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AMAÇ VE KAPSAM

Türk Osteoporoz Dergisi, Türkiye Osteoporoz Derneği'nin süreli yayın organı olup, osteoporoz ve metabolik kemik hastalıkları içerikli, yayın dili Türkçe ve İngilizce olan, bağımsız ve önyargısız hakemlik (peer-review) ilkelerine dayanan uluslararası, periyodik bir dergidir. Türk Osteoporoz Dergisi, Nisan, Ağustos ve Aralık aylarında olmak üzere yılda 3 sayı çıkar.

Türk Osteoporoz Degisi'nin hedefi uluslararası düzeyde nitelikli, sürekli ve osteoporoz konusunda özgün bir periyodik olarak klinik ve bilimsel açıdan en üst düzeyde orijinal araştırmaları yayınlamaktır. Bununla birlikte eğitim ile ilgili temel yenilikleri kapsayan derlemeler, editöryel kısa yazılar, olgu sunumları, orijinal görüntüler ve geniş fiziksel tıp, romatoloji, rehabilitasyon ve jinekoloji kesimlerinin konular hakkındaki deneyimlerini ve eleştirilerini içeren mektuplar ve sosyal konulu yazılar yayınlamaktır.

Osteoporoz ve kemik hastalıklarına ilgi duyan birinci basamak tıp hizmeti veren pratisyen hekim, iç hastalıkları, jinekoloji, romatoloji ve fiziksel tıp ve rehabilitasyon uzmanlarının "bilmesi gerekli olanları" iyice saptayarak; bunları Türk Osteoporoz Dergisi'nde bulmaları için gerekli düzenlemeler yapılacaktır.

Türk Osteoporoz Dergisi, Emerging Sources Citation Index (ESCI), DOAJ, EBSCO Database, Gale/Cengage Learning, CINAHL, Index Copernicus, Embase, Scopus, Proquest, J-Gate Academic Keys, TÜBİTAK/ULAKBİM, Hinari, Oare, Ardi, Goali, Türk Medline Ulusal Atıf İndeksi ve CABI tarafından indekslenmektedir.

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Derginin açık erişim politikası 'Budapest Open Access Initiative(BOAI) kuralları esas alınarak uygulanmaktadır.

Açık Erişim, "[hakem değerlendirmesinden geçmiş bilimsel literatürün], İnternet aracılığıyla; finansal, yasal ve teknik engeller olmaksızın, serbestçe erişilebilir, okunabilir, indirilebilir, kopyalanabilir, dağıtılabilir, basılabilir, taranabilir, tam metinlere bağlantı verilebilir, dizinlenebilir, yazılıma veri olarak aktarılabilir ve her türlü yasal amaç için kullanılabilir olması"dır. Çoğaltma ve dağıtım üzerindeki tek kısıtlama yetkisi ve bu alandaki tek telif hakkı rolü; kendi çalışmalarının bütünlüğü üzerinde kontrol sahibi olabilmeleri, gerektiği gibi tanınmalarının ve alıntılanmalarının sağlanması için, yazarlara verilmelidir.

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Türk Osteoporoz Dergisi, ülkemizde görev yapan fiziksel tıp ve rehabilitasyon uzmanlarına, akademisyenlerine ve osteoporoz'a ilgi duyan diğer tüm tıp branşlarına mensup uzmanlara ücretsiz olarak dağıtılmaktadır. Derginin tüm sayılarına ücretsiz olarak www.turkosteoporozdergisi.org adresinden tam metin ulaşılabilir. Dergiye abone olmak isteyen kişiler Türkiye Osteoporoz Derneği'ne başvurmalıdır.

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AIMS AND SCOPE

Turkish Journal Of Osteoporosis is the regular publishing organ of the Turkish Osteoporosis Society. This periodical journal covers osteoporosis and metabolic bone diseases subjects. It is a periodic international journal, published in Turkish and English languages and is independent, being based on peer-review principles. The journal is published 3 times per year (April, August and December).

The aim of the journal "Turkish Journal Of Osteoporosis" is to continuously publish original research papers of the highest scientific and clinical values specifically on osteoporosis, on an international level. Additionally, reviews on basic developments in education, editorial short notes, case reports, original views, letters from the fields of physical medicine, rheumatology, rehabilitation, gynaecology containing experiences and comments as well as social subjects are published.

Thing that must be known' subjects for general practitioners giving first line medical service who are interested in osteoporosis and metabolic bone diseases, specialists in internal medicine, gynecology, rheumatology and physiotherapy will be determined It will then be possible to make the necessary adjustments to the journal "Turkish Journal Of Osteoporosis" according to their needs.

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Turkish Journal Of Osteoporosis is sent free to physiotherapy specialists, academicians in our country as well as other specialists in all branches of medicine interested in osteoporosis. All published volumes can be reached full text without fee through the web site www.turkosteoporozdergisi.org. Those who wish to subscribe to the journal should apply to the Turkish Osteoporosis Association.

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YAZARLARA BİLGİ

Türk Osteoporoz Dergisi, Türkiye Osteoporoz Derneği'nin resmi yayın organıdır.
Dergi, osteoporoz, metabolik kemik hastalıkları ve rehabilitasyon alanlarını ilgilendiren tüm konulardaki yazıları yayınlar. Dergide orijinal makalelerin dışında derleme yazıları, orijinal olgu sunumları, editöre mektuplar, bilimsel mektuplar, eğitim yazıları, yeni literatür özetleri ve gelecek kongre/toplantı duyuruları da yayınlanır.
Dergide yayınlanacak yazıların seçimine temel teşkil eden hakem heyeti, dergide belirtilen danışmanlar ve gerekirse yurt içi/dışı otörler arasından seçilir.
Yazılarda Türk Dil Kurumu'nun Türkçe Sözlüğü ve Yazım Kılavuzu temel alınmalıdır. İngilizce yazılan yazılar özellikle desteklenmektedir.
Makaleletin formatı 'Uniform reqiuirements for Manuscripts Submitted to Biomedical Journals' (http.//www.icmje.org) kurallarına göre düzenlenmelidir.
Editör tarafından, etik kurul onayı alınması zorunluluğu olan klinik araştırmalarda onay belgesi talep edilecektir. İnsan üzerinde yapılan deneysel araştırmaların bildirildiği yazıların metnin içerisinde, yazarların bu araştırmanın prosedürünün sorumlu olan etik kurulun insan üzerine deney yapılma etik standartlarına (kurumsal ve ulusal) ve 2013 yılında revize edilen1964 Helsinki Deklarasyonuna uyulduğunu ve hastaların onaylarının alındığını belirtilmelidir. Hayvan üzerinde yapılan deneysel araştırmalarda, yazarlar yapılan prosedürlerin hayvanlar haklarına uygun olduğunu belirtilip (Guide for the care and use of laboratory animals. www.nap.edu/catalog/5140html) ayrıca etik kurulu onayı'nı alınmalıdır.
Yazıların içeriğinden ve kaynakların doğruluğundan yazarlar sorumludur.
Yazarlar, gönderdikleri çalışmanın başka bir dergide yayınlanmadığı ve/veya yayınlanmak üzere incelemede olmadığı konusunda garanti vermelidir. Daha önceki bilimsel toplantılarda 200 kelimeyi geçmeyen özet sunumlarının yayınları, durumu belirtilmek koşulu ile kabul edilebilir.
Tüm yazarların çıkar çatışma olmadığını, bilimsel katkı ve sorumluluklarını bildiren toplu imza ile yayına katılmalıdır.
Tüm yazılar, editör ve ilgili editör yardımcıları ile en az üç danışman hakem tarafından incelenir. Yazarlar, yayına kabul edilen yazılarda, metinde temel değişiklik yapmamak kaydı ile editör ve yardımcılarının düzeltme yapmalarını kabul etmiş olmalıdırlar.

Genel Kurallar

Yazılar sadece "online" olarak kabul edilmektedir. Yazarların makale gönderebilmesi için Journal Agent web sayfasına (www.journalagent.com/osteoporoz) kayıt olup şifre almaları gereklidir. Bu sistem on-line yazı gönderilmesine ve değerlendirilmesine olanak tanımaktadır. Makale gönderimi yapılırken sorumlu yazarın ORCID (Open Researcher ve Contributor ID) numarası belirtilmelidir. http://orcid.org adresinden ücretsiz olarak kayıt oluşturabilir.
Bu sistem ile toplanan makaleler ICMJE-www.icmje.org, Index Medicus (Medline/PubMed) ve Ulakbim-Türk Tıp Dizini kurallarına uygun olarak sisteme alınmakta ve arşivlenmektedir. Yayına kabul edilmeyen yazılar, sanatsal resimler hariç geriye yollanmaz.
Yazının tümünün 5000 kelimeden az olması gerekmektedir. İlk sayfa hariç tüm yazıların sağ üst köşelerinde sayfa numaraları bulunmalıdır. Yazıda, konunun anlaşılmasında gerekli olan sayıda ve içerikte tablo ve şekil bulunmalıdır.
Başlık sayfası, kaynaklar, şekiller ve tablolar ile ilgili kurallar bu dergide basılan tüm yayın türleri için geçerlidir.

Orijinal Makaleler

1) Başlık Sayfası (Sayfa 1)
Yazı başlığının, yazar(lar)ın bilgilerinin, anahtar kelimelerin ve kısa başlıkların yer aldığı ilk sayfadır.
Türkçe yazılarda, yazının İngilizce başlığı da mutlaka yer almalıdır; yabancı dildeki yayınlarda ise yazının Türkçe başlığı da bulunmalıdır. Türkçe ve İngilizce anahtar sözcükler ve kısa başlık da başlık sayfasında yer almalıdır.
Yazarların isimleri, hangi kurumda çalıştıkları ve açık adresleri belirtilmelidir. Yazışmaların yapılacağı yazarın adresi de ayrıca açık olarak belirtilmelidir. Yazarlarla iletişimde öncelikle e-posta adresi kullanılacağından, yazışmaların yapılacağı yazara ait e-posta adresi belirtilmelidir. Buna ek olarak telefon ve faks numaraları da bildirilmelidir.
Çalışma herhangi bir bilimsel toplantıda önceden bildirilen koşullarda tebliğ edilmiş ya da özeti yayınlanmış ise bu sayfada konu ile ilgili açıklama yapılmalıdır.
Yine bu sayfada, dergiye gönderilen yazı ile ilgili herhangi bir kuruluşun desteği sağlanmışsa belirtilmelidir.
2) Özet (Sayfa 2)
İkinci sayfada yazının Türkçe ve İngilizce özetleri (her biri için en fazla 200 sözcük) ile anahtar sözcükler belirtilmelidir.
Özet bölümü; Amaç, Gereç ve Yöntem, Bulgular, Sonuç şeklinde alt başlıklarla düzenlenir. Derleme, vaka takdimi ve eğitim yazılarında özet bölümü alt başlıklara ayrılmaz. Bunlarda özet bölümü, 200 kelimeyi geçmeyecek şekilde amaçlar, bulgular ve sonuç cümlelerini içermelidir.
Özet bölümünde kaynaklar gösterilmemelidir. Özet bölümünde kısaltmalardan mümkün olduğunca kaçınılmalıdır. Yapılacak kısaltmalar metindekilerden bağımsız olarak ele alınmalıdır.
3) Metin (Özetin uzunluğuna göre Sayfa 3 veya 4'den başlayarak)
Genel Kurallar bölümüne uyunuz.
Metinde ana başlıklar şunlardır: Giriş, Gereç ve Yöntem, Bulgular, Tartışma.
Giriş bölümü çalışmanın mantığı ve konunun geçmişi ile ilgili bilgiler içermelidir. Çalışmanın sonuçları giriş bölümünde tartışılmamalıdır.
Gereç ve yöntem bölümü çalışmanın tekrar edilebilmesi için yeterli ayrıntılar içermelidir. Kullanılan istatistik yöntemler açık olarak belirtilmelidir.
Bulgular bölümü de çalışmanın tekrar edilebilmesine yetecek ayrıntıları içermelidir.
Tartışma bölümünde, elde edilen bulguların doğru ve ayrıntılı bir yorumu verilmelidir. Bu bölümde kullanılacak literatürün, yazarların bulguları ile direkt ilişkili olmasına dikkat edilmelidir.
Teşekkür mümkün olduğunca kısa tutulmalıdır. Çalışma için bir destek verilmişse bu bölümde söz edilmelidir.
Çalışmanın kısıtlılıkları başlığı altında çalışma sürecinde yapılamayanlar ile sınırları ifade edilmeli ve gelecek çalışmalara ilişkin öneriler sunulmalıdır.
Sonuç başlığı altında çalışmadan elde edilen sonuç vurgulanmalıdır.
Metinde fazla kısaltma kullanmaktan kaçınılmalıdır. Tüm kısaltılacak terimler metinde ilk geçtiği yerde parantez içinde belirtilmelidir. Özette ve metinde yapılan kısaltmalar birbirinden bağımsız olarak ele alınmalıdır. Özet bölümünde kısaltması yapılan kelimeler, metinde ilk geçtiği yerde tekrar uzun şekilleri ile yazılıp kısaltılmalıdırlar.
4) Kaynaklar
Kaynakların gerçekliğinden yazarlar sorumludur.
Kaynaklar metinde geçiş sırasına göre numaralandırılmalıdır. Kullanılan kaynaklar metinde parantez içinde belirtilmelidir.
Kişisel görüşmeler, yayınlanmamış veriler ve henüz yayınlanmamış çalışmalar bu bölümde değil, metin içinde şu şekilde verilmelidir: (isim(ler), yayınlanmamış veri, 19..).
Kaynaklar listesi makale metninin sonunda ayrı bir sayfaya yazılmalıdır. Altıdan fazla yazarın yer aldığı kaynaklarda 6. isimden sonraki yazarlar için "et al" ("ve ark") kısaltması kullanılmalıdır. Dergi isimlerinin kısaltmaları Index Medicus'taki stile uygun olarak yapılır. Tüm referanslar Vancouver sistemine göre aşağıdaki şekilde yazılmalıdır.
a) Standart makale:
Intiso D, Santilli V, Grasso MG, Rossi R, Caruso I. Rehabilitation of walking with electromyographic biofeedback in foot-drop after stroke. Stroke 1994;25:1189-92.
b) Kitap:
Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.
c) Kitap Bölümü:
Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk, CN: Appleton and Lange; 1995. p. 361-80.
Birden fazla editör varsa: editors.
d) Toplantıda sunulan makale:
Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561-5.
e) Elektronik formatta makale:
Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 1(1):[24 screens]. Available from:s URL:http://www/cdc/gov/ncidoc/ EID/eid.htm. Accessed December 25, 1999.
f) Tez:
Kaplan SI. Post-hospital home health care: the elderly access and utilization (thesis). St. Louis (MO): Washington Univ; 1995.
5) Tablolar-grafikler-şekiller-resimler
Tüm tablolar, grafikler veya şekiller ayrı bir kağıda basılmalıdır. Her birine metinde geçiş sırasına göre numara verilmeli ve kısa birer başlık yazılmalıdır. Kullanılan kısaltmalar alt kısımda mutlaka açıklanmalıdır. Özellikle tablolar metni açıklayıcı ve kolay anlaşılır hale getirme amacı ile hazırlanmalı ve metnin tekrarı olmamalıdır. Başka bir yayından alıntı yapılıyorsa yazılı baskı izni birlikte yollanmalıdır. Fotoğraflar parlak kağıda basılmalıdır. Çizimler profesyonellerce yapılmalı ve gri renkler kullanılmamalıdır.

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3) Editöre Mektuplar:
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5) Eğitim Yazıları:
Bu kategoride otörler osteoporoz, metabolik kemik hastalıkları ve rehabilitasyon konularındaki güncel bilgileri özetlerler.

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Türk Osteoporoz Dergisi

TURKISH JOURNAL OF OSTEOPOROSIS

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Türk Osteoporoz Dergisi
TURKISH JOURNAL OF OSTEOPOROSIS

Editörden / Editorial

Sevgili Meslektaşlarımız,

Ülkemizi ve Dünyayı etkisi altına alan Koronavirüs hastalığı 2019 nedeniyle tüm sağlık personelinin üstün sorumluluk bilinci ve büyük özveriyle çalıştığı bu çok zor günlerin en kısa sürede bitmesini gönülden diliyoruz. Pandemi sürecinde de meslektaşlarımızın akademik faaliyetlere yönelik çabaları devam ederek, dergimize basım için yayın akışı sürmüştür. Türkiye Osteoporoz Derneği Yönetim Kurulu üyeleri tarafından konuyla ilgili son görüşlerin paylaşıldığı "Osteosarkopeni: Klinik Perspektif" isimli bir derleme hazırlanmış ve bu sayıda basımına karar verilmiştir.

Bu salgın nedeniyle yapılması planlanan birçok bilimsel kongre iptal edilmiştir ve Nisan ayında Barselona- İspanya'da yapılacak olan Osteoporoz, Osteoartrit ve Kas İskelet Sistemi Hastalıkları Dünya Kongresi (WCO-IOF-ESCEO) önce 20-23 Ağustos 2020 tarihine ertelenmiş, daha sonra da pandemi koşullarının devam etmesi nedeniyle osteoporoz, osteoartrit ve sarkopeni alanında dünyanın en büyük kongresi olan bu toplantının aynı tarihlerde sanal kongre olarak düzenlenmesine karar verilmiştir. Kongre bilimsel kurulu bu ilk sanal WCO-IOF-ESCEO kongresine şimdiden 5166 delegenin kaydolduğunu bildirmiş ve bu nedenle ana sponsorlara teşekkür etmiştir. Bu kongre kapsamında daha önceki yıllarda olduğu gibi; Türkiye Osteoporoz Derneği Yönetim Kurulu üyeleri tarafından bir sempozyum düzenlenmiş olup, bu yıl tema olarak "Non-pharmacological Approaches in the Management of Osteoporosis" konusu belirlenmiştir. Ayrıca kongrede organize edilen sanal "Ulusal Dernekler Köyü" kapsamında yine daha önceki yıllarda olduğu gibi, derneğimiz son bir yıl içinde gerçekleştirdiği aktiviteleri içeren "Osteotrain" çalışması ile yer alacaktır.

Türkiye Osteoporoz Derneği ev sahipliğinde ve International Osteoporosis Foundation bilimsel desteği ile gerçekleştirilecek olan 7. Ulusal Osteoporoz Kongresi OSTEO2020'nin 08-11 Ekim 2020 tarihlerinde Sheraton Otel Çeşme, İzmir'de yapılması planlanmıştır. Kongre ile ilgili tüm hazırlıklar kongre düzenleme kurulunca tamamlanmıştır. Ancak pandemi ile ilgili gelişmeler yakından takip edilmekte olup, kongre ile ilgili olabilecek değişiklikler sizlerle anında paylaşılacaktır.

Ayrıca derneğimizin bilgi güncellemeye yönelik "Osteoakademi" eğitim etkinlikleri düzenlenme aşamasındadır.

Siz değerli meslektaşlarımıza bu zor pandemi günlerinde kolaylıklar diler; güzel günlerde görüşmek arzusuyla, sevgi ve saygılarımı sunarım.

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Osteosarkopeni: Klinik Perspektif

Osteosarcopenia: Clinical Perspective

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Öz

Osteosarkopeni yaşlanma ile ilişkili iki kronik kas iskelet sistemi sorunu olan osteoporoz ve sarkopeninin birlikteliğini tanımlayan bir geriatrik sendromdur. Bu sendrom düşmelere ve kırıklara, morbidite, mortalite ve yeti yitiminde artışa ve yaşam kalitesinde azalmaya yol açabilir. Osteosarkopenin etiyopatogenezi multifaktöriyeldir; mekanik, biyokimyasal, genetik ve yaşam tarzı ile ilişkili faktörler ortaya çıkmasında önemli rollere sahiptir. Prevalansı %5 ile %37 arasında bildirilmiştir. Prevalanstaki bu değişkenlik, muhtemelen çalışma popülasyonlarındaki heterojeniteye veya farklı tanı kriterlerin kullanılmasına bağlıdır. Osteosarkopeni tanısı detaylı klinik değerlendirme (örneğin; tarama ve risk hesaplama araçları, kavrama kuvveti ölçümü, fiziksel performans testleri), laboratuvar testleri ve görüntüleme yöntemleri ile konulabilir. Osteoporoz tanısına yönelik olarak kemik mineral yoğunluğunu ölçmek için en sık kullanılan dual enerjili X-ışını absorbsiyometri yöntemidir. Sarkopenide meydana gelen iskelet kas kütlesindeki kaybı saptamak amacıyla kullanılan görüntüleme teknikleri ise dual enerjili X-ışını absorbsiyometri, bilgisayarlı tomografi, ultrasonografi ve manyetik rezonans görüntülemedir. Osteosarkopeninin tedavi seçenekleri arasında egzersiz, besin takviyeleri (protein, D vitamini, kalsiyum ve kreatin), yaşam tarzı değişiklikleri ve farmakolojik tedaviler yer almaktadır. Osteosarkopeni gelişiminin altında yatan mekanizmalar daha iyi anlaşıldıkça hem kası hem de kemiği hedef alan terapötik ajanların geliştirilmesi, yeni bir araştırma alanı haline gelmiştir. Bu derlemede, konuyla ilgili güncel literatür ışığında, osteosarkopenin epidemiyolojisi, patogenezi, tanı ve tedavisi özetlenmiştir.

Anahtar kelimeler: Osteoporoz, sarkopeni, kemik mineral yoğunluğu, kas kuvveti, fiziksel performans, yaşlı

Abstract

Osteosarcopenia is a geriatric syndrome characterised by the co-existence of osteoporosis and sarcopenia, two chronic musculoskeletal conditions associated with ageing. This syndrome may lead to falls and fractures, increased morbidity, mortality and disability, and reduced quality of life. The etiopathogenesis of osteosarcopenia is multifactorial; mechanical, biochemical, genetic and lifestyle factors all play important roles. Its prevalence has been reported between 5% and 37%. The varied prevalence is likely due to the heterogeneous populations or non-unified diagnostic criteria for this syndrome. Osteosarcopenia can be diagnosed by detailed clinical assessment (e.g. screening and risk calculation tools, grip strength, physical performance tests), laboratory tests and imaging methods. Dual-energy X-ray absorptiometry is the most common method used in measuring bone mineral density for the diagnosis of osteoporosis. The imaging techniques used to detect loss of skeletal muscle mass in sarcopenia are dual-energy X-ray absorptiometry, computed tomography, ultrasonography and magnetic resonance imaging. Treatment options for osteosarcopenia include exercise, nutritional supplements (protein, vitamin D, calcium and creatine), life style modifications and pharmacological therapy. With increasing understanding of the underlying mechanisms of osteosarcopenia, the development of therapeutic agents targeting both muscle and bone has become a new area of investigation. This review summarises the epidemiology, pathophysiology, diagnosis and treatment of osteosarcopenia in the light of the relevant literature.

Keywords: Osteoporosis, sarcopenia, bone mineral density, muscle strength, physical performance, ageing

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Giriş

İleri yaştaki kişilerde herhangi bir hastalık grubuna girmeyen klinik durumlar "geriatrik sendromlar" olarak adlandırılmakta olup, bu tablolar çoklu faktörlerin etkileşimleri ile ortaya çıkmakta, karmaşık ve çeşitli risk faktörlerinin sinerjistik etkileri ile gelişmektedir (1). Geriatrik sendromlar arasında yer alan "kırılganlık" bireyi küçük stres faktörleriyle karşılaştığında riske sokan, yeti kayıplarına, morbiditeye, hospitalizasyona ve hatta mortaliteye neden olabilen bir durumdur. En yaygın belirti ve bulguları; istemsiz kilo kaybı, kas güçsüzlüğü, yorgunluk, yavaş yürüme hızı ve progresif fonksiyonel kayıplardır (2). Kırılganlık ile birlikte en sık görülen sorunlar osteoporoz ve sarkopenidir.

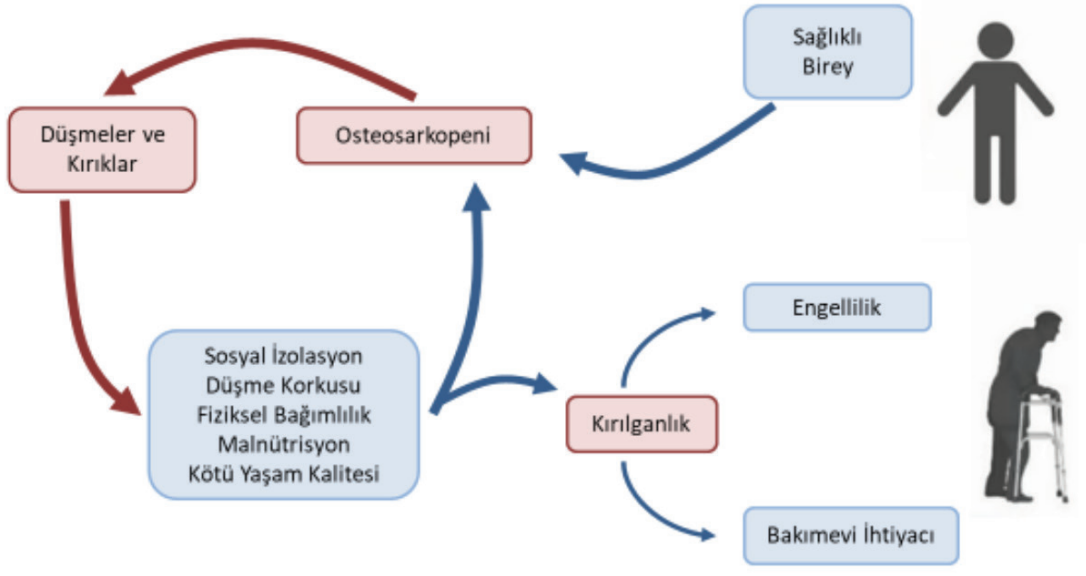
Tanım

Osteoporoz düşük kemik kütlesi ve kemik dokusunun mikromimarisinin bozulmasına bağlı olarak kemik kırılganlığının ve kırık olasılığının artması ile sonuçlanan progresif bir metabolik kemik hastalığıdır (3). Sarkopeni ise kas kütlesi ve kuvvetinin progresif olarak azalmasına bağlı jeneralize fonksiyon kaybı, kırılganlık, düşmeler ve mortalite nedeni olabilen iskelet kası bozukluğudur (4). Sarkopeninin patofizyolojisinde nörojenik, muskulojenik, sinaptojenik ve vaskülojenik sistemlerin dejenerasyonu, mitokondriyal disfonksiyon, metabolik faktörler ve enflamatuvar mekanizmalar olduğu görülmektedir (5). Hayatın 6. dekadından itibaren her yıl kemik mineral yoğunluğu (KMY) %1-1,5, kas kütlesi ise %1 kadar azalmaktadır, bu da osteoporoz ve sarkopeni gibi hastalıkların riskini 2 kat artırmaktadır (6).
Osteosarkopeni, yaşlanma ile ilişkili iki kronik kas iskelet sistemi hastalığı olan osteoporoz ve sarkopeninin birlikteliğini tanımlayan bir sendromdur. Her iki durumda hem örtüşen risk faktörlerini ve patogenezi paylaşır, hem de morbidite, mortalite açısından ön plana çıkan ve önemli sosyoekonomik maliyetleri olan sorunlardır (Şekil 1).

Etiyolojisi çok faktörlüdür, mekanik, biyokimyasal, genetik ve yaşam tarzı faktörleri kemik-kas ünitesinin inşasına katkıda bulunur (7-9). Kas, kemik üzerine mekanik yüklenme yaparak fonksiyonelliği sağlamaktadır. Mekanik etki dışında, endokrin ve parakrin sinyaller yoluyla da bu iki doku birbirleriyle iletişim kurarak gelişme, yüklenme ve yaralanmaya yanıtta da koordinasyon sağlamaktadır. Dolayısıyla ileri yaşın önemli iki kas iskelet sistemi sorunu olan osteoporoz ve sarkopeninin gelişiminde ortak birtakım yolakların sorumlu olabileceği ve birlikte görülme olasılıklarını artırabileceği ifade edilmektedir (10). Yaşlı erişkinlerin fiziksel fonksiyonları açısından yapılan değerlendirmeler, sadece osteoporoz veya sadece sarkopenisi olan kişilerle karşılaştırıldığında, osteosarkopeni tanısı almış olguların fiziksel işlev bozukluklarının diğerlerine göre daha ön planda olduğunu göstermektedir (11). Dolayısıyla, yaşlanan popülasyonlarda osteosarkopeni gelecekte giderek daha da önem kazanacak olan bir halk sağlığı sorunudur.

Epidemiyoloji

Osteosarkopeni tanısı için bir görüş birliği olmaması nedeni ile prevalansı çok değişkendir. Toplum içerisinde yaşayan 65 yaş üstü bireylerde prevalansı %5-37 olarak bildirilmiştir (6). Sıklığı yaşla birlikte artar; prevalansı 60-70 yaşlarındaki bireylerde %5-13 iken 80 yaş üstünde %11-50 bulunmuştur (7). Kadınlarda erkeklere kıyasla daha sık görülmektedir. Osteosarkopeni prevalansı erkeklerde 60-64 yaş arasında %14,3, 75 yaş üstünde ise %59,4 iken kadınlarda ise 60-64 yaş arasında %20,3, 75 yaş üstünde %48,3 olarak tespit edilmiştir (12). Yapılan çalışmalarda osteoporozun sarkopeni riskini artırdığı veya sarkopeninin osteoporoz riskini artırdığı gösterilmiştir (6). Beş yüz doksan postmenopozal kadının dahil edildiği bir çalışmada; sarkopenisi olanlarda olmayanlara göre 12,9 kat fazla osteoporoz saptanmıştır (13). Başka bir çalışmada ise "olası



Şekil 1. Osteosarkopenin birey üzerindeki olumsuz etkileri

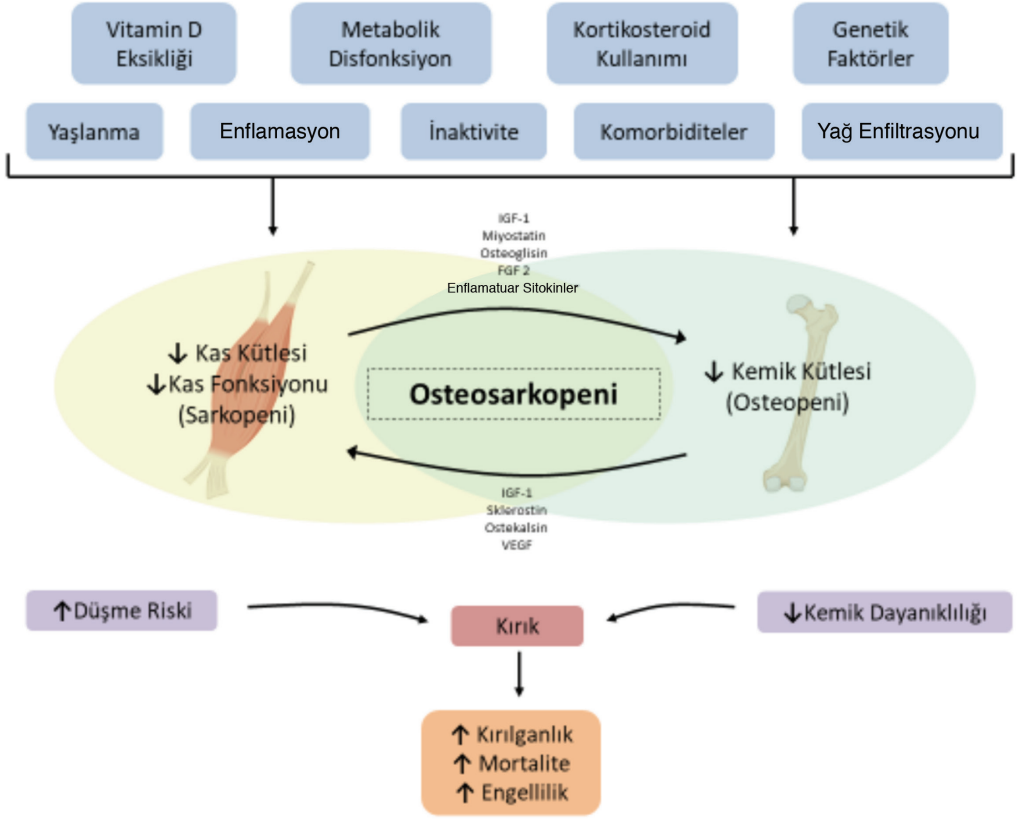
veya kesin sarkopenisi" olanların olmayanlara kıyasla daha düşük KMY değerlerine sahip olduğu belirlenmiştir (14). Kırık öyküsü olan 680 yaşlıda osteosarkopeni prevalansı %37 olarak bildirilmiş ve bu hastalarda daha sık komorbidite, azalmış mobilite ve depresyon olduğu ortaya konmuş, aynı zamanda mortalitede de anlamlı artışa neden olduğu gösterilmiştir (15). Kalça kırığı olan yaşlılarda bir yıllık mortalite hızı %15,1 olarak bildirilmiş, bu oran sadece osteoporozu olanlara (%5,1) ya da sarkopenisi olanlara (%10,3) göre daha yüksek bulunmuştur (16). Altmış beş yaş üzeri 316 bireyin dahil edildiği bir başka çalışmada; erkeklerde %10,4, kadınlarda %15,1 oranında osteosarkopeni saptanmış, osteosarkopenisi olanlarda kırılganlık oranının da tek başına osteoporotik veya sarkopenik olanlara kıyasla daha yüksek olduğu belirlenmiştir (17).

Patogenez

Yaşlanma ile birlikte kas dokusundaki protein ve iskelet sistemindeki kemik yapım-yıkım dengesi bozulmakta, bu bozulma inaktivite, travma gibi durumlarda daha da artmaktadır. Bu dengesizlik belli bir eşiğe gelince KMY'de, kas kütlesinde, kuvvetinde ve kas iskelet sistemi fonksiyonunda sinerjistik bir kayıp gerçekleşmekte ve osteosarkopeni gelişmektedir. Osteosarkopeni, kas ve kemik hücrelerinin kökeni olan mezenkimal kök hücrelerin yaşlanması ile farklılaşma ve çoğalma yeteneğinde azalmanın sonucudur. Kas ve kemik birbiriyle etkileşim içinde olan dokulardır. Bu etkileşimi etkileyen mekanik, biyokimyasal, genetik ve yaşam stili ile ilişkili faktörler, komorbiditeler ve bunların tedavisinde kullanılan çeşitli ilaçlar osteosarkopeninin patogenezinde rol oynamaktadır (Şekil 2) (7,9).

Hareket gerçekleşirken kaslar kemiklere mekanik olarak yük uygular. Kas kütlesi arttıkça kasın periosta uyguladığı gerim de artacak ve bu da kemik yapımını uyaracaktır. Fiziksel aktivite hem kas, hem de kemik kütlesini artırabilmektedir. Yaşlılıkta fiziksel aktivitenin azalmasıyla kas ve kemik arasındaki mekanik etkileşimin azalması osteosarkopeni gelişimini tetiklemektedir (18).

Kas ve kemik, miyokin ve osteokin adı verilen bazı faktörler üretmektedir. Bu faktörler kas-kemik etkileşiminde rol oynamaktadır. Kas kontraksiyonu ile stimüle olan miyokinler kemik yapım ve yıkımına karışmaktadır. Miyositler tarafından üretilen insülin benzeri büyüme faktörü-1 (İBF-1), fibroblast büyüme faktörü-2 (FGF-2) hem kas hem de kemikler için anabolik faktörlerdir. Başka bir miyokin olan interlökin-6 (IL-6) ise kemik yıkımını tetiklemektedir. Benzer şekilde, kemik iliğindeki stromal hücreler tarafından üretilen osteokinler de kas hücrelerini etkileyebilmektedir (19). Yaşlanma ile kas ve kemik iliğine yağ infiltrasyonu artmakta ve salınan yağ asitleri ve adipokinler tarafından bu etkileşim bozulmaktadır. Osteosarkopenik



Şekil 2. Osteosarkopeni patofizyolojisi

FGF-2: Fibroblast büyüme faktörü-2, İBF-1: İnsülin benzeri büyüme faktörü-1, VEGF: Vasküler endotelial büyüme faktörü
(Kirk B, Al Saedi A, Duque G. Osteosarcopenia: A case of geroscience. Aging Med (Milton) 2019;2:147-56'dan uyarlanmıştır.)

kişilerde dolaşımda IL-6, adiponektin, leptin gibi adipokinler yüksek konsantrasyonlarda tespit edilmiştir (20). Bunların dışında büyüme hormonu (BH), gonodal cinsiyet hormonları, D vitamini gibi endokrin faktörler de yaşla birlikte azalmakta ve osteosarkopeni gelişiminde rol oynamaktadır.

