis. However, it should be noted that the low rate of ADs in other relatives could also be attributed to the patients' lack of knowledge about their relatives' medical history. In addition, the prevalence of SLE, autoimmune hepatitis, MG, PBS, autoimmune hemolytic anemia, connective tissue disease, Sjögren's syndrome, and scleroderma are less than the prevalence of type 1 DM, Hashimoto's disease, Graves' disease, and RA was low due to our study groups scale remained relatively small. Therefore, we could not analyze the less common diseases due to insufficient data to evaluate the relationship between the study groups. Consequently, we think the results might differ in more extensive multicenter studies.

Study Limitations

Our study had several limitations. First of all, data were obtained through verbal questionnaires. Therefore, there is a risk of missing data in this study. Our study was designed to have a relatively small sample size at a single center, and the number of children of individuals in the study population was not recorded at the time of data collection. However, we still think detecting a significant difference in OR is valuable. Another weakness is the differences between the BC and the control groups. BC group was older than the control group. Since the frequency of AD diseases increases with age,[9] the finding of more common ADs in the first-degree relatives of the BC group compared to the control group, could partly be attributed to the difference in the mean age between the groups; however, it is unlikely to be the sole reason. In addition, our study did not include data regarding the age of relatives, which could affect differences in the frequency of ADs. The mean BMI of the patient group was also significantly higher than that of the control group. However, this is compatible with the previous research that demonstrated obesity to be associated with an increased incidence of BC[10-20] and unlikely to have any influence on the results of the study. Our study was planned to investigate the frequency of ADs in the relatives of the patient and control groups, and a possible limitation was that we did not record the presence of ADs in the patient and control groups, which could potentially impact the results.

The prevalence of ADs in the relatives of patients with BC has not been previously studied in detail; therefore, our study might shed light on this association and might guide future studies to elucidate this issue.

Conclusion

Our results suggest that the first-degree relatives of BC patients could be at increased risk of developing ADs, and common genetic factors might play roles in the pathogenesis of these two different categories of diseases.

Ethics

Ethics Committee Approval: The Research Ethics Committee of Gazi University granted ethical approval to our study (no: 2017-114 dated: 03.07.2017).

Informed Consent: Written informed consent form was obtained from each patient.

Authorship Contributions

Concept: A.A., B.G., M.A.Ö., A.T., Ş.H., H.B., A.Ö., A.Ü., N.G., G.T., Design: A.A., B.G., M.A.Ö., A.T., Ş.H., H.B., A.Ö., A.Ü., N.G., G.T., Data Collection or Processing: A.A., G.T., Analysis or Interpretation: A.A., B.G., Literature Search: A.A., Writing: A.A., B.G.

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Genetic variations in Familial Mediterranean fever related *MIR197* gene in Turkish population

Türk popülasyonundaki Ailevi Akdeniz ateşi ilişkili *MIR197* genindeki genetik varyasyonlar

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Abstract

Objective: Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease caused by the gain of function mutations in the *MEFV* gene, which encodes pyrin protein. This study aimed to determine single nucleotide polymorphisms in the *MIR197* gene locus in FMF patients and healthy controls in Turkish population. We have previously identified miR-197-3p as a differentially expressed miRNA in FMF patients according to disease severity.

Methods: DNA was isolated from peripheral blood samples of six FMF patients and 12 healthy controls. The *MIR197* gene region was amplified by polymerase chain reaction and Sanger sequencing was performed. DNA sequence analysis results were analyzed with the Chromas (version 2.33). Additionally, open access GWAS data (Harvard Dataverse, V2; Turkish_A1_A2.txt) covering 1011 healthy Turkish people was analyzed using R.

Results: Genetic variants in the *MIR197* region were not detected in study group. Also, we couldn't find any genetic variants in the *MIR197* region through the analysis of a GWAS study (Harvard Dataverse, V2; Turkish_A1_A2.txt).

Conclusion: In this study, we demonstrated that the dysregulated miR-197-3p profile seen in FMF patients is not explained by variations in the *MIR197* gene locus. These results suggest that other factors such as promotor methylation, histone modifications, other non-coding RNAs and alterations in post-transcriptional processing may be involved in the changes in miRNA expression and should be investigated further.