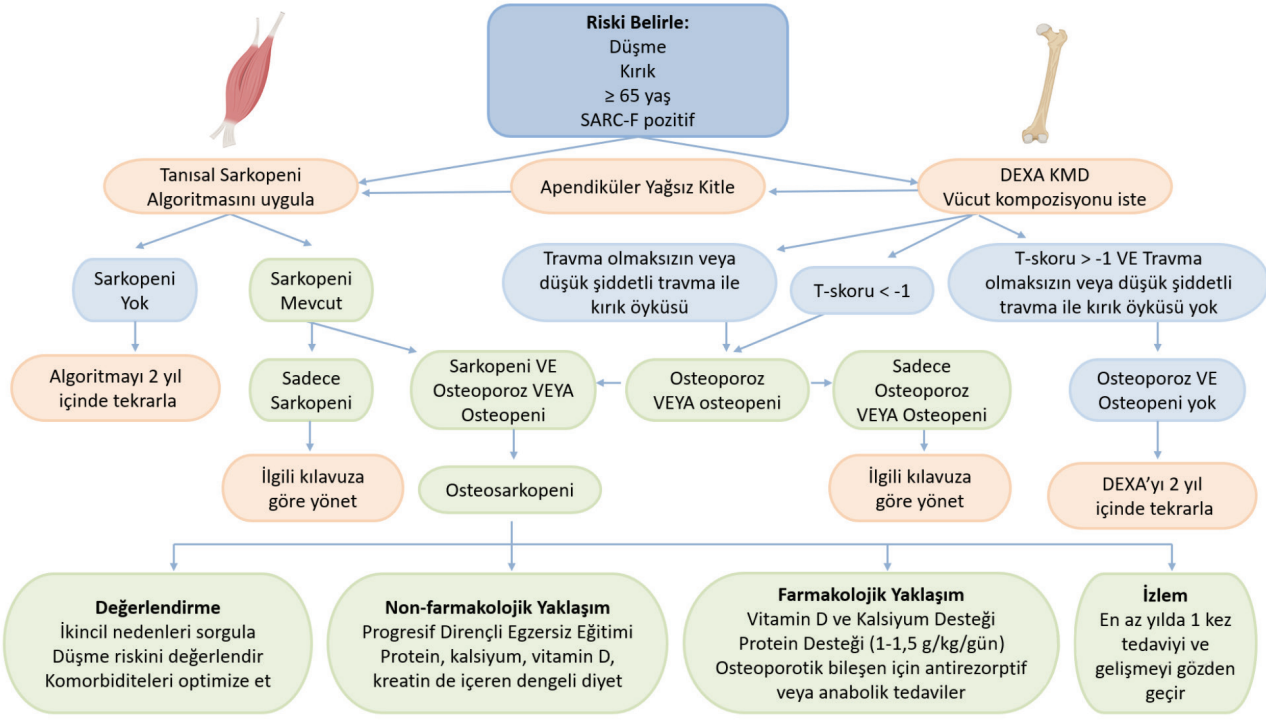
Bazı genetik polimorfizmler de osteosarkopeni patogenezinde rol oynamaktadır. Kas ve kemik hücreleri mezenkimal kök hücrelerinden köken aldığı için benzer genetik faktörlerden etkilenmesi doğaldır. Androjen ve östrojen reseptör, İBF-1, vitamin D reseptör, miyostatin, α-aktinin-3 genleri bunlardan bazılarıdır. Osteoporoz ve sarkopeninin kalıtılabilirliği %60-70 oranlarındadır (21).

Hipertiroidizm, hiperparatiroidizm, diyabet, hiperlipidemi gibi durumların osteosarkopeni ile ilişkileri gösterilmiştir. Diyabette oluşan ileri glikasyon son ürünleri kemik yapımını ve miyoblast profilerasyonunu azaltmakta ve apoptozisi indüklemektedir (9). Glukokortikoid tedavisi ise kemik yeniden şekillenme döngüsünü azaltmakta, aynı zamanda kas protein sentezini de bozmaktadır (22).

Yaşlanma ile fiziksel aktivitenin azalması dışında, kas kuvvetinde önemli olan protein ve D vitaminin diyetle alımının azalması ve D vitaminin deriden sentezinin azalması da osteosarkopeni gelişimine katkıda bulunmaktadır. Protein alımının azalması ile düşük kas ve kemik kütlesi arasında ilişki bildirilmektedir (23). Gözlemsel çalışmalar D vitamini ve kas-kemik sağlığı arasında etkileşim olabileceğini düşündürmektedir (24). Bu konuda yapılan bir hayvan çalışmasında miyositlerdeki vitamin D reseptör eksikliği ile kas kuvvet ve fonksiyonunda azalma arasında ilişki olduğu gösterilmiştir (25). D vitamini düşüklüğü ve kas kuvvetinin azalması düşme riskini de artırmakta ve düşmeler de kas ve kemiği olumsuz etkilemektedir. Ayrıca sigara ve alkol gibi alışkanlıklar da osteoporoz gelişimi için risk faktörleridir.

Klinik Ölçme ve Değerlendirme

Osteosarkopeninin klinik değerlendirmesi hem osteoporoz hem de sarkopeni değerlendirmesinin eş zamanlı yapılmasını gerektirir. Bu bağlamda osteosarkopenin değerlendirme ve tanısı, detaylı öykü (tıbbi ve sosyal öykü, düşme ve kırık öyküsü, ilaç kullanımı), risk faktörlerinin belirlenmesi, fiziksel değerlendirme, görüntüleme yöntemleri ve laboratuvar testlerini içermektedir (6). Osteosarkopeni için başlıca risk faktörleri; yaşlanma, fiziksel inaktivite, beslenmeyle ilgili faktörler (düşük protein alımı, D vitamini eksikliği, aşırı alkol alımı, obezite, kaşeksi, malabsorpsiyon), komorbid durumlar (Tip 2 diyabet, hipogonadizm, tiroid hastalıkları, erken menopoz, enflamatuvar hastalıklar, maligniteler, organ yetmezlikleri) ve ilaç kullanım (glukokortikoid, kemoterapötikler, heparin, antiepileptikler, aromataz inhibitörleri, aşırı tiroksin, gonadotropin salgılatıcı hormon agonistleri) öyküsüdür. Osteosarkopenin değerlendirmesine ve tedavisine yönelik Kirk ve ark.'nın (6) önerdiği klinik algoritma Şekil 3'te gösterilmiştir. Bu algoritma, rutin klinik uygulamada osteosarkopeniye yaklaşıma ışık tutması açısından önemlidir (6).



Şekil 3. Osteosarkopeniye klinik yaklaşım algoritması
DXA: Dual enerji X-ray absorbsiyometri, KMD: Kemik mineral dansitesi
Kirk B, Zanker J, Duque G. Osteosarcopenia: epidemiology, diagnosis, and treatment- facts and numbers. J Cachexia Sarcopenia and Muscle 2020;11:609-18.'den uyarlanmıştır.)

Osteoporoz

Osteoporoz tanısı için dual enerjili X-ışını absorbsiyometri (DXA) ile KMY ölçümü yapılmaktadır. Osteoporoza bağlı kırık riskinin belirlenmesinde ise "kırık riski değerlendirme aracı (FRAX®)" kullanılmaktadır (26). FRAX®, 10 yıllık kalça kırığı ve majör osteoporotik kırık (kalça, klinik vertebra, el bileği, proksimal humerus) geçirme olasılığını hesaplayan web tabanlı bir algoritmadır (27). 2008 yılında geliştirilmiş olup, kullanımı birçok kılavuzda önerilmektedir. Ülkeye özel FRAX modelleri oluşturulmuştur; Türkiye'nin de içinde bulunduğu 66 ülkede kullanılmaktadır. FRAX, yedi klinik risk faktörünü (geçirilmiş kırık, ebeveynde kalça kırığı, sigara kullanımı, sistemik kortikosteroid kullanımı, alkol kullanımı, romatoid artrit, sekonder oseoporoz), yaş, cinsiyet ve vücut kitle indeksiyle birlikte değerlendirerek 10 yıllık kalça ve majör kırık riskini hesaplar. Opsiyonel olarak femur boyun KMY'si (g/cm^2) girilerek de hesaplama yapılmaktadır (Erişim Adresi: https://www.sheffield.ac.uk/FRAX/index.aspx?lang=tu).

Sarkopeni

Sarkopeni tanısı için üç kriterin varlığı önemlidir: 1) kas gücünde azalma, 2) kas kantite (kütle) ve kalitesinde azalma, 3) fiziksel performansta azalma (28). 2018'de Avrupa Sarkopeni Çalışma Grubu (EWGSOP) tarafından yenilenen sarkopeni tanımına göre birinci kriterin varlığı "olası sarkopeni", ek olarak ikinci kriterin de bulunması "kesin sarkopeni", her üç kriterin birlikte mevcudiyeti ise "ağır sarkopeni" olarak tanımlanmaktadır (29). Klinik uygulamada sarkopeni riskini belirlemede tarama testi olarak SARC-F önerilmektedir. SARC-F anketi, kişinin kendi bildirimine dayalı 5 sorudan (kuvvet, yürüme, sandalyeden kalkma, merdiven çıkma ve düşme) oluşmakta, toplam puan 0-10 arasında değişmekte olup, ≥4 puan sarkopeni riski bulunduğunu göstermektedir. SARC-F'nin sarkopeniyi belirlemedeki hassasiyeti orta derecede, özgüllüğü ise yüksektir (28). SARC-F'nin Türkçe versiyonu bulunmaktadır (30).

Kişide sarkopeni riskinin saptanması durumunda kesin tanı için yukarda belirtilen üç kriterin değerlendirilmesi gerekmektedir. Kas kuvvetindeki azalmayı belirlemek için el kavrama kuvveti ölçümü ideal test olarak kabul edilmekte ve Jamar dinamometre ile ölçülmektedir. Her iki el için üçer kez ölçüm yapılmakta ve en yüksek ölçüm esas alınmaktadır. Kavrama gücünün vücut kitle indeksine göre kadın ve erkekler için kesim (cut-off) değerleri belirlenmiştir (31). Kas kuvvetini değerlendirmek amacıyla kullanılan bir diğer test ise "sandalye kalkma testi"dir. Bu testte, kişinin oturur pozisyonda iken el ve kollarıyla tutunmadan sandalyeden 5 kez kalkıp oturması için gerekli süre ölçülmektedir. Test, alt ekstremitelerin kas kuvvetini yansıtması açısından değerlidir.

Fiziksel performans, hareketle ilişkili genel vücut fonksiyonlarının objektif bir ölçümü olup, sadece kas fonksiyonlarını değil, periferik ve santral sinir sistemi fonksiyonlarını da içeren bir kavramdır. Fiziksel performansın değerlendirilmesinde; yürüme hızı, "kısa fiziksel performans bataryası", "zamanlı kalk ve yürü testi" ve "400 metre yürüme testi" kullanılabilir. Yürüme hızını değerlendirmede en sık kullanılan test "4 metre normal yürüme hızı testi"dir (28). Bu test, EWGSOP tarafından fiziksel performansın değerlendirilmesi için önerilmekte ve kesim değeri olarak ≤0,8 metre/saniye ağır sarkopeninin bir göstergesi olarak kabul edilmektedir (29). Kısa fiziksel performans bataryası; yürüme hızı, denge ve sandalyeden kalmayı birlikte değerlendirmekte ve ≤8 puan kötü fiziksel performansı göstermektedir. Zamanlı kalk ve yürü testi; kişinin sandalyeden kalkıp, 3 metre yürüyüp geri dönüp sandalyeye oturmasına kadar geçen süreyi dikkate alan bir testtir. Dört yüz metre yürüme hızı testinde ise kişinin 20 metrelik bir mesafeyi olabildiğince hızlı olarak 20 kez yürümesi istenmektedir. Bu testlerin hepsinin mortaliteyi ve sarkopeni ile ilişkili sonuç parametrelerini belirleyici oldukları gösterilmiş olmakla birlikte demansı ya da yürüme ve denge sorunları olan yaşlılarda uygulanmaları mümkün olmayabilir. Sarkopeninin kesin tanısı için gerekli olan kas kütlesi ve kalitesi değerlendirilmesi ise görüntüleme yöntemleriyle yapılmaktadır.

Görüntüleme Yöntemleri

Osteoporoz

Kemik kuvvetini etkileyen değişik faktörler arasında KMY ortalama %70'den sorumlu olup, klinik pratikte kolaylıkla kantifiye edilebilir. KMY'nin ölçülmesi sadece osteoporoz tanısıyla ilişkili değildir; aynı zamanda kırık riski olasılığını değerlendirmede ve farmakolojik tedavi alan hastaların izleminde de önemlidir. *In vivo* KMY ölçümü DXA, bilgisayarlı tomografi (BT) ve ultrason (US) ile yapılabilir. Bunlar içerisinde hem klinik pratikte hem de araştırma çalışmalarında en sık kullanılan yöntem DXA'dır (32). Bu kantitatif yöntem alansal KMY ölçümü verir ve g/cm^2 olarak ifade edilir. DXA'nın avantajları arasında doğal ortam radyasyonu (2,4 mSv) ile karşılaştırıldığında hastalara çok düşük doz (1-6 μSv) vermesi sayılabilir. İkinci olarak, osteoporotik kırıklarla en ilişkili bölgelerden (proksimal femur ve lomber vertebra) KMY ölçümü yapılır. Daha yüksek kırık riski belirleyicilik değeri nedeniyle tanı için femur boynu referans bölge olarak seçilmiştir. Ancak lomber bölge ölçümleri tedavi ile oluşan değişiklikleri izlemek açısından daha etkindir. Üçüncü olarak da, DXA cihazları düşük tarama zamanları (1-3 dk) ile tüm dünyada yaygın olarak bulunmaktadır. Bununla birlikte, DXA ölçümlerinin bazı kısıtlılıkları da vardır. Yaşlılarda sık görülebilen osteoartroz ve kırık gibi sorunlara bağlı olarak ortaya çıkan lomber vertebra dansitesindeki değişiklikler KMY'yi artırabilir. Uygun DXA çekimi için teknisyenin hasta demografik verileri, hasta pozisyonlama ve veri analizi gibi bazı konulara çok dikkat etmesi gerekmektedir. DXA ile elde edilen KMY değerleri T-skoru veya Z-skoru olarak ifade edilir. Dünya Sağlık Örgütü tarafından yapılan tanımlamaya göre; lomber vertebra total veya femur boynu veya total kalça veya radius distal 1/3'ü T-skoru ≤-2,5 standart sapma (SS) olması durumunda osteoporoz, -1 ve -2,5 SS arasında olduğunda ise osteopeni tanısı konulmaktadır. Çeşitli nedenlerle (dejeneratif artrit, vertebra kırıkları, spinal cerrahi, total kalça artroplastisi) lomber bölge veya kalça ölçülemediğinde veya hiperparatiroidisi olan hastalarda önkol KMY değerleri de tanı için kullanılabilir.

DXA cihazı ile KMY dışında ek kantitatif ölçümler yapılabilir. Proksimal kalça aksis uzunluğu, boyun şaft açısı gibi parametrelerle kalça geometrisi değerlendirilebilir. Trabeküler kemik skoru (TBS), DXA cihazı ile elde edilebilir ve KMY'den bağımsız bir kırık riski belirleyicisidir. Daha yüksek TBS değerleri daha iyi bir mikromimari ile korele iken, daha düşük TBS değerleri daha zayıf bir mikromimari belirtir. Ayrıca, kantitatif vertebral morfometri de DXA cihazının lateral görüntülerinden elde edilerek vertebra yüksekliği ölçümleri için kullanılabilir.

DXA dışında görüntüleme yöntemleri konvansiyonel radyografi, BT ve US'dir. Osteoporozun radyografik özellikleri ışın geçirgenliğinde artış ve kortikal incelmedir. Ancak bu özellikler hastalığın ileri safhalarında, kemik kaybı %30 civarında olduğu zaman saptanabilir. Radyografiler kırıkların saptanması, değerlendirilmesi ve izleminde kullanılabilir. Kantitatif BT volümetrik KMY değerleri verir, g/cm^3 olarak ifade edilir. DXA'dan çok daha yüksek doz radyasyona maruz kalınır. US kullanımında ise radyasyon söz konusu olmayıp, osteoporoz tanısı koymak amacıyla değil, taramaya yönelik olarak kullanılmaktadır.

Sarkopeni

Sarkopeni tanısında görüntüleme yöntemleri giderek daha fazla önem kazanmakta olup, bu amaçla DXA, BT, US ve manyetik rezonans görüntüleme (MRG) kullanılmaktadır (32). Sarkopeni şüphesi durumunda vücut kompozisyonu (VK) değerlendirilmesi bu yöntemlerle yapılır. Ancak moleküler seviyede VK değerlendirmesi için DXA en sık kullanılan tekniktir, VK'nin üç kompartmanlı modeli olan yağ kütlesi, yağ dışı kütle ve vücut mineral içeriği verilerini sağlar. Ancak bu üç komponentin direkt ölçümünü vermediği için DXA VK ölçümü için altın standart teknik değildir. Sarkopeninin güncel tanımlaması hem kas kantitesi, hem de kas kalitesindeki bozulmayı içerir. Kas kütlesinin kantitatif değerlendirmesi DXA ile yapılır. DXA ile elde edilen "Apendiküler Yağ Dışı Kütle indeksi" sarkopeni değerlendirmesinde en sık kullanılan ölçümdür (33). BT ve MRG, yağ ve yağ dışı kütlenin segmental ve total ölçümüne izin veren çapraz kesitsel görüntüler sundukları için iskelet kas kütlesini kantifiye etmede altın standarttır. Ancak her iki yöntem de pahalı ve zaman alıcı olduğu için araştırma amaçlı kullanılmaktadır. Hastalarda yağ dışı kütlenin değerlendirmesi için yüksek güvenirliliği, düşük maliyeti ve düşük radyasyon dozları nedeniyle DXA klinik uygulamalarda en sık kullanılan tekniktir. Bununla birlikte DXA temelli yağ dışı kütle değerleri için popülasyona özgü referans verileri halen sınırlıdır (34).

Laboratuvar Yöntemleri

Osteoporoz

Osteoporoz tanı ve izleminde önerilen laboratuvar incelemeleri; rutin olarak yapılması önerilenler ve gerekli olduğunda yapılması önerilenler olmak üzere iki ana grupta incelenmektedir. Gerekli olduğunda yapılması önerilen testler ayırıcı tanı açısından öncelik kazanmaktadır. Rutin olarak yapılması önerilenler; tam kan sayımı, eritrosit sedimentasyon hızı veya C-reaktif protein, serum kalsiyum, fosfor, alkalen fosfataz, karaciğer transaminazları, kreatinin, serum 25 hidroksi vitamin D (bazı kılavuzlarda rutin olarak ölçülmesi önerilmektedir) ve tiroid fonksiyon testleridir. Gerekli olduğunda yapılması önerilen testler; serum immünelektroforez ve idrarda Bence Jones proteini, paratiroid hormon, idrarda kalsiyum, serum testosteron, seks hormonları bağlayıcı protein, folikül uyarıcı hormon, lüteinleştirici hormon, kemik döngü belirteçleri (rezorbsiyon için: serumda tip 1 kollajenin C terminal telopeptidi, idrarda N terminal telopeptidi, formasyon için: serum prokollajen tip I N propeptid, 24 saatlik serbest kortizol, gecelik Deksametazon Supresyon testi, endomisyal ve doku transglutaminaz antikorlarıdır (35-37).

Sarkopeni

Sarkopeni tanısı ve izlemi açısından tek bir biyobelirteç geliştirilmesi ve validasyonu kolay ve uygun maliyetli bir yol olabilir. Bununla birlikte, sarkopeninin karmaşık patofizyolojisi nedeniyle, genç ve yaşlı insanların heterojen popülasyonundaki durumu tanımlayabilen tek bir biyobelirteç olması olası görünmemektedir. Bunun yerine, potansiyel serum belirteçleri ve doku belirteçleri de dahil olmak üzere bir biyobelirteç panelinin geliştirilmesi düşünülmektedir. Günümüzde bazı potansiyel biyobelirteçler, nöromüsküler kavşak belirteçleri, kas proteini döngüsü, davranış aracılı yollar, enflamasyon aracılı yollar, redoks ile ilgili faktörler ve hormonlar veya diğer anabolik faktörler söz konusu olmaktadır (38,39). Ayrıca İBF-1 aktivitesinin iskelet kasının idamesinde potansiyel bir rolü olduğunu gösteren araştırmalar da vardır. Fakat kemik kütlesine etki söz konusu değildir. Araştırmacılar çalışmaların yaş ve cinsiyet farkları gözetilerek ilerletilmesini önermekte, osteosarkopeni fenotipinin belirleyicilerinin gençlik döneminde daha fazla araştırılmasına ve kesin tanı kriterlerinin tanımlanması sonrasında çalışmalara hız verilmesine vurgu yapmaktadırlar (40).

Kreatin, karaciğer ve böbrek tarafından üretilen ve ayrıca et açısından zengin diyet ile alınan doğal bir amino asittir. Bir kısmı her gün kas hücreleri tarafından alınır ve geri dönüşü olmayan bir şekilde yüksek enerjili bir metabolit olan fosfokreatine dönüştürülür. Dolaşımdaki aşırı kreatin, kreatinin olarak değiştirilir ve idrarla atılır. Kreatinin atılım oranı, tüm vücut kas kütlesini tahmin etmek için umut verici bir temsili (proxy) ölçü olarak görülmektedir (41). İdrardaki D3-kreatinin zenginleştirmesinden toplam vücut kreatin havuzu büyüklüğü ve kas kütlesi hesaplanabilmektedir. Kreatin seyreltme testi sonuçlarının, kas kütlesinin MRG tabanlı ölçümlerle ve DXA ölçümleriyle ilişkili bulunduğunu bildiren araştırmalar vardır (42,43). Kreatin dilüsyon testi şu anda çoğunlukla araştırmalarda kullanılmaktadır, bu nedenle bu metodolojinin klinik ortamlarda kullanım açısından pratik ve güvenilir hale getirilmesi için daha fazla iyileştirme yapılması gerekmektedir (5).

Osteoporoz ve sarkopeninin hem örtüşen, hem de ayrışan karmaşık patofizyolojik yapıları nedeniyle klinik açıdan osteosarkopeni tanısı ve izleminde kullanılacak geçerli ve güvenilir özgün laboratuvar testlerin geliştirilmesi ve rutin pratik uygulamalara yansıması zaman alacak gibi görünmektedir.

Farmakolojik Tedavi

Osteosarkopeni tedavisi için çeşitli farmakolojik olmayan yaklaşımlar benimsenmiş olmakla birlikte ne yazık ki halen etkinliği ve güvenirliliği kanıtlanmış spesifik bir farmakolojik tedavisi bulunmamaktadır. Bununla birlikte, osteosarkopeninin altında yatan mekanizmalar anlaşıldıkça bu konuda yapılan çalışmalar hızlanmış ve gelecek vadeden bulgular elde edilmiştir.

Denosumab

Denosumab nükleer faktör kappa-B reseptör aktivatörü (RANK) ligandına karşı geliştirilmiş insan monoklonal antikorudur. Osteoklast aktivasyonunu, differansiyasyonu ve fonksiyonunu inhibe ederek kemik rezorbsiyonunu azaltır ve böylece KMY artar. İlacın etkinliğini ve güvenirliliğini değerlendirmek amacıyla tasarlanan FREEDOM çalışmasında; kırık riskinde azalmanın yanı sıra denosumab kullanan hastalarının daha az sıklıkta düştüğü de gözlenmiştir (44). Bu gözlemsel bulgudan yola çıkarak, özellikle osteoporozu ve/veya sarkopenisi olanlarda denosumabın kas kuvveti üzerine etkisini incelemek amacıyla Bonnet ve ark. (45) bir çalışma planlamıştır. İlk olarak, ortalama 3 yıl süreyle denosumab kullanmakta olan postmenopozal osteoporozlu kadınlarla tedavi almayanlar veya bifosfonat kullananlar karşılaştırılmıştır. Hem denosumab hem de bifosfonat kullananlarda KMY değerleri artış gösterirken, sadece denosumabın apendiküler yağsız vücut kütlesini ve kavrama kuvvetini artırdığı tespit edilmiştir. İkinci aşamada, RANK ligandı inhibitörlerinin kas üzerine direkt etkisini incelemek amacıyla hayvan deneyi gerçekleştirilmiş ve görülmüştür ki RANK ve RANK ligandı iskelet kaslarında da eksprese olmaktadır. Farelerde RANK ligandının aşırı ekspresyonu; trabeküler ve kortikal kemik hacminde ciddi azalmaya neden olurken, kas kütlesinde/kuvvetinde azalma ve sarkopenide olduğu gibi kaslarda yağ infiltrasyonu da yol açmıştır. Kaslarda meydana gelen bu değişiklikler, miyostatin ve protein tirozin fosfataz reseptör tip G adı verilen kasta yer alan antimiyojenik/enflamatuvar belirteçlerin artmış ekspresyonu ile ilişkili bulunmuştur. Bu bulgular ışığında, RANK/RANK ligandı/osteoprotegerin sisteminin kas metabolizmasında ve sarkopeni gelişiminde anahtar role sahip olduğu öne sürülmüştür. Denosumabın kas kuvveti ve fonksiyonları üzerine etkilerini tam olarak ortaya koyacak prospektif çalışmalara gereksinim vardır.

Testosteron

Testosteron düzeylerinin yaşla birlikte azalması, kemik kaybına ve kas kuvvetinde azalmaya yol açar. Bu nedenle, testosteronun osteosarkopeni gelişiminde önemli bir faktör olduğu düşünülmektedir. Testosteron kullanımı ile KMY'de ve protein sentezini artırarak kas kütlesinde ve kuvvetinde artış sağlandığı gösterilmiştir. Fakat yan etkilerinden çekinildiği için son yıllarda çalışmalar selektif androjen reseptör modülatörleri üzerinde yoğunlaşmaya başlamıştır. Bu ilaçlar, testosteron gibi kas ve kemik üzerinde anabolik etkiye sahipken doz sınırlayıcı androjenik etkiler (örneğin; prostat büyümesi, akne) göstermezler. Her ne kadar elde edilen ilk bulgular kas ve kemik üzerinde olumlu etkileri olduğu yönünde olsa da bu ajanların uzun süreli etkilerini değerlendirecek ileri çalışmalar yapılması gereklidir (46,47).

Büyüme Hormonu

Yaşlanmayla birlikte BH ve İBF-1 düzeylerinin azaldığı bilinmektedir. Sağlıklı yaşlılarda BH tedavisinin etkinliğini ve güvenirliliği değerlendirmek amacıyla yapılan bir sistematik derlemede; ortalama 27 hafta süreli tedavi ile vücut ağırlığı değişmeksizin yağsız vücut kütlesinin arttığı fakat KMY değerlerinde herhangi bir değişiklik olmadığı belirlenmiştir. Bununla birlikte tedavi alanlarda yumuşak doku ödemi, artralji, karpal tünel sendromu, jinekomasti ve glukoz intoleransı ya da diabetes mellitus gibi yan etkiler daha sık görülmüştür. Bu nedenle de, yaşlanma karşıtı tedavi olarak kullanılması önerilmemiştir (48). 2018 yılında yayınlanan ve 8 çalışmanın dahil edildiği bir başka metaanalizde ise; BH tedavisi ile postmenopozal osteoporozu olan kadınlarda kırık riskinde azalma sağlanabileceği fakat KMY üzerinde olumlu bir etkisinin olmadığı sonucuna varılmıştır (49).

Anti-miyozin Antikorları

Miyostatin iskelet kasında sentezlenen ve kas büyümesini inhibe eden bir proteindir. Böbrek yetmezliği, kronik obstrüktif akciğer hastalığı ve HIV gibi çeşitli hastalıklarda görülen kas kaybı kısmen myostatin artışıyla açıklanmıştır (50). Anti-miyozin antikorlarının farelerde kas kütlesini ve kuvvetini artırdığı tespit edilmiştir (51). Düşme öyküsü olan 75 yaş ve üstü bireylerin dahil edildiği bir faz 2 çalışmada da; yağsız vücut kitlesinde artışla birlikte kas gücüyle ilişkili bazı fonksiyonel ölçümlerde (merdiven çıkma zamanı, 5 tekrarlı sandalyeye otur kalk testi, yürüme hızı) iyileşme olduğu saptanmıştır (52). Her ne kadar hayvan deneylerinde bu antikorların kemik kütlesini de artırdığı yönünde bulgular olsa da insanlarda da benzer etkiler oluşturduğu klinik çalışmalarla kanıtlanmalıdır.

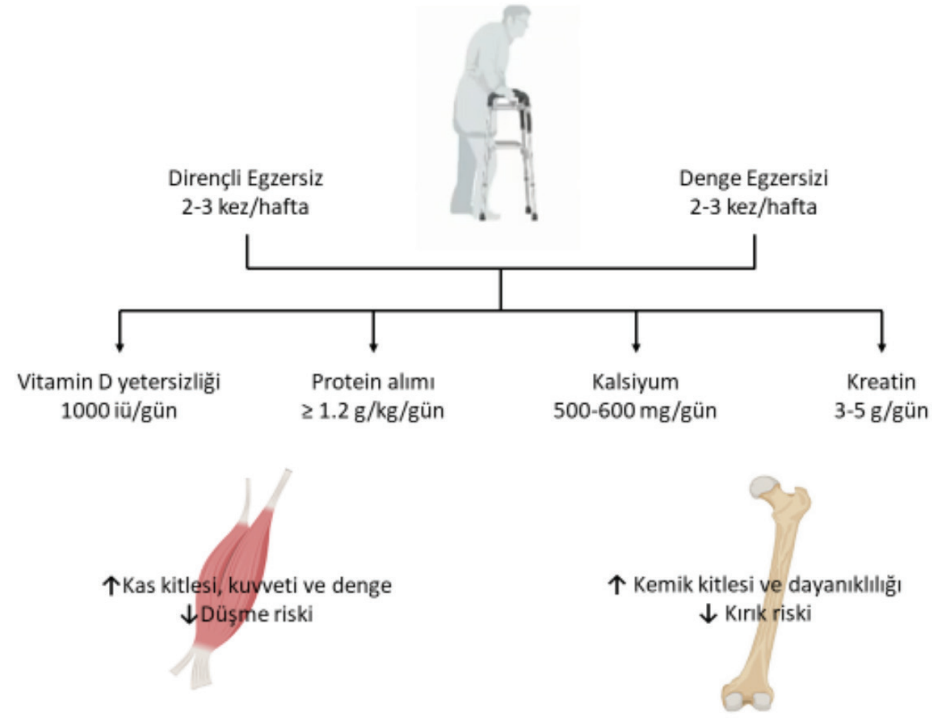
Farmakolojik Olmayan Tedaviler

Osteosarkopenide farmakolojik olmayan tedavi seçenekleri arasında egzersiz, protein, kalsiyum, D vitamini ve kreatin takviyeleri ve yaşam tarzı değişikleri yer almaktadır (Şekil 4).

Egzersiz

Dinamik bir doku olan kemik, fiziksel ve mekanik uyarıların başlatacağı; kontraksiyon, traksiyon ve vibrasyon etkilerine gerek kemik, gerekse kas yapılanması ile osteoporozun ve sarkopeninin tedavisi açısından olumlu yanıt verir. Etkin egzersizin şekli, süresi, sıklığı gibi halen tartışmalı konularda standardizasyon sağlanamamış olsa da egzersiz reçetelerinin zaten kişiye özel planlanması gerektiği de unutulmamalıdır (53). Egzersiz reçetesinin kişiye uygunluğunu sağlamak için vücut ağırlığına karşı yapılan tüm egzersizlerde alt ekstremitelerde yük taşıyan eklemlerin durumu ve diğer sistemlerle ilgili mevcut tanı ve riskler iyi değerlendirilmelidir.

Osteoporozun önlenmesi ve tedavisi için, yavaş hızda (<4 km/saat) yapılan tempolu yürüyüşlerin ve kondisyon bisikleti gibi zemin tepkime kuvvetini yansıtmayan ve vücut ağırlığı ile yüklenmenin



Şekil 4. Osteosarkopeninin farmakolojik olmayan tedavi seçenekleri
(Kirk B, Zanker J, Duque G. Osteosarcopenia: epidemiology, diagnosis, and treatment- facts and numbers. J Cachexia Sarcopenia and Muscle 2020;11:609-18.'den uyarlanmıştır.)

olmadığı aerobik egzersizlerin KMY'yi artırmada etkisiz olduğu son yılların yayınlarında belirtilmektedir (54). En az 6 km/saat hızda yapılan tempolu yürüyüş programları, koşu (6-9 km/saat) ve atlama sıçrama gibi yüksek zemin tepkime kuvvetlerine karşı vücut ağırlığı yüklenmesi ile yapılan egzersizlerin KMY artışında etkin olacağı görüşü artık hakimdir (55,56).

Progresif dirençli egzersizlerin uygulanmasıyla, osteoblastogenezisinin ve kas protein sentezinin uyarıldığını gösterilmiştir. Böylece, kemik mikromimarisinde düzelme, kas kütlesinde ve kuvvetinde artış, fiziksel fonksiyonel iyileşme olması osteoporotik ve sarkopenik ileri yaş grubunda önemli kazanımlar sağlar. 12-24 hafta süreyle ve haftada 3 defa uygulanan dirençli egzersiz programıyla bu etkilerin sağlanması mümkündür. Dirençli egzersizlerin denge ve postür çalışmaları ile desteklenmesi, dönüşümlü ve kombine programların uygulama süresi, sıklığı bireyin potansiyeline göre düzenlenmelidir (57-59).

Total vücut vibrasyon sistemlerinin dirençli egzersizlerin etkisini artırabileceği savunulmuşsa da; çalışmalar vibrasyon uygulanmasında kalıcı bir etki elde edilmediğinden, bunun da doz, frekans, süre düzenlenmesindeki optimum değerlerin belirlenme zorluğundan kaynaklandığını açıklamaktadır (60). Etkisinden daha emin olduğumuz ve uzun yıllardır kas kuvvetlendirme programlarında kullanılan elektrostimülasyon sistemlerinden yararlanmakta da mümkündür, ancak bireyler için uygulama kolaylığı ve devamlılığı yönünden kişiye özel ev egzersiz programı ile birlikte, protein, kalsiyum, D vitamini ve benzeri düzenlemeler daha etkin sonuç verecektir (61).

Protein Takviyesi

Beslenme ile yeterli protein alınması veya ek protein desteği kas ve kemik dokunun temel yapıtaşı oluşu nedeni ile önemlidir. Protein, kalsiyum emiliminde artışının sağlanması, paratiroid hormon regülasyonu ve İBF-1'in salgılanmasındaki etkileri üzerinden kemik-kas fonksiyonlarının dengesine katkı sağlar (62). Özellikle lösin aminoasidi içeren protein desteği ile (çizgili kasta mTORC1'in temel uyaranı) protein sentezini desteklemek, kas kuvvetinde ve fonksiyonellikte artış sağlamak mümkündür (63).

Sağlıklı kişiler için, yaş ve cins gözetilmeksizin önerilen protein alımı 0,8 gr/kg/gündür. Ancak, 65 yaş üstü bireylerde, ilerleyen yaşla birlikte kas iskelet sisteminin protein yararlanım hassasiyeti azaldığı için günlük protein ihtiyacı artar ve önerilen protein miktarı 1,2 gr/kg/güne yükselir (64). Bakım ve beslenme problemleri olan ve düşük protein (≤0,45 gr/kg/gün) içeren gıda ile beslenen 65 yaş üstü erişkinlerde kas atrofisi daha yaygın saptanmışken, protein takviyesiyle 3-24 ay beslenen ileri yaş grubunda sarkopeni bulgularında azalma olmuş ve kas kuvvetleri de artmıştır. Bu nedenle, ileri yaş grubunda 1-1,2 gr/kg/gün protein alımı veya öğünlere 25-30 gram protein takviyesi tavsiye edilmektedir (47).

Kalsiyum ve D vitamini Takviyesi

Dirençli kuvvetlendirme egzersizlerinin olumlu etkileri yeterli protein alınması ile artarken, protein de optimal D vitamini ve kalsiyum seviyeleri ile aktive olmaktadır. D vitamini kas ve kemik fizyolojisinin temel yapı moleküllerinden biridir.

Kalsiyum ve fosfat absorbsiyonunu artırıcı etkisi ile kontraktilite, mitokondriyal fonksiyonlar ve insülin hassasiyeti üzerinde etkilidir (65). D vitamini, kas ve kemik dokuda aracı görevi üstlenerek, miyokinlerin (miyostatin, vasküler endotelyal büyüme faktörü, İBF-1, osteoglisin) ve osteokinlerin (sklerostin, osteokalsin, FGF-2) regülasyonunu sağlar (66).

D vitamini ile sarkopeni arasındaki ilişkiyi incelemek amacıyla ileri yaş erkeklerde yapılan bir çalışmada; D vitamini seviyesi <40 nmol/L olanlarda 5 yıl içinde sarkopeni geliştirme insidansı yüksek bulunmuştur (67). Bir başka çalışmada; D vitamini seviyesi düşük olan (<25 nmol/L) 65 yaş üstü kadınlara 1.000 IU D vitamini takviyesi ile kas kütlesinde ve kuvvetinde artış olduğu tespit edilmiştir (68). Günlük D vitamini takviyesinin dozu, doğal beslenme alışkanlığı ve serum düzeyi ile ilişkilidir. Serum D vitamini düzeyinin 50-60 nmol/L arasında olması ve 100 nmol/L'nin üst limit olarak kabul edilmesi benimsenmiştir. Genellikle 800-1.000 iu/gün D vitamini ile birlikte 500 mg/gün kalsiyum desteğinin önerilmektedir (47).

Kalsiyum, kemiğin en önemli yapı mineralidir ve kas kontraksiyonunu sağlar. Sarkopeni riskinin azalması için yeterli miktarda alınması çok önemlidir. Optimal kemik sağlığı için diyetle 1.000-1.300 mg/gün kalsiyum alınmalıdır. Eğer diyetle alımda yetersizlik varsa 500 mg/gün kalsiyum desteği takviye olarak yapılmalıdır. Diyetle alınan veya yetersiz alındığı düşünülen kalsiyumu desteklemek için yüksek miktarlarda takviye alınması (>2,000 mg/gün), kardiyovasküler yan etki riskini artırabilir (69).

Kreatin

Kreatin (3-5 gr/gün) takviyesi ile dirençli egzersizlerin etkisinin artırılabildiği, kas kütle ve kuvvetinde iyileşme olduğuna dair bildirimler vardır ancak etkilerinin daha ayrıntılı araştırılması da önerilmektedir (6).

Yaşam Tarzı Değişiklikleri

Sigara ve alkol kullanımının gerek kemik, gerekse kas sağlığına olumsuz etkilerini bildiren çok sayıda çalışmalar mevcuttur. Sigara ve alkol kullanımına ara verilmesi durumunda ise; kırık riskinin azaldığı bildirilmiştir (6,47).

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Demographic, Clinical and Serological Characteristics of the Patients with Sjögren's Syndrome: A Tertiary Clinic Experience

Sjögren Sendromlu Hastaların Demografik, Klinik ve Serolojik Özellikleri: Üçüncü Basamak Deneyimi

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Abstract

Objective: This study aimed to evaluate the demographic, clinical and serological characteristics of patients with Sjögren's syndrome (SS).
Materials and Methods: Forty-nine patients with SS admitted to our outpatient clinic between January 2015 and April 2019 were included in this study. Patients were evaluated retrospectively in terms of age, gender and primary/secondary SS state; concomitant diseases with secondary SS, the presence of other related chronic diseases, minor salivary gland biopsy and autoantibody evaluation results were recorded.
Results: The mean age of the 49 patients (46 females, 3 males) included in the study was 48.39±11.45 years (minimum: 18, maximum: 81). Female/male ratio was 15.3/1. Thirty-four (69.4%) of the patients had primary SS, while 15 (30.6%) patients were diagnosed as secondary SS. The most common symptom at the time of diagnosis was dry eye (98%) and dry mouth (92%). Antinuclear antibody positivity was found to be 40.8% and rheumatoid factor positivity as 28.6%. Anti-SS-A and anti-SS-B was positive in 46.9% and 26.5% of the patients, respectively.
Conclusion: SS is characterised by heterogeneity of clinical manifestations, serological markers and symptoms. The symptom severity and variety of the patients are also affected by the other concomitant rheumatic diseases.
Keywords: Sjögren's syndrome, sicca symptoms, primary Sjögren's syndrome, secondary Sjögren's syndrome, auto-antibodies

Öz

Amaç: Bu çalışmada kliniğimize başvuran Sjögren sendromu (SS) tanılı hastalarımızın demografik, klinik ve serolojik özelliklerin değerlendirmesi amaçlandı.
Gereç ve Yöntem: Çalışmaya Ocak 2015 ve Nisan 2019 tarihleri arasında polikliniğimize başvuran SS tanılı 49 hasta dahil edildi. Hastaların geriye dönük olarak yaş, cinsiyet, SS'nin primer/sekonder olma durumu; sekonder ise hangi hastalığa eşlik ettiği, ilişkili olabilecek diğer kronik hastalıkların varlığı, tükürük bezi biyopsisi ve otoantikor değerlendirme sonuçları kaydedildi.
Bulgular: Çalışmaya katılan 49 hastanın (46 kadın, 3 erkek) yaş ortalaması 48,39±11,45 yıl (minimum: 18, maksimum: 81) idi. Kadın/erkek oranı 15,3/1 idi. Hastaların 34'ü (%69,4) primer SS tanısı alırken, 15'i (%30,6) sekonder SS idi. En yaygın başvuru yakınması kuru göz (%98) ve kuru ağız (%92) idi. Çalışmamızda anti-nükleer antikorlar pozitifliği %40,8 olarak saptanırken, romatoid faktör pozitifliği %28,6 idi. Hastaların %46,9'unda Anti-SS-A; %26,5'inde ise anti-SS-B pozitifti.
Sonuç: SS'de klinik bulgular, serolojik belirteçler ve semptomlar heterojendir. Hastaların semptom şiddeti ve çeşitliliği diğer eşlik eden romatizmal hastalıklardan da etkilenir.
Anahtar kelimeler: Sjögren sendromu, sikka semptomları, primer Sjögren sendromu, sekonder Sjögren sendromu, otoantikorlar

Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease; which causes dry eye and dry mouth (sicca symptoms) due to lymphocytic infiltration in the exocrine glands (1). Although sicca symptoms are the most common clinical findings; there are different clinical manifestations in SS (1).

In SS except lacrimal and salivary glands; other exocrine glands, lungs, kidneys and blood vessels may also been involved. The presence of the disease itself, is defined as "primary" SS (pSS); while in the presence of another concomitant autoimmune disease, the "secondary" SS (sSS) term is used. The most common accompanying diseases in patients with SS are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE),

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scleroderma, mixed connective tissue disease (MCTD), primary biliary cirrhosis (PBC), myositis, vasculitis, thyroiditis, chronic active hepatitis, mixed cryoglobulinemia. The disease is more common in women than men (9/1), most commonly seen in the 4th and 5th decades of life (2). However, it can be observed in adolescents and young adults (2). In a study of 837 women aged between 18-90; the prevalence of pSS was found to be 0.8% (3).

Among the autoimmune diseases, SS is associated with the highest risk of lymphoma. Five to ten percent of the patients will have a B cell lymphoma; mostly a low-grade type developing from mucosa-associated lymphoid tissue (4,5). Increased risk of developing lymphoma is the most important complication of SS and it is the most important factor affecting mortality rate in these patients (6).

In SS; clinical findings can vary from mild glandular manifestations to a wide range of symptoms; including vasculitis, glomerulonephritis, neuropathies and even lymphomas. There may be a pre diagnosis period of 8 to 10 years, most of which is accompanied by non-specific clinical findings (7). Early and accurate diagnosis of SS will prevent development of many complications associated with this disease. In this study, by the demographic, clinical and serological evaluations of the patients with the diagnosis of SS; we aimed to increase the data on SS, which has low clinical awareness among the patients and physicians.

Materials and Methods

The approval of Tokat Gaziosmanpaşa University Faculty of Medicine Ethics Committee was obtained for our study (approval number: 16.04.2019/19-KAEK-117). Forty-nine patients (46 females, 3 males; mean age 48.39±11.45 years) who were clinically diagnosed with SS; between January 2015 and April 2019; were included in the study. The data of the patients were evaluated retrospectively from the electronic health records in the hospital database. Therefore, informed consent form could not be obtained from the patients. The clinical diagnosis of SS is based on the American College of Rheumatology Classification Criteria for SS (at least 2 of the 3 criteria are required for diagnosis) (8). Those not fulfilling the criteria were excluded from the study. Serology screening for hepatitis B, hepatitis C and HIV was done in all patients and only those with negative serology for these viral agents were included in the study. Patients with radiotherapy to the head and neck region, sarcoidosis, amyloidosis, graft-versus-host disease, lgG4-related disease history and those with a history of drug using leading to sicca-like symptoms were excluded from the study. Histopathology results of the minor salivary gland biopsy from the lower lip were noted. Schirmer's test was used as the objective evidence for ocular involvement. Commercial ELISA kits (Euroimmun, Lubeck, Germany) were used for detection of rheumatoid factor (RF), anti- cyclic citrullinated peptide (anti-CCP), anti-nuclear antibody (ANA), anti-double stranded DNA antibody, anti-Sjögren's syndrome-related antigen A (Ro/SS-A), anti-Sjögren's-syndrome-related antigen B (La/SS-B), anti-histidyl transfer RNA synthetase and anti-topoisomerase I (anti-Scl 70) 70. The results of each test exceeding their own thresholds were considered to be positive. Clinical presentations including glandular and extraglandular manifestations; demographic features including age, gender; serological profile and others were noted.

We assessed the clinical outcomes of the patients in terms of sicca symptoms, joint symptoms and systemic involvement at the last recorded follow up visit. Major systemic involvement was defined as any significant involvements of musculoskeletal, renal, cardiovascular, gastrointestinal and neurological systems.

The study adhered to the principles of the Helsinki Declaration.

Statistical Analysis

IBM SPSS version 19.0 software was used for data analysis (IBM SPSS Statistics 19, Somers, New York). Descriptive statistics were given as number (n), percent (%), mean and standard deviation. A p value of <0.05 was considered to be statistically significant.

Results

The mean age of 49 patients (46 female, 3 male) included in the study was 48.39±11.45 years [minimum (min): 18, maximum (max): 81]. Female/male ratio was 15.3/1. Thirty four (69.4%) of the patients were pSS; fifteen (30.6%) patients were diagnosed as sSS. The distribution of the concomitant rheumatic diseases in patients with sSS is given in Table 1. All patients with sSS were female. The most common subjective presenting feature at the time of the diagnosis was dry eye (98%) and dry mouth (92%). Minor salivary gland biopsy was found positive in 43 (87.8%) patients. Arthralgia was seen in 37 (75.5%) patients; while the number of the patients with chronic arthritis was 10 (20.4%). Two of the three patients with Raynaud phenomenon, had concomitant scleroderma; one patient had MCTD. Of the

Table 1. Distribution of the concomitant rheumatic diseases in patients with secondary Sjögren's syndrome and the thyroid pathologies in all patients

Variables	n	%
Rheumatic diseases		
SLE	4	8.2
MCTD	4	8.2
RA	3	6.1
Scleroderma	2	4.1
FMF	2	4.1
Thyroid pathologies		
Hashimato thyroiditis	4	8.2
Multinodular goiter	3	6.1
Thyroid papillary cancer	1	2.0

SLE: Systemic lupus erythematosus, MCTD: Mixed connective tissue disease, RA: Rheumatoid arthritis, FMF: Familial Mediterranean fever

10 patients with chronic arthritis; three had RA, one had MCTD and one had SLE. The remaining five patients were diagnosed as pSS.

Eight patients (16.3%) had thyroid pathologies. The distribution of the thyroid pathologies in all patients is in Table 1. The patient with thyroid papillary cancer was also diagnosed with RA and PBC.

Two patients with renal involvement were diagnosed with pSS. One of the patients with renal involvement had tubulointerstitial nephritis; while the other one had renal tubular acidosis. Two of the patients had pericardial effusion; one of these patients also had a diagnosis of RA, while the other was diagnosed with pSS. Six patients (12.2%) had neurological involvement. In four of the patients with neurological involvement; vasculitic lesions were detected in the central nervous system, two patients had transverse myelitis. Serological characteristics of the patients are shown in Table 2. In four (66.7%) of the patients with neurological involvement, ANA was positive. However, only one patient with neurological involvement was also diagnosed with SLE; the other five patients were diagnosed with pSS. Two patients with positive anti-Scl 70 were diagnosed with scleroderma.

Discussion

In our study, 34 of the patients were diagnosed with pSS; while 15 patients were diagnosed with sSS. The mean age of our patients was 48.39±11.45 years (min:18, max:81). The female/male ratio of the patients was 15.3/1. Compared to the literature, the mean age of our patients was lower and the female/male ratio was higher (9).

SS is characterized by a heterogeneity of clinical manifestations, serological markers and symptoms. In SS, the incidence of extraglandular systemic symptoms is about one third. The symptom severity and variety of the patients is also affected by the concomitant rheumatic diseases. In patients with SS, typically the lacrimal and salivary glands are involved. It is known that patients often present with complaints of dry eye and dry mouth. Skin, lung, heart, gastrointestinal system, central and peripheral nervous system, musculoskeletal system and kidneys can also been involved by SS (9,10).

Table 2. Serological characteristics of the patients with Sjögren's syndrome

ANA	Positive/Negative	20 (40.8)/29 (59.2)
Anti-dsDNA	Positive/Negative	2 (4.1)/47 (95.9)
RF	Positive/Negative	14 (28.6)/35 (71.4)
Anti-CCP	Positive/Negative	2 (4.1)/47 (95.9)
Anti Ro/SS A	Positive/Negative	23 (46.9)/26 (53.1)
Anti La/SS B	Positive/Negative	13 (26.5)/36 (73.5)
Anti-Jo-1	Positive/Negative	1 (2)/48 (98)
Anti-Scl 70	Positive/Negative	2 (4.1)/47 (95.9)

Data are shown as n (%). ANA: Antinuclear antibody, Anti-dsDNA: Anti-double stranded DNA antibody, RF: Rheumatoid factor, Anti-CCP: Anti-cyclic citrullinated peptide, Anti Ro/SS A: Anti-Sjögren's syndrome related antigen A, Anti-La/SS B: Anti-Sjögren's-syndrome-related antigen B, anti-JO-1: Anti-histidyl transfer RNA synthetase, Anti-Scl 70: Anti-topoisomerase I

The most common rheumatic diseases associated with sSS are RA and SLE (11). Familial Mediterranean fever (FMF) and SS co-occurrence were reported as case reports in the literature (12,13). Three (6.1%) of our patients with sSS had RA, four (8.2%) with SLE, four (8.2%) with MCTD, two (4.1%) with scleroderma and two (4.1%) with FMF. Both of the patients with FMF were followed up with FMF for years. The clinic of SS was established over the time in these patients.

The musculoskeletal system findings of the SS include arthralgia, mostly non-erosive arthritis and sometimes myositis accompanied by elevation of muscle enzymes, myalgia and tenosynovitis which can lead to Jaccoud arthropathy (14).

The most common symptoms of the patients included in our study were dry eye and dry mouth; three quarters of the patients had arthralgia and approximately one-fifth of the patients had arthritis. The symptoms of arthritis and arthralgia were prominent in our patients with concomitant RA (7).

Systemic involvement in SS is well known; however, obvious cardiac manifestations are extremely rare although clinically silent involvements are fairly common on echocardiography (15). Two (4.1%) of our patients had pericardiac effusion due to cardiac involvement; one of our patients with cardiac involvement was sSS (with RA); the other patient was pSS.

Renal involvement in SS is not rare. The most common renal disease is tubulointerstitial nephritis. Renal tubular acidosis may develop in these patients (16). In three retrospective studies about overt renal involvement in pSS showed that renal involvement was seen in 5% and 4.3% of the patients, respectively (17,18). In our study, two (4.1%) patients were diagnosed with renal involvement; one patient was diagnosed as interstitial nephritis and one patient had renal tubular acidosis. Both of the patients with renal involvement were diagnosed with pSS.

Raynaud's phenomenon can be seen in one third of the cases with pSS (19). García-Carrasco et al. (20) found the frequency of Raynaud's phenomenon to be 13% in a study with 320 pSS patients and it was showed that joint involvement, skin vasculitis and serological findings were more common in the Raynaud phenomenon group. In our study, three (6.1%) patients had Raynaud phenomenon; two of the patients had concomitant scleroderma; one patient had MCTD. The frequency of Raynaud's phenomenon in our study group was lower than the literature (20).

Peripheral sensory or motor-sensory neuropathy can be seen at a frequency of 10-20% in pSS. Central nervous system involvement findings such as epilepsy and transverse myelitis have also been reported (21-23). Neurological involvement ratio was 12.2% in our study group. Our results were consistent with the literature (21-23). In four of the six patients with neurological involvement, vasculitic lesions were detected in the central nervous system; two patients had transverse myelitis. In four of these six patients, ANA was positive. One of these four patients had SLE. Particular attention should be paid to the development

of neurological symptoms in patients with SS who are positive for ANA autoantibody.

Autoantibodies are frequently found positive in SS. ANA positivity is 55-97%; RF positivity is 36-74% in SS. Anti-CCP positivity is 3-10%. There are anti-Ro/SS-A (50-70%) and anti-La/SS-B (25-40%) autoantibodies against the ribonucleoprotein antigen (24). The SS-B autoantibody is more specific, but less sensitive than the SS-A autoantibody. SS-A autoantibody is also found positive in other autoimmune diseases (25). In our study, ANA positivity was found to be 40.8% and RF positivity was 28.6%. Anti-SS-A positivity was 46.9% in our patients. In 26.5% of the cases, anti-SS-B was positive. Our data were compatible with the literature.

The main superiority of our study is that this is the first study evaluating the demographic, clinical and serological characteristics of patients with SS without primary-secondary discrimination. Thus, data on this disease in which there is a diagnostic delay of 8-10 years, will be increased and this study will contribute to the increase of patient-physician awareness to SS.

Study Limitations

Because of the retrospective design of our study, it is possible that some glandular and extraglandular findings have not been reported. Since it is a single-center study, the number of the patients is limited. Therefore, our results may not reflect the whole community. Long-term prospective studies are needed to determine the increased risk of malignancy in SS.

Conclusion

SS is characterized by a heterogeneity of clinical manifestations, serological markers, and symptoms. In SS, the incidence of extraglandular systemic symptoms is approximately one-third. The symptom severity and variety of the patient is also affected by accompanying rheumatic diseases. Although the most common symptom is sicca symptoms, there is a need for prospective studies about this disease, which has a wide symptomatology ranging from severe neurological involvement to lymphomas.

Ethics

Ethics Committee Approval: The approval of Tokat Gaziosmanpaşa University Faculty of Medicine Ethics Committee was obtained for our study (approval number: 16.04.2019/19-KAEK-117).

Informed Consent: Informed consent form could not be obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Y., Concept: N.Y., O.D., Design: N.Y., O.D., Data Collection or Processing: N.Y., Analysis or Interpretation: O.D., Literature Search: N.Y., O.D., Writing: N.Y., O.D.

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Ortopedi Doktorlarında Osteoporoz Farkındalığı

Awareness of Osteoporosis in Orthopaedic Surgeons

Tuğba Aydın

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Öz

Amaç: Bu çalışmanın amacı ülkemizde çalışan ortopedi doktorlarının primer osteoporozun tanı ve takibindeki farkındalığı ortaya koymaktır.
Gereç ve Yöntem: Bu çalışma açık erişimli, web tabanlı, çevrimiçi anket çalışması olarak planlandı. Üniversite hastanesi, eğitim araştırma hastanesi, devlet ve özel hastanelerde çalışan 166 ortopedi doktoru çalışmaya dahil edildi.
Bulgular: Doktorların %30,1'i postmenopozal hastalardan, %41,02'si 65 yaş üstü hastalardan, %38,6'sı kalça kırığı ile gelen hastalardan, %34,9'u vertebra kırığı ile gelen hastalardan, %4,8'i ön kol kırığı ile gelen hastalardan dual enerji X-ray absorbsiyometri (DXA) isterken, doktorların %30,1'i hiçbir hastadan DXA istemediklerini belirtti. Doktorların %63,9'u 65 yaş üstü kırıkla gelen hastayı osteoporoz açısından değerlendirmediğini söyledi. Frajilite kırığı tespit ettikleri hastalardan ortopedi doktorlarının %36,1'i D vitamini seviyesini istemediğini belirtti. Primer osteoporozda tedaviyi ortopedi doktorlarının %79,5'i DXA'nın T-skoruna, %15,7'si DXA'nın Z-skoruna, %55,4'ü yaşa, %37,7'si cinsiyete, %51,8'i frajilite kırığı varlığına, %37,3'ü daha önce kullandığı osteoporoz ilaçlarına, %13,3'ü FRAX risk sınıflamasına göre planladıklarını söyledi. Primer osteoporozda D vitamini düşüklüğü olan hastalara doktorların %22,9'u 300,000 IU 25 hidroksi vitamin D'yi [25(OH)D] içeren ampülleri oral olarak, %1,2'si bu ampülleri intramüsküler olarak verdiğini; doktorların %15,7'si 50,000 IU 25(OH)D içeren şişenin tümünü haftada bir oral olarak, %10,8'i bu şişeyi her gün damla olarak verdiğini söyledi.
Sonuç: Ortopedi doktorlarının osteoporoz hastalarının tanı ve takibindeki bilgi düzeyi ve farkındalığı beklenenden daha düşüktür. Kırık tedavisinden sorumlu olan ortopedi doktorlarında bu durumu iyileştirmek için ek çalışmalar ve müdahale programları gereklidir.
Anahtar kelimeler: Osteoporoz, ortopedi, anket

Abstract

Objective: In this study, we aimed to evaluate the awareness of orthopaedic surgeons working in Turkey regarding the diagnosis and follow-up of primary osteoporosis.
Materials and Methods: In this study designed as an open-access, web-based, online survey, 166 orthopaedic surgeons working in university hospitals, educational research hospitals and public and private hospitals were included.
Results: Overall, 30.1% doctors stated that they request for a dual-energy X-ray absorptiometry (DXA) scan in postmenopausal patients, 41.02%, 38.6%, 34.9% and 4.8% in patients aged >65 years, those with hip fractures, with vertebral fractures and with forearm fracture, respectively, whereas 30.1% doctors stated that they did not request for a DXA scan from any patient. Further, 63.9% doctors reported that they did not evaluate patients aged >65 years with fractures for osteoporosis. Of the patients with fragility fractures, 36.1% orthopaedic doctors stated that they did not request for vitamin D results. In primary osteoporosis, 79.5% orthopaedic surgeons stated that they treated with DXA's T-score, 15.7% with DXA's Z-score, 55.4% with age, 37.7% with gender, 51.8% in fragility fractures, 37.3% of the osteoporosis drugs previously used and 13.3% according to the FRAX risk classification. In primary osteoporosis, 22.9% doctors stated that they administered patients low vitamin D ampoules containing 300,000 IU 25 (OH) vitamin D orally and 1.2% administered it intramuscularly; moreover, 15.7% doctors administered these patients 50,000 IU 25 (OH) vitamin D bottle orally once a week, and 10.8% prescribed the vitamin to be taken as drops daily.
Conclusion: The knowledge and awareness of orthopaedic doctors in the diagnosis and follow-up of primary osteoporosis is lower than expected. Orthopaedic doctors involved in the treatment of fractures require additional studies and intervention programmes to improve their knowledge regarding this condition.
Keywords: Osteoporosis, orthopaedics, survey

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Giriş

Osteoporoz, düşük kemik kütlesi ve kemik dokusunun mikro-mimarisinin bozulması sonucunda kemik kırılabilirliğinde ve kırık riskinde artışla sonuçlanan progresif bir metabolik kemik hastalığıdır (1).

Osteoporoz, dünya çapında yılda yaklaşık 9 milyon kırığa neden olmaktadır (2). Sağlıklı kemikte kırık oluşturmayacak düzeydeki düşük düzeyli ve düşük enerjili travma olarak bilinen mekanik güçler sonucu oluşan kırığa frajilite kırığı denilir. Dünya Sağlık Örgütü'ne göre bu mekanik güç, ayakta durma pozisyonu ya da daha düşük mesafeden düşmeye denk olan güçtür. Frajilite kırıkları en çok vertebra, proksimal femur ve distal radiusta izlenir (2). Frajilite kırığı olan hastaların ilk bir yıl içinde tekrar frajilite kırığı geçirme riski %5,8 olup, bu oran her geçen yıl artmaktadır (3). Bu kırıklar yüksek mortalite, morbidite ve fonksiyonel bağımsızlık kaybına neden olmaktadır (4). Risk altında olduğu düşünülen hastalarda frajilite kırıklarının önlenmesi veya daha önce frajilite kırığı olan hastalarda yeni kırık oluşumunu önlemek için çeşitli tedaviler bulunmaktadır (2). Ancak osteoporozu olan birçok hasta frajilite kırığı oluşana kadar osteoporoz tanısı almamaktadır. Hatta çoğu zaman frajilite kırık tanısı alan hastalarda bile osteoporoz tanısı konulamamaktadır (5). Oysa kırık sonrası başlanan osteoporoz tedavisinin yeni kırık oluşumunu ve mortaliteyi azalttığı çalışmalarda gösterilmiştir (6,7).

Genellikle osteoporotik kırığı olan hastaları ilk değerlendiren ve tedavi eden doktorlar ortopedi doktorlarıdır. Bu nedenle ortopedi doktorları kırık ile başvuran hastalarda osteoporoz tanı ve tedavisini başlatarak, uzun vadeli sağlık sonuçlarını değiştirmek (sonraki kırılmanın önlenmesi, dizabilite ve mortalitenin azaltılması) için benzersiz bir fırsata sahiptirler (8). Ancak literatür incelendiğinde doğru osteoporoz tanı ve tedavisi alan osteoporotik kırık hastalarının oranının oldukça düşük olduğu görülmüştür (9-11). Bu durum bize ortopedi hekimlerinin osteoporoz için hastaları değerlendirmeyi ve osteoporozu tedavi etmeyi yeterince önemsemediklerini düşündürmüştür.

Bu çalışmada, ülkemiz ortopedi doktorlarının primer osteoporozun tanısı, takibi ve frajilite kırıkları konusundaki farkındalığını ortaya koymayı amaçlamıştır.

Gereç ve Yöntem

Bu çalışma online doldurulan web tabanlı bir ankettir. Çalışma protokolü, Helsinki Deklarasyonu'na uygun olarak 2019/18 onay numarası ile İstanbul Bakırköy Dr. Sadi Konum Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından onaylandı. Katılımcılar çalışma hakkında bilgilendirildi ve sözlü onamları alındı. Açık erişimli çevrimiçi SurveyMonkey yazılımı (SurveyMonkey, CA, U.S.A.; http://www.surveymonkey.com), anketimizi oluşturmak ve yönetmek için kullanıldı. Anket linki; üniversite hastanesi, eğitim araştırma hastanesi, devlet hastanesi ve özel hastanelerde çalışan; anketi doldurmaya gönüllü olan tüm ortopedi doktorlarına e-posta yolu ile gönderildi (n=180). Aktif olarak çalışmayan doktorlar ve asistanlık süresi 3 seneden az olan asistan hekimler çalışmaya alınmadı.

Ankette demografik bilgiler ve primer osteoporoz ile ilgili, iki farklı başlık altında incelenen sorular vardı. Sorular çoktan seçmeli olarak hazırlandı. Bazı soruların birden fazla cevabı vardı. Bazı soruların birden fazla cevabı olduğu anketin girişi bölümüne yazıldı.

İstatistiksel Analiz

Verilerin tanımlayıcı istatistiklerinde ortalama, standart sapma, medyan, en düşük, en yüksek, frekans ve oran değerleri kullanılmıştır. Nitel bağımsız verilerin analizinde ki-kare test kullanıldı. Analizlerde SPSS 22.0 programı kullanılmıştır.

Bulgular

Ankete katılmayı kabul eden 180 doktorun, 166 tanesinin anketi eksiksiz doldurduğu görüldü. Araştırmaya katılan doktorların yaş ortalaması 35,4±9,1 yıldı. Doktorların %42,2'si asistan, %47'si uzman, %7,2'si doçent, %3,6'sı profesör doktor idi. %14,5 doktor devlet hastanesinde, %53 doktor eğitim araştırma hastanesinde, %10,8 doktor özel sektörde, %21,7 doktor üniversite hastanelerinde çalışmaktaydı (Tablo 1).

Ortopedi doktorlarına günlük pratiklerinde hangi hastalardan dual enerji X-ray absorbsiyometri (DXA) istedikleri soruldu. Postmenopozal hastalardan doktorların %30,1'i, 65 yaş üstü hastalardan doktorların %41'i, kalça kırığı ile başvuran hastalardan doktorların %38,6'sı, vertebra kırığı ile başvuran hastalardan doktorların %34,9'u, ön kol kırığı ile başvuran hastalardan doktorların %4,8'i DXA isterken, doktorların %30,1'i hiçbir hastadan DXA istemediklerini belirtti (Tablo 1).

Primer osteoporozda tedavi ve takibi doktorların %6'sı hastalarını dahiliye hekimine, %60,2'si hastalarını fizik tedavi ve rehabilitasyon (FTR) hekimine yönlendirirken; doktorların %33,7'si tedavi ve takibi kendilerinin yaptıklarını söyledi (Tablo 1).

Altmış beş yaş üstü kırıkla gelen hastayı ortopedi doktorların %36,1'i osteoporoz açısından değerlendirirken, %63,9'u bu hastaları osteoporoz açısından değerlendirmediğini söyledi (Tablo 1).

Frajilite kırığı tespit ettikleri hastalarda ortopedi doktorlarının %36,1'i, D vitamini seviyesi istemezken, %63,9'u D vitamini seviyesini istemektedir. Yine aynı hasta grubunda doktorların %37,3'ü hastalardan serum kalsiyum (Ca), fosfor (P), kreatinin, alkalen fosfataz (ALP), parathormon (PTH) değerlerini isterken, doktorların %62,7'si istememektedir (Tablo 1).

Primer osteoporozda tedaviyi neye göre planlarsınız sorusuna ortopedi doktorlarının %79,5'i DXA T-skoruna göre cevabını, %15,7'si DXA Z-skoruna göre cevabını, %55,4'ü yaşa göre cevabını, %37,7'si cinsiyete göre cevabını, %51,8'i frajilite kırığı varlığına göre cevabını, %28,9'u frajilite kırığının lokalizasyonuna göre cevabını, %26,5'i mevcut hastalıklarına göre cevabını, %37,3'ü daha önce kullandığı osteoporoz ilaçlarına göre cevabını, %13,3'ü kırık riski değerlendirme aracı (FRAX) risk sınıflamasına göre cevabını seçti (Tablo 1).

Primer osteoporozda D vitamini düşüklüğü tespit ettiğiniz hastalara D vitamini tedavisini nasıl verdiklerini sorduğumuzda,

Tablo 1. Ortopedi doktorlarında osteoporoz değerlendirme anket verileri					
		Minimum-maksimum		Medyan	Ortalama ± SS/ (n-%)
Yaş (yıl)		25	66	33	35,4±%9,1
Uzmanlık	Asistan	-	-	-	70±%42,2
	Uzman	-	-	-	78±%47
	Doçent	-	-	-	12±%7,2
	Profesör	-	-	-	6±%3,6
Çalışılan kurum	Devlet hastanesi	-	-	-	24±%14,5
	Eğitim araştırma hastanesi	-	-	-	88±%53
	Özel sektör	-	-	-	18±%10,8
	Üniversite	-	-	-	36±%21,7
Günlük pratiğinizde hangi hastalardan DXA istiyorsunuz					
Postmenopoz bütün hastalardan		-	-	-	50±%30,1
65 yaş üstü bütün hastalardan		-	-	-	68±%41
Kalça kırığı ile başvuran bütün hastalardan		-	-	-	64±%38,6
Vertebra kırığı ile başvuran bütün hastalardan		-	-	-	58±%34,9
Ön kol kırığı ile başvuran bütün hastalardan		-	-	-	8±%4,8
Hiçbir hastadan DXA istemiyorum		-	-	-	50±%30,1
Primer osteoporozda tedavi ve takip					
Dahiliye hekimine yönlendiririm		-	-	-	10±%6
Fizik tedavi ve rehabilitasyon hekimine yönlendiririm		-	-	-	100±%60,2
Tedaviyi ve takibi kendim yaparım		-	-	-	56±%33,7
65 yaş üstü kırıkla gelen hastayı osteoporoz için	Değerlendirmem	-	-	-	60±%36,1
	Değerlendiririm	-	-	-	106±%63,9
Frajilite kırığı tespit ettiğim hastalarda	D vitamini seviyesi istemem	-	-	-	60±%36,1
	D vitamini seviyesi isterim	-	-	-	106±%63,9
Frajilite kırığı olan hastalarda Ca (Ca, P, kreatinin, ALP, PTH) parametrelerini	İstemem	-	-	-	62±%37,3
	İsterim	-	-	-	104±%62,7
Primer osteoporozda tedaviyi kendiniz yaparsanız, tedavi planınızı neye göre yaparsınız?					
DXA T-skoruna göre		-	-	-	132±%79,5
DXA Z-skoruna göre		-	-	-	26±%15,7
Yaşa		-	-	-	92±%55,4
Cinsiyete		-	-	-	62±%37,3
Frajilite kırığı varlığına		-	-	-	86±%51,8
Frajilite kırığının lokalizasyonuna		-	-	-	48±%28,9
Diğer mevcut hastalıklarına		-	-	-	44±%26,5
Daha önce kullandığı osteoporoz ilaçlarına göre		-	-	-	62±%37,3
FRAX risk sınıflamasına göre		-	-	-	22±%13,3
Primer osteoporozda D vitamini düşüklüğü tespit ettiğim hastalara					
300.000 IU 25(OH)D içeren ampulleri oral olarak veririm		-	-	-	38±%22,9
300.000 IU 25(OH)D vitamini içeren ampulleri intramuskuler olarak veririm		-	-	-	2±%1,2
50.000 IU 25(OH)D içeren şişenin tümünü haftada bir oral olarak veririm		-	-	-	26±%15,7
50.000 IU 25(OH)D içeren şişeyi her gün damla olarak veririm		-	-	-	18±%10,8
Sadece Ca ile kombine şekilde bulunan D vitamini preparatları veririm		-	-	-	32±%19,3
Diğer branşlara yönlendiririm		-	-	-	50±%30,1
Primer osteoporozda D vitamini düşüklüğü tespit ettiğim hastalara Ca replasmanı					
Başlamam		-	-	-	70±%42,2
Başlarım		-	-	-	96±%57,8

SS: Standart sapma, DXA: Dual enerji X-ray absorbsiyometri, Ca: Kalsiyum, P: Fosfor, ALP: Alkalen fosfataz, PTH: Parathormon

%22,9 ortopedi doktorunun 300,000 IU 25(OH)D vitamini içeren ampulleri oral olarak verdiğini, %1,2 doktorun 300.000 IU 25(OH)D vitamini içeren ampulleri intramuskuler olarak verdiğini, %15,7 doktorun 50.000 IU 25(OH)D vitamini içeren şişenin tümünü haftada bir oral olarak verdiğini, %10,8 doktor 50.000 25(OH)D vitamini içeren şişeyi hergün damla olarak verdiğini, %19,3 doktor sadece Ca ile kombine şekilde bulunan D vitamini preparatları verdiğini söyledi. %30,1 ortopedi doktoru ise D vitamini düşüklüğü tespit ettiği hastasını diğer branşlara yönlendirdiğini belirtti (Tablo 1).

Primer osteoporozda D vitamini düşüklüğü tespit ettiğinizde hastalarınıza Ca replasmanı da başlar mısınız diye sorduğumuzda ise doktorların %42,2'si replasman vermezken, %57,8'i Ca replasmanı yaptığını söyledi (Tablo 1).

Asistan (eğitiminin 3. senesini bitirmiş) ve uzmanlar (uzman, doçent ve profesörler) arasındaki anket verilerini karşılaştıran verilere Tablo 2'de yer verilmiştir. Buna göre uzmanlarda 65 yaş üstü hastalardan DXA isteme oranı ve kalça kırığı olan hastalardan DXA isteme oranı asistanlardan anlamlı ($p<0,05$) olarak daha fazlaydı. Hiçbir hastadan DXA istememe oranı ise asistanlarda uzmanlardan anlamlı ($p<0,05$) olarak daha fazlaydı (Tablo 2).

Uzmanlarda primer osteoporoz tedavisi kendisini yapma oranı, asistanlarda ise primer osteoporoz tedavisini FTR uzmanına yönlendirme oranı anlamlı ($p<0,05$) olarak daha fazlaydı (Tablo 2).

Uzmanlarda 65 yaş üstü kırıkla gelen hastaları osteoporoz açısından değerlendirme oranı asistanlardan anlamlı ($p<0,05$) olarak daha fazlaydı (Tablo 2).

Uzmanlarda primer osteoporozda tedaviyi DXA T-skoruna göre başlama oranı asistanlardan anlamlı ($p<0,05$) olarak daha fazlaydı, yine uzmanlarda tedaviyi DXA Z-skoruna göre başlama oranı ise asistanlardan anlamlı ($p<0,05$) olarak daha düşüktü. Asistanlarda primer osteoporozda tedaviyi FRAX sınıflamasına göre başlama oranı uzmanlardan anlamlı ($p<0,05$) olarak daha fazlaydı (Tablo 2).

Tartışma

Bu çalışma ülkemizde ortopedi doktorlarının osteoporoz konusundaki bilgi düzeyini sorgulayan ortopedi doktorlarına yapılan ilk anket çalışmasıdır. Osteoporoz, progresif kırık oluşana kadar sıklıkla asemptomatik kalan sessiz bir hastalıktır. Türkiye'de 2010 yılında yapılan Fraktürk çalışmasında 50-64 yaş arası kişilerde kalça kırığı 1 yılda toplam 24.000 kişide görülmektedir (12). Frajilite kırığı oluşumunda bilinen en önemli risk faktörü önceki frajilite kırığıdır. Bu nedenle ortopedistlerin bu yeni kırıkları önlemedeki rolü oldukça önemlidir (13). Ortopedi doktorları osteoporoz konusundaki farkındalığının artması, osteoporoz tedavisine aktif katılımı ile frajilite kırığı olan hastalara osteoporoz tedavisinin başlanma oranının arttığı çalışmalarla da gösterilmiştir (14,15).

Amerikan Ulusal Osteoporoz; 65 yaş ve üzeri tüm kadınlardan, 70 yaş üstü tüm erkeklerden; kırık için risk faktörü olan postmenopozal kadınlar, menopoza geçiş evresinde olan kadınlar ve 50-69 yaş erkeklerden; 50 yaş üzeri kırığı olan erişkinlerden DXA istenmesini tavsiye etmektedir (16). Anket çalışmamızda ise ortopedi doktorlarına hangi hastalardan DXA istedikleri sorulduğunda %30,1 doktorun postmenopozal kadınlardan, %41 doktorun 65 yaş üstü hastalardan, %38,9 doktorun kalça kırığı teşhisi konulan hastalardan, %34,9 doktorun vertebra kırığı teşhisi konulan hastalardan ve %4,8 ortopedi hekiminin ön kol kırığı ile başvuran hastalardan DXA istediği belirlenmiştir. Çalışmamıza göre %30,1 ortopedi hekimi ise hiçbir hastasından DXA istememektedir. Yine araştırmamıza göre 65 yaş üstü kırıkla gelen hastaları %36,1 ortopedi doktoru osteoporoz açısından değerlendirmediği tespit edilmiştir. Kalça kırığı ardından osteoporoz tedavisini araştıran çalışmalar incelendiğinde kırık sonrası osteoporoz tedavisi başlama oranlarının %5 ile %30 arasında değiştiği izlenmiştir (12). Ülkemizde ortopedi hekimlerinin kırık sonrası DXA isteme oranının çalışmamızda da düşük olması, kırık sonrası osteoporoz tedavi oranlarının düşüklüğünü açıklar niteliktedir. Gong ve ark. (17), 50 yaş üstü kırık öyküsü olan kadın hastaları taradıkları çalışmalarında kalça kırığı olan hastaların %22,5'ine, vertebra kırığı olan hastaların %28,8'ine, el bilek kırığı olan hastaların %8,7'sine DXA istendiği belirtmişlerdir. Bu oranlar bizim çalışmamızdaki sonuçları desteklemektedir.