Keywords: FMF, microRNA, genetic variations, SNPs, *MIR197* gene

Öz

Amaç: Ailevi Akdeniz ateşi (AAA), pyrin proteinini kodlayan *MEFV* genindeki fonksiyon kazanımı mutasyonlarının neden olduğu kalıtsal otoenflamatuvar bir hastalıktır. Bu çalışmanın amacı, Türk toplumundaki AAA hastalarında ve sağlıklı kontrollerde *MIR197* gen lokusundaki tek nükleotit polimorfizmlerini incelemektir. Grubumuzun daha önceki çalışmalarında, miR-197-3p'nin AAA hastalarında hastalık şiddetine göre değişken ifade gösteren bir miRNA olduğu tanımlanmıştır.

Yöntem: Altı AAA hastası ve 12 sağlıklı kontrolün periferik kan örneklerinden DNA izolasyonu yapılmıştır. *MIR197* gen bölgesi polimeraz zincir reaksiyonu ile çoğaltılmış ve Sanger dizilemesi yapılmıştır. DNA dizi analizi sonuçları Chromas (sürüm 2.33) ile analiz edilmiştir. Ayrıca Türk popülasyonundan 1011 sağlıklı katılımcıyı kapsayan açık erişimli GWAS verileri (Harvard Dataverse, V2; Turkish_A1_A2.txt) R programı kullanılarak analiz edilmiştir.

Bulgular: Çalışma gruplarında *MIR197* gen bölgesinde herhangi bir genetik varyasyon saptanamamıştır. Türk toplumundan 1011 sağlıklı kontrolü içeren GWAS çalışmasının (Harvard Dataverse, V2; Turkish_A1_A2.txt) analizi sonucunda da *MIR197* gen bölgesinde herhangi bir genetik varyant tespit edilememiştir.

Sonuç: Bu çalışmada, AAA hastalarında görülen miR-197-3p ifade değişikliğinin nedeninin *MIR197* gen lokusundaki varyasyonlarla açıklanmadığını belirlenmiştir. Bu sonuçlar, promotor metilasyonu, histon modifikasyonları, diğer kodlamayan RNA'lar ve transkripsiyon sonrası modifikasyonlar gibi diğer faktörlerin miRNA ekspresyonundaki değişikliklerde rol oynayabileceğini ve daha ileri araştırmaların yapılması gerektiğini göstermektedir.

Anahtar Kelimeler: AAA, mikroRNA, genetik varyasyonlar, SNPs, *MIR197* geni

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Introduction

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease caused by the gain of function mutations in the *MEFV* gene, which encodes pyrin protein.[1] A variety of phenotypic differences between FMF patients with identical mutations and changing severity of the disease pathogenesis imply a role for epigenetic regulation in this disease.[2] There is growing evidence that microRNAs (miRNAs) as epigenetic regulators may serve as promising candidates for FMF.

miRNAs are a class of small non-coding RNAs that play crucial roles in various biological processes, including gene expression regulation and post-transcriptional gene silencing. miRNAs, typically composed of 18-25 nucleotides, are highly conserved across species and have been found to be involved in numerous cellular processes such as cell proliferation, differentiation, and apoptosis.[3] miRNA biogenesis comprises a multi-step process that ends with the production of a mature miRNA.[4] The mature miRNA is loaded onto the RNA-induced silencing complex. This complex guides the miRNA to its target mRNA sequence through base pairing, leading to gene silencing through translational repression or mRNA degradation.[4] Although the canonical function of miRNAs is defined by this silencing effect, studies show that it can have diverse effects on translational and transcriptional activity.[5] The dysregulation of miRNA expression can result from genetic variations, including single nucleotide polymorphisms, in the genes involved in miRNA biogenesis, regulation, and miRNA sequence itself.[6-8]