Serum 25(OH)D vitamini eksikliği kemik sağlığını olumsuz yönde etkilemektedir (18). Bu duruma ek olarak özellikle yaşlı hastalarda 25(OH)D vitamini eksikliğinin düşme riskini artırdığı, D vitamini takviyesinin ise düşmeleri azalttığı gösterilmiştir (19). D vitamini eksikliği kemik metabolizması ve düşme riski üzerine etkileri nedeni ile kırık riskini artırmaktadır (18). Bu nedenler ile 25(OH) D vitamini ölçülmesi osteoporoz tanı ve takibinde önerilmektedir. Tedavide hedef, 25(OH)D vitamini seviyesini 30 ng/mL üzerinde tutmaktır. 25(OH)D düzeyi <20 ng/mL düzeyinde olan hastalarda; serum Ca, P, ALP, PTH, kreatinin ölçülmesi de öneriler arasındadır (20). D vitamini eksikliğinin osteoporoz hastalarının takibinde bu kadar önemli olmasına rağmen anket çalışmamızda frajilite kırığı tespit ettiğikleri hastalarda ortopedi doktorların %36,1'inin D vitamini seviyesi, %37,3'ünün ise Ca parametreleri (Ca, P, Kreatinin, ALP, PTH) istemedikleri görülmüştür.

Osteoporoz tanısı kemik mineral yoğunluğunun kantitatif değerlendirmesine dayanır. Bu değerlendirme genellikle DXA ile yapılır. T-skorunun -2,5 standart sapma (SS) altında olması osteoporoz tanısı koydurur (21). Uluslararası Klinik Dansitometri Derneği sekonder osteoporozu olan premenapozal kadınlar, 50 yaş altı erkekler ve çocukların osteoporoz tanısında Z-skoru kullanılması tavsiye eder. Z-skoru -2,0 SS ve altı ise kronolojik yaşa göre beklenenden düşük kemik kütlesinden bahsedilir. Primer osteoporoz tanısında Z-skoru tercih edilmemektedir (22). Yaş, cinsiyet, önceki frajilite kırığı varlığı, bu kırığın lokalizasyonu, kronik başka hastalıkların varlığı, kırık riski için değerlendirmede kullanılan klinik risk faktörleri arasında sayılmaktadır. Osteoporoz tanı ve tedavisine yol göstermesi için bu durumlar hastalarda sorgulanması önerilmektedir (21). Dünya Sağlık Örgütü tarafından hastalardaki kırık riskini tespit etmek için

Tablo 2. Asistan ve uzmanlar (uzman, doçent ve profesörler) arasında anket verilerinin karşılaştırılması

		Asistan		Uzman		p	
		n	%	n	%		
Günlük pratiğinizde hangi hastalardan DXA istiyorsunuz?							
Postmenopoz bütün hastalardan		16	%22,9	34	%35,4	0,082	χ^2
65 yaş üstü bütün hastalardan		20	%28,6	48	%50	**0,006**	χ^2
Kalça kırığı ile başvuran bütün hastalardan		20	%28,6	44	%45,8	**0,024**	χ^2
Vertebra kırığı ile başvuran bütün hastalardan		20	%28,6	38	%39,6	0,142	χ^2
Ön kol kırığı ile başvuran bütün hastalardan		2	%2,9	6	%6,3	0,313	χ^2
Hiçbir hastadan DXA istemiyorum		32	%45,7	18	%18,8	**0,000**	χ^2
Primer osteoporozda tedavi ve takip							
Dahiliye hekimine yönlendiririm		6	%8,6	4	%4,2	**0,005**	χ^2
Fizik tedavi hekimine yönlendiririm		50	%71,4	50	%52,1		
Tedaviyi ve takibi kendim yaparım		14	%20	42	%43,8		
65 yaş üstü kırıkla gelen hastaları osteoporoz için	Değerlendirmem	34	%48,6	26	%27,1	**0,004**	χ^2
	Değerlendiririm	36	%51,4	70	%72,9		
Frajilite kırığı tespit ettiğim hastalarda	D vitamini seviyesi istemem	26	%37,1	34	%35,4	0,819	χ^2
	D vitamini seviyesi isterim	44	%62,9	62	%64,6		
Frajilite kırığı olan hastalarda Ca (Ca, P, kreatinin, ALP, PTH) parametrelerini	İstemem	30	%42,9	32	%33,3	0,210	χ^2
	İsterim	40	%57,1	64	%66,7		
Primer osteoporozda tedaviyi kendiniz yaparsanız, tedavi planınızı neye göre yaparsınız?							
DXA T-skoruna göre		50	%71,4	82	%85,4	**0,027**	χ^2
DXA Z-skoruna göre		16	%22,9	10	%10,4	**0,029**	χ^2
Yaşa		36	%51,4	56	%58,3	0,377	χ^2
Cinsiyete		28	%40	34	%35,4	0,547	χ^2
Frajilite kırığı varlığına		32	%45,7	54	%56,3	0,180	χ^2
Frajilite kırığının lokalizasyonuna		22	%31,4	26	%27,1	0,542	χ^2
Diğer mevcut hastalıklarına		24	%34,3	20	%20,8	0,052	χ^2
Daha önce kullandığı osteoporoz ilaçlarına göre		24	%34,3	38	%39,6	0,486	χ^2
FRAX risk sınıflamasına göre		14	%20	8	%8,3	**0,029**	χ^2
Primer osteoporozda D vitamini düşüklüğü tespit ettiğim hastalara							
300.000 IU 25(OH)D içeren ampulleri oral olarak veririm		16	%22,9	22	%22,9	0,858	χ^2
300.000 IU 25(OH)D vitamini içeren ampulleri intramuskuler olarak veririm		2	%2,9	0	%0	0,344	χ^2
50.000 IU 25(OH)D içeren şişenin tümünü haftada bir oral olarak veririm		12	%17,1	14	%14,6	0,816	χ^2
50.000 IU 25(OH)D içeren şişeyi her gün damla olarak veririm		6	%8,6	12	%12,5	0,163	χ^2
Sadece Ca ile kombine şekilde bulunan D vitamini preparatları veririm		12	%17,1	20	%20,8	0,692	χ^2
Diğer branşlara yönlendiririm		22	%31,4	28	%29,2	0,886	χ^2
Primer osteoporozda D vitamini düşüklüğü tespit ettiğim hastalara Ca replasmanı	Başlamam	34	%48,6	36	%37,5	0,154	χ^2
	Başlarım	36	%51,4	60	%62,5		

χ^2: ki-kare test, DXA: Dual enerji X-ray absorbsiyometri, Ca: Kalsiyum, P: Fosfor, ALP: Alkalen fosfataz, PTH: Parathormon

FRAX kullanılması önerilmektedir. FRAX https://www.shef.ac.uk/frax/ web adresinden hastalara ait bilgiler doldurularak hastaların 10 yıllık kırık riskini değerlendirir (23). Çalışmamızda primer osteoporozda tanı ve tedavi planını yaparken ortopedi doktorlarının %79,5'inin DXA T-skoru, %15,7'sinin DXA Z-skoru, %55,4'ünün yaşı, %37,3'ünün cinsiyeti, %51,3'ünün frajilite kırığı varlığını, %51,8'inin frajilite kırığı lokalizasyonunu, %26,5'inin diğer mevcut hastalıkları, %37,3'ünün daha önce kullandığı osteoporoz ilaçlarını, %13,3'ünün ise FRAX riski sınıflamasını dikkate aldığını gördük.

Avrupa Osteoporoz ve Osteoartrit Klinik ve Ekonomik Yönleri Derneği (ESCEO); 25(OH)D düzeyi <10 ng/mL düzeyinde olanlarda kemiklerde mineralizasyon defekti olduğunu; 25(OH) D düzeyi <20 ng/mL olanlarda kemik döngüsü ve/veya serum PTH seviyesinde artma olduğunu; 20 ng/mL <25(OH)D <30 ng/mL olanlarda nötral etki (kemik döngüsü ve PTH normal) ve yine bu düzeyde kırık riskinde, düşme riskinde ve mortalitede azalma izlendiğini belirtmiştir. 25(OH)D ≥30 ng/mL olmasının özellikle kırılgan geriatrik hastalarda kırık, düşme ve mortalitenin azalması için optimal hedef olduğunu vurgulamıştır. 25(OH) D vitaminin 50 ng/mL üstünde olmasında advers olaylar görülebileceğini söylemiştir (24). ESCEO tarafından sekiz yüz IU/gün D vitamini alınması önerilmektedir (25). D vitamini düşüklüğünde hedef, serum 25(OH)D vitamini düzeyini 30 ng/mL ve üzerine çıkarılması olmalıdır. D vitamini eksikliği (<10-20 ng/mL) olanlarda 50.000 IU/hafta, 6-8 hafta süre ile D vitamini oral olarak verilmelidir. Hedef düzeye ulaşınca günlük idame dozuna geçilmelidir. Hedef düzeye ulaşılamadı ise tedaviye 50.000 IU/hafta, 3-6 hafta süre ile devam edilmelidir (20,26). Ortopedi hekimlerimize D vitamini düşüklüğü bulunan hastalara D vitamini takviyesini nasıl yaparsınız diye sorduğumuzda %22,9'unun 300.000 IU 25(OH)D vitamini içeren ampuller oral olarak verdiğini, %1,2 ortopedi hekiminin ise aynı ampulleri intramuskuler yolla verdiği görüldü. %15,7 doktorun 50,000 IU 25(OH)D vitamini içeren şişeyi haftada bir oral olarak vermeyi tercih ederken, %10,8 doktorun ise aynı şişeyi damla damla verdiğini gözlemledik. %19,3 ortopedi hekimi ise serum D vitamini eksikliği tespit ettikleri hastalarda sadece Ca ile kombine halde bulunan oral preperatları tercih ettiğini söyledi. Ortopedi doktrolarının %30,1'i D vitamini eksiliği tespit ettikleri hastaları diğer branşlara yönlendirdiğini ifade etti.

D vitamini ile birlikte yeterli Ca alımı sağlanmalıdır (19-70 yaş: 1.000 mg/gün, >70 yaş: 1.200 mg/gün) (20). Ancak ortopedi hekimlerimize D vitamini düşüklüğü bulunan hastalarınıza Ca replasmanı yapar mısınız diye sorduğumuzda %42,2'sinin Ca vermediği görüldü.

Osteoporoz tedavisi birçok branş tarafından yapılmasına rağmen, hastaların kemik kırığı oluştuğunda karşılaştığı ilk doktor ortopedi hekimleri olmaktadır (27). Ortopedi doktorlarının osteoporozu iyi bilmeleri beklenmelidir. Anketimizin sonuçlarını incelediğimizde ortopedi hekimlerinin, primer osteoporozda tedavi ve takip için %6'sının hastalarını dahiliye hekimine, %60,2'sinin fizik tedavi hekimine yönlendirdiğini, %33,7 ortopedi doktorunun ise tedavi takibi kendisinin yaptığı görüldü. Sorbi ve ark. (8) yaptıkları çalışmada ortopedi doktorlarının ve dahiliye hekimlerin osteoporoz değerlendirmesi ve tedavisi konusundaki tıbbi bilgilerini karşılaştırmışlardır. Bu çalışmaya göre ortopedi doktorlarının çoğu, kırık sonrası hastaları tıbbi konsültasyon için ilgili ekibe yönlendirmekte genel bir motivasyon eksikliği sergilemişlerdir. Aynı zamanda bu çalışmada dahiliye hekimlerin, frajilite kırığı olan hastaların osteoporozunu değerlendirme ve tedavi etme konusunda daha fazla bilgili olduğu gösterilmiştir (8). Kendi çalışmamızın ve bu çalışmanın sonuçları bize ortopedi hekimlerinin osteoporozun tanısının ve erken tedavisinin başlatılması konusunda aktif rol oynamasının uygun olduğunu, sonrasında ortopedi doktorlarının osteoporoz tedavisinden sorumlu olan FTR, iç hastalıkları gibi dahili branşlardan konsültasyon istemesi gerektiğini, aksi takdirde komplikasyonların ortaya çıkabileceğini düşündürmüştür.

Genel olarak anket sonuçlarını ortopedi asistanlığının üçüncü senesini bitirmiş hekimler ve ortopedi uzmanlık eğitimini bitiren hekimler (uzman, doçent ve profesörler) arasında karşılaştırdığımızda, uzmanlık eğitimini bitirmiş grupta osteoporoz konusunda farkındalığın daha yüksek olduğunu ancak yine de bu farkındalığın yeterli olmadığı düşünmekteyiz.

Sonuç

Ortopedi doktorlarının osteoporoz tanı ve takibinde bilgi düzeyi ve farkındalığı beklenildiğinden düşüktür. Frajilite kırıklarının tanı ve tedavisinde çok önemli yeri olan ortopedi doktorlarının bilgi ve farkındalığını artırmak için ek çalışmalar ve müdahale programları gereklidir.

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Postmenopozal Türk Kadınlarında Vücut Kompozisyonu ve Fiziksel Aktivitenin Kemik Mineral Yoğunluğu ile İlişkisi

The Relationship of Body Composition and Physical Activity with Bone Mineral Density in Turkish Women in Postmenopausal Stage

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Öz

Amaç: Vücut bileşenlerinin kemik mineral yoğunluğu ile ilişkisinde vücut ağırlığından başka etkileri olup olmadığı tartışmalıdır. Bu çalışmanın amacı postmenopozal Türk kadınlarında vücut kompozisyonu ve fiziksel aktivitenin kemik mineral yoğunluğu ile ilişkisini değerlendirmektir.
Gereç ve Yöntem: Bu kesitsel çalışma Çanakkale Onsekiz Mart Üniversite Hastanesi kayıtlarından kemik mineral yoğunluğu değerlerine ulaşılabilen 95 postmenopozal kadın üzerinde yürütülmüştür. Vücut bileşenlerinin kemik mineral yoğunluğu ile olan ilişkisi vücut ağırlığı kovaryant iken ve değilken ayrı ayrı incelenip karşılaştırılmıştır.
Bulgular: Katılımcıların yaş ortalaması 61,7±7,2 idi. Katılımcıların vücut kitle indeksi (r=0,270, p=0,009), bel çevresi (r=0,308, p=0,003), kalça çevresi (r=0,277, p=0,007), yağ kitlesi (r=0,256, p=0,014), yağ yüzdesi (r=0,185, p=0,077), yağsız kitle (r=0,311, p=0,003), total kas kitlesi (r=0,311, p=0,003), iskelet kası indeksi (r=0,260, p=0,012), apendiküler yağsız kütle indeksi (r=0,279, p=0,007), apendiküler iskelet kası indeksi (r=0,280, p=0,007) kemik mineral yoğunluğu ile korelasyon gösterirken, vücut ağırlığı kontrol edildiğinde hiçbirinde anlamlı korelasyon yoktu. Boy ve bel/kalça oranı hem vücut ağırlığı kontrol edildiğinde hem de edilmediğinde kemik mineral yoğunluğu ile anlamlı ilişkili yoktu. Fiziksel aktivite ile kemik mineral yoğunluğu arasında anlamlı bir korelasyon saptanmadı (r=0,032, p=0,799).
Sonuç: Postmenopozal Türk kadınlarında vücut ağırlığı ile kemik mineral yoğunluğu arasında pozitif korelasyon vardır. Vücut bileşenlerinin neden oldukları vücut ağırlığı nedeniyle kemikler üzerine mekanik yük oluşturmak dışında kemik mineral yoğunluğu üzerinde etkisizdir.
Anahtar kelimeler: Osteoporoz, kemik mineral yoğunluğu, vücut kompozisyonu, fiziksel aktivite

Abstract

Objective: The effects of body components, other than body weight, on bone mineral density remain a controversial issue. The purpose of this study is to evaluate the relationship between body composition and physical activity with bone mineral density in Turkish women in postmenopausal stage.
Materials and Methods: We conducted this cross-sectional study on 95 women in postmenopausal stage whose bone mineral density values were obtained from the records of Çanakkale Onsekiz Mart University Hospital. We examined the relationship of body components with bone mineral density and compared them separately when the body weight was a covariant and when it was not a covariant.
Results: The mean age of the participants was 61.7±7.2 years. Body mass index (r=0.270, p=0.009), waist circumference (r=0.308, p=0.003), hip circumference (r=0.277, p=0.007), fat mass (r=0.256, p=0.014), fat percentage (r=0.185, p=0.077), lean mass (r=0.311, p=0.003), total muscle mass (r=0.311, p=0.003), skeletal muscle index (r=0.260, p=0.012), appendicular lean mass index (r=0.279, p=0.007) and appendicular skeletal muscle index (r=0.280, p=0.007) correlated with bone mineral density, but none of them significantly correlated when the body weight was controlled. Both the height and waist/hip ratio were not significantly associated with the bone mineral density when the body weight was controlled and not controlled. No significant correlation was found between physical activity and bone mineral density (r=0.032, p=0.799).
Conclusion: Body weight is positively correlated with bone mineral density among Turkish women at postmenopausal stage. Body components have no effects on bone mineral density except for contributing to the body weight that generate mechanical loads on bones.
Keywords: Osteoporosis, bone mineral density, body composition, physical activity

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Giriş

Osteoporoz azalmış kemik gücüyle birlikte artan kırık riskini ifade eder ve azalmış kemik kütlesiyle birlikte kemik mikro-yapısında bozulmayla karakterize iskelet sistem hastalığı olarak tanımlanabilir (1). Osteoporoz son yıllarda ciddi bir sorun olarak kabul edilmektedir (2). Osteoporoz tüm dünyada milyonlarca insanı etkileyen ve yaygınlığı gitgide artan bir hastalıktır ve aynı şekilde Türkiye'de de sıklığı özellikle son 20 yılda ciddi artış göstermiştir. Ülkemizde 2010 yılında yapılan 'FRAKTÜRK' çalışmasına göre 50 yaş üstü kadınlarda osteoporoz görülme sıklığı %33,3 iken erkeklerde %7,5'tir (3). Özellikle kadınlarda menopoz sonrası osteoporoz gelişmesi için yüksek risk söz konusudur (4).

Osteoporozun tanısında Dual enerji X-ray absorbsiyometri (DEXA) kemik mineral yoğunluğunu (KMY) belirlemede basit, güvenilir ve tekrarlanabilir bir araçtır ve lomber omurga, kalça KMY ölçümleri osteoporoz tanısı için altın standarttır (1). Dünya Sağlık Örgütü tanımlarına göre T-skoruna dayalı tanı konmaktadır: T-skoru >-1 ise normal, >-2,5 ise osteopeni ve <-2,5 ise osteoporoz şeklinde tanımlanmıştır (5).

Fiziksel aktivite, kemik sağlığı için önemlidir. KMY'yi artırır, korur ve kemik kırığı riskini azaltır (6). Fiziksel aktivitenin kemik üzerine olan etkileri, kemik dokusunun sürekli olarak yeniden şekillendirilen bir doku olup mekanik uyarılara cevap vermesi ile açıklanmaktadır (7). Özellikle ağırlık taşıyan veya yerçekimine karşı yapılan aktivitelerin KMY üzerine etkili olduğu gösterilmiştir (8). Osteoporozla ilgili birçok rehber ağırlık taşıyıcı ve kas güçlendirici aktiviteleri önermektedir (9).

Vücut kompozisyonu, kilo, alkol tüketimi, sigara, güneş ışığı alma süresi, besleyici durum, yeme alışkanlıkları ve fiziksel aktivitelerin KMY üzerinde önemli bir etkiye sahip olduğu bilinmektedir. Bu değiştirilebilir yaşam tarzı faktörleri osteoporozun ana nedeni olarak rapor edilmiştir. Bu faktörlerin arasında en çok vücut ağırlığı üzerinde durulmaktadır. Yüksek vücut ağırlığına sahip bireylerin daha yüksek KMY'ye sahip olduğu gösterilmiştir (5,10). Son zamanlarda vücut ağırlığının koruyuculuğuna alternatif olarak hangi vücut bileşenlerinin osteoporozda önemli olduğunu araştırmak gerekliliği doğmuştur. Abdominal obezite, kas kitlesi, toplam yağ kitlesi ve yağsız vücut kitlesinin obezite ile ilişkisini inceleyen birçok çalışma mevcuttur. Bu çalışmalarda farklı sonuçlar vermektedir ve hangi parametrenin kullanılacağına kesin karar verilmiş değildir (11-13). Bu çalışmanın amacı postmenopozal Türk kadınlarında vücut kompozisyonu ve fiziksel aktivitenin KMY ile ilişkisini değerlendirmektir.

Gereç ve Yöntem

Evren ve Örneklem

Çalışma Çanakkale Onsekiz Mart Üniversitesi (ÇOMÜ) Uygulama ve Araştırma Hastanesi kayıtlarında Eylül 2015 - Eylül 2016 yapılmış DEXA ile L1-4 omurga KMY tespiti bulunan 45 yaş üstü postmenopozal kadınlarda yürütülmüştür. Son 12 aydır amenore öyküsü olan hastalar postmenopozal kabul edildi. Son 12 ay içerisinde steroid veya osteoporoz tedavisi alanlar çalışma dışı bırakıldı.

Hastane kayıtlarından belirlenen 957 kişiye, çalışmaya davet etmek amacı ile telefon edilerek ulaşılmaya çalışıldı. Ulaşılabilen 416 kişiden 319'u çalışmaya katılmayı reddetti. Katılımcılardan 2'si çalışma metoduna uyumu engelleyecek hastalık ya da engeli bulunduğu için çalışmaya alınmadı. Son bir yıl içerisinde steroid kullanım öyküsü olan katılımcı yoktu.

Veri Toplama Araçları

Araştırmada veriler bir anket uygulaması, antropometrik ölçümler, vücut kompozisyonunun ölçümü ve hastane kayıtlarındaki veriler kullanılarak toplanmıştır.

Katılımcıların fiziksel aktivite düzeyini belirlemek için Uluslararası Fiziksel Aktivite Anketi (IPAQ)-kısa form (14) kullanılmıştır. Hastaların kilo ve vücut kompozisyonunun ölçümü biyoelektriksel empedans analiz cihazı ile yapılmıştır. Biyoelektrik impedans analizi cihazının çalışma şekli basitçe vücut dokularının az miktarda zararsız elektrik akımına maruz bırakılıp, farklı dirençlerinin ölçülmesi şeklindedir. Çalışmamızda kullandığımız "Tanita Body Composition Analyzer Tanita BC - 418 Japan" biyoelektrik impedans analizörünün (BIA) geçerlilik çalışmaları yapılmış olup ölçümler üreticinin talimatlarına göre yapılmıştır (15). Kompozisyon değerleri [yağ kitlesi (kg), yağ yüzdesi (%), yağsız kitle (kg), iskelet kas indeksi (SMI) (kg/m^2)] hesaplanmıştır. Çalışmamızda Sarkopeni Avrupa çalışma grubu tarafından BIA ile kas tahmini yöntemlerinden sayılan, toplam tahmini kas kitlesinin yüksekliğin metre cinsinden karesine bölünmesi ile elde edilen değer SMI olarak; dört ekstremitenin kas kitlesi toplamını apendiküler iskelet kası kütlesi olarak tanımlayarak bu değeri yüksekliğin metre cinsinden karesine bölünmesi ile hesaplanan değer apendiküler iskelet kası indeksi (ASMI) olarak; apendiküler yağsız kitleyi vücut büyüklüğüne uyarlamak için yüksekliğin metre cinsinden karesine bölerek elde edilen değer apendiküler yağsız kütle indeksi (ALMI) olarak belirtilmiş ve kullanılmıştır (16).

Hastaların KMY durumlarını belirlemek üzere ÇOMÜ Araştırma Uygulama Hastanesi kayıtlarında bulunan, Lunar Prodigy DF+350624 cihazı ile son bir yıla ait L1-4 omurga DEXA çekimi sonuçları kullanılmıştır.

İzin ve Onamlar

Çalışmaya başlamadan önce 21.09.2016 tarihinde 27/2016-E.99849 no'lu araştırmamız için ÇOMÜ Tıp Fakültesi Klinik Araştırmalar Etik Kurulu onayı alındı. Çalışmaya katılım için davet edilen hastalara çalışma hakkında sözel bilgi verilip yazılı onamları alındı.

İstatistiksel Analiz

Verilerin analizinde IBM SPSS v20 istatistik programı kullanıldı. Verilerin normal dağılıma uygunluğu Kolmogorov-Smirnov testi ile değerlendirildi. Normal dağılıma uymayan verilere dönüşüm uygulanarak (log, karekök, yansıtma vs) normal dağılıma uygunlukları sağlandı. Ortalama karşılaştırmaları için uygun olduğu yerde bağımsız örneklem t-testi veya ANOVA kullanıldı. Korelasyon uygulanan değişkenler arasındaki ilişkinin lineerliği test uygulanmadan önce Scatter/Dot grafikleri ile kontrol edildi.

Ordinal değişkenlerin korelasyonunda Kendall' tau b, sürekli değişkenlerin korelasyonunda ise Pearson korelasyon testi uygulandı. Öncelikle yaş ve menapoz süresi kontrol edilerek, bağımsız değişkenlerin KMY ile parsiyel korelasyonlarına bakıldı. Daha sonra vücut ağırlığının mekanik yük etkilerini ortadan kaldırarak bağımsız değişkenlerin KMY ile olan ilişkisini değerlendirebilmek için vücut ağırlığı da kovaryant olarak yaş ve menopoz süresine eklenerek tekrar parsiyel korelasyon değerleri incelendi. Her bir istatistik testi için uygun olan etki büyüklükleri test sonuçları ile beraber verildi. Cohen's d için 0,2-0,5-0,8, η^2 için 0,01-0,06-0,14, Pearson korelasyon katsayısı için ise 0,1-0,3-0,5 sırası ile küçük-orta-büyük etki sınırları olarak kabul edildi (17). Anlamlılık sınırı olarak p<0,05 kabul edildi.

Bulgular

Araştırmaya katılan 95 postmenopozal kadın bireyin yaş ortalaması 61,7±7,2 (47-77) olup KMY ile anlamlı korele değildi (r=-0,119, p=0,251). Katılımcıların eğitim süresi (8,1±4,3) (r=0,020, p=0,792), çay tüketim miktarları (4,3±2,7 bardak/gün) (tau b=0,128, p=0,080) ve kahve tüketim miktarları (0,53±0,56) (tau b=0,092, p=0,241) ile KMY değerlerinde arasında anlamlı korelasyon yoktu. Medeni durum (t=-0,211, p=0,833 Cohen's d:-0,05), çalışma durumu (F=0,531, p=0,590, η^2=0,011), sigara kullanımı (F=0,121, p=0,886, η^2=0,003) ve alkol kullanımı (t=-0,328, p=0,744, Cohen's d:- 0,09) grupları arasında KMY açısından anlamlı fark yoktu. Katılımcıların sosyodemografik özellikleri ve alışkanlıklarına ait özellikleri Tablo 1'de verilmiştir. Menopoza giriş şekli 75 (%79) kadında doğal, 19 (%20) kadında cerrahi idi. Bir katılımcı Turner sendromu tanılı idi ve hiç adet görmediğini belirtti. Kadınların menopoza girme yaşı ortalama 47,2±5,3 (34-55) idi. Menopoz süresi 14,6±7,4 (1-35) yıl olup KMY ile anlamlı koreleydi (r=-0,267, p=0,009). Katılımcıların 23'ü (%24,2) daha önce majör travma olmaksızın kemik kırığı yaşamıştı. Katılımcıların 11'i (%11,6) ebeveyninde kırık öyküsü olduğu belirtildi. Katılımcılarda en sık rastlanan hastalıklar hipertansiyon (%42,1), hipotiroidi (%24,2) diabetes mellitus (%17,9) ve hiperlipidemi (%14,7) idi.

Tablo 1. Sosyodemografik özellikler ve alışkanlıklar

Yaş		61,7±7,2 (47-77)
Eğitim süresi (yıl)		8,1±4,3 (0-16)
Medeni durum	Evli	74 (%77,9)
	Bekar, dul, boşanmış	21 (%22,1)
Çalışma durumu	Aktif çalışan	8 (%8,4)
	Emekli	38 (%40)
	Çalışmayan	49 (%51,6)
Sigara kullanımı	Hiç içmemiş	70 (%73,7)
	Bırakmış	16 (%16,8)
	İçiyor	9 (%9,5)
Alkol kullanımı	Hiç kullanmıyor	77 (%81,1)
	Kullanıyor	18 (%18,9)
Çay kullanımı		4,3±2,7 (1-12) bardak
Kahve kullanımı		0,53±0,56 (0-2) bardak

Öncelikle yaş ve menopoz süresi kontrol edilerek bağımsız değişkenler olan vücut ağrılığı, boy, beden kitle indeksi (BKİ), bel çevresi, kalça çevresi, bel/kalça oranı, yağ kitlesi, yağ yüzdesi, yağsız kitle, total kas kitlesi, SMI, ALMI, ASMI, IPAQ Continious skoru (Log_e), oturma süresinin KMY ile parsiyel korelasyonuna bakılmış olup boy, bel/kalça oranı, IPAQ, Log_e ve oturma süresi hariç diğerlerinin anlamlı pozitif korele olduğu saptanmıştır (Tablo 2). Daha sonra bu bağımsız değişkenlerin, yaş ve menopoz süresine ek olarak kilodan kaynaklanan varyanslarını kontrol ederek KMY ile yapılan parsiyel korelasyon incelemesinde değerlendirilen hiçbir bağımsız değişkenin anlamlı korele olmadığı saptanmıştır. Tüm değişkenlerin istatistik sonuçları Tablo 2'de ayrıntılı olarak verilmiştir.

Tartışma

Çalışmamızdaki bağımsız değişkenlerden vücut ağrılığı, BKİ, bel çevresi, kalça çevresi, yağ kitlesi, yağ yüzdesi, yağsız kitle, total kas kitlesi, SMI, ALMI, ASMI'nın yaş ve menopoz süresi kontrol edildikten sonra KMY ile anlamlı ilişkili olduğu gösterilmiştir. Yaş ve menopoz süresine ek olarak kovaryantlara vücut ağırlığı da eklendiğin de hiçbir bağımsız değişkenin KMY ile anlamlı ilişkisi olmadığı saptanmıştır. Yapılan bir meta-analizde (18) postmenopozal kadınlar için KMY'nin yağ kitlesi ile korelasyon değeri r=0,31 (0,26-0,35) iken yağsız kitle ile korelasyon değeri r=0,34 (0,30-0,39) saptanmış olup çalışmamızda saptanan değerler ile (sırasıyla r=0,256 ve r=0,311) uyumlu görünmektedir. Bu çalışmada saptanan korelasyon değerlerinin meta-analizde saptanan değerlerin alt sınırında olmasının nedeni bu çalışmada menopoz süresi ve yaş kontrol edildikten sonra parsiyel korelasyon kullanılması olabilir.

Bu çalışmada da gösterildiği gibi vücut ağırlığı KMY ile güçlü şekilde ilişkilidir (10). Genel kabul mekanik yük nedeni ile kemik yapımının tetiklenmesi olsa da yağ kitlesini oluşturan adipositlerden salgılanan östrojenin osteoklast inhibe edici fonksiyonun yağ kitlesinin KMY ile olan ilişkisine katkıda bulunduğu düşünülmektedir (19). Yağ kitlesi ile KMY ilişkisi açısından tartışmalı sonuçlar mevcuttur (20) hatta premenopozal dönemde artan yağ kitlesinin KMY ile ters orantılı olduğu gösterilmiştir (21). Yağ kitlesine göre yağsız kitlenin KMY ile daha güçlü ilişkili olduğu gösterilmiştir (20,22). Bu çalışmada vücut bileşenlerinin KMY ile olan ilişkisindeki mekanik etkilerini kontrol altına alabilmek için yaş ve menopoz süresine ek olarak ikinci değerlendirme vücut ağırlığı da istatistiksel olarak kontrol edilmiştir. Yaş ve menopoz süresi kontrol edilmişken KMY ile anlamlı ilişkili olduğu saptanan boy, BKİ, bel çevresi, kalça çevresi, yağ kitlesi, yağ yüzdesi, yağsız kitle, total kas kitlesi, SMI, ALMI, ASMI değerlerinin tamamı vücut ağırlığı kontrol edildikten sonra yapılan değerlendirmede KMY ile ilişkisiz saptanmıştır. Bu

Tablo 2. Bağımsız değişkenlerin kemik mineral yoğunluğu ile parsiyel korelasyon incelemeleri

Bağımsız değişken	Ortalama ± standart sapma (minimum-maximum)	Yaş ve menopoz süresi kontrol edildiğin de KMY ile parsiyel korelasyon	Yaş, menopoz süresi ve kilo kontrol edildiğinde KMY ile parsiyel korelasyon
Menopoz süresi	14,6±7,4 (1-35) yıl	-	-
Vücut ağrılığı	74±13,6 (46,6-110) kg	r=0,308 p=0,003	-
Boy	155,9±6 (141-171) cm	r=0,119 p=0,257	r=0,070 p=0,507
BKİ	30,6±5,9 (19,5-54,7) kg/m^2	r=0,270 p=0,009	r=-0,004 p=0,967
Bel çevresi	97,3±12,7 (70-142) cm	r=0,308 p=0,003	r=0,097 p=0,360
Kalça çevresi	110,5±11,7 (85-154) cm	r=0,277 p=0,007	r=0,033 p=0,759
Bel/kalça oranı	0,88±0,06 (0,72-1,04)	r=0,159 p=0,131	r=0,070 p=0,456
Yağ kitlesi	29,1±9,3 (10,7-60) kg	r=0,256 p=0,014	r=-0,122 p=0,249
Yağ yüzdesi	38,4±6,4 (20,3-55,1)	r=0,185 p=0,077	r=-0,086 p=0,419
Yağsız kitle	44,9±5,6 (33,1-60,2) kg	r=0,311 p=0,003	r=0,102 p=0,335
Total kas kitlesi	42,7±5,3 (31,3-57,1)	r=0,311 p=0,003	r=0,104 p=0,325
SMI	17,6±2,1 (13,8-23,3) kg/m^2	r=0,260 p=0,012	r=0,043 p=0,686
ALMI	8,1±1,1 (6,2-11,2) kg/m^2	r=0,279 p=0,007	r=0,050 p=0,640
ASMI	7,7±1 (5,8-10,5) kg/m^2	r=0,280 p=0,007	r=0,053 p=0,619
IPAQ, Log_e	2,7±0,4 (1,82-3,69)	r=0,032 p=0,799	r=0,109 p=0,393
Oturma süresi	5,4±2,8 (0-13) saat/gün	r=-0,075 p=0,501	r=-0,038 p=0,733

ALMI: Apendiküler yağsız kütle indeksi, ASMI: Apendiküler iskelet kası indeksi, BKİ: Beden kitle indeksi, IPAQ: Uluslararası Fiziksel Aktivite Anketi, KMY: Kemik mineral yoğunluğu, SMI: İskelet kas indeksi, Loge: Continious skoru

da vücut bileşenlerinin mekanik etkileri dışında KMY üzerine etkileri olmadığını gösteriyor olabilir. Çalışmamıza metodolojik olarak benzer bir çalışmada postmenopozal Çinli kadınlarda yağ kitlesi KMY ile doğru orantılıyken vücut ağırlığı istatistiksel olarak kontrol edildikten sonra yağ kitlesi ile KMY'nin ters orantılı olduğu saptanmıştır (23). Postmenopozal Brezilyalı kadınlarda ise vücut ağırlığı kontrol edildiğinde yağ kitlesi ile KMY'nin ilişkisiz olduğu gösterilmiştir (24). Bir Kore çalışmasında postmenopozal kadınlarda bel çevresi ile bilgisayarlı tomografi ölçümü ile elde edilen toplam yağ alanı, KMY ile pozitif korele iken yaş ve vücut ağırlığı kontrol edildikten sonra bu ilişki gösterilememiştir (21). Yine aynı çalışmada bizim çalışmamızda saptandığı gibi sadece yaşın kontrol edildiği parsiyel korelasyonlarına bakılsa dahi yağ yüzdesi ve bel/kalça oranı ile KMY arasında ilişki olmadığı gösterilmiştir.

Çalışmamızda katılımcıların fiziksel aktivite durumları ile KMY arasında anlamlı bir ilişki saptanamamıştır. Bir meta analizde ise fiziksel aktivite ile KMY'nin ilişkili olduğu söylenmektedir (6). Fiziksel aktivitenin IPAQ skoru kullanılarak tanımlandığı bir çalışmada premenopozal kadınların (25) sedanter olanlar ile orta derecede fiziksel aktif olanlar arasında KMY açısından anlamlı bir fark saptanamamış iken tüm gruplar beraber değerlendirildiğin de KMY ile fiziksel aktivite arasında pozitif yönde anlamlı ilişki gösterilmiş olup çalışmamızdaki yüksek derecede fiziksel aktif katılımcı azlığı nedeni ile KMY ile fiziksel aktiflik durumu arasındaki olası ilişkiyi saptayamamış olabiliriz. Her ne kadar bu çalışma da fiziksel aktivite ile KMY arasında ilişki saptanmamış olsa da fiziksel aktivite ile gerileme sağlanan sarkopeninin (özellikle apendiküler) osteoporotik kırıklar için bağımsız bir risk faktörü olduğu unutulmamalıdır (6,26).

Sonuç olarak bu çalışmada postmenopozal Türk kadınlarında vücut ağırlığı KMY ile pozitif korele olup vücut bileşenlerinin etkiledikleri vücut ağırlığı nedeniyle kemikler üzerine mekanik yük oluşturmak dışında KMY üzerine etkileri saptanamamıştır. Ayrıca yine aynı grupta fiziksel aktivite ile KMY arasında anlamlı bir ilişki gösterilememiştir. Bu sonuçları pratikte kullanırken KMY'nin osteoporotik kırıkları öngörmede çok önemli bir risk faktörü olduğunu fakat tek risk faktörü olmadığını dolayısı ile vücut bileşenlerinin ve fiziksel aktivitenin diğer risk faktörleri üzerine olan etkisi olabileceğini unutmamak önemlidir.