Single nucleotide polymorphisms (SNPs), or single nucleotide polymorphisms, are the most common type of genetic variation that can occur within miRNA genes or target sites in the human genome. They occur when a single nucleotide base in the DNA sequence is altered. These SNPs can affect miRNA biogenesis, function, and regulation, ultimately impacting gene expression and contributing to the development of various human complex diseases. According to the miRNASNP-v3, there are 46,826 SNPs and 4,712 DRVs (Disease Related Variants) located in pre-miRNA loci in the human genome.[9]

miRNA SNPs or polymorphisms may have varying downstream effects depending on the miRNA function and the region of SNP.[10] The regulatory functions of miRNAs exclusively depend on the sequence alignment of their seed region to their target mRNA. SNPs located in the seed region may disrupt this binding.[11] On the other hand, SNPs or mutations that result in perfect matching with the target site can result in the degradation of the mRNA, instead of transcriptional silencing.[12] A seed sequence SNP of miR-125a prevents Drosha binding to the other arm and inhibits its transcription.[13] Seed sequence mutations are important in this manner because they are directly related to the function of the miRNA causing a disease state in the organism.

miRNA gene loci also include sequences for directing the biogenesis and their regulation with other factors. SNPs and mutations in these regions can cause alterations in biogenesis, changes in miRNA level, altered precision of processing, biased 5p/3p strand selection, and malfunctioning in the target silencing. miRNA clusters and individual miRNA genes form hairpin structures during transcription that generate a 3D form for DROSHA and other proteins to recognize and process the pri- to pre-transformation. Nucleotide changes may generate unstable hairpins or changed distributions of these loops causing disruption in pri-miRNA processing. These changes in the stability of the 3D structure can alter the expression patterns of miRNA. SNPs may also affect specific modifications on RNA nucleotides, which is important for their further localization and processing.

Polymorphism studies on miRNAs showed that decreased seed sequence ratios are seen in the human population, but different populations have a high frequency of specific polymorphisms in *MIR-146A* gene.[11] miR-146a is mainly expressed in immune cells, a SNP from G to C change in this miRNA, disturbs DROSHA cleavage in biogenesis, and this polymorphism was linked to a higher risk for multiple sclerosis in women along with a lower risk of ankylosing spondylitis and psoriasis.[11,14,15] This polymorphism is one of the most studied ones and has many ties with different cancer types and inflammatory diseases. miRNA SNP research on Mendelian disorders highlighted the many miRNAs germ line mutation's role in familial diseases. Non-syndromic hearing loss was one of the first miRNA-related Mendelian disorder in which many candidate genes showed no mutation correlations but only mutant miR-96's role could explain the disease progression.[16] Different studies on atherosclerosis phenotype differences, SNPs effecting pri-miRNA formation and pre-miRNA processing in a variety of populations causing the phenotypic differences in stages of atherosclerosis.[17] A study on miR-146a polymorphism found that in Behçet's cases, decreased homozygous rs2910164 CC genotype and C allele effecting the miR-146 level reduction in Chinese BD patients.[18] A meta-analysis study confirms this polymorphism effect on BD susceptibility in Caucasians.[19] miR-499 is another well studied miRNA, especially in autoimmune diseases. One polymorphism

in this miRNA, rs3746444, is associated with an elevated risk of autoimmune diseases in Caucasian and Asian populations.[20]

miR-197-3p is encoded from the *MIR197* gene from chromosome one and its dysregulation profile is mostly observed in different cancer studies.[21-23] New research broadens the miR-197's role in inflammatory processes[24,25] such as miR-197-3p's effect on endothelial cells in Takayasu disease.[26] In our previous study, miR-197-3p was found to be decreased (FCH: -2,22) in M694V/M694V homozygotes FMF patients compared to healthy controls.[27] Our group also showed that miR-197-3p, which directly targets the interleukin-1beta (IL-1β) receptor type I gene (*IL1R1*), is differentially expressed in FMF patients.[28] In this paper, possible genetic variations of *MIR197* gene were searched in FMF patients to explain the altered miR-197-3p expressions between patients and controls.