Çalışmanın Kısıtlılıkları

Çalışmamız bir üçüncü basmak hastanede yapıldığı için topluma genellerken dikkatli olunmalıdır. Vücut ağırlığı ile osteoporotik kırıkların ilişkisinin vücut bölgelerine göre değişebileceği gösterilmiş olup (27), bu etki vücut bileşenleri için de geçerli olabileceği için sadece lomber vertebra KMY'nin değerlendirilmesi çalışmamız için bir kısıtlılık sayılabilir.

Bağımsız değişkenlerin her biri için ayrı ayrı parsiyel korelasyon değerlendirilmesi yapılması Tip I hataya düşme riskini artırmaktadır fakat çalışmamızda ki gibi birbirinden türetilen veya birbirini tamamlayan bağımsız değişkenler söz konusu olduğunda ortaya çıkan çoklu doğrusallık sorunu çalışmada ki analizlerin tek seferde regresyon ile yapılmasını engellemiştir.

Başta Tip II hatayı artırmak gibi birçok diğer kısıtlılığa neden olduğu ve son zamanlarda kullanımın oldukça kısıtlı olması yönündeki görüşler nedeni ile çalışmamızda anlamlılık sınırı için Bonferroni düzeltmesi kullanılmamıştır.

Sonuç

Postmenopozal Türk kadınlarında vücut ağırlığı KMY ile doğru orantılıdır. Vücut bileşenlerinin neden oldukları vücut ağırlığı nedeniyle kemikler üzerine mekanik yük oluşturmak dışında KMY üzerinde etkisizdir. Fiziksel aktivite ile KMY arasında anlamlı bir ilişki yoktur.

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Does Bone Mineral Density Have an Affect on the Visual Analogue Scale Pain Score?

Kemik Mineral Dansitesinin Vizüel Analog Skala Ağrı Skoruna Etkisi Var mıdır?

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Abstract

Objective: The objective of this study is to evaluate the Visual Analogue scale (VAS) pain scale in elderly patients with obesity and without obesity, and determine whether the VAS pain score is associated with obesity in patients with osteoporosis.
Materials and Methods: We included 192 patients in this study (69 patients with body mass index (BMI) <30 and 99 patients with BMI ≥30). We determined the values of bone mineral density (BMD) by the dual-energy X-ray absorptiometry method. Importantly, we evaluated the VAS pain scores in the range of "without pain" (score=0) and "the worst pain" (score=10), and divided them into three groups according to the World Health Organization's pain severity scale: mild pain (score: <3), mild-moderate pain (score: 3-6), and moderate-severe pain (score: >6). Additionally, we used a multivariate logistic regression model to identify the independent risk factors of VAS pain score in patients with osteoporosis.
Results: The VAS pain score was higher in patients with obesity than the patients without obesity (4.49±2.76 and 3.49±.42, respectively. P=0.014). Advanced age [Odds ratio (OR)=1.094, 95% confidence interval (CI)=1.018-1.175, p=0.014] and obesity (OR=0.225, 95% CI=0.055-0.928, p=0.039) were associated with higher VAS pain score in patients with osteoporosis. Otherwise, only advanced age (OR=1.157, 95% CI=1.045-1.280, p=0.005) was associated with higher VAS pain score in patients with normal BMD. Advanced age (OR=1.141, 95% CI=1.093-1.192, p=<0.001) and osteoporosis (OR=0.001, 95% CI=0.00-0.014, p=<0.001) were associated with higher VAS pain score in all patients.
Conclusion: We believe that reducing obesity, which is a variable risk factor, will benefit in pain reduction and sedentary lifestyle, and improve BMD in patients with osteoporosis.
Keywords: Osteoporosis, VAS pain score, obesity

Öz

Amaç: Bu çalışmada, obez ve obez olmayan yaşlı hastalarda Vizüel Analog skala (VAS) ağrı skalasını değerlendirmeyi ve ayrıca VAS ağrı skorunun osteoporozlu hastalarda obezite ile ilişkili olup olmadığını belirlemeyi amaçladık.
Gereç ve Yöntem: Çalışmaya toplam yüz doksan iki hasta dahil edildi [vücut kitle indeksi (VKİ) <30 olan 69 hasta ve VKİ ≥30 olan 99 hasta]. kemik mineral yoğunluğu (KMY) değerleri, dual-enerjili X-ışını absorpsiyometrisi yöntemi ile belirlenmiştir. VAS ağrı skoru "ağrısız" (skor=0) ve "en kötü ağrı" (skor=10) olarak değerlendirildi ve Dünya Sağlık Örgütü'nün ağrı şiddeti ölçeğine göre 3 gruba ayrıldı: skor <3 hafif ağrı, 3-6 hafif-orta derecede ağrı ve >6 orta-şiddetli ağrı. Osteoporoz hastalarında VAS ağrı skorunun bağımsız risk faktörlerini belirlemek için çok değişkenli bir lojistik regresyon modeli kullanıldı.
Bulgular: Obez hastalarda VAS ağrı skoru obez olmayan hastalardan daha yüksekti (4,49±2,76 ve 3,49±2,42, p=0,014). Osteoporoz hastalarında ileri yaş [Olasılık oranı (OR)=1,094, %95 güven aralığı (GA)=1,018-1,175, p=0,014] ve obezite (OR=0,225, %95 GA=0,055-0,928, p=0,039), VAS ağrı skoru ile ilişkili idi. Normal KMY olan hastalarda sadece ileri yaş VAS ağrı skoru ile ilişkili idi (OR=1,157, %95 GA=1,045-1,280, p=0,005). Tüm hastalarda ileri yaş (OR=1,141, %95 GA=1,093-1,192, p=<0,001) ve osteoporoz (OR=0,001, %95 GA=0,00-0,014, p=<0,001) VAS ağrı skoru ile ilişkiliydi.
Sonuç: Değişken bir risk faktörü olan obezitenin azaltılmasının, ağrı ve sedanter yaşam tarzını azaltacağını ve osteoporozu olan hastalarda KMY'yi iyileştireceğini düşünüyoruz.
Anahtar kelimeler: Osteoporoz, VAS ağrı skoru, obezite

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Introduction

Osteoporosis is a serious health problem in the elderly population (1). Worldwide, osteoporosis was 27.5 million in 2010, and it is estimated to be 33.9 million in 2025 and increase by 23% (2). Risk factors of osteoporosis are advanced age, female gender, genetic, calcium-poor, vitamin D deficiency, protein-rich nutrition, smoking, alcohol and coffee consumption, immobilization, sedentary life and steroid-like drug use affecting bone resorption (3). Nowadays, sedentary life, which has increased as a result of the change in eating habits and technological developments, has caused obesity to become a significant health problem like osteoporosis (4). Hu et al. (5) reported that osteoporosis and obesity have some common pleiotropic genes. Neglia et al. (6) said that increased body mass index (BMI) was associated with the raised rate of osteoporosis. Also, when bone mineral density (BMD) was evaluated with dual-energy X-ray absorptiometry (DXA) and high-resolution peripheral quantitative computed tomography was not shown the difference between obese and non-obese elderly (7).

Pain is an important complaint in osteoporotic elderly population, especially in postmenopausal women (8). The findings of Ohtori et al. (9) support that increased back pain as a result of bone resorption occurs in patients with osteoporosis. Also, studies have shown that obesity is also associated with pain (10). Mohd Sallehuddin et al. (11) reported that the Visual Analogue scale (VAS) pain score was increased in obese older and younger women, and the VAS pain score was higher in obese older women than younger obese women.

Osteoporosis and increased age are manifested as the increase of pain, withdrawal from daily life, and transition to a sedentary life. In light of current findings, obesity may affect the severity of pain in the elderly population with osteoporosis. In our study, we aimed to evaluate the VAS pain scale in obese and non-obese elderly patients, and additionally determine whether the VAS pain score is associated with obesity in patients with osteoporosis.

Materials and Methods

A total of one hundred and ninety-two patients were included in the study. These patients were admitted to the outpatient clinic of Beyşehir State Hospital and whose BMD and T-scores were determined in the last year. Because, BMD scanning time varies according to the age of osteoporosis-related fracture risk factors such as pre-fragility fracture, steroid use, family history of hip fracture, age, low body weight, smoking and decreased vision. Eventually, the time of re-BMD changes according to the threshold value of BMD to evaluate the effectiveness of the treatment in osteoporosis (12). Also, DXA analysis showed no significant difference in BMD in the elderly without any risk factors within 24 months (13). In our study, when we look at the following exclusion criteria; patients without additional risk factors, without any medication, causing any change in bone density, and no indication for re-measurement of BMD. BMD values were determined by the DXA method (DXA, Stratos dR 2D Fan Beam Dexa, DMS GROUP). BMI was calculated by the formula of kilogram/height square meters. BMI ≥30 was accepted as obese and BMI <30 as non-obese according to the World Health Organization (WHO) classification. BMD was measured from the lumbar spine level (L1-L4), and the hips (femoral neck, trochanter, and intertrochanteric) and the unit was g/cm^2. Osteoporosis and osteopenia were determined according to the T-scores of the above specific localizations regions according to the WHO, T-score ≤-2.5 was accepted as osteoporosis and T-score between -2.5 and -1 were accepted as osteopenia.

Patients were excluded if any of the following disorders were present: spontaneous and/or post-traumatic fractures, ankylosing spondylitis, myasthenia graves, received chemotherapy and radiotherapy due to a history of bone tumor and/or systemic tumor, received medication such as biphosphonate, calcium, which could cause a change in BMD for at least one year or longer. All participants provided a written informed consent and the study protocol was approved by the Necmettin Erbakan University Meram Faculty of Medicine Local Ethics Committee (approval date: 05.04.2019, decision no: 1794).

All patients who participated in the study were evaluated at admission. Clinical histories were evaluated, and anthropometry measurements, clinical examinations were performed. VAS pain score was evaluated in the patients. Especially walking, standing, climbing stairs, squatting, pain status with sitting and/or staying were evaluated in pain assessment of VAS pain scores. The VAS pain score was assessed as " without pain" (score =0) and "the worst pain" (score =10) (14). VAS pain scale was divided into three groups according to the WHO's pain severity scale as follows: score <3 mild pain, 3-6 mild-moderate pain, and >6 moderate-severe pain (15). BMD measurements of patients who were admitted to our hospital within the last year were recorded. The study protocol was performed according to the principles of the Declaration of Helsinki and approved by the local Ethical Committee.

Routine laboratory automated techniques were used to determine serum biochemical markers of serum C-reactive protein (CRP), calcium, phosphorus, sodium, potassium and vitamin B12 [CRP (0-6 mg/L), calcium (8.2-10.2 mg/dL), phosphorus (2.5-5 mg/dL), sodium (135-145 mmol/L), potassium (3.5-5.1 mmol/L), vitamin B12 (210-915 pg/mL) and vitamin D (9.5-39.6 ng/mL). Complete blood count (CBC) parameters were measured by automated blood counter Cell-Dyn 3700 automated hemocytometer (Abbott, IL, USA).

Statistical Analysis

The sample size required for the study was performed with the G-Power program (16). A minimum sample size of one hundred and twenty-six was needed to detect anticipated effect size of 0.3 for the regression equation, at a power level of 0.95 (β=0.95) and a probability level of 0.05 (α=0.05).

BM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Variables were tested for normality by the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± standard deviations. Categorical comparisons were performed using the χ^2 -test. We used the independent samples t-test for parametric variables between BMI <30 and BMI ≥30 groups. Univariate and multivariate logistic regression analysis was used to determine if a relationship between severe VAS pain score and obesity, serum biochemical and/or CBC parameters were present in patients with osteoporosis and normal BMD patients. A p value <0.05 was considered as significant.

Results

A total of 168 participants (69 BMI <30 and 99 BMI ≥30 patients) were enrolled in the study. The anthropometric and biochemical characteristics, CBC parameters, VAS pain score, and BMD measurements are given in Table 1. There were no statistically significant differences among age, CRP, calcium, phosphorus, sodium, potassium and vitamin B12, white blood cell counts, mean corpuscular volume, neutrophil lymphocyte ratio, platelet lymphocyte ratio values between groups. Osteoporosis and osteopenia distribution rates were not statistically significant between groups (Table 1). Serum vitamin D level was 10.49±3.12 ng/mL in the obese group, 9.09±3.06 ng/mL in the non-obese group, and was statistically significantly higher in the obese group (p=0.009). The median VAS pain score was 4.49±2.76 and 3.49±2.42 in BMI ≥30 and BMI <30 groups. VAS pain scores were higher in obese patients than non-obese patients (p=0.014) (Table 1).

Univariate and multivariate logistic regression analysis was then used to determine a relationship between VAS pain score and biochemical, CBC parameters, and BMI in osteoporosis and normal BMD patients. Advanced age [odds ratio (OR) =1.094, 95% confidence interval (CI) =1.018-1.175, p=0.014] and BMI ≥30 (OR =0.225, 95% CI =0.055-0.928, p=0.039) were associated with VAS pain score in osteoporosis patients (Table 2). Otherwise, only advanced age (OR =1.157, 95% CI =1.045-1.280, p=0.005) was associated with VAS pain score in normal BMD patients (Table 2).

Univariate and multivariate logistic regression analysis was then used to determine a relationship between VAS pain score and other variables in all patients. Advanced age (OR =1.141, 95% CI =1.093-1.192, p=<0.001) and osteoporosis (OR =0.001, 95% CI =0.00-0.014, p=<0.001) were associated with VAS pain score in all patients (Table 3). BMI and other variables were not significantly associated with VAS pain score in all patients (Table 3).

Table 1. Anthropometric and biochemical characteristics, laboratory parameters, and BMD measurements of BMI <30 and BMI ≥30 groups

		BMI <30 n=69	BMI ≥30 n=99	p*
Age (year)		57.38±9.36	55.49±9.09	0.194
VAS pain score		3.49±2.42	4.49±2.76	0.014
CRP (mg/L)		3.81±4.95	4.05±5.54	0.770
Sedimentation (mm/hr)		15.01±1.78	15.22±3.94	0.958
Calcium (mg/dL)		8.79±0.63	8.81±0.59	0.858
Phosphorus (mg/dL)		3.53±1.43	3.27±0.59	0.120
Sodium (mmol/L)		139.70±2.56	136.54±20.06	0.195
Potassium (mmol/L)		4.17±0.36	4.34±1.44	0.333
Vitamin B12 (pg/mL)		269.54±181.17	325.87±243.97	0.105
WBC (µl/mL)		7.45±1.89	7.58±1.89	0.676
MCV (fL)		80.23±10.66	80±6.49	0.857
Vitamin D (ng/mL)		9.09±3.06	10.49±3.12	0.009
NLR		2.07±0.93	2.11±1.01	0.834
PLR		108.95±42.08	111.64±51.43	0.720
BMD	**Osteoporosis**	21 (30.4%)	26 (26.3%)	0.785
	Osteopenia	18 (26.1%)	25 (25.3%)	
	Normal	30 (43.5%)	48 (48.5%)	

*p<0.05 is considered as statistically significant. Independent sample-test, mean ± SD, BMI: Body mass index, VAS: Visual Analogue scale, BMD: Bone mineral density, WBC: White blood cells, MCV: Mean corpuscular volume, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, BMD: Bone mineral density, SD: Standard deviation, n: Number, CRP: C-reactive protein

Table 2. Regression analysis of relationship factors with VAS pain score in osteoporosis and normal BMD patients

		VAS pain score							
		Osteoporosis				Normal BMD			
		Univariate		Multivariate		Univariate		Multivariate	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (year)		1.107 (1.030-1.189)	**0.005**	1.094 (1.018-1.175)	**0.014**	1.134 (1.031-1.248)	**0.010**	1.157 (1.045-1.280)	**0.005**
CRP (mg/L)		0.923 (0.711-1.198)	0.549	-	-	0.992 (0.919-1.070)	0.831	-	-
Calcium (mg/dL)		0.473 (0.143-1.559)	0.219	-	-	1.714 (0.587-5.004)	0.324	-	-
Phosphorus (mg/dL)		2.221 (0.707-6.973)	0.172	-	-	1.199 (0.377-3.813)	0.758	-	-
Sodium (mmol/L)		1.184 (0.950-1.476)	0.132	-	-	1.067 (0.844-1.349)	0.586	-	-
Potassium (mmol/L)		0.904 (0.616-1.326)	0.604	-	-	2.254 (0.402-12.628)	0.355	-	-
Sedimentation (mm/hr)		0.991 (0.964-1.019)	0.522	-	-	1.034 (0.985-1.086)	0.177	-	-
Vitamin B12 (pg/mL)		1.002 (0.999-1.005)	0.131	-	-	1.000 (0.997-1.004)	0.869	-	-
WBC (µl/mL)		1.136 (0.868-1.487)	0.353	-	-	0.914 (0.691-1.211)	0.532	-	-
MCV (fL)		0.996 (0.952-1.043)	0.878	-	-	1.018 (0.891-1.163)	0.796	-	-
Vitamin D (ng/mL)		1.111 (0.930-1.328)	0.247	-	-	1.008 (0.815-1.247)	0.942	-	-
NLR		1.026 (0.724-1.454)	0.885	-	-	0.977 (0.541-1.766)	0.939	-	-
PLR		1.004 (0.993-1.015)	0.489	-	-	1.002 (0.994-1.010)	0.658	-	-
BMI	**BMI ≥30**	0.185 (0.051-0.677)	**0.011**	0.225 (0.055-0.928)	**0.039**	0.536 (0.159-1.804)	0.314	0.308 (0.074-1.285)	0.106
	BMI <30	0.971 (0.840-1.009)	0.077	-	-	1.111 (0.991-1.245)	0.070	-	-

*Logistic regression analysis (single and multiple categorical variables with Binary Logistik Regression analysis), *p value <0.05 is considered as statistically significant. BMI: Body mass index, VAS: Visual analogue scale, WBC: White blood cells, MCV: Mean corpuscular volume, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, BMD: Bone mineral density, OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein

Discussion

In our study, we found that the VAS pain score was higher in the elderly obese group than in a non-obese group. Additionally, in the present study, increased age and BMI ≥30 were found to be associated with VAS pain score in osteoporosis, and only increased age was found to be associated with VAS pain score in normal BMD patients.

Osteoporosis and obesity can be treated as the most important health problems worldwide. The aging of the world population, changes in dietary habits and increasing sedentary life, increases the rate of these diseases, and acute and chronic diseases such as heart disease, diabetes, and bone fractures. However, the rates of acute and chronic diseases such as diabetes, heart disease, and bone fractures are increasing because of osteoporosis and obesity (17). Nowadays, osteoporosis and obesity prevention and treatment are carried out to reduce treatment costs, minimize and prevent diseases worldwide. In the treatment of osteoporosis, drugs that inhibit bone resorption such as bisphosphonates, calcium, calcitonin, vitamin D, and regulate bone formation such as parathyroid hormone and strontium salts reused (18). Otherwise, lifestyle changes essential as much as the medications as mentioned above

Table 3. Regression analysis of relationship factors with VAS pain score in patients

	VAS pain score			
	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age (year)	1.135 (1.088-1.185)	**<0.001**	1.141 (1.093-1.192)	**<0.001**
BMI (kg/m²)	1.051 (1.001-1.103)	**0.045**	1.38 (0.997-1.121)	0.064
Osteoporosis	0.003 (0.00-0.025)	**<0.001**	0.001 (0.00-0.104)	**<0.001**
CRP (mg/L)	1.049 (0.997-1.104)	0.68	-	-
Calcium (mg/dL)	0.743 (0.465-1.190)	0.216	-	-
Phosphorus (mg/dL)	0.952 (0.664-1.366)	0.789	-	-
Sodium (mmol/L)	1.001 (0.987-1.014)	0.918	-	-
Potassium (mmol/L)	0.930 (0.623-1.308)	0.590	-	-
Sedimentation (mm/hr)	1.003 (0.991-1.015)	0.635	-	-
Vitamin B12 (pg/mL)	1.001 (0.999-1.002)	0.335	-	-
WBC (µl/mL)	0.942 (0.809-1.097)	0.440	-	-
MCV (fL)	1.022 (0.967-1.080)	0.441	-	-
Vitamin D (ng/mL)	1.007 (0.904-1.121)	0.903	-	-
NLR	1.072 (0.846-1.358)	0.564	-	-
PLR	1.004 (0.998-1.010)	0.156	-	-

*Logistic regression analysis (single and multiple categorical variables with Binary Logistik Regression analysis), *: p value <0.05 is considered as statistically significant. BMI: Body mass index, VAS: Visual analogue scale, WBC: White blood cells, MCV: Mean corpuscular volume, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, BMD: Bone mineral density, OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein

for the prevention of osteoporosis (18). Chen et al. (19) reported that obesity was associated with low BMD and additionally showed a significant relationship between increased BMI and low BMD. Ilich et al. (20) observed that bone and muscle mass decreased with increasing fat content, and as a result, they stated that immobilization, bone fracture rate, and pain increased. However, some studies suggest that obesity may be protective against osteoporosis and osteopenia in the elderly population (21). Some research shown that pain and obesity were positively correlated in elderly patients, and obesity was a risk factor in the development of pain and decreased the quality of life (22). National Institute for Health and Care Excellence stated that weight loss is an important treatment for pain management. Pain leads to a decrease of mobilization, loss of walking, and balance (23), restricts physical activity and increases the risk of falling in elderly patients (24,25). Increased pain and bone fracture rates are serious morbidity and mortality reasons in patients with osteoporosis (26). In light of the studies as mentioned above, it is seen that osteoporosis and obesity are important factors in pain formation and also treating these diseases reduces pain and improves the quality of life in the elderly population.

Conclusion

As a result of our study, we found that obesity and age are important risk factors that increase VAS pain score in elderly osteoporosis patients. We think that decreasing obesity, which is a variable risk factor, will benefit reduction pain and sedentary lifestyle and improve BMD in patients with osteoporosis. Limitations of our study were the absence of other biochemical markers in which BMD was evaluated, and lack of assessment of elderly life quality scale.

Ethics

Ethics Committee Approval: The study protocol was approved by the Necmettin Erbakan University Meram Faculty of Medicine Local Ethics Committee (approval date: 05.04.2019, decision no: 1794).

Informed Consent: All participants provided a written informed consent.

Peer-review: Internally peer-reviewed.

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The Effect of Postural Correction and Exercise on Neck Pains in Cell Phone Users

Cep Telefonu Kullanıcılarında Postür Düzeltilmesi ve Egzersizin Boyun Ağrılarına Etkisi

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Abstract

Objective: Using a cell phone in the head forward posture for a long time is a risk factor for the induction of trigger points (TP) and myofascial pain syndromes (MPS). The purpose of this study was to evaluate the association between cell phone use-related neck pain and MPS in the trapezius, sternocleidomastoideus and levator scapulae (LS) muscles as well as to determine an appropriate treatment approach.
Materials and Methods: In total, 49 patients who had neck pain and reported using a cell phone were included in this study and divided randomly into two groups. Taut band existence and TP pain severity were evaluated in the trapezius, sternocleidomastoideus and LS muscles. In addition, neck pain severity and range of motion (ROM) were assessed. Group 1 received a structured exercise programme and posture correction advice, whereas group 2 did not receive any treatment. The patients were re-evaluated again after 1 month, and these parameters were compared with those at the first examination.
Results: A total of 47 patients completed this study. In group 1, the neck pain score was found to be significantly decreased ($p<0.001$), and the taut band of the right LS muscle to have significantly disappeared ($p=0.004$). A significant decrease in TP pain severity was found on the 2nd point of the left sternocleidomastoideus ($p=0.039$), left trapezius ($p=0.031$), and right LS ($p=0.012$) muscles. In addition, a borderline decrease in pain was found in the 2nd point of the left LS muscle in group 1, although it did not reach statistical significance ($p=0.056$). On the other hand, there were no significant changes in terms of neck pain score, taut band existence and TPs pain severity in group 2. Pain and limitation of ROM showed no significant difference between the first and second examinations in both groups.
Conclusion: Limiting the duration of mobile phone usage, performing regular exercises and correcting the head forward position by increasing awareness can be helpful in preventing the development of text neck syndrome.
Keywords: Cell phone, neck pain, trapezius, sternocleidomastoideus, levator scapulae, trigger points, exercise, text neck syndrome

Öz

Amaç: Yanlış postürde uzun süreli cep telefonu kullanımı, tetik nokta (TN) ve miyofasiyal ağrı sendromu (MAS) oluşumu açısından risk oluşturmaktadır. Bu çalışmanın amacı trapez, sternokleidomastoid ve levator skapula (LS) kaslarındaki cep telefonu kullanımı ilişkili boyun ağrısı ve MAS arasındaki ilişkiyi değerlendirmek ve doğru tedavi yaklaşımını belirlemektir.
Gereç ve Yöntem: Bu çalışmaya boyun ağrısı olan ve cep telefonu kullanan 49 hasta katıldı ve randomize olarak iki gruba ayrıldı. Boyun ağrısı şiddeti, boyun hareket açıklığı ve trapez, sternokleidomastoid ve LS kaslarında gergin bant varlığı ile TN ağrı şiddeti değerlendirildi. Grup 1'deki hastalara yapılandırılmış boyun egzersizleri ve postür düzeltme önerileri verilirken, grup 2'deki hastalar herhangi bir tedavi almadı. Bir ay sonucunda hastalar yukarıdaki parametreler açısından tekrar değerlendirildi.
Bulgular: Toplamda 47 hasta araştırmayı tamamladı. Grup 1'de boyun ağrısında ($p<0,001$) ve sağ LS'de bulunan gergin bantlarda anlamlı bir azalma görüldü ($p=0,004$). Ayrıca grup 1'de sol sternokleidomastoid 2. noktasında ($p=0,039$), sol trapez 2. noktasında ($p=0,031$), ve sağ LS 2. noktasında ($p=0,012$) TN ağrı şiddetinde anlamlı azalma bulundu; ayrıca sol LS 2. noktasında ağrı şiddetinde sınıra yakın bir azalma bulunsa da bu azalma anlamlı bulunmadı ($p=0,056$). Buna karşın grup 2'de boyun ağrısı şiddeti, gergin bant varlığı ve TN ağrı şiddeti açısından anlamlı bir değişim tespit edilmedi. Ayrıca iki grupta da boyun hareket açıklığı muayenesi sırasında oluşan ağrı ve kısıtlılık açısından anlamlı bir fark saptanmadı.
Sonuç: Cep telefonu kullanımına bağlı boyun ağrısı ve MAS gelişen hastalarda farkındalığı artırarak, text neck sendromu gelişimini önlemek için telefon kullanımının kısıtlanması, düzenli egzersiz yapılması ve telefon kullanımı sırasında doğru boyun postürünün sağlanması önerilmektedir.
Anahtar kelimeler: Cep telefonu, boyun ağrısı, trapez, sternokleidomastoid, levator skapula, tetik nokta, egzersiz, text neck sendromu

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Introduction

Neck pain is a major musculoskeletal complaint in the young population. The overall prevalence of neck pain in the general population was found to be 23.1% (1). Myofascial pain syndromes (MPS) were defined as one of the leading causes of neck and thoracic pain (2). MPS are characterized by trigger points (TP), taut bands, pressure sensitivity, and referred pain (3).

Using a cell phone in abnormal posture for a long time puts increased strain on neck muscles and causes the induction of TPs and MPS. It was also reported that avoiding the aggravating factors had a significant role in the prevention or worsening of MPS (4). In the neutral position of the head, which is 0 degrees, the weight carried by the neck is approximately 5 kilograms (kg). This weight increases to nearly 12 kg with flexion of the head for 15 degrees, 18 kg with 30 degrees, 22 kg with 45 degrees and 27 kg with 60 degrees (5).

In the last years, the increased rate of cell phone usage and prolongation of using periods are responsible for increased neck muscle-related complaints. As a result, long-term fatigue, acute and chronic pain of the musculoskeletal system, and postural changes are detected in patients. If this condition is left untreated, it may be responsible for permanent changes such as flattening of the cervical spinal curve, spinal misalignment, and early spinal degenerations (6).

Along with steadily increasing in their usage, cell phones are becoming more and more important in our lives. As a result of that "text neck" which is the term for cervical spinal degeneration resulting from frequent forward head flexion while looking down at the of mobile devices, is becoming more common (7). According to a recent study, 79% of the population between the age of 18-44 spend 2 hours without their cell phones during their waking hours (6). Furthermore, 75% of the world's population spends hours while hunched over their handheld devices with their heads flexed forward (7).

Relationship between cell phone using and neck complaints has been shown by previous studies. Gustafsson et al. (8) found a relationship between text messaging and the neck/upper back pain. Berolo et al. (9) also found an association between cell phone using and pain in the neck and shoulder area.

Awareness about text neck syndrome was found to be very low in the population. According to a recent study, only 8% of the population was aware of text neck syndrome, 65% of them had never heard about it, while 27% reported having heard about it but did not know what it was. Also, 75% of these patients stated that although they thought this syndrome is preventable, they did not know the method for prevention (10). These results show that people should be informed about text neck syndrome and prevention methods.

In our study, three of the frequently involved muscles, trapezius, sternocleidomastoideus and levator scapulae (LS) were evaluated due to their essential functions. The trapezius muscle is one of the primary responsible muscle for posture, perceived neck/shoulder pain intensity, and muscle tenderness (11). The sternocleidomastoideus frequently contains multiple TPs and is responsible for flexion of head and neck. LS is also one of the primary muscles for developing TP and neck pain. TPs in LS is usually responsible for "stiff neck" (markedly limited rotation) (3). The correlation between cervical posture and TPs were addressed in a previous study, and a significant increase in TPs of the LS was reported in chronic neck pain patients (12). The function of LS is to help the extension and rotation of the neck (3). In addition to the mentioned features of these muscles, their accessibility during the physical examination was considered for their choice in our study.

In this study, we aimed to increase awareness among the population and prevent text neck syndrome. Another goal of this study was to evaluate the association between cell phone use related-neck pain and MPS in trapezius, sternocleidomastoideus and LS muscles as well as determining an appropriate treatment approach by providing a structured exercise program and posture correction advice.

Materials and Methods

This study was carried out at the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Physical Medicine and Rehabilitation, İstanbul, Turkey. Approval was obtained from the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee. A total of 49 patients (21 female and 28 male) who were cell phone users and complained of neck pain attended this research. Occupations of the patients included desk workers and students.

Inclusion criteria were neck pain complaint, using a cell phone for at least two hours per day for five years and being between 15 and 40 years old.

Exclusion criteria were previous neck-head trauma, history of surgical intervention in the neck area, neurological deficit, severe neck pain which required medical treatment, cervical disc disease with radiculopathy, inflammatory or malignant type of pain, and systematic diseases.

Patients who applied to the outpatient clinic of our department with complaints of musculoskeletal system pain of different regions were evaluated. Those who had neck pain and fulfilled inclusion and exclusion criteria were determined to be suitable patients for our clinical study. The patients were randomly divided into two groups as group 1 [treatment group (n=21)], and group 2 [control group (n=28)]. Patients in group 1 received a structured exercise program and verbal as well as written posture correction advice, while group 2 patients did not receive any treatment.

Before the examination, all patients were informed in detail about the study and written consent forms were obtained. The examination consisted of four parts, including medical history, inspection, palpation, and neck range of motion (ROM) examination.

All examinations were performed simultaneously by an intern and a physiatrist. Patients' history was asked in detail and age, body mass index (BMI) occupation, daily usage of cell phone and computer, number of years since regular cell phone using, duration of pain, pain characteristic and reference pattern, aggravating and alleviating factors, position during cell phone use, sport activity and smoking history were recorded.

Pain severity was measured by the Visual Analog scale (VAS) during the first examination and second examination which is one month later. Also, VAS measurements were saved as millimeters.

During the inspection, patients were evaluated for shoulder asymmetry, cervical lordosis, and dorsal postural deformities.

During palpation, two different points of sternocleidomastoideus (Figure 1), three different points of trapezius (Figures 2.1, 2.2) and two different points of LS (Figure 3) were palpated and evaluated in terms of taut muscle bands and TP existence. While pression of these points, patients were asked to classify TP pain severity as grade 1 (mild pain), grade 2 (moderate pain) or grade 3 (severe pain).

During the neck ROM examination patients were assessed for pain and limitation in neck movements. Patients in group 2 were instructed to continue their regular life and not to receive any additional medication or treatment.

Patients in group 1 received a structured, exercise program consisting of neck muscles stretching and posture exercises also they were informed to perform exercises as 10 repeats and 2 sets in every day. In addition to exercises, they received advice for posture correction and limitations during cell phone usage.

Neck exercises compromised neck rotation (Figure 4), isometric

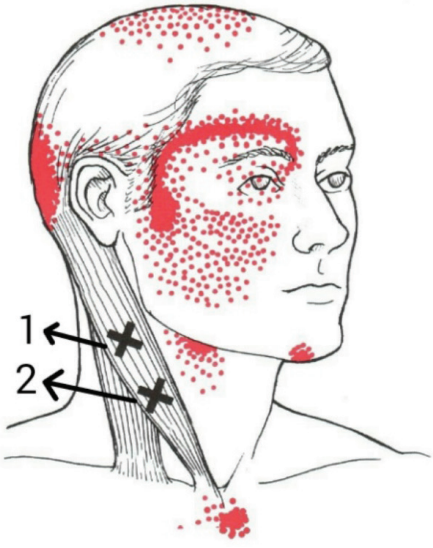

Figure 1. M. sternocleidomastoideus 1st and 2nd trigger points (12)

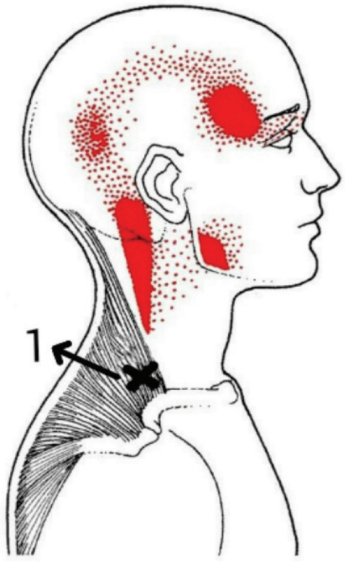

Figure 2.1. M. trapezius 1st trigger point (12)

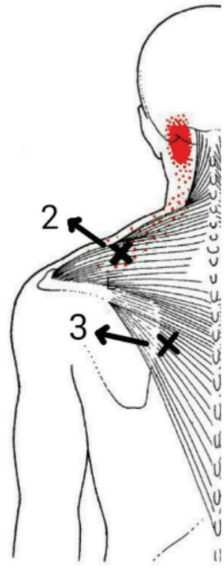

Figure 2.2. M. trapezius 2nd and 3rd trigger points (12)

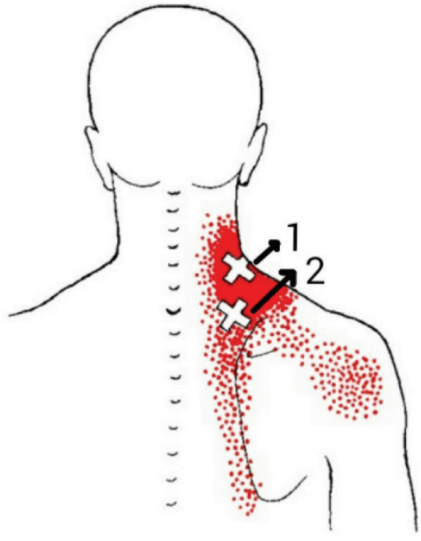

Figure 3. M. levator Scapulae 1st and 2nd trigger points (12)

Figure 4. Neck rotation exercise

Figure 5. Isometric neck extension exercise

Figure 6. Levator scapulae stretch

neck extension (Figure 5), LS stretch (Figure 6), lateral neck stretch in standing (Figure 7) and lying position (Figure 8), standing chest stretch (Figure 9), shoulder roll (Figure 10), corner chest stretch (Figure 11), and trapezius muscle stretch in lying position (Figure 12).

The written posture advice was:

- While using a cell phone, personal computer and other electronic devices please hold them at eye level.
- Please give a break in every 20 minutes during using of these devices.
- While using big and heavy electronic devices such as Tablets and large cell phones, please hold them with both hands.
- During reading books or newspapers please hold them at eye level.
- While using cell phone, avoid high repetitive typing and scrolling the screen for a long time.
- Try not to hunch forward during electronic devices.

Additionally, patients in group 1 were informed about a mobile phone application which warns about changes in the head posture by a notification.

All patients were informed to reach the physician immediately if any adverse events or a significant increase in pain severity occurred.

One month after the first examination, patients were called for control. In the follow-up examination, patients' pain severity was measured again by VAS. Taut bands, TPs, and neck ROM were assessed.

Statistical Analysis

Mc Nemar test was utilized to determining significance of taut band existence and pain or limitation during ROM assessment in groups. For evaluating VAS Pain score, Mann-Whitney U test was applied. Wilcoxon Signed Ranks test was used for determination of pain severity in TPs. SPSS 21.0 (IBM, USA) was used for all the statistical analyses and statistical significance was assumed when p-value was lowered than 0.05.

Figure 7. Lateral neck stretch in standing position

Figure 8. Lateral neck stretch in lying position

Results

From a total of 49 patients, 21 patients in group 1 and 26 patients in group 2 completed the study. Two patients from group 2 were eliminated. The first patient was eliminated due to the diagnosis of fibromyalgia syndrome and the second one was eliminated because he had to take additional medicational treatment. Patient demographic data and pain characteristics were recorded during the first examination and they were shown in Table 1. Males compromised 57.4% (n=27) and females compromised 42.6% (n=20) of patients. The mean

Figure 9. Standing chest stretch

age of participants was 27.6±7.4 [mean ± standard deviation (SD)], and the mean BMI was 23.5±3.1 (mean ± SD). All patients complained of a mechanical type of neck pain. 63.8% of patients described referral of pain to different regions, especially to shoulders, head, back, and arms.

In the physical examination, cervical lordosis was found to be decreased in 55.3% of patients. Shoulder asymmetry, especially depression of one shoulder, was inspected in 30.4% of patients. Neck pain severity was assessed by VAS pain score in the beginning and after one month. Pain score in group 1 was 43.3±16.3 (mean ± SD) in the first assessment, while it was 21.9±13.3 (mean ± SD) in the second assessment. According to VAS neck pain score results, a significant decrease was found in group 1 ($p<0.001$). In contrast, there were no significant changes found in group 2 ($p=0.123$). Group 2 pain severity scores were recorded as 37.0±16.9 (mean ± SD) in the first and 30.3±15.3 (mean ± SD) in the second assessment (Table 2).

Patients were evaluated in terms of the existence of the taut band and TP pain severity during palpation. In group 1, only the taut band of right LS had significantly disappeared ($p=0.004$);

Figure 10. Shoulder roll exercise

Figure 11. Corner chest stretch

however, there were no significant changes in group 2 with regard to examined muscles.

TPs pain severity was found to be significantly decreased at the 2nd point of the left sternocleidomastoideus (p=0.039), left trapezius (p=0.031), and right LS (p=0.012) muscles in group 1. In the 2nd point of the left side in LS, pain decrease was found borderline, although it did not reach statistical significance (Table 3). There were no significant changes with regards to TP pain in group 2 (Table 4).

Pain and limitation during neck ROM examination revealed no significant changes between the first and second examination in group 1 and 2.

Discussion

In our study, we aimed at describing the relationship between neck pain, MPS and treatment outcome in mobile phone users. Neck pain and its relationship to using electronic devices and the correlation with MPS have been discussed extensively. This study measured changes in patients' VAS neck pain score, TP's pain, taut band existence, and neck ROM and compared results in treatment and control groups.

In our study, students (44.7%) and desk workers (55.3%) constituted the population. Along with using electronic devices frequently and spending extended time with head forward posture, neck pain complaint is becoming very common among students and desk workers in the population. According to recent studies, 46% of students (13) and 50 to 60% of desk workers reported neck pain (14). Our findings and previous research's results show that patients who belong to these two occupation groups should be informed by physicians about neck pain development and effective prevention methods.

Most cases with neck pain run an episodic course over a lifetime and, thus, relapses are frequent (1). In 91.5% (n=43) of our patients, the duration of neck pain was over six months, that denoted if neck pains are not treated adequately they tend to develop chronic musculoskeletal pain condition.

Spending a long time using a cell phone, frequently talking, texting, and gaming was described as a risk factor for developing neck pain (9,15,16).

In this study, 46.3% of patients reported that their daily phone usage was between 3 to 6 hours. This finding was consistent with the study conducted by Berolo et al. (9), who reported a mean of 4.6±5.6 (mean ± SD) hours. 55.3% of our patients

Table 1. Patient data and pain characteristics			
Age (years)	27.6 ±7.4	**Number of years since regular cell phone using (years)**	
Body mass index	23.5±3.1	<10	36.2% (n=17)
Gender		10-20	55.3% (n=26)
Female	42.6% (n=20)	20>	8.5% (n=4)
Male	57.4% (n=27)	**Daily phone usage (hours)**	
Occupation		<3	29.8% (n=14)
Student	44.7% (n=21)	3-6	46.3% (n=22)
Desk workers	55.3% (n=26)	>6	21.3% (n=10)
Referred pain		**Posture during phone use**	
Yes	63.8% (n=30)	Sit and bend forward	78.7% (n=37)
No	36.2% (n=17)	Lie on back	8.5% (n=4)
Onset of pain (months)		Both	12.8% (n=6)
<1	4.3% (n=2)	**Pain aggrevating posture during phone use**	
1-6	4.3% (n=2)	Sit and bend forward	84.6% (n=22)
>6	91.5% (n=43)	Lie down	7.7% (n=2)
Is pain continuous or intermittent		Both	7.7% (n=2)
Continiuous	36.2% (n=17)	**Daily personal computer usage (hours)**	
Intermittent	63.8% (n=30)	<3	36.2% (n=17)
Frequency of pain (in one week)		3-6	10.6% (n=5)
>3	41.2% (n=14)	>6	53.2% (n=25)
<3	58.8% (n=20)	**Smoking**	
Aggravating factors of pain		Yes	32.6% (n=15)
Phone using	58.7% (n=27)	No	67.4% (n=31)
Others	41.3% (n=19)	**Regular sport activities**	
Alleviating factors of pain		Yes	44.7% (n=21)
Stretching	46.9% (n=15)	No	55.3% (n=26)
Resting	37.5% (n=12)	**Cervical lordosis**	
Both	15.6% (n=5)	Decreased	55.3% (n=26)
		Normal	44.7% (n=21)
		Shoulder asymmetry	30.4% (n=14)

stated that they have been using a cell phone for 10 to 20 years. Hegazy et al. (16), stated a shorter average duration of owning a cell phone [7.8±1.9 years (mean ± SD)]. The mean age of our patients [27.6±7.4 years (mean ± SD)] was older than in Hegazy et al.'s (16) study [21±1.1 years (mean ± SD)], which could elucidate this difference.

Along with cell phones becoming more popular, neck pain complaints keep increasing. In our study, 58.7% of patients stated that cell phone use caused or increased their neck pain. Complaints due to using mobile devices for a long time were studied by different researchers, and the most common symptom was found to be neck pain. The results for frequency of neck pain symptom was reported in different studies to change between 40.9% [Shan et al. (17)], 55.8% [Kim and Kim. (18)], 68% [Berolo et al. (9)], and 71.2% [Alzarea and Patil (19)]. We found that the most frequently described posture by our patients during phone use was sitting and bending forward position (78.7%). Also, these patients stated that this posture was responsible for the aggravation of neck pain (84.6%). Gold et al. (20), observed almost two-thirds of their patients were using a cell phone in neck flexed posture. This finding was consistent with our results. The relationship between flexed neck posture and neck pain has also been studied by different researchers. Gustafsson et al. (8) mentioned that two prospective cohort studies have shown an increased risk for neck or neck/shoulder pain during work with neck flexion position. Two recent studies reported that an increase in cervical flexion degree caused a significant increase in muscle fatigue and pain in the upper trapezius muscle (21,22). Also, Syamala et al. (23) stated that holding cell phone at eye level with proper body support during usage can reduce the biomechanical stress in the neck and upper extremities.

Figure 12. Trapezius muscle stretch in lying position

Table 2. Comparison of patients' Visual Analog scale neck pain score between the 1st and 2nd measurement

	1st Measurement	2nd Measurement	
	Mean ± SD (mm)	Mean ± SD (mm)	*p
Group 1	43.3±16.3	21.9±13.3	p<0.001*
Group 2	37.0±16.9	30.3±15.3	p=0.123

*p<0.05, thereby indicating a significant difference in patients' Visual Analog scale neck pain score, SD: Standard deviation

In our study, we did not find a significant change in patients' limitation and pain during neck ROM examination in the two groups. However, Kong et al. (24) found a significant increase in neck ROM after four weeks of modified cervical exercise program. A possible explanation of this difference could be that our patients did not perform exercises on a regular basis. Another explanation could be that limitation in neck ROM was not an inclusion criterion in our study, and therefore, a change could not be detected.

Cervical lordosis was found to be decreased in 55.3% (n=26) of the patients. According to a recent research, cell phone use causes a decrease in cervical lordosis (25). Our findings were consistent with that of Öğrenci et al. (26), who reported a significant correlation between decreased cervical lordosis and the duration of phone usage.

After a one-month exercise program and posture correction advice, we found a significant decrease in VAS neck pain score ($p<0.05$) in the treatment group. Jagdhari et al. (2), evaluated pain score by using VAS at the 1st, 30th, and 60th days and found a significant decrease in exercise group in consistency with our result.

TPs and taut bands were present in different locations and different muscles in all of our patients. TPs are often located in muscles in the neck and thoracic region, also secondary TPs development is quite often (7,27). Our results showed that the presence of TPs in the sternocleidomastoideus was associated with the presence of TPs in the trapezius muscle and the LS. These findings were parallel to Fernández-de-las-Peñas et al.'s (28) study.

In our study after patients performed the exercise program and followed posture advice for one month, TPs pain severity was

Table 3. Group 1 patients' trigger point pain severity and significance of difference between 1st and 2nd examinations in different locations

	1st Examination				2nd Examination				
Trigger point location	**Painless**	**Mild pain**	**Moderate pain**	**Severe pain**	**Painless**	**Mild pain**	**Moderate pain**	**Severe pain**	***p**
M. sternocleidomastoideus right 1st	52.4% (n=11)	14.3% (n=3)	23.8% (n=5)	9.5% (n=2)	76.2% (n=16)	9.5% (n=2)	14.3% (n=3)	-	p=0.176
M. sternocleidomastoideus right 2nd	52.4% (n=11)	23.8% (n=5)	14.3% (n=3)	9.5% (n=2)	76.2% (n=16)	9.5% (n=2)	4.8% (n=1)	9.5% (n=2)	p=0.092
M. sternocleidomastoideus left 1st	61.9% (n=13)	9.5% (n=2)	23.8% (n=5)	4.8% (n=1)	85.7% (n=18)	9.5% (n=2)	4.8% (n=1)	-	p=0.388
M. sternocleidomastoideus left 2nd	52.4% (n=11)	28.6% (n=6)	14.3% (n=3)	4.8% (n=1)	90.5% (n=19)	9.5% (n=2)	-	-	p=0.039*
M. trapezius right 1st	57.1% (n=12)	14.3% (n=3)	28.6% (n=6)	-	52.4% (n=11)	19.0% (n=4)	28.6% (n=6)	-	p=0.717
M. trapezius right 2nd	33.3% (n=7)	28.6% (n=6)	23.8% (n=5)	14.3% (n=3)	42.9% (n=9)	23.8% (n=5)	19% (n=4)	14.3% (n=3)	p=0.381
M. trapezius right 3rd	66.7% (n=14)	14.3% (n=3)	9.5% (n=2)	9.5% (n=2)	61.9% (n=13)	19% (n=4)	14.3% (n=3)	4.8% (n=1)	p=0.509
M. trapezius left 1st	57.1% (n=12)	14.3% (n=3)	28.6% (n=6)	-	61.9% (n=13)	23.8% (n=5)	14.3% (n=3)	-	p=0.959
M. trapezius left 2nd	42.9% (n=9)	23.8% (n=5)	23.8% (n=5)	9.5% (n=2)	76.2% (n=16)	9.5% (n=2)	14.3% (n=3)	-	p=0.031*
M. trapezius left 3rd	61.9% (n=13)	23.8% (n=5)	14.3% (n=3)	-	61.9% (n=13)	23.8% (n=5)	14.3% (n=3)	-	p=1
LS right 1st	66.7% (n=14)	14.3% (n=3)	19% (n=4)	-	76.2% (n=16)	14.3% (n=3)	9.5% (n=2)	-	p=0.619
LS right 2nd	33.3% (n=7)	23.8% (n=5)	33.3% (n=7)	9.5% (n=2)	81% (n=17)	14.3% (n=3)	4.8% (n=1)	-	p=0.012*
LS left 1st	57.1% (n=12)	19% (n=4)	23.8% (n=5)	-	66.7% (n=14)	14.3% (n=3)	19% (n=4)	-	p=0.550
LS left 2nd	33.3% (n=7)	23.8% (n=5)	42.9% (n=9)	-	57.1% (n=12)	4.8% (n=1)	38.1% (n=8)	-	p=0.056

LS: Levator Scapulae muscle, *p<0.05, thereby indicating significant difference in patients' trigger point pain severity

found to be significantly decreased at the 2nd point of the left sternocleidomastoideus (p=0.039), left trapezius (p=0.031), and right LS (p=0.012) muscles in group 1. Also, the 2nd point of the left side in LS (p=056) pain decreased but did not reach statistical significance. There were no significant changes with regards to TPs pain in group 2. Taut bands in LS significantly disappeared in group 1 (p<0.05). Also, Jagdhari et al.'s (2) study, detected a reduction in muscle tenderness in the exercise group. Additionally, decreased myofascial TP sensitivity in response to passive stretch in patients with myofascial head and neck pain was reported (29).

The strong point of our study was that despite many studies pointing out the correlation between neck pain and cell phone usage, only very few of them focused on treatment. In our study, the patients received a structured neck exercise program and recommendations for posture correction and limitations during cell phone usage. A follow-up examination of all patients was carried out after one month of treatment.

Study Limitations

The limitations of our study were that examinations were not performed blind. The other limitation was that exercises should be performed for two to three months to show optimal improvement. A prospective follow-up of patients for more prolonged periods could be advisable in future research studies.

Conclusion

Cell phone using rates have increased in recent years. As a result of this, the number of people who have cell phone use-related neck pain complaints has been on the rise. Limiting the duration of mobile phone usage and correcting forward head position by increasing awareness should be recommended. Furthermore, a structured neck exercise program performed on a regular basis also should be helpful to prevent the development and treatment of text neck syndrome.

Table 4. Group 2 patients' trigger point pain severity and significance of the difference between 1st and 2nd examinations in different locations

	1st Examination				2nd Examination				
Trigger point location	**Painless**	**Mild pain**	**Moderate pain**	**Severe pain**	**Painless**	**Mild pain**	**Moderate pain**	**Severe pain**	**p**
M. sternocleidomastoideus right 1st	65.4% (n=17)	3.8% (n=1)	26.9% (n=7)	3.8% (n=1)	50% (n=13)	19.2% (n=5)	26.9% (n=7)	3.8% (n=1)	p=0.085
M. sternocleidomastoideus right 2nd	57.7% (n=15)	19.2% (n=5)	11.5% (n=3)	11.5% (n=3)	61.5% (n=16)	3.8% (n=1)	19.2% (n=5)	15.4% (n=4)	p=0.321
M. sternocleidomastoideus left 1st	61.5% (n=16)	15.4% (n=4)	11.5% (n=3)	11.5% (n=3)	65.4% (n=17)	11.5% (n=3)	15.4% (n=4)	7.7% (n=2)	p=0.717
M. sternocleidomastoideus left 2nd	61.5% (n=16)	11.5% (n=3)	19.2% (n=5)	7.7% (n=2)	53.8% (n=14)	7.7% (n=2)	26.9% (n=7)	11.5% (n=3)	p=0.752
M. trapezius right 1st	61.5% (n=16)	26.9% (n=7)	7.7% (n=2)	3.8% (n=1)	53.8% (n=14)	23% (n=6)	19.2% (n=5)	3.8% (n=1)	p=0.842
M. trapezius right 2nd	69.2% (n=18)	11.5% (n=3)	7.7% (n=2)	11.5% (n=3)	50% (n=13)	7.7% (n=2)	26.9% (n=7)	15.4% (n=4)	p=0.324
M. trapezius right 3rd	80.8% (n=21)	3.8% (n=1)	7.7% (n=2)	7.7% (n=2)	73.1% (n=19)	7.7% (n=2)	11.5% (n=3)	7.7% (n=2)	p=0.286
M. trapezius left 1st	76.9% (n=20)	7.7% (n=2)	11.5% (n=3)	3.8% (n=1)	69.2% (n=18)	7.7% (n=2)	19.2% (n=5)	3.8% (n=1)	p=0.478
M. trapezius left 2nd	69.2% (n=18)	7.7% (n=2)	15.4% (n=4)	7.7% (n=2)	50% (n=13)	30.8% (n=8)	7.7% (n=2)	11.5% (n=3)	p=0.099
M. trapezius left 3rd	88.5% (n=23)	3.8% (n=1)	3.8% (n=1)	3.8% (n=1)	80.8% (n=21)	3.8% (n=1)	11.5% (n=3)	3.8% (n=1)	p=0.459
LS right 1st	42.3% (n=11)	30.8% (n=8)	15.4% (n=4)	11.5% (n=3)	57.7% (n=15)	26.9% (n=7)	11.5% (n=3)	3.8% (n=1)	p=0.403
LS right 2nd	61.5% (n=16)	7.7% (n=2)	19.2% (n=5)	11.5% (n=3)	57.7% (n=15)	19.2% (n=5)	19.2% (n=5)	3.8% (n=1)	p=0.301
LS left 1st	53.8% (n=14)	26.9% (n=7)	7.7% (n=2)	11.5% (n=3)	65.4% (n=17)	19.2% (n=5)	7.7% (n=2)	7.7% (n=2)	p=0.615
LS left 2nd	69. 2% (n=18)	11.5% (n=3)	7.7% (n=2)	11.5% (n=3)	61.5% (n=16)	15.4% (n=4)	11.5% (n=3)	11.5% (n=3)	p=0.396

LS: Levator scapulae muscle, *p<0.05, thereby indicating significant difference in patients' trigger point pain severity

Ethics

Ethics Committee Approval: Approval was obtained from the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (date: 07.03.2016, approval no: 89638).

Informed Consent: Written consent forms were obtained.

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Serum Melatonin Levels in Patients with Family Mediterranean Fever

Ailevi Akdeniz Ateşi Olan Hastalarda Serum Melatonin Düzeyleri

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Abstract

Objective: Melatonin (MLT) has been reported to play a role in the immunopathogenesis and aetiology of many chronic inflammatory diseases. Therefore, we aimed to investigate the possible relationship between disease severity and serum MLT levels in patients with Familial Mediterranean fever (FMF).

Materials and Methods: A total of 30 patients diagnosed with FMF who had experienced no episodes for at least 1 month (mean age, 36.4±12.2 years; range, 19-68 years), including 14 men and 16 women, and 30 healthy controls (mean age, 38.4±12.5 years; range, 19-65 years), 12 men and 18 women, matched for age and gender, were included in this study. Demographic data, laboratory data and clinical characteristics of the participants were recorded and serum MLT levels were determined. In addition, the relationship between serum MLT level and disease severity was evaluated.

Results: A significant difference was observed between the groups in terms of serum MLT levels ($p<0.05$). However, there were no significant relationships between serum MLT levels and demographic data, such as sex and age, and body mass index, erythrocyte sedimentation rate, C-reactive protein and fibrinogen levels and disease severity scores of the FMF patients. There was a statistically significant difference in serum MLT levels between patients having a history of acute arthritis (n=7) and those without arthritis (n=23), ($p=0.019$).

Conclusion: Our findings suggest that MLT may play a possible role in the immunopathogenesis of FMF and those with a history of FMF-related arthritis. However, because the immune regulatory role of MLT is very complex and the mechanisms are not yet fully understood, we think that more comprehensive studies in the future are needed to confirm our findings.

Keywords: Familial Mediterranean fever, melatonin, arthritis, relationship

Öz

Amaç: Melatoninin (MLT) birçok kronik enflamatuvar hastalığın immünopatogenezinde ve etiyolojisinde rol oynayabileceği bildirildiğinden dolayı, çalışmamızda ailevi akdeniz ateşi (AAA) olan hastaların serum MLT seviyelerinin belirlenerek hastalık şiddeti ile arasında olası bir ilişki olup olmadığını incelemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya AAA hastalığı tanısı konulan ve en az 1 aydır (ortalama yaş, 36,4±12,2 yıl; aralık, 19-68 yıl) atak geçirmeyen 14 erkek ve 16 kadın olmak üzere toplam 30 hasta (ortalama yaş, 38,4±12,5 yıl; aralık, 19-65 yıl) ile yaş ve cinsiyetleri benzer olan 12 erkek ve 18 kadın toplam 30 sağlıklı kontrol (ortalama yaş 38,4±12,5 yıl; yaş aralığı; 19-65 yıl) bulunmaktaydı. Katılımcıların demografik verileri, laboratuvar ve klinik özellikleri kaydedilerek, serum MLT seviyeleri belirlendi. Ayrıca serum MLT seviyesi ile hastalık şiddeti arasındaki ilişki değerlendirildi.

Bulgular: Gruplar arasında serum MLT seviyeleri açısından anlamlı fark olduğu belirlendi ($p<0,05$). AAA hastalarının cinsiyet, yaş ve vücut kitle indeksi gibi demografik verileri, eritrosit sedimentasyon hızı, C-reaktif protein ve fibrinojen değerleri ve hastalık şiddet skoru ile serum MLT seviyesi arasında anlamlı bir ilişki bulunmadı. AAA hastalarında artrit varlığına göre; akut artrit öyküsü olanlar (n=7 kişi) ile artriti olmayanlar (n=23 kişi) arasında serum MLT düzeyleri açısından istatistiksel olarak anlamlı fark bulundu ($p=0,019$).

Sonuç: Bulgularımız MLT'nin AAA'nın immünopatogenezinde ve AAA'ya bağlı artrit öyküsü olanlarda olası bir rol oynadığına dair kanıt sunmaktadır. Ancak MLT'nin immün düzenleyici rolü çok karmaşık ve mekanizmaları henüz tam olarak anlaşılamadığından dolayı bulgularımızın gelecekte daha kapsamlı araştırmalarla desteklenmesi gerektiğini düşünüyoruz.

Anahtar kelimeler: Ailevi akdeniz ateşi, melatonin, artrit, ilişki

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Introduction

Familial Mediterranean fever (FMF) is a recurrent and self-limiting hereditary auto inflammatory disease characterized by fever and painful polyserositis attacks with a very intense acute phase response (1). Although it was reported that B and T lymphocyte dysfunction and immunological abnormalities related to the production of proinflammatory cytokines, incorrectly regulated immune response and over-response to very small stimuli or to the delayed deactivation of the immune response play role in the course of the disease, the pathophysiology of the disease it is not clear (2-4). It has also been reported that decreased antioxidant capacity and impaired oxidant/antioxidant balance may be associated with FMF pathogenesis (5).

Melatonin (MLT) is the hormone that is secreted from the pineal gland and regulates the circadian rhythm, and it is thought that as a result of disruption of the circadian rhythm, it will deteriorate in immune response, abnormal immune cells will occur and may lead to FMF attacks (6-8). Many studies of MLT have emphasized its antioxidant properties as one of the most potent endogenous free radical scavengers (9,10). In addition, MLT has been reported to have immunomodulatory and anti-inflammatory functions in clinical studies (11,12). However, the immune regulatory role of MLT is very complex and its mechanisms are not yet fully understood (13). Because of these properties, it has been suggested that MLT may play a role in the immunopathogenesis and etiology of many chronic inflammatory diseases and can also be used in their treatment. In addition, due to the relationship between circadian MLT secretion and the rhythmic symptoms and symptoms of some chronic inflammatory diseases, it may have a role in the pathophysiology of these diseases (13). However, there is a study in the literature examining the relationship between FMF disease and MLT, and the relationship between MLT and disease severity was not evaluated in that study.

In our study; we aimed to investigate the possible relationship between disease severity and serum MLT levels in patients with FMF.

Materials and Method

This study was conducted between November 2019 and December 2019 at Atatürk University Faculty of Medicine, Department of Physical Medicine and Rehabilitation and Department of Rheumatology. The study protocol was approved by the Atatürk University Faculty of Medicine Ethics Committee (decision no: 17, date: 07.11.2019). A written informed consent was obtained from each subject. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 30 FMF patients diagnosed based on the criteria defined by Livneh et al. (14) and 30 healthy individuals with similar age and gender were included. All patients were diagnosed and evaluated by the same physician. None of the patients had an FMF attack. Patients who did not have an attack for at least 1 month were included in the study. The control group was constituted of healthy individuals.

In our study, FMF patients with additional immunological, rheumatologic or systemic disease, acute or chronic infection, complete urinalysis and abnormal biochemical results in blood analysis were excluded from the study.

Gender, age, body mass index (BMI), duration of disease, duration and dose of colchicine were recorded. Eighteen patients were on 1 mg/day oral colchicine treatment and 12 patients were on 1.5 mg/day oral colchicine treatment. Disease severity of FMF patients was evaluated in clinical examination.

The FMF disease severity scores were calculated based on age at disease onset (>31, 21-31, 11-20, 6-10, and <6 years, respectively, 0, 1, 2, 3, 4 points), number of attacks per month, (1, 2, 3 points if <1, 1-2,>2 respectively), arthritis status (2 and 3 points respectively if acute or protracted), amyloidosis status (3 points if present), colchicine dose (1, 1.5, 2 and >2 mg, respectively, 1, 2, 3 and 4 points) and the presence or absence of erysipelas-like erythema at the time of admission. Scores of 3-5, 6-8, and ≥9 were considered to reflect mild, moderate and severe disease, respectively (15). Distribution of the number of patients according to the scores obtained from disease severity parameters is shown in Table 1.

Healthy controls and FMF patients were rested in sitting position between 8.00-9.00 in the morning, and blood samples were obtained from antecubital region by using a vacutainer. Venous blood samples were stored in biochemistry tube for C-reactive protein (CRP) and MLT measurements and in hemogram tubes with ethylenediaminetetraacetic acid for erythrocyte sedimentation rate (ESR) measurements. Biochemistry samples were centrifuged at 4.000 rpm for 15 minutes after the clotting process at room temperature was completed and serum

Table 1. Distribution of the number of patients according to scores obtained from disease severity parameters

Number of patients according to disease severity parameters	Disease severity score				
	0 point	1 point	2 point	3 point	4 point
n (Age at disease onset; 0-4 point)	6	11	8	4	1
n (Number of attacks per month; 1-3 point)	-	21	9	-	-
n (Arthritis status; 2/3 point)	23	-	7	-	-
n (Erysipelas-like erythema status; 0/2 point)	25	-	5	-	-
n (Amyloidosis status; 0/3 point)	27	-	-	3	-
n (Colchicine dose; 1-4 point)	-	18	12	-	-

n: Number of patients

samples were aliquoted for MLT measurement and stored until analyzed at -80 °C. The analysis was performed in the Medical Biochemistry Laboratory of our hospital.

The ESR (0-20 mm/h) was measured with the Western Green method using Interrliner XN (Sysmex Corporation, Kobe, Japan) automatic ESR analysis device and the CRP (0-5 mg/mL) was quantitatively measured with the immunoturbidometric method using Beckman Coulter AU5800 autoanalyser (Beckman Coultr Inc. Ca, USA). Fibrinogen (mg/dL) levels were measured by Clauss clotting method on STA Compact (Diagnostica Stago, France) coagulation analyzer. MLT levels were analyzed by enzyme-linked immunosorbent assay (ELISA) method on Dynex brand automated ELISA reader device (Dynex Technologies Headquarters, Chantilly, USA) according to the standard protocol recommended by SunLong brand (Cat No: SL1169Hu, Sunlung Biotech Co., Ltd., HangZhou, China). The intra-assay cofficient of variation (CV) value of the kit was below 10% and the inter-assay CV was below 12%.

Statistical Analysis

In our study, power analysis for serum MLT level was performed at 95% power and 95% confidence interval. The mean values for the MLT level were 23±2.8 pg/mL for the patient group and 16.4±3.8 pg/mL for the control group. Statistical analysis was performed using SPSS 20.0 (SPSS, Chicago IL, United States). Results were given as mean ± standard deviation (SD) and minimum (min) - maximum (max). The suitability of the parameters to normal distribution was evaluated by Kolmogorov-Smirnov test. One-Way ANOVA test and t-test (independent samples t-test, or student t-test) were used to compare normal distribution parameters. The non-normal distribution parameters were compared with Mann-Whitney U test. Pearson correlation analysis was used for correlation analysis.

Results

A total of 30 patients (14 males and 16 females, mean age 36.4±12.2 years; range 19 to 68 years), with FMF disease, and 30 healthy controls (12 males and 18 females, mean age 38.4±12.5 years; range 19 to 65 years), were included in the study.

Demographic characteristics, laboratory characteristics, disease duration, disease severity score and serum MLT levels of patients and healthy individuals are shown in Table 2. There was no statistically significant difference between the groups in terms of age, gender, BMI, ESR, CRP and fibrinogen levels. The mean disease duration in the patient group was 10±11 years (range 1-50 years). The mean disease severity score was 5±2 There was a significant difference between the groups in terms of serum MLT levels ($p<0.05$), (Table 2).

There was no significant relationship between serum MLT level and demographic data such as gender, age and BMI, ESR, CRP and fibrinogen values, disease severity score of FMF patients (Table 3).

When the arthritis, FMF disease severity score parameters were assessed, there was a statistically significant difference in serum MLT levels between patients with a history of acute arthritis (n=7) and those without arthritis (n=23) (p=0.019), but no significant difference was found in other clinical severity parameters (Figure 1).

Discussion

The aim of the study was to investigate the clinical and physopathological effect of MLT hormone on FMF. Our study was the first to evaluate the relationship between serum MLT levels and disease severity. In our study, we found that serum MLT levels were higher in the FMF patient group than in the control group. In addition, serum MLT levels of FMF patients with a history of arthritis were significantly higher than those without a history of arthritis.

Circadian rhythm allows the body to adapt to environmental changes. Disruption of this rhythm usually has a negative effect. For example; Jet Lag syndrome, which is a collection of spontaneous symptoms that lasts for a few days as a result of

Table 2. Demographic, laboratory and clinical characteristics of Familial Mediterranean fever patients and healthy controls

	Patients (n=30)	Controls (n=30)	p
Gender (f/m)	16/14	12/18	0.602
Age (mean ± SD)	36.4±12.2	38.4±12.5	0.541
BMI (kg/m^2)	26.3±4	27±3.5	0.484
Disease duration [(mean ± SD, (minimum-maximum), year)]	10±11 (1-50)	-	-
ESR (mean ± SD) (mm/h)	13.2±13.9	11.2±8.1	0.52
CRP (mean ± SD) (mg/mL)	11.4±12.5	6.8±5.6	0.218
Fibrinogen (mg/dL)	334±76.4	306±70.4	0.144
Serum melatonin level (mean ± SD) (pg/mL)	23±2.8	16.4±3.8	0.001**
Disease severity scores	5.2±2	-	-

f: Female, m: Male, SD: Standard deviation, BMI: Body mass index, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, *p<0.05, **p<0.01: Statistically significant difference between groups

Table 3. Demographic characteristics of Familial Mediterranean fever patients and the relationship between serum melatonin levels and erythrocyte sedimentation rate, C-reactive protein, fibrinogen and disease severity score

	r	p
Age (mean ± SD)	0.064	0.626
BMI (kg/m^2)	-0.028	0.83
ESR (mean ± SD) (mm/h)	-0.077	0.556
CRP (mean ± SD) (mg/mL)	0.131	0.318
Fibrinogen (mg/dL)	0.162	0.216
Disease severity scores	-0.142	0.455

SD: Standard deviation, BMI: Body mass index, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, p<0.05: Statistically significant difference between groups

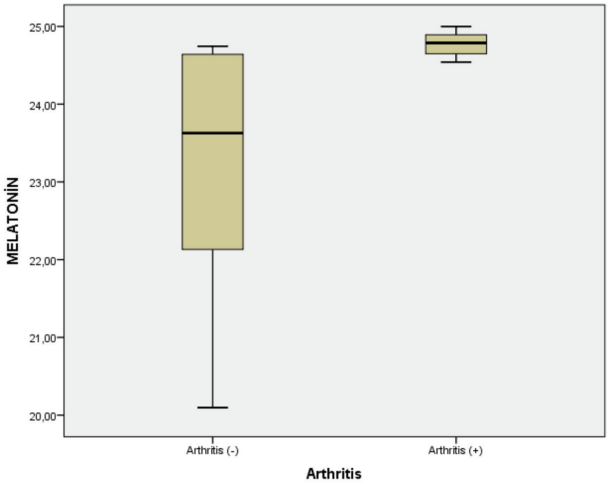

Figure 1. Serum melatonin levels of Familial Mediterranean fever patients according to arthritis history

disruption of the circadian rhythm, resembles the FMF attacks that last for several days and usually end with a pattern of onset and termination. Therefore, it is stated that disruption of the circadian rhythm may cause FMF attacks (16,17). In addition, common factors such as physical and emotional stress or high-fat diet may lead to disruption of the circadian rhythm and FMF attacks. It also suggests that MLT, the main regulatory hormone of the circadian rhythm, may have a possible role in the pathophysiology or clinic of FMF, which is known as a neutrophil-related disease, since MLT causes monocytes, natural killer cells, and in particular neutrophil activation (18,19).

MLT levels in FMF were evaluated by Musabak et al. (13) serum MLT levels were reported to be significantly higher in both acute exacerbations and non-exacerbations than in the control group, similar to our study. Again, no significant correlation was found between ESR and fibrinogen levels and serum MLT levels. It has been suggested that MLT may play a role in the immunopathogenesis of many autoimmune and auto inflammatory diseases including FMF. Our study makes a contribution to the literature and differs from the study of Musabak et al. (13) in terms of evaluating the relationship between serum MLT levels and disease severity and detecting higher serum MLT levels in the group with arthritis history.

Makay and Unsal (16) have suggested that changes in circadian rhythm may disrupt the immune response and affect the functions of the hypothalamic-pituitary-adrenal (HPA) axis, an important component of the neuroendocrine and immune system. Furthermore, they reported that any dysfunction in the HPA axis would affect the release of proinflammatory cytokines in the immune system and that HPA axis could have an active role in FMF attack (16,20,21).

In our study, FMF patients who were not at attack were evaluated. Therefore, ESR, CRP and fibrinogen values were within normal limits and were similar to those of the control group. In addition, similar to literature, there was no significant relationship between MLT levels and demographic data such as age, gender and BMI (22). In the literature, in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS), it was reported that serum MLT levels were significantly higher than in the control group, similar to our results (13,23). These results may suggest that MLT may have a role in the pathophysogenesis of FMF disease and subclinical inflammation. In addition, many studies reported that MLT may increase as a compensatory response to inflammation by stating its antioxidant and anti-inflammatory properties (24).

In the literature, as a result of studies investigating the relationship between rhythmic symptoms and signs in some autoimmune diseases such as RA and AS and the secretion of circadian MLT; It has been reported that serum MLT levels are higher than control groups and there is a significant relationship between disease activities and serum MLT levels and it is reported that MLT may play a role in the pathophysogenesis of these diseases (25,26). In these studies, it was stated that high serum MLT levels in the morning may be a cause of symptoms such as stiffness and joint swelling in patients with arthritis (10,25,26). It was also reported that MLT may play a role in the formation of a more active inflammatory response during the night by increasing the synthesis of proinflammatory cytokines (16). However, there are studies reporting that high MLT values in the morning are not associated with disease activity (22). In addition, there are studies reporting that serum MLT levels are lover in patients with systemic lupus erythematosus, psoriasis, and multiple sclerosis in compared to healthy individuals (27). This suggest that it is not clear how and where MLT plays a role due to the different immunopathogenetic processes involved in the formation of autoimmune diseases. In the light of these results; we can say that the immunopathological and clinical effects of MLT have not been fully elucidated due to the fact that different immunopathogenetic mechanisms are effective in different autoimmune diseases and the different effects of MLT are examined.

In our study; we could not find a statistically significant relationship between disease severity score and MLT levels.

This may be due to the inclusion of a low number of FMF patients, low disease severity score, and disadvantages in evaluating the disease severity score. However, MLT levels were significantly higher in patients with arthritis history than those without arthritis. El-Awady et al. (25) reported that there was a significant relationship between the presence of arthritis, an indicator of disease activity score, and MLT levels in patients with RA, similar to our study. In a study, specific MLT binding sites and synovial fluid MLT levels were found to be high in synovial fluid macrophages of RA patients (10). In addition, it has been demonstrated in mice that exogenous MLT administration reported to increase the severity of arthritis (28). However, it is reported that MLT has anti-inflammatory and antioxidant effects by inhibiting the release of many pro-inflammatory mediators in many ways (24). It is not yet clear in the literature whether high serum MLT values are caused by arthritis or because of the need for more antioxidant activity or anti-inflammatory activity for compensatory purposes. Similar to studies in which inhibition of MLT synthesis or administration of antagonists has been reported to have a therapeutic effect as an adjuvant for RA (23), we think that it may have a positive effect on adjuvant therapy in FMF patients.

Study Limitations

The most important limitation of our study was that blood samples were obtained only between 8 and 9 am in the morning when MLT was the lowest and there was not a complete response to the circadian MLT release. In addition, we think that the number of patients is low and the results should be supported by studies in larger patient groups.

Conclusion

Our findings provide evidence that MLT plays a role in the immunopathogenesis of FMF and in those with a history of FMF-related arthritis. However, since the immune regulatory role of MLT is very complex and its mechanisms are not yet fully understood, we think that our findings should be supported by more comprehensive research in the future.

Ethics

Ethics Committee Approval: The study protocol was approved by the Atatürk University Faculty of Medicine Ethics Committee (decision no: 17, date: 07.11.2019).

Informed Consent: A written informed consent was obtained from each subject.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.K., N.Ö., K.S., F.B., Concept: A.K., N.Ö., Design: A.K., Data Collection or Processing: A.K., N.Ö, K.S., F.B., Analysis or Interpretation: A.K., N.Ö., Literature Search: A.K., Writing: A.K., N.Ö.