Materials and Methods

Study Group

The study consisted of six FMF patients who were homozygous for the M694V mutation (M694V/M694V)[27] who showed a severe phenotype and 12 healthy individuals as a control group. The study group consisted of adults between 19-48 years of age. All patients displayed a typical phenotype with attacks of 12-72 hours duration. 10 mL of blood was taken from the individuals into DNA blood tubes. Blood samples were taken for sedimentation and determination of C-reactive protein and complete blood count levels from all individuals in the study group. Since the homozygote patients had a severe disease phenotype, five of them were also receiving anti-IL-1β therapy. Median ages were 28 years for homozygote patients and 34 years for healthy controls. Written consent was acquired from the patients and controls involved in the study and approved by national ethics committee (23.01.2013 date, GO13/54-07 number - Hacettepe University Non-invasive Clinical Research Ethics Committee).

Polymerase Chain Reaction

Polymerase chain reaction (PCR) primers used to amplify the *MIR197* gene region are provided in Table 1. Reactions were carried out in the Gene Amplification PCR System 9700 (Applied Biosystem). The sizes of the amplification products and the specificity of the amplification were determined by agarose gel electrophoresis.

DNA Sequencing

After the successful amplification of *MIR197* gene region, DNA sequencing studies were carried out. The amplicons were purified using Promega Wizard™ SV Gel and PCR Cleanup System (Fisher Scientific, CA) according to the manufacturer's instructions. Sequencing was performed using the BigDye Terminator kit v. 3.1 and cleaned up with BigDye XTerminator v. 3.1 (Applied Biosystems, Foster City, CA). The purified products of the cycle sequencing were analysed on the ABI 3130 Genetic Analyser (Applied Biosystems). DNA sequence analysis results were analyzed with the Chromas (version 2.33) program in Applied Biosystems 3130 Genetic Analyzer.

Analysis of GWAS Data

The GWAS data (Harvard Dataverse, V2; TurkishA1A2.txt)[29] was analyzed and *MIR197* locus was screened by using R Core Team (2023). _R: A Language and Environment for Statistical Computing_. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>.

Results

To investigate the possibility that the decreased expression of miR-197-3p identified in our cohort of severe phenotype patients were due to variations the in *MIR197* locus, sequence analysis was performed for the *MIR197* gene in six *M694V/M694V* patients and 12 control individuals.

According to the results of sequence analysis of miR-197-3p gene of homozygous (*M694V/M694V*) individuals; no genetic variants were observed in either group (Figure 1).[30]

To expand our search for *MIR197* SNPs to a larger population, we analyzed open access GWAS data on 1011 healthy Turkish people *MIR197* SNPs, and consistent with our study results, no SNPs were observed.[29]

Discussion

In this study, *MIR197* gene variations were analyzed in severe FMF patients with low expression levels of miR-197-3p. Since variations in miRNA genes can affect the functionality or expression levels of miRNA, the fact that no difference was observed between patient and control

Table 1. Primer sequences of *MIR197* gene region for PCR

Exon	Forward (F) primer	Reverse (R) primer	PCR product (bp)
MIR197	5'GCCCAACACCGAAATCCTT 3'	5'ACGGTGAGACATAACAGCA 3'	181