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Frequency of Anaemia in Patients with Musculoskeletal Pain

Kas-iskelet Sistemi Ağrısı Olan Hastalarda Anemi Görülme Sıklığı

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Abstract

Objective: This study aimed to determine the frequency of anaemia in patients with musculoskeletal pain who were admitted to our clinic.
Materials and Methods: Three hundred and thirty-eight patients with muscloskeletal pain were divided into 2 groups as follows: Group 1, with diffuse pain, and group 2, with local pain. Serum iron, ferritin, total iron-binding capacity, vitamin B12 and plasma haemoglobin levels were analysed retrospectively.
Results: Patients with iron deficiency and iron-deficiency anaemia were evaluated retrospectively. There was iron deficiency in 35.7% of all patients with musculoskeletal pain and iron-deficiency anaemia in 11.2% of all patients. Iron deficiency was identified in both groups when the patients were evaluated separately according to the painful area. The rates of iron deficiency in the groups were 28.3% in the diffuse pain group and 37.1% in the local pain group.
Conclusion: We suggest that serum iron and ferritin levels should be measured, and if necessary, supplemented for better treatment success in patients with musculoskeletal pain.
Keywords: Anaemia, frequency, musculoskeletal diseases

Öz

Amaç: Bu çalışmada kliniğimize kas-iskelet sistemi ağrısı şikayeti ile başvuran hastalarda görülen anemi sıklığının belirlenmesi amaçlandı.
Gereç ve Yöntem: İskelet-kas sistemi ağrısı olan 338 hasta grup 1 (yaygın ağrı) ve grup 2 (lokal ağrı) olmak üzere 2 gruba ayrıldı. Hastaların serum demir, ferritin, total demir bağlama kapasitesi, vitamin B12 ve plazma hemoglobin düzeyleri geriye dönük olarak analiz edildi.
Bulgular: Demir eksikliği ve demir eksikliği anemisi olan hastalar geriye dönük olarak değerlendirildi. Kas-iskelet sistemi ağrısı olan tüm hastaların %35,7'sinde demir eksikliği, %11,2'sinde demir eksikliği anemisi vardı. Hastalar ağrı bölgesine göre ayrı ayrı değerlendirildiğinde her iki grupta da demir eksikliği olduğu görüldü. Demir eksikliği oranları yaygın ağrı grubunda %28,3 ve lokal ağrı grubunda %37,1 olarak saptandı.
Sonuç: Kas-iskelet sistemi ağrısı olan hastalarda serum demir ve ferritin düzeylerinin ölçülmesini ve tedavi başarısının artırılması için gerekirse tedavi edilmesini öneriyoruz.
Anahtar kelimeler: Anemi, kas-iskelet sistemi hastalıkları, sıklık

Introduction

Musculoskeletal disorders are painful conditions and lead to disability. Musculoskeletal system diseases are a group of diseases that may have different causes in terms of pathophysiology, but common characteristics are pain and impaired physical function. The prevalence of musculoskeletal system diseases is high worldwide. World Health Organization (WHO) reports that 1/3 to 1/5 people (including children) have musculoskeletal diseases in a period of their lives (1).

Iron is an important element for almost all life. Nearly two-thirds of the iron involves to the structure of heme and as it is well known the oxygen transport function of hemoglobin in erythrocytes is essential. Additionally, some other proteins containing heme such as myoglobin, cytochrome P450, and the cytochromes a, b, and c have key roles on mitochondrial respiration and adenosine triphosphate synthesis (2).

Iron-deficiency and iron-deficiency anemia are both common though preventable nutritional problems not only in Turkey but also all over the world (3). Determining iron deficiency, particularly before iron-deficiency anemia develops, is very important for the success of treatment. For this purpose, ferritin is used as a reliable marker of iron storage. It has been shown that ferritin is the most valuable test for the detection and follow-up of iron deficiency. Measurement of serum ferritin

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levels is useful for the treatment of iron-deficiency before the development of anemia (4).

Normal iron function and hemostasis have crucial importance for the normal function of the central nervous system due to the role of iron having a cofactor role in the function of many enzymes involved in neurotransmitter synthesis such as serotonin, norepinephrine, and dopamine (5). Decreased synthesis of these neurotransmitters may take part in pain generation, particularly in neuropathic pain generation (6).

There are very few studies investigating the possible relationship between iron-deficiency and pain. One experimental animal study has demonstrated that iron-deficiency increases acute and chronic pain responses in mice (7). One clinical study with a small sample size has shown that serum ferritin levels are significantly lower in patients with chronic neck pain compared to healthy controls (8).

The lack of a comprehensive descriptive study in the literature investigating the possible association between anemia in a wide range of muscoloskletal pain conditions prompted us to perform this study.

This study aimed to determine anemia frequency of patients who have musculoskeletal system pain, retrospectively.

Materials and Methods

Five hundred and fifty patients suffering from musculoskeletal pain admitted to Physical Medicine and Rehabilitation outpatient clinic of our hospital within the last five years (between January 1, 2014 and December 1, 2018) were analyzed retrospectively using hospital automation system and patient file archives.

The inclusion criteria were as follows:

1. Patients with musculoskeletal pain
2. Patients who have test results of serum ferritin, iron, vitamin B12 concentrations, total iron-binding capacity (TIBC) and plasma hemoglobin levels.

The exclusion criteria were as follows:

1. Acute and chronic infections (since ferritin is an acute phase reactant)
2. Inflammatory diseases
3. Rheumatic diseases
4. Malignancies
5. Depression
6. Pregnancy and breastfeeding

After the inclusion and exclusion criteria were applied, the study was completed with the data of the remaining 338 patients divided into 2 groups as follows:

Group 1: Diffuse pain

Group 2: Local pain (artralgia, upper extremity pain, lower extremity pain, neuropathic pain, spinal pain)

Demographic data and serum ferritin, iron, TIBC, vitamin B12 levels and plasma hemoglobin levels were recorded.

Serum ferritin levels of less than 15 ng/dL were evaluated as iron deficiency. In addition to iron deficiency, patients with hemoglobin values below 12 g/dL in premenopausal women and 13 g/dL in postmenopausal women and men were evaluated as iron-deficiency anemia (9). Serum total vitamin B12 concentrations of less than 300 pg/mL values were evaluated as vitamin B12 deficiency and less than 200 pg/mL values were evaluated as vitamin B12 insufficiency (10). In our laboratory, the reference range of serum iron level is 37-145 ug/dL and the reference range of serum TIBC level is 127-450 (pg/dL). A classification was made by applying these criteria and patients were identified as follows: patients with iron deficiency, patients with iron-deficiency anemia, patients with vitamin B12 deficiency, patients with vitamin B12 insufficiency, iron level under the reference range and TIBC level outside the reference range.

Ethical Issues

The study met the approval of Turkish Statistical Institute (with authorization number 23.08.2019/19496) and the approval of Atatürk University Faculty of Medicine Local Clinical Research Ethics Committee (approval date: 26.09.2019, decision no: 423).

Statistical Analysis

The results were evaluated in SPSS 23 package program. Descriptive statistics (mean, standard deviation, frequency) were made. Independent samples t-test was performed to determine the difference of age and biochemical parameters between independent groups (comparison of group 1-group 2 and comparison of male-female in all patients, in group 1 and in group 2). P<0.05 values were accepted as statistically significant in a 95% confidence interval.

Results

The ages and biochemical parameters of all musculoskeletal pain patients and of the patients divided into 2 groups were demonstrated in Table 1, Table 2 and Figure 1.

The mean age of all patients was 44.7±14.4 years, and there was no statistically significant difference between the ages of male and female patients (p<0.05).

Table 1. Demographic characteristics and biochemical parameters of patients

	Diffuse pain (n=53)	Local pain (n=285)	p (Diffuse pain- local pain)
Age (year)	43.8±14.4	44.9±14.4	0.619
Hemoglobin (g/dL)	13.5±1.5	14±7.6	0.681
Iron (ug/dL)	73.9±32.5	71.4±31.9	0.602
Ferritin (ng/mL)	44.2±41.5	37.8±39.4	0.287
TIBC (pg/dL)	287.8±89	288.8±91.8	0.941
Vitamin B12 (pg/mL)	363.5±154.3	361±187	0.925

TIBC: Total iron-binding capacity, results were given as mean ± standard deviation, p: Independent samples t-test statistics p value

Table 2. Distribution of parameters by gender				
All patients	**All patients (n=338)**	**Female patients (n=311)**	**Male patients (n=27)**	**p (Male-female)**
Age (year)	44.7±14.4	45±14.2	40.9±16.4	0.151
Hemoglobin (g/dL)	13.9±7	13.8±7.3	15.2±1.8	0.325
Iron (ug/dL)	71.8±32	70.2±30.6	90.3±41.6	0.002
Ferritin (ng/mL)	38.8±39.7	35.9±36.7	72.9±55.4	<0.001
TIBC (pg/dL)	288.6±91.2	292.1±92.1	248.5±70.3	0.017
Vitamin B12 (pg/mL)	361.4±182.1	358±160.6	400.2±347.3	0.249
Group 1 (Diffuse pain)	**All patients (n=53)**	**Female patients (n=47)**	**Male patients (n=6)**	**p (Male-female)**
Age (year)	43.8±14.4	44.8±14.2	35.8±15.1	0.151
Hemoglobin (g/dL)	13.5±1.5	13.3±1.4	15.3±0.9	0.002
Iron (ug/dL)	73.9±32.5	68.7±28.7	114.3±34.5	0.001
Ferritin (ng/mL)	44.2±41.5	40.5±40.2	72.6±44.2	0.075
TIBC (pg/dL)	287.8±89	295.3±91	228.7±37.2	0.084
Vitamin B12 (pg/mL)	363.5±154.3	362.7±160.7	370.1±100.9	0.913
Group 2 (Local pain)	**All patients (n=285)**	**Female patients (n=264)**	**Male patients (n=21)**	**p (Male-female)**
Age (year)	44.9±14.4	45.1±14.2	42.3±16.9	0.403
Hemoglobin (g/dL)	14±7.6	13.9±7.9	15.2±2	0.460
Iron (ug/dL)	71.4±31.9	70.4±31	83.4±41.5	0.073
Ferritin (ng/mL)	37.8±39.4	35±36	73±59.2	<0.001
TIBC (pg/dL)	288.8±91.8	291.5±92.5	254.2±77	0.073
Vitamin B12 (pg/mL)	361±187	357.2±160.9	408.8±392.3	0.224

TIBC: Total iron-binding capacity, Results were given as mean ± standard deviation, p: Independent samples t-test statistics p value

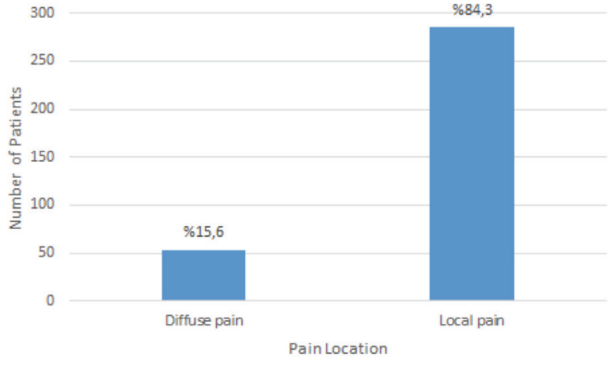

Figure 1. Number and frequency distribution of patients with musculoskeletal pain by pain location

In the independent group comparisons between female and male patients, both serum ferritin and serum iron levels were significantly lower in female patients than in male patients (p<0.001 and p<0.05, respectively).

Serum TIBC levels were significantly higher in female patients than in male patients (p=p<0.05).

There was no statistically significant difference between serum vitamin B12 levels and plasma hemoglobin levels between male and female patients (p>0.05 for both parameters).

The differences of parameters between pain groups (diffuse pain group and local pain group) were also evalulated with independent samples t-test. There were no significant differences in all parameters (age, hemoglobin, iron, ferritin, TIBC, vitamin B12) between all group comparisons (all group 1 patients-all group 2 patients, female group 1 patients-female group 2 patients, male group 1 patients-male group 2 patients) (p>0.05 for all parameters in all comparisons) (Table 3).

Percentages of patients with iron deficiency, iron-deficiency anemia, vitamin B12 deficiency, vitamin B12 deficiency, the iron level below the reference range and TIBC level outside the reference range were determined in all patients and in the patients divided into 2 groups (Table 4, Figures 2, 3).

Discussion

Our retrospective analysis results have shown that there was iron-deficiency in 35.7% of all patients with musculoskeletal system pain and iron-deficiency anemia in 11.2% of all patients. Iron-deficiency was determined in both groups when the patients were evaluated separately according to the pain area. Iron-deficiency rates were determined as follows: in diffuse pain: 28.3% and in spine pain: 37.1%.

In addition to iron deficiency, iron-deficiency anemia was determined in both groups with the rates 11.7% in upper

Table 3. Distribution of parameters between diffuse pain and local pain patients			
Female and male patients	**Group 1 (Diffuse pain)**	**Group 2 (Local pain)**	**p (group 1-group 2)**
Age (year)	43.8±14.4	44.9±14.4	0.619
Hemoglobin (g/dL)	13.5±1.5	14±7.6	0.681
Iron (ug/dL)	73.9±32.5	71.4±31.9	0.602
Ferritin (ng/mL)	44.2±41.5	37.8±39.4	0.287
TIBC (pg/dL)	287.8±89	288.8±91.8	0.941
Vitamin B12 (pg/mL)	363.5±154.3	361±187	0.925
Female patients	**Group 1 (Diffuse pain)**	**Group 2 (Local pain)**	**p (group 1-group 2)**
Age (year)	44.8±14.2	45.1±14.2	0.910
Hemoglobin (g/dL)	13.3±1.4	13.9±7.9	0.629
Iron (ug/dL)	68.7±28.7	70.4±31	0.727
Ferritin (ng/mL)	40.5±40.2	35±36	0.345
TIBC (pg/dL)	295.3±91	291.5±92.5	0.796
Vitamin B12 (pg/mL)	362.7±160.7	357.2±160.9	0.829
Male patients	**Group 1 (Diffuse pain)**	**Group 2 (Local pain)**	**p (group 1-group 2)**
Age (year)	35.8±15.1	42.3±16.9	0.402
Hemoglobin (g/dL)	15.3±0.9	15.2±2	0.903
Iron (ug/dL)	114.3±34.5	83.4±41.5	0.110
Ferritin (ng/mL)	72.6±44.2	73±59.2	0.989
TIBC (pg/dL)	228.7±37.2	254.2±77	0.444
Vitamin B12 (pg/mL)	370.1±100.9	408.8±392.3	0.815
TIBC: Total iron-binding capacity, results were given as mean ± standard deviation, p: Independent samples t-test statistics p value			

extremity pain, 11.3% in diffuse pain and 11.2% in lcoal pain.

Determining iron-deficiency accurately is an important issue for clinicians. For this purpose, measurement of serum ferritin levels is used as a reliable and non-invasive method to indirectly show iron stores of the body and decreased serum ferritin level is considered as a sign of iron depletion (11).

Although there is a wide consensus on the determinative role of ferritin in iron deficiency, different expert organizations recommend various cut-off limits for the diagnosis of iron deficiency. In our study, we used the highly accepted cut-off limit recommended by WHO, which defines iron-deficiency with the ferritin levels less than 15 ng/dL (9).

However, the concentration of ferrite required to maintain the normal function of muscle tissue and other organs has not been fully established. It has been recommended that, when ferritin levels are below 50 ng/mL, the targeted ferritin concentration in the treatment of iron-deficiency 50 ng/mL (12).

Iron, a cofactor of the cytochrome oxidase enzyme system, has a vital role in the energy production of muscle. Thus, iron-deficiency causes a deterioration in muscle energy production and contributes to the development of muscle fatigue, poor endurance and myofascial pain (13).

An experimental mouse model study has demonstrated that iron-deficiency triggers a reducement in pain threshold and an increment in pain feeling (7,14).

Another perspective for the relationship of iron deficiency and anemia is focused on the role of iron as an essential cofactor of several enzymes which are key elements of neurotransmitter synthesis, particularly tryptophan hydroxylase (in serotonin synthesis) and tyrosine hydroxylase (in norepinephrine and dopamine synthesis) (5,6).

At this point, it is necessary to examine the relationship between serotonin and pain. Serotonin, a neurotransmitter derived from tryptophan, is produced by neurons in the brainstem. Serotonin is broadly circulated throughout the cortex, limbic system, and thalamus by the connections of serotonergic neurons and thus it has inhibitory effects on some pain pathways. There is increasing evidence pointing out the important role of serotonin [5-hydroxytryptamine, (5-HT)] in the modulation of nociceptive transmission. Various 5-HT receptor subtypes have been identified in the central nervous system (15), and in the spinal cord. Experimental studies have shown that 5-HT produces antinociception and several 5-HT receptors take part in the mediation of antinociception (16).

Due to the cofactor role of iron tyrosine hydroxylase enzyme (leading norepinephrine and dopamine synthesis), determining

Table 4. The incidence of clinical conditions accompanying patients' pain complaints			
Musculoskeletal pain	**All patients (n=338) %**	**Female patients (n=311) %**	**Male patients (n=27) %**
Iron deficiency	35.7	37.6	14.8
Iron-deficiency anemia	11.2	11.5	7.4
Vitamin B12 deficiency	43.1	42.1	55.5
Vitamin B12 insuffuciency	9.1	9.3	7.4
Iron level under the ref. range	12.4	12.2	14.8
TIBC level outside the ref. range	5.3	5.4	3.7
Group 1: Diffuse pain	**All patients (n= 53) %**	**Female patients (n=47) %**	**Male patients (n=6) %**
Iron deficiency	28.3	29.7	16.6
Iron-deficiency anemia	11.3	12.7	0
Vitamin B12 deficiency	37.7	38.2	33.3
Vitamin B12 insuffuciency	11.3	12.7	0
Iron level under the ref range	16.9	19.1	0
TIBC level outside the ref. range	11.3	8.5	0
Group 2: Local pain	**All patients (n=285) %**	**Female patients (n=264) %**	**Male patients (n=21) %**
Iron deficiency	37.1	39	14.2
Iron-deficiency anemia	11.2	11.3	9.5
Vitamin B12 deficiency	44.2	42.8	61.9
Vitamin B12 insuffuciency	8.7	8.7	9.5
Iron level under the ref. range	11.5	10.9	19
TIBC level outside the reference range	6.6	5.3	4.7
TIBC: Total iron binding capacitiy, ref.: Reference			

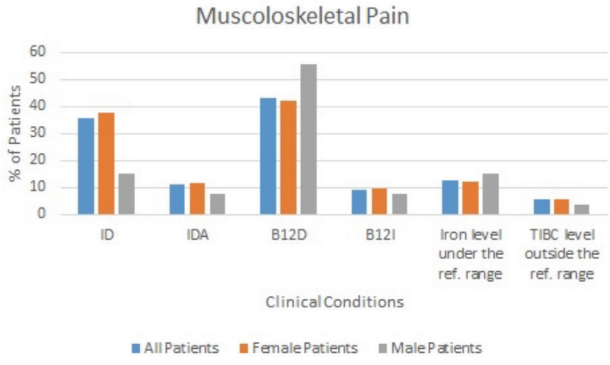

Figure 2. The frequency of clinical conditions associated with pain complaints in patients with musculoskeletal pain
ID; Iron-deficieny, IDA; Iron-deficiency anemia, B12D: Vitamin B12 deficiency, B12I: Vitamin B12 insufficiency, ref.:reference, TIBC: Total iron-binding capacity

the possible role of dopaminergic neurotransmission in chronic pain is an important field of interest for researchers.

Dopaminergic neurotransmission is thought to play a pivotal role in moderating pain sensation and analgesia. Researchers reporting decreased dopamine levels in Fibromyalgia syndrome have concluded that abnormal dopaminergic neurotransmission may be responsible for the painful conditions of fibromyalgia and painful diabetic neuropathy. Another evidence supporting the potent relationship between iron, pain sensation and dopaminergic system is the curative effect achieved by using dopamine agonists in Restless Leg syndrome patients (17).

Here is an important point is to note that, experimental animal studies have demonstrated that while analgesia is induced by the activation of mesolimbic dopamine neurons by acute stress, chronic stress conditions trigger a reverse effect on pain sensation and lead to hyperalgesia by decreasing mesolimbic dopaminergic output (18).

Although investigating the relationship between pain and Fibromyalgia syndrome is out of the scope of our study, we note that reduced concentration of dopamine, norepinephrine, and serotonin is reported in FMS patients, who have different pain perception from that of the broad population, consequence of degenerated pain processing pathways in the central nervous system (5,19).

An issue must be considered in the planning of a study design investigating ferritin levels is that is the possibility that elevated ferritin levels may be arisen from inflammation conditions because ferritin is an acute-phase reactant. In this study, we excluded patients with inflammatory diseases and rheumatic diseases based on the detailed anamnesis of patients.

The limited studies available in the literature aimed to investigate the possible relationship between iron-deficiency and pain have

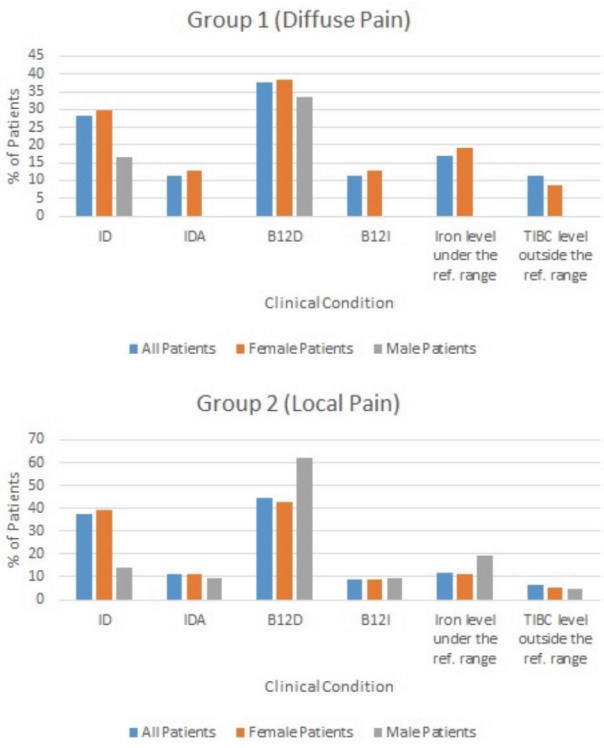

Figure 3. The frequency of clinical conditions accompanying pain complaints in patients with musculoskeletal pain divided into different groups

ID: Iron-deficieny, IDA: Iron-deficiency anemia, B12D: Vitamin B12 deficiency, B12I: Vitamin B12 insufficiency, ref.: reference, TIBC: Total iron-binding capacity

small sample sizes (8). Our study was performed with larger sample size.

Study Limitations

Our study has a limitation with the study design being retrospective.

Conclusion

To the best of our knowledge, this is the first study in English literature, reporting iron-deficiency and iron-deficiency anemia rates in a large number of sample size in various musculoskeletal system pain conditions. Based on our results, we suggest that serum iron and ferritin levels should be measured and, if necessary, treated to improve treatment success in patients with musculoskeletal system pain.

Ethics

Ethics Committee Approval: The study met the approval of Turkish Statistical Institute (with authorization number 23.08.2019/19496) and the approval of Atatürk University Faculty of Medicine Local Clinical Research Ethics Committee (approval date: 26.09.2019, decision no: 423).

Informed Consent: Informed consent is not appliciable.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.B., A.K., Concept: F.B, A.K., Design: F.B., A.K., Data Collection or Processing: F.B, Analysis or Interpretation: F.B., Literature Search: F.B., A.K., Writing: F.B., A.K.

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

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Serum Melatonin Levels in Patients with Behçet's Disease

Behçet Hastalığı Olan Hastalarda Serum Melatonin Düzeyleri

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Abstract

Objective: Melatonin (MLT) hormone has been reported to play a role in the immunopathogenesis and aetiology of many chronic inflammatory diseases. We aimed to investigate the role of MLT in Behçet's disease (BD) by determining the serum MLT levels of patients with BD.

Materials and Methods: A total of 40 patients (mean age, 35.3±9.0 years; age range, 19-57 years), including 19 women and 21 men, and 40 healthy individuals, including 20 women and 20 men, matched for age and gender (mean age, 37.7±11.2 years; age range, 19-65 years) were included in this study. Serum MLT levels of the participants were determined, and their demographic data, laboratory parameters, and clinical features were recorded. Disease activity was evaluated according to the BD current activity form 2006. The relationship between disease activity and serum MLT level was examined.

Results: There were no significant differences in the demographic characteristics and other laboratory parameters between the groups, except for serum MLT levels and mean platelet volume values ($p<0.05$). Serum MLT values were found to be significantly lower in patients having headache than in those without headache ($p<0.05$), but there was no significant difference in other clinical parameters. No significant correlation was found between the serum MLT levels of patients with BD and laboratory parameters and disease activity scores.

Conclusion: Although this study provides evidence that MLT plays a possible role in the immunopathogenesis of BD in patients with a headache history, there was no association between MLT level and disease activity. We suggest that further studies are needed to determine the possible role of MLT in BD and that our findings should be evaluated by future research.

Keywords: Behçet's disease, melatonin, headache, immunopathogenesis

Öz

Amaç: Melatoninleri (MLT) hormonunun birçok kronik enflamatuvar hastalığın immünopatogenezinde ve etiyolojisinde rol oynayabileceği bildirildiğinden dolayı, çalışmamızda Behçet hastalığı (BH) olan hastaların serum MLT seviyelerinin belirlenerek hastalık aktivitesi ile arasında olası bir ilişki olup olmadığını incelemeyi amaçladık.

Gereç ve Yöntem: Çalışmada 19 kadın ve 21 erkek olmak üzere toplam 40 hasta (ortalama yaş; 35,3±9,0 yıl; yaş aralığı; 19-57 yıl) ile yaş ve cinsiyetleri benzer olan 20 kadın ve 20 erkek toplam 40 sağlıklı kontrol (ortalama yaş; 37,7±11,2 yıl; yaş aralığı;19-65 yıl) bulunmaktaydı. Katılımcıların demografik verileri, laboratuvar ve klinik özellikleri kaydedilerek serum MLT seviyeleri belirlendi. BH anlık aktivite form-2006'ya göre hastalık aktivitesi değerlendirildi. Hastalık aktivitesi ile serum MLT seviyesi arasındaki ilişki incelendi.

Bulgular: Gruplar arasında serum MLT düzeyleri ve ortalama trombosit hacmi değerleri hariç ($p<0,05$) demografik özellikler ve diğer laboratuvar parametreleri arasında anlamlı bir fark yoktu. Hastalık aktivitesinin değerlendirilmesinde kullanılan klinik parametrelerin hastalardaki varlığına göre yapılan incelemede; baş ağrısı olanlarda olmayanlara göre serum MLT değerlerinin anlamlı şekilde daha düşük olduğu bulunurken ($p<0,05$), diğer klinik parametrelerde anlamlı bir fark yoktu. BH olan hastalarının değerlendirilen laboratuvar parametreleri ve hastalık aktivite skorları ile serum MLT seviyesi arasında anlamlı bir ilişki bulunmadı.

Sonuç: MLT'nin BH immünopatogenezinde ve baş ağrısı hikayesi olanlarda olası bir rol oynadığına dair kanıt sunmasına rağmen MLT düzeyi ile hastalık aktivitesi arasında bir ilişki bulunmadı. BH'de MLT'nin olası rolünü belirlemek için daha fazla çalışmaya ihtiyaç olduğunu ve bulgularımızın gelecekteki araştırmalarla desteklenmesi gerektiğini öneriyoruz.

Anahtar kelimeler: Behçet hastalığı, melatonin, baş ağrısı, ilişki

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Introduction

Behçet's disease (BD) is a chronic systemic inflammatory vasculitis with unknown etiology including oral aphthous ulcers, genital ulcers, skin lesions, ocular lesions, gastrointestinal and central nervous system abnormalities and other pathologies. Vascular inflammation affects arteries and veins in all types, diameters and localization, causing endothelial cell dysfunction (1). Although immunological abnormalities play an important role in the development and progression of the disease, oxidative stress increases due to overproduction of free oxygen radicals occurring in the disease process or the effectiveness of antioxidant defense systems (1,2).

Melatonin (MLT) is a hormone secreted from the pineal gland and primarily regulates the circadian rhythm. In addition to its regulatory properties such as mood, sleep, reproductive and immune system regulation, it has antioxidant and anti-inflammatory effects (3). It has been reported that the immune system regulatory feature is in the form of pleiotropic action or buffering, since MLT can have an immune stimulating effect in basal conditions or under immunosuppressive conditions, or it may show an anti-inflammatory activity by performing an inhibitory effect in the immune system in the presence of chronic inflammation (4,5). In addition, thanks to its antioxidant and anti-inflammatory properties, it directly cleans free radicals and indirectly decreases the tissue damage that occurs during inflammation by reducing the production of agents (cytokines and adhesion molecules) that contribute to cellular damage (6). Despite this information, the immune regulatory role of MLT is very complex and its mechanisms are not yet fully understood (4). Due to these features, it has been suggested that MLT may play a role in the immunopathogenesis and etiology of many chronic inflammatory diseases and can also be used in their treatments (7). However, there is no study in the literature examining serum MLT level and the relationship between disease activity and MLT in BD.

In our study; we aimed to investigate whether there is a possible relationship between disease activity and MLT levels by determining serum MLT levels of patients with BD.

Materials and Methods

This study was conducted between November 2019 and December 2019 by Atatürk University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Division of Rheumatology. The study protocol was approved by the Atatürk University Faculty of Medicine Ethics Committee (decision no: 16, date: 07.11.2019). A written informed consent was obtained from each subject. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The study included 40 patients based on BD diagnostic criteria recommended by the international study group and 40 age-matched healthy controls (8). All patients were evaluated by the same physician.

In the study, patients with BD who meet the international study group diagnostic criteria, who have a disease activity score one and above, between 18-65 years, are included while patients with any additional systemic inflammatory or autoimmune and rheumatological diseases, acute or chronic infection, hematological disease, diabetes mellitus, history of malignancy, vision problems and drug use that would affect MLT release (antidepressant, sleep and beta blocker etc) were not included.

The participants' gender, age, body mass index (BMI), disease duration, hemogram parameters [White blood cell count (WBC), neutrophil (Neu), lymphocyte (Lym), monocyte (Mon), platelet, mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), Neu/Lym ratio and platelet/Lym ratio] values, erythrocyte sedimentation rate (ESR; mm/h) and C-reactive protein (CRP; mg/mL) levels and serum MLT level (pg/mL) It was evaluated. Disease activities of the patients were evaluated using the Behçet's Disease Current Activity Form-2006 (BDCAF) score. Thirty-four patients were on colchicine, 9 were on tumor necrosis factor-alpha inhibitors, 12 were on azathioprine, 2 were on cyclophosphamide and 5 were on corticosteroid medication. In order to determine the disease activity, BDCAF, which was translated into Turkish by Hamuryudan et al. (9), was used. This form includes only the evaluation of clinical findings. In this form, which does not include pathergy test or laboratory findings, each symptom occurring according to the system affected by BD is scored and evaluated based on the duration in the last four weeks. Patients are evaluated based on symptoms such as headaches, oral ulcers, genital ulcers, skin lesions such as erythema and pustules, joint findings such as arthritis and arthralgia, and gastrointestinal system findings (nausea, vomiting, abdominal pain/diarrhea, bloody stool). It is evaluated as 0 point for absence and 1 point for presence of the symptoms. Symptoms vascular, nervous system and eye involvement are also questioned. The total score of the form is between 0-12.

Venous blood samples were taken to biochemistry and ethylenediaminetetraacetic acid hemogram tubes between 8:00-9:00 in the morning using a vacutainer after the participants rested in sitting position. As blood samples were taken for ESR and hemogram parameters measurement, their immediate transfer to the laboratory was provided, and for CRP measurements, the blood samples were stored at the room temperature for 30 minutes for coagulation and analyzed daily after centrifugation. WBC, Neu absolute count, Neu percentage (%), Lym absolute count, Lym %, Mon absolute count, Mon %, platelet count (PLT) and MPV, PDW, PCT values were recorded. Serum samples for MLT measurement were aliquoted and stored at -80 ˚C until analyzed. The analysis was performed in the Medical Biochemistry Laboratory of our hospital.

The ESR (0-20 mm/h) was measured with the Western Green method using Interrliner XN (Sysmex Corporation, Kobe, Japanese) automatic ESR analysis device and the CRP (0-5 mg/mL) was quantitatively measured with the immunoturbidometric method using Beckman Coulter AU5800 autoanalyser (Beckman Coultr Inc. Ca, USA). Sysmex XN 1000 (Sysmex Corporation,

Kobe, Japan) device was used for complete blood count. MLT levels measurement was performed by using SunLong (Cat No: SL1169Hu, Sunlung Biotech Co., Ltd., HangZhou, China) kit and measured by enzyme-linked immunosorbent assay (ELISA) method following the experimental stages according to the proposed protocol. Dynex automated ELISA reader device was used (Dynex Technologies Headquarters, Chantilly, USA).

Statistical Analysis

Power analysis for serum MLT level was performed at 95% strength and 95% confidence interval. The mean values for the MLT level were 23.6±2.5 pg/mL for the patient group and 16.4±3.7 pg/mL for the control group. Statistical analyzes were performed by using SPSS 20.0 (SPSS, Chicago IL, United States) program. Results were given as mean ± standard deviation and minimum-maximum. The suitability of the parameters to normal distribution was evaluated with the Kolmogorov-Smirnov test. The t-test (independent samples t-test, or Student's t-test) was used to compare the parameters that showed normal distribution, and the Mann-Whitney U test was used to compare parameters that did not show normal distribution. Pearson and spearman methods used for correlation analysis.

Results

A total of 40 patients (19 women and 21 men) (mean age 35.3±9 years; range: 19 to 57 years) diagnosed with BD, and a total of 40 healthy controls (mean age: 37.7±11.2 years; range: 19 to 65 years) were included in the study.

Demographic, laboratory and clinical features of the patients and healthy individuals are shown in Table 1. There was no significant difference between the other demographic characteristics and laboratory parameters, except serum MLT levels and mean MPV values ($p<0.05$). The mean disease duration in the patient group was 86.7±75.6 (range: 1-348 months) months. The mean value of BDCAF score of the patients was 3.7±1.9 (Table 1).

Data on the frequency and percentage of BDCAF clinical parameters and serum MLT levels in Behçet's patients are shown in Table 2. In the examination made according to the presence of clinical parameters used in evaluating the disease activity in BD patients; serum MLT values were found to be significantly lower in patients with headache (23.4 pg/mL) compared to patients without headache (24.6 pg/mL) ($p<0.05$). But there was no significant difference in other clinical parameters (Table 2).

Data showing the relationship between Behçet patients' laboratory parameters, disease duration, BDCAF scores and serum MLT level are shown in Table 3. No relation was found between the parameters evaluated and the BDCAF score and serum MLT levels (Table 3).

Discussion

This is the first study evaluating the relationship between MLT levels and disease activity in BD patients. In our study, serum MLT hormone levels were significantly higher in the BD group compared to the control group, but there was no significant relationship between disease activity. In addition, patients with

Table 1. Comparison of the demographic, laboratory and clinical characteristics of patients with Behçet's disease and healthy control individuals.

	Patients (n=40)	Controls (n=40)	p
Gender (f/m)	19/21	20/20	0.823
Age (mean ± SD)	35.3±9	37.7±11.2	0.289
BMI (kg/m^2)	25.4±4.3	26.8±3.3	0.111
Disease duration (month) (mean ± SD)	86.7±75.6	-	-
WBC (x10^3/µL)	8.4±2.7	7.7±1.9	0.163
Neutrophil (x10^3/µL)	5±2.3	4.9±1.7	0.734
Lymphocyte (x10^3/µL)	2.5±0.6	2.5±0.8	0.756
Monocyte (x10^3/µL)	0.7±0.2	0.6±0.2	0.227
Platelet (x10^3/µL)	293±69	285±54	0.568
MPV (fL)	10±0.8	9.6±1	0.032*
PDW (%)	11.5±1.7	12.4±2.7	0.056
PCT (%)	0.3±0.1	0.3±0.1	0.147
NLR	2.1±1	2.2±1.1	0.905
PLR	124±34	122±37	0.800
ESR [mean ± SD (minimum-maximum)] (mm/h)	11.3±9.2 (2-47)	8.2±5.9 (1-22)	0.078
CRP (mean ± SD) (mg/mL)	5.9±4.7 (3-23)	4.4±1.9 (2-10)	0.413
Serum melatonin level (mean ± SD) (pg/mL)	23.8±1.7	16.4±3.4	0.001**
BDCAF score	3.7±1.9	-	-

f: Female, m: Male, SD: Standard deviation, BMI: Body mass index, WBC: White blood cell, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, BDCAF: The Behçet's Disease Current Activity Form-2006, *$p<0.05$: Statistically significant difference between groups, **$p<0.01$: Statistically significant difference between groups

Table 2. The frequency and percentage of Behçet's Disease Current Activity Form-2006 parameters in patients with Behçet's disease

Clinical symptoms and signs		with; n (%)	without; n (%)	p
Headache		26 (65%)	14 (35%)	0.027*
Oral ulcer		26 (65%)	14 (35%)	0.943
Genital ulcer		7 (18%)	33 (82%)	0.460
Skin lesions	Erythema	16 (40%)	24 (60%)	0.987
	Pustule	25 (63%)	15 (37%)	0.912
Joint involvement	Arthralgia	29 (73%)	11 (27%)	0.175
	Arthritis	6 (15%)	34 (85%)	0.630
GIS involvement	Abdominal pain	13 (33%)	27 (67%)	0.246
	Bloody diarrhea	-	40 (100%)	-
Eye involvement (active uveitis)		1 (3%)	39 (97%)	-
Nervous system involvement		-	40 (100%)	-
Great vascular involvement		-	40 (100%)	-

n: Number of patients with Behçet's disease with symptoms or signs, %: Percentile, GIS: Gastrointestinal system
*p<0.05: Statistically significant difference between those with and without clinical symptoms and signs

Table 3. The relationship between laboratory, clinical and Behçet's Disease Current Activity Form-2006 scores and serum melatonin level in Behçet's disease patients

	r	p
WBC	0.198	0.078
Neutrophil	0.109	0.336
Lymphocyte	-0.085	0.454
Monocyte	0.207	0.066
Platelet	0.008	0.946
MPV	0.183	0.103
PDW	-0.195	0.083
PCT	0.097	0.391
NLR	0.112	0.323
PLR	0.061	0.592
ESR (mean ± SD) (mm/h)	0.202	0.070
CRP (mean ± SD) (mg/mL)	-0.059	0.602
Disease duration (mean ± SD)	0.135	0.408
BDCAF score	-0.251	0.118

WBC: White blood cell, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, BDCAF: The Behçet's Disease Current Activity Form, *Correlation is significant at the p<0.05

headache were found to have significantly lower serum MLT levels than those without headaches.