bp: Base pair, PCR: Polymerase chain reaction

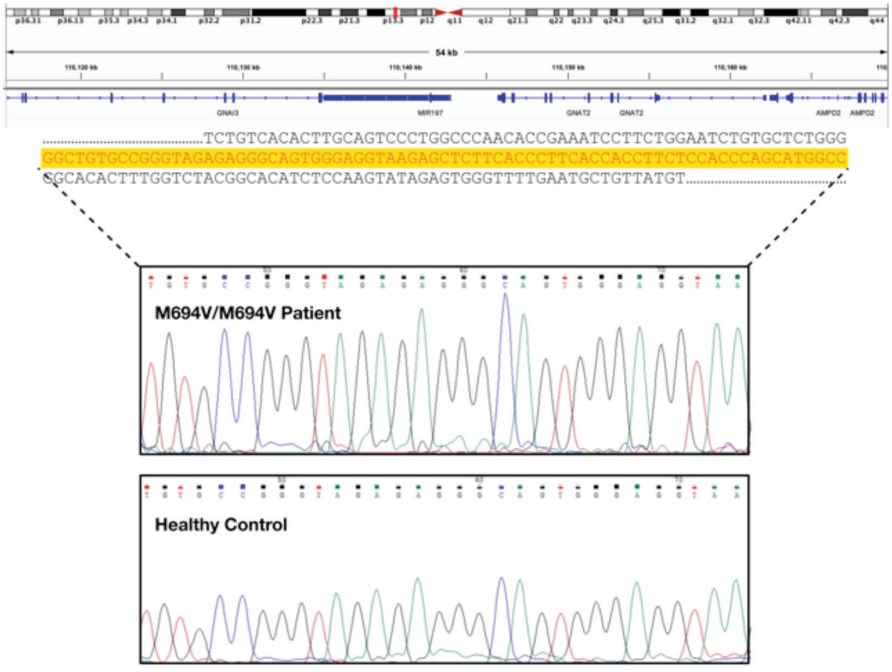

Figure 1. Sequencing results of the *MIR197* locus. In the chromosomal region, *MIR197* gene was showed in blue and the gene sequence was highlighted with yellow[30]

individuals with sequence analysis showed that the miRNA expression differences we identified in our patients were not due to genetic variations in the *MIR197* coding region.

The dysregulation of miRNAs can lead to the disruption of biological pathways and the development of various diseases. Studies have shown that miRNAs are closely related to the pathogenesis of many autoinflammatory and autoimmune diseases.[31]

Genetic variations in miRNA sequences are very important as they can affect both the expression levels and the functionality of miRNA. SNPs may influence miRNA expression at every step of the miRNA biogenesis. It is known that differences in the sequence may cause damage to the hairpin stem structure and subsequent disruption of its processing, resulting in the degradation of miRNA.

Due to their variety of functions, the regulation of miRNA activity is a complex process involving various mechanisms. These mechanisms include transcriptional regulation, epigenetic modifications, RNA editing, and regulation by other proteins or non-coding RNAs.[32] DNA methylation and histone modifications are transcriptional regulation mechanisms that can affect miRNA expression levels by controlling the transcription machinery's access to the miRNA gene locus. Post-transcriptional regulatory mechanisms include alternative splicing and enzymatic modifications of RNA. Additionally, alternative Drosha cutting generates different types of pre-miRNA products, increasing their diversity and, in some situations, leading to the degradation of specific miRNAs.[33] These modifications can also modulate the half-life of miRNAs for the regulation of their activity in a time-wise manner. Non-coding RNAs like lncRNA may capture newly synthesized pri-miRNAs or regulate transcription to alter miRNA expression. Every cellular molecule involved in miRNA biogenesis and function can be responsible for the altered miRNA profile in disease situations.[34] Genetic code differences of these epigenetic molecules and target mRNA 3'UTR sites may lead to increased or decreased synthesis, altered functions, splicing variants, and disrupted protein-protein interactions.

Conclusion

In this study, we determined that the previously demonstrated dysregulation in miR-197-3p expression seen in FMF patients is not explained by variations in the *miR-197* gene locus. We also did not find any SNPs upon analyzing open-access GWAS data on the Turkish population.[29] To our knowledge, ours is the first study to investigate *MIR197* variations in autoinflammatory diseases. This study is limited by the small sample size, and only the coding region was analyzed. Increasing the sample size and sequencing the promoter region may provide better information about the altered expression of miR-197-3p in FMF patients. Our results suggest that further investigation of other epigenetic factors such as promotor methylation, histone modifications, other non-coding RNAs, and alterations in post-transcriptional processing may be implicated in the differential expression of miR-197-3p.

Ethics

Ethics Committee Approval: Approved by national ethics committee (23.01.2013 date, GO13/54-07 number - Hacettepe University Non-invasive Clinical Research Ethics Committee).

Informed Consent: Written consent was acquired from the patients and controls involved in the study.

Authorship Contributions

Concept: L.K., Design: L.K., Y.Z.A.U., Data Collection or Processing: E.N., L.K., Analysis or Interpretation: E.N., B.Ş., Literature Search: E.N., Writing: E.N., B.Ş., Y.Z.A.U.

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