In previous studies, different laboratory parameters as well as clinical findings were used to determine the activity of BD. Although acute phase proteins, immunoglobulin, complement levels, autoantibodies, surface markers, cytokines, Lyms and many other hemogram parameters have been investigated, there is no specific laboratory marker for BD (10). However, some laboratory abnormalities associated with the disease activation can be detected, although not in all patients. It has been reported that ESR, CRP levels and Neu activation, which are among the frequently used indicators, are associated with systemic inflammation and are not significant in reflecting disease activity, but when these parameters increase in an inactive patient, they may be instructive for a detailed research (11). Platelets play role in inflammation and the cytokines and chemokines, released from activated platelet membranes, play an important role in immune response and the size of activated platelets increase. In other words, increased MPV is an indication that the platelet is activated (12). There are conflicting results about the increase or decrease of MPV values in BD, as well as its relationship with disease activity (13,14). However, it is known that patients with thrombosis have significantly higher MPV values than those who do not, and this increases the risk of deep venous thrombosis (14,15).

In the laboratory parameters evaluated in our study, there was no significant difference between the groups except for the average MPV value. The mean MPV values in our study were within normal limits in both groups (normal; 5.9-11.3 fL). However, mean MPV values were significantly higher in the patient group than in the control group. Based on our findings, we cannot say that there is an isolated MPV increase in patients with BD. This result may be derived from the low number of patients, the low disease activity and the normal ESR, CRP, WBC, PLT and other systemic inflammation parameter values. In addition, no significant correlation was found between MPV values and serum MLT levels in our study. However, our patients did not have any symptoms or signs such as pain in the arm, leg or face, swelling, discoloration, which would indicate an increased coagulative condition due to vascular involvement. This may be due to the MPV values in our patients being within normal limits.

In addition to the immune regulatory role, MLT shows anti-inflammatory and antioxidant activity by reducing the production of agents (cytokines and adhesion molecules) that contribute to cellular damage in the presence of chronic inflammatory status (4,16). It also has protective functions against vascular endothelial dysfunction in various pathological conditions due to the protecting effects on endothelial damage, vasoconstriction, platelet aggregation and leukocyte infiltration. The presence of MLT receptors throughout the body, including vascular endothelial cells and platelets, supports the ability to perform these functions (4,16). In many studies, it has been reported that MLT plays a role in the development and pathogenesis of autoimmune and/or rheumatological diseases (17,18). In addition to being involved in the regulation of the immune system and rheumatological diseases, it is also effective in reducing oxidative stress and apoptosis (7). Similar to the results of our study in many studies investigating rheumatological diseases; Increased MLT levels were found in patient groups. For example, in studies investigating the relationship between rhythmic symptoms and findings in autoimmune diseases such as rheumatoid arthritis (RA) and ankylosing spondylitis, and circadian MLT release; it was reported that serum MLT levels of patients were higher than control groups and that there was a significant relationship between disease activities and serum MLT levels, and it was reported that MLT may play a role in the pathophysiology of these diseases (19-21). However, there are studies reporting that although MLT levels are higher in RA patients compared to control groups, it is not associated with disease activity (22). In addition, there are studies reporting that serum MLT levels are higher in systemic lupus erythematosus patients than in control groups, but there are studies reporting that serum MLT levels are lower or the same compared to control groups (23-25).

In our study, serum MLT level was significantly higher in BD patients. This may be due to the deterioration of the circadian rhythm of MLT and/or the need for more antioxidant activity or anti-inflammatory activity in order to compensate chronic inflammation. However, there was no significant relationship between MLT level and disease activity in our study. This may be due to the low number of patients, the low activity of the disease, the disadvantages of the form used to assess the disease activity, or the effects of immunosuppressive therapy on MLT levels. In this context, given the other rheumatological diseases, we can say that how and where the MLT hormone plays a role in different autoimmune diseases is not well understood due to the different effects of the MLT hormone, and the immunopathological and clinical effects of the MLT hormone are not yet fully elucidated.

Headache is a common symptom in BD patients with or without neurological involvement. The presence of tension or migraine type of headache is not considered as neurological involvement (26,27). In BD, the evaluation of headache is difficult and correct diagnosis is very important since secondary headache causes can be devastating especially in neuro-BD with parenchymal involvement (28). There are studies that MLT has a role in the physiopathology of many types of headaches and is useful in the treatment of these headaches (29,30). In addition, it has been reported that increased oxidative stress and decreased antioxidant capacity trigger headaches by disrupting the brain blood flow (31).

In our study, there were no patients with symptoms or signs that could be considered as nervous system involvement according to BDCAF. However, it was determined that there were 26 patients (65%), including 18 women and 8 men with headache symptoms that are within the BDCAF criteria. Serum MLT levels were found to be significantly lower in patients with headache than those without. A lower MLT level in those with headaches may show us that the antioxidant capacity may have decreased, and this may be a trigger for headaches. For this reason, we think that MLT hormone may have a role in the physiopathology of headache in BD, but more detailed and comprehensive studies are needed. The mean age of patients with headache was 34.7 and 36.4 in patients without headache and were statistically similar. It is also known that MLT release is not affected by gender factor (32). Therefore, we can say that serum MLT levels were not affected by factors such as age and female gender. However, it has been reported that headache is more common in female gender since women are more affected by psychological stresses (33). In this sense, the presence of female domination in patients with headache in our study seems to be compatible with the literature.

Study Limitations

Limitations of our study can be listed as the timing of blood sample obtaining since the blood samples were obtained only between 8-9 am, when the MLT is the lowest, it does not fully reflect the circadian MLT hormone release, the low number of patients, and the immunosuppressive therapy.

Conclusion

Although we found that MLT plays a possible role in BD immunopathogenesis in BD patients with a headache history, there was no association between MLT level and disease activity. We suggest that further studies are needed to determine the possible role of MLT in BD and that our findings should be supported by future research.

Ethics

Ethics Committee Approval: The study protocol was approved by the Atatürk University Faculty of Medicine Ethics Committee (decision no: 16, date: 07.11.2019).

Informed Consent: A written informed consent was obtained from each subject.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.K., N.Ö., Y.A., F.B., Concept: A.K., N.Ö., Design: A.K., Data Collection or Processing: A.K.,

N.Ö., Y.A., F.B., Analysis or Interpretation: A.K., N.Ö., Literature Search: A.K., Writing: A.K, N.Ö.

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Naif İnsan Bağışıklık Yetmezliği Virüsü ile Enfekte Bireylerde Kemik Mineral Yoğunluğunun Değerlendirilmesi

Evaluation of Bone Mineral Density in Treatment-naive Patients with Human Immundeficiency Virus Infection

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Öz

Amaç: İnsan Bağışıklık Yetmezliği virüsü (HIV) enfeksiyonu, düşük kemik mineral yoğunluğu (KMY) için bir risk faktörüdür. Uluslararası HIV/AIDS kılavuzları her hasta için KMY taramasını önermemektedir. Bu çalışmada tedavi naif HIV enfeksiyonu olup rutin KMY taraması önerilmeyen hastalar ile 50 yaşın üzerindeki erkekler, menopoz sonrası kadınlar gibi olası osteoporoz/osteopeni risk faktörlerine sahip ve rutin KMY taraması önerilen hastalarda osteoporoz/osteopeni gelişimi için risk faktörlerini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Enfeksiyon hastalıkları polikliniğinde Ocak 2015 - Haziran 2019 tarihleri arasında takip edilen HIV ile enfekte bireylerin ilk başvurularındaki demografik, klinik ve laboratuvar özelliklerinin kaydedildiği bir veri tabanı oluşturulmuştur. Başvuru anında ve antiretroviral tedavi öncesi dual enerji X-ray absorbsiyometri (DXA) ölçümü yapılan 284 HIV ile enfekte hasta çalışmaya dahil edilmiştir. Osteoporoz/osteopeni tanısı alan ≥50 yaş/postmenapozal ve <50 yaş naif HIV ile enfekte bireylerin özellikleri karşılaştırılmıştır.

Bulgular: Çalışmaya dahil edilen 284 naif HIV ile enfekte bireylerin 131'inde (%46) DXA ile osteoporoz/osteopeni tanısı konulmuş olup, <50 yaş osteoporoz/osteopeni oranı %42,9 (106/247) iken ≥50 yaş olanlarda %67,6 (25/37) saptanmıştır (p=0,007). Yirmi altı hastada osteoporoz saptanmış olup, 16'sı (%61,5) 50 yaş altındadır. Yaşlı bireylerde KMY azalmasının en fazla femoral bölgede olduğu, genç bireylerde femoral bölge yanında lomber bölgede de görüldüğü belirlenmiştir (p<0,001).

Sonuç: Çalışmamız genç ve antiretroviral tedaviye maruziyeti olmayan hastalarımızda yüksek oranda KMY'de azalma olduğu ortaya koymaktadır. Osteopeni/osteoporoz varlığının erken saptanması, hayat kalitesinin artırılması ve ilaç yükünün azaltılması için önemlidir. Bu nedenle, düşük KMY tespiti, erken tedavisi için herhangi bir yaşta ve naif hastalarda da tedaviden bağımsız olarak tanısal testlerin yapılmasını öneriyoruz.

Anahtar kelimeler: HIV, kemik mineral yoğunluğu, osteoporoz, osteopeni

Abstract

Objective: Human Immundeficiency virus (HIV) infection is a risk factor for low bone mineral density (BMD). International HIV/AIDS guidelines do not recommend BMD screening for every patient. In this study, we aimed to compare the risk factors for the development of osteoporosis/osteopenia between patients with treatment naive HIV infection, to whom routine BMD screening is not recommended and patients with osteoporosis/osteopenia risk factors like men over 50 years of age, postmenopausal women to whom routine BMD screening is recommended.

Materials and Methods: A database was created in which the demographic, clinical and laboratory features of patients with HIV infection were recorded in the infectious diseases outpatient clinic between January 2015 and June 2019. A total of 284 HIV-infected patients with dual-energy X-ray absorptiometry (DXA) measurements at admission and before antiretroviral treatment were included in the study. The characteristics of those aged ≥50 years/postmenopausal and <50 years naive HIV-infected patients with osteoporosis/osteopenia were compared.

Results: Overall, 131 (46%) of 284 treatment-naive HIV-infected individuals were diagnosed with osteoporosis/osteopenia by DXA. The osteoporosis/osteopenia rate was 42.9% (106/247) and 67% (25/37) in those aged <50 and ≥50 years, respectively (p= 0.007). Osteoporosis was detected in 26 patients and 16 (61.5%) were <50 years. Further, decrease in BMD was most commonly observed in the femoral region among the elderly and in the lumbar and femoral regions among the young individuals (p<0.001).

Conclusion: This study reveals a high rate of decrease in BMD among our young patients who were not exposed to antiretroviral therapy. The early detection of the presence of osteoporosis/osteopenia is important to increase the quality of life and to decrease the drug load. Therefore, we recommend performing diagnostic tests at any age in naive patients for low BMD detection and early treatment, regardless of the treatment.

Keywords: HIV, bone mineral density, osteoporosis, osteopenia

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Giriş

İnsan Bağışıklık Yetmezliği virüsü (HIV) ile enfekte bireylerde tanı ve erken tedavi erişim olanakları arttıkça yaşam süreleri uzamakta ve beraberinde komordit hastalıklarda artış görülmektedir. HIV enfeksiyonu kemik mineral yoğunluğu (KMY) düşüklüğü için bir risk faktörü olup, pro-enflamatuvar yanıt ve immün aktivasyonla ve kullanılan antiretroviral tedavi (ART) etkisiyle kemik demineralizasyonuna neden olabilmektedir (1,2). Osteoporoz, düşük kemik kütlesi ve kemik dokusunun mikro-mimarisinin bozulması sonucunda kemik kırılabilirliğinde artışla sonuçlanan progresif bir metabolik kemik hastalığıdır. Günümüzde 200 milyondan fazla insanın osteoporotik olduğu tahmin edilmektedir (3). Türkiye'de 2010 yılında yapılmış FRAKTÜRK araştırmasında, 50 yaş üzerinde osteoporoz prevalansı kadınlarda %12,9 ve erkeklerde %7,5'tir. 2010 yılı verilerine göre 24,000 kadında osteoporoza bağlı kalça kırığı olduğu tahmin edilmiştir (4). Kalça kırıkları, osteoporozun en önemli komplikasyonudur; 2000 yılında tüm dünyada 9 milyon osteoporotik kırık olgusu görülmüştür; bunların 1,6 milyonu kalça kırığıdır (5). KMY ölçümünde günümüzde önerilen yöntem dual enerji X-ray absorbsiyometridir (DXA). DXA ile KMY ölçümü sadece tanıda değil, kırık riskini belirlemede, farmakolojik tedaviye başlama kararında, tedavi monitorizasyonunda da faydalıdır (3). HIV enfekte hastaların takibinde kullanılan ulusal ve uluslararası rehberler, KMY'de azalmaya neden olan glukokortikoid kullanımı, hipogonadizm, frajilite kırığı gibi klasik risk faktörlerine sahip olgular yanı sıra 50 yaş üzeri erkekler ve postmenopozal HIV ile enfekte bireylerde rutin DXA ile KMY takibini önermektedir (6). Buna karşın yapılan çalışmalarda 50 yaş altındaki HIV ile enfekte bireylerde de DXA ile KMY'de azalma olduğu bildirilmektedir. Osteoporoz, kırıklar oluşmadan da tanısı konabilen, gerekli önlemlerle ve tedavilerle, kırıkların yaratacağı sağlık sorunlarının önlenebildiği bir hastalıktır. Çalışmamızda rehberlerin rutin olarak KMY taraması önerdiği ve önermediği hasta grupları içinde tanımlanan naif HIV ile enfekte bireylerde, osteoporoz/osteopeni gelişimi için risk faktörlerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem

Hastanemiz enfeksiyon hastalıkları polikliniğinde Ocak 2015 - Haziran 2019 tarihleri arasında takip edilen HIV ile enfekte bireylerin ilk başvurularındaki demografik, klinik ve laboratuvar özelliklerinin kaydedildiği bir veri tabanı oluşturulmuştur. Başvuru anında ve ART öncesi DXA ölçümü yapılan 284 HIV ile enfekte hasta çalışmaya dahil edilmiştir. Hastalardan ≥50 yaş olanlar ileri yaş, <50 yaş genç bireyler olarak kabul edilmiştir (7). Postmenopozal kadınlarda ve 50 yaş üzeri erkeklerde T-skoru -2,5 ve altı olanlar, menopoz öncesi kadınlar ve 50 yaşından küçük erkeklerde Z-skoru -2 ve altı olanlar osteoporoz olarak kabul edilmiştir. T-skoru -1 ile -2,5 arasında olması osteopeni olarak kabul edilmiştir (8,9). Osteoporoz/osteopeni tanısı alan ≥50 yaş/postmenapozal ve <50 yaş naive HIV ile enfekte bireylerin özellikleri karşılaştırılmıştır. Hastaların yaş, cinsiyet, vücut kitle indeksi (VKİ), olası bulaş yolları, D vitamini düzeyleri, CD4 T lenfosit ve HIV, ribonükleik asit düzeyleri, tanı alış nedenleri, sigara, alkol, uyuşturucu kullanımları, birlikte ilaç kullanımı olup olmadığı ve DXA ölçümleri karşılaştırma kapsamına alınmıştır. Tanı anında kardiyovasküler ve nöropsikiyatrik sistem hastalıklarına ait ilaçlar, tiroid ilaçları, antidiyabetik ilaçlar, proton pompa inhibitörleri ve steroid kullanımı komedikasyon olarak tanımlanmıştır. Uyuşturucu kullanımına intravenöz, oral ve inhaler tüm madde kullanımı dahil edilmiştir. Ağır alkol içiciliği kavramı kadınlarda 120 gr/hafta, erkeklerde 160 gr/hafta olarak belirlenmiştir. Çalışma için İstanbul Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'ndan 10.06.2019 tarihinde 2019-11-01 numarası ile onay alınmıştır. Retrospektif planlanan çalışma için hasta onamı alınmamıştır.

İstatistiksel Analiz

Kategorik değişkenler ki-kare testi ile, sürekli değişkenler ise Kruskal-Wallis testi ile karşılaştırılmıştır. Sonuçlar, p değerinin 0,05'ten küçük olduğu durumlarda istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular

Çalışmaya dahil edilen 284 naif HIV ile enfekte bireyin 131'inde (%46) osteopeni/osteoporoz tanımlanmıştır. Hastaların 105'inde (%37) osteopeni, 26'sında (%9,15) osteoporoz saptanmıştır. Osteopeni/osteoporoz saptanan 131 hastanın 106'sı (%81) 50 yaş altında olup, hastaların ortalama yaşı 32±7,72 (18-49 yaş), 50 yaş üzeri 57±5,05 (%19) hastanın yaş ortalaması ise 57±5 (50-70 yaş) olarak bulunmuştur. Çalışma kapsamında olan 284 hastanın 26'sında (%9,15) osteoporoz saptanmış olup, bu hastaların 16'sı (%61,5) 50 yaş altında, 10'u (%38,5) 50 yaş üzerindedir. Elli yaş altı hastaların 16'sında (%15) osteoporoz ve 90'ında (%85) osteopeni saptanmıştır. Elli yaş üzerinde ise 10 hastada (%40) osteoporoz mevcut iken, 15 hastada (%60) hastada osteopeni saptanmıştır. Yaşlı bireylerde KMY azalmasının en fazla femoral bölgede olduğu, buna karşılık genç bireylerde femoral bölge yanında lomber bölgede de görüldüğü belirlenmiştir (p=0,0001). Elli yaştan küçük olan hastalarda erkek hasta oranı, ≥50 yaş hastalarda kadın hasta oranı yüksek bulunmuştur (p=0,011). Elli yaştan küçük olan hastalarda erkekle seks yapan erkek (MSM) bireyler anlamlı yüksek saptanmış ve yine bu yaş grubunda VKİ anlamlı olarak düşük bulunmuştur (p=0,007, p=0,001). Komedikasyon varlığı da ≥50 yaş hastalarda yüksek saptanmıştır (p=0,004). 25-hidroksi vitamin D [25(OH)D] düzeyi gruplar arasında farklılık görülmemiştir. Sadece bir hastada frajilite kırığı saptanmıştır. Tablo 1'de uluslararası rehberlerin rutin KMY taraması önerdiği ve önermediği yaş gruplarındaki HIV ile enfekte bireylerde osteoporoz/osteopeni tanısı almış olguların demografik, laboratuvar ve klinik özelliklerinin karşılaştırılması sunulmuştur.

Tablo 1. Naif osteoporozlu/osteopenili İnsan Bağışıklık Yetmezliği virüsü ile enfekte <50 yaş ve ≥50 yaş bireylerin karşılaştırılması

Bireylerin özellikleri (n=131)	<50 yaş (n=106)	≥50 yaş (n=25)	p
Cinsiyet			
Erkek	100 (94,3)	19 (76)	**0,011**
Kadın	6 (5,7)	6 (24)	
Bulaş yolu			
Heteroseksüel	39 (39,4)	17 (70,8)	**0,007**
MSM	60 (60,6)	7 (29,2)	
Tanı nedeni			
Tarama testleri	20 (19,9)	3 (12)	
Kendi isteği	13 (12,4)	2 (8)	
Partneri pozitif	14 (13,3)	4 (16)	0,736
Cinsel yolla bulaşan hastalık (+)	10 (9,5)	1 (4)	
HIV ilişkili durum	26 (24,8)	9 (36)	
HIV dışı durum tetkik	22 (21)	6 (24)	
VKİ [medyan (IQR)]	23,2 (21-25,2)	25,1 (23,9-28,3)	**0,001**
Sigara kullanımı			
Hiç içmemiş	40 (37,7)	9 (36)	0,240
Bırakmış	13 (12,3)	5 (20)	
Halen içiyor	46 (43,4)	7 (28)	
Alkol kullanımı			
İçmiyor	49 (46,2)	13 (52)	0,177
Sosyal içici	33 (31,1)	3 (12)	
Ağır içici	10 (9,4)	5 (20)	
Uyuşturucu kullanımı			
Evet	8 (7,5)	1 (4)	0,056
Hayır	62 (58,5)	9 (36)	
CD4 [hücre/mm³, medyan (IQR)]	389 (284,3-558)	298 (154,5-519,5)	0,099
HIV-RNA [kopya/mL, medyan (IQR)]	145088,0 (44830, 5-531780,0)	115902 (29034,5-420810,5)	0,643
Komedikasyon			
Var	26 (24,5)	14 (56)	**0,004**
Yok	80 (75,5)	11 (44)	
HBV koenfeksiyonu			
Var	2 (1,9)	2 (8,3)	0,159
Yok	102 (98,1)	22 (91,7)	
HCV koenfeksiyonu			
Var	-	1 (4)	0,194
Yok	104 (100)	24 (96)	
Sifiliz			0,410
Var	21 (21,2)	7 (30,4)	
Yok	78 (78,8)	16 (69,6)	
Kemik mineral yoğunluğu en çok azaldığı bölge			
L1	33 (31,1)	3 (12)	
L2	-	1 (4)	
L3	1 (0,9)	-	
L4	1 (0,9)	2 (8)	**<0,0001**
Trokanter major	9 (8,5)	1 (4)	
Femur boynu	46 (43,4)	13 (52)	
Trokanter minor	15 (14,2)	-	
Wards alanı	1 (0,9)	5 (20)	
25(OH)D vitamini			
Eksik <20 ng/mL	25 (45,5)	6 (40)	0,890
Yetersiz 20-30 ng/mL	15 (27,3)	5 (33,3)	
Yeterli >30 ng/mL	15 (27,3)	4 (26,7)	

RNA: Ribonükleik asit, 25(OH): 25-hidroksi, HBV: Hepatit B, HCV: Hepatit C, HIV: İnsan Bağışıklık Yetmezliği virüsü, VKİ: Vücut kitle indeksi, IQR: Çeyrek değerler genişliği, MSM: Erkekle seks yapan erkek

Tartışma

HIV ile yaşayan bireylerin yaşam beklentisi, genel popülasyondakiyle aynı süreye ulaşmaktadır. Beklenen yaşam süresi uzadıkça osteoporoz gibi komorbiditelerin görülme sıklığı da artmaktadır. Klasik risk faktörlerinin yanı sıra, HIV enfeksiyonunun kendisi ve ART rejimi (özellikle tenofovir disoproksil fumarat ve proteaz inhibitörleri) de kemik kaybına katkıda bulunmaktadır (10).

Çalışmamızda HIV rehberleri doğrultusunda risk için belirlenen yaş grubu olan, 50 yaş altı ve 50 yaş üzeri hastalar osteopeni/osteoporoz varlığı açısından değerlendirilmiştir. Çalışmaya dahil edilen 284 naif HIV ile enfekte bireyin 131'inde (%46) osteopeni/osteoporoz tanımlandığı ve hastaların 105'inde (%37) osteopeni, 26'sında (%9,15) osteoporoz saptanmıştır. Bu olguların %81'inin 50 yaş altında olduğu görülmüştür. Elli yaş altında osteoporoz/osteopeni saptanan HIV ile enfekte bireylerde erkek cinsiyet ve MSM bireyler fazla bulunmuştur (p=0,011, p=0,007). Osteoporoz için klasik risk faktörü olan VKİ düşüklüğü 50 yaş altındaki bireylerde daha fazla bulunmuş (p<0,001) ve 50 yaş üzeri bireylerde komedikasyon varlığı istatistiksel olarak anlamlı oranda yüksek saptanmıştır (p=0,004). Yaşlı bireylerde KMY azalmasının en fazla femoral bölgede olduğu, genç bireylerde femoral bölge yanında lomber bölgede de görüldüğü belirlenmiştir (p<0,001).

HIV ile enfekte hastalarda osteonekroz, osteomalazi ve osteoporoz olarak üç patolojik kemik ilişkili durum tanımlanmıştır. Osteoporoz en yaygın olanıdır ve HIV ile enfekte hasta popülasyonunda artan morbidite ile ilişkilidir (11). Bazı kohort çalışmalarında HIV ile enfekte hastalarda kırık insidansı genel popülasyona göre artmış bulunmuştur. HIV popülasyonunda kırılma riski ile ilgili uzun vadeli veriler sınırlı olmakla birlikte, özellikle uzun süredir ART kullanan yaşlı hastalar kırık insidansı artmış olarak bulunmuştur. Kırk yaşından büyük HIV pozitif erkeklerde kırık insidansına yönelik prospektif bir çalışmada, 50-59 yaş arası HIV pozitif tüm erkeklerde kırık görülme sıklığı HIV negatif kontrollere göre daha yüksek bulunmuş ve kırık insidansının yaklaşık 10 yıl önce arttığını belirtilmiştir. HIV enfeksiyonunun kendisi ve ART rejimi (özellikle tenofovir ve proteaz inhibitörleri) de kemik kaybına katkıda bulunur. Kemik kaybının çoğunluğu virüs aktivitesi sırasında ve ART başlangıcında (bağışıklığın yeniden yapılandırılması) ortaya çıkar ve kemik rezorpsiyonunun artmasıyla ilişkilendirilmiştir (10). Brezilya'da yapılan bir çalışmada 108 HIV ile enfekte birey çalışmaya dahil edilmiştir. Hastaların medyan yaşı 42 [çeyrek değerler genişliği (IQR) 36-48], HIV tanı zamanı 4,01 yıl (IQR 2-11 yıl) ve %70,3'ü erkek olarak bildirilmiştir. Hastaların 25'inde (%23) düşük KMY saptanmış olup, çalışmamıza benzer şekilde erkek hasta oranı fazla iken daha düşük oranda KMY'de azalma saptanmıştır. Hastaların 15'i (%60) osteopeni ve 10'u (%40) osteoporoz olarak presente olmuştur. Klasik risk faktörlerinden sigara içmek ve ≥50 yaş olmak ilişkili risk faktörü olarak saptanmıştır. Sigara çalışmamızda bir risk faktörü olarak belirlenmemiştir (12). Escota ve ark. (13) tarafından yapılan çalışmaya %77'si erkek, 653 HIV ile enfekte birey dahil edilmiştir. Yaş ortalamaları 41 olan hastaların, %29'u siyah ırk olup, ART öncesi %51'inde osteopeni ve %10'unda osteoporoz saptanmıştır. Hastalarda düşük VKİ, siyah ırk, daha uzun tenofovir disoproksil fumarat maruziyeti, ileri yaş, işsiz veya emekli olmak bağımsız olarak osteoporoz ile ilişkilendirilmiştir. Çalışmamıza benzer şekilde istatistiksel olarak anlamlı oranda femur boyunda KMY düşüklük saptanmıştır. Dört yıllık takip sonunda 170 virolojik suprese ve KMY takipleri yapılan hastanın %31'inde bazal KMY'den %5 düşüş saptanmış ve hastaların üçte birinde kemik kaybı ile karşılaştıkları vurgulanmıştır. Çalışmamızda olduğu gibi hastaların yüksek oranda erkek ve genç yaşta olduğu ve naif hastalarda yaklaşık %60'ında KMY'de düşüklük saptandığı görülmüştür. ART altında KMY'de bazalden düşüş oluşu beklenen bir sonuçtur.

Gümüşer ve Arslan (14) yaptıkları çalışmaya, 18-65 yaş arası erkek olup, ek hastalığı olmayan ve tiroid uyarıcı hormon, parathormon, D vitamini, testosteron, fosfor ve kalsiyum düzeyleri normal, 135 HIV ile enfekte hasta dahil edilmiştir. ART alan (%43,7) ve almayan (%56,3) hastalar osteopeni/osteoporoz açısından değerlendirilmiştir. Tedavi alan grupta %50 osteopeni, %20,3 osteoporoz ve almayan grupta %44,7 osteopeni, %13,2 osteoporoz saptanmış ve 2 grup arasında hem osteopeni hem osteoporoz varlığı açısından istatistiksel fark saptanmamıştır. ART almayan ve ek hastalığı olmayan tedavi naif erkek hasta grubunda da tedavi deneyimli hastalara benzer osteopeni/osteoporoz varlığı dikkat çekici olarak görülmüştür. Aydın ve ark. (15) 126 HIV ile enfekte hasta ile yaptıkları çalışmada hastaların %84'ü erkek ve yaş ortalamaları 40,1 yaş (20-70 yaş) olarak bildirilmiştir. Hastaların %37,5'i tedavi naif olup, tüm hastaların %53,9'unda osteopeni ve %23,8'inde osteoporoz saptanmıştır. Erkeklerde osteoporoz oranı kadınlardan fazla görülmüş (p=0,042) ve yüksek viral yük, ART kullanımı ve ART kullanım süresinin uzunluğu ile kemik kaybı arasında istatistiksel anlamlı bir ilişki saptanmıştır. Düşük KMY'de hem HIV'nin kendisinin hem de ART'nin önemi vurgulanmıştır. Hasta grubu benzer şekilde genç erkeklerdir ve osteoporoz erkeklerde anlamlı yüksek bulunmuştur. Çimen ve ark.'nın (16) yaptıkları çalışmaya 72 HIV ile enfekte, <50 yaş erkek ve premenopozal kadın hasta dahil edilmiştir. Hastaların yaş ortalaması 38 yaş ve %90,3'ü erkek olarak saptanmıştır. Hepsi ART kullanmakta olan ve viral yük negatif olan bu hastaların %19,3'ünde düşük kemik kütlesi olduğu görülmüş ve sadece düşük VKİ ile istatistiksel anlamlı ilişki saptanmıştır. KMY düşüklüğünün genç nüfusta da görülebileceği ama >50 yaş ve postmenopozal kadınlara göre daha az görüldüğü vurgulanmıştır. Hastaların %90'ının genç erkek olduğu bu çalışma grubunda, hastaların %90'ından fazlası tenofovir disoproksil fumarat kullanmakta olup hastalarda çalışmamıza göre düşük bir KMY düşüklüğü saptanmıştır. Brown ve ark. (17) 331 HIV ile enfekte birey ile yaptıkları çalışmada naif, ART almayan hastalar çalışmaya dahil edilmiş ve çalışmamıza benzer şekilde hastaların %31'inde KMY'de düşüklük saptanmıştır. Hastaların yaklaşık %90'ı erkek ve yaş ortalamaları 36 yıl olup, VKİ'de düşüklük çalışmamıza benzer şekilde KMY düşüklüğü ile istatistiki olarak anlamlı bulunmuştur.

Çalışmanın Kısıtlılıkları

Hasta grubumuzda beslenme düzeni ve aile öyküsü verileri değerlendirilememişir. Komedikasyon varlığı bütünsel olarak değerlendirilmiş olup hasta bazlı özellikle osteoporoz olan hastalar için kullanılan ilaçlar tek tek belirtilmemiştir. 25(OH) D düzeyi hastane politikası nedenli aralıkla bölümümüzce istenememekte olup tüm hastalarda ilk sonuçlar verilememiştir.

Sonuç

Çalışmamız klasik risk faktörlerine sahip olmayan ve rutin tarama önerilmeyen 50 yaş altı genç, antiretrovirallere maruziyeti olmayan hastalarımızda yüksek oranda KMY'de azalma olduğu ve düşük 25(OH)D seviyeleri gösterdiklerini ortaya koymaktadır. Özellikle HIV ile enfekte bireyler içinde artış görülen genç MSM bireylerde osteopeni/osteoporoz görülme oranının fazlalığı rutin tarama yapılan ve klasik risk faktörleri dışında kalan grup için de KMY azalmasının ve taramanın önemine dikkat çekmektedir. Osteopeni/osteoporoz varlığının erken saptanması, hayat kalitesinin artırılması ve ilaç yükünün azaltılması konusunda önemlidir. Bu nedenle, düşük KMY ve D vitamini eksikliğinin tespiti erken tedavisi için herhangi bir yaşta ve naif hastalarda da tedaviden bağımsız olarak tanısal testlerin yapılmasını öneriyoruz.

Etik

Etik Kurul Onayı: Çalışma etik komite onayı İstanbul Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'ndan alınmıştır (tarih: 10.06.2019, karar no: 2019-11-01).

Hasta Onayı: Retrospektif planlanan çalışma için hasta onamı alınmamıştır.

Hakem Değerlendirmesi: Editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazarlık Katkıları

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Factors Affecting Bone Mineral Density in Male Patients with Primary Progressive Multiple Sclerosis

Primer Progresif Multipl Sklerozlu Erkek Hastalarda Kemik Mineral Yoğunluğunu Etkileyen Faktörler

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Abstract

Objective: Osteoporosis (OP) is one of the most frequent metabolic bone disorders worldwide, male OP is still underestimated and undertreated. Primary progressive multiple sclerosis (PPMS) is considered as an important cause of secondary OP in males and there is limited data on this condition in Turkey. This study aimed to evaluate the bone mineral density (BMD) of male PPMS patients and the possible clinical and laboratory interacting factors as well as to also define the correlation between BMD and bone turnover markers (BTM).

Materials and Methods: In this study, 26 male PPMS patients and 20 age-matched healthy volunteers were evaluated by the Expanded Disability Status Scale (EDSS), femoral and lumbar BMD, biochemical and hormonal tests and BTMs.

Results: Demographic characteristics were statistically similar between the groups. Mean values for patient age, disease duration and EDSS score were 42.5±10.0 years, 3.5±1.5 years and 4.6±1.6, respectively. Although we found a significant difference in BMD and carboxy-terminal telopeptide levels between PPMS patients and the control group, there were no significant correlations between sex hormone binding globülin levels, EDSS, BMD scores, BTMs and other biochemical variables.

Conclusion: BMD scores were lower in the patient group compared to the control group. This study highlights the importance of considering bone health in male PPMS patients and reminds that strategies should be developed as part of the management plan.

Keywords: Multiple sclerosis, bone mineral density, osteoporosis

Öz

Amaç: Osteoporoz (OP) dünya çapında en sık görülen metabolik kemik bozukluklarından biri olmasına rağmen, erkek OP'si halen yeterince göz önüne alınmamakta ve tedavi edilmemektedir. Primer progresif multipl skleroz (PPMS), erkeklerde ikincil OP'nin önemli bir nedeni olarak kabul edilmekte olup, Türkiye'de konu ile ilgili veriler sınırlıdır. Bu araştırmada erkek PPMS hastalarının kemik mineral yoğunluklarının (KMY) incelenmesi, etkileşen olası klinik ve laboratuvar faktörlerin saptanması ve ayrıca KMY ile biyokimyasal kemik döngü belirteçleri (BKDB) arasındaki korelasyonun tanımlanması amaçlanmıştır.

Gereç ve Yöntem: Yirmi altı erkek PPMS hastası ve 20 yaş uyumlu sağlıklı gönüllü Genişlemiş Özürlülük Durum Ölçeği (EDSS), femoral ve lomber KMY, biyokimyasal ve hormonal testler ve BKDB ile değerlendirildi.

Bulgular: Demografik özellikler gruplar arasında istatistiksel olarak benzerdi. Hastaların yaş, hastalık süresi ve EDSS skoru için ortalama değerler sırasıyla 42,5±10,0 yıl, 3,5±1,5 yıl ve 4,6±1,6 idi. PPMS hastaları ile kontrol grubu arasında KMY ve karboksi terminal telopeptid düzeylerinde anlamlı bir fark bulunmuş olsa da cinsiyet hormonu bağlayıcı globulin düzeyleri, EDSS, KMY skorları, BKDB'ler ve diğer biyokimyasal değişkenler arasında anlamlı korelasyon saptanmadı.

Sonuç: KMY skorlarının hasta grubunda kontrol grubuna göre daha düşük olduğu belirlendi. Bu çalışma erkek PPMS hastalarında kemik sağlığının göz önünde bulundurmanın önemini vurgulamakta ve tedavi planının stratejik bir parçası olarak ele alınması gerektiğini hatırlatmaktadır.

Anahtar kelimeler: Multipl skleroz, kemik mineral yoğunluğu, osteoporoz

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Introduction

Osteoporosis (OP) is one of the most frequent metabolic bone disorders worldwide and male OP is still underestimated and undertreated, which has significant clinical and social consequences (1). About two-thirds of men have secondary OP and since diagnosis is important to define the prognosis and to choose the appropriate treatment, it is recommended to investigate young individuals and men under 65 years of age for other underlying causes of OP (1-3).

Multiple sclerosis (MS) is considered as an important cause of secondary OP (4). Since MS is predominantly seen in females, OP in male primary progressive MS (PPMS) patients are underrated. Drake et al. (5) identified multiple risk factors for osteoporotic fractures in men, but concluded that, usefulness for stratifying and selecting men for bone mineral density (BMD) testing remains uncertain. So not only the BMD but clinical and laboratory contributing factors should also be evaluated in males.

There is limited data about the effects of MS on male OP in Turkey.

This study aimed to evaluate BMD among male PPMS patients excluding factors such as chronic immobilization and oral glucocorticoid use, which can be two importing confounding factors. Bone tunover markers (BTM) commonly used as bone formation marker include serum osteocalcin (OC), and serum Carboxyterminal telopeptide of collagen I (CTX) as bone resorption marker for the evaluation of bone turnover (6). We also aimed to define the correlation between BMD and BTM for use in clinical practice to give information about bone metabolism earlier in a cheaper, reproducible way that does not have any radiation risk.

Materials and Methods

Ethics Statement

This study was approved by the Hacettepe University Non-interventional Clinical Research Ethics Committee (decision no: GO 14/524-06) and carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study Design and Participants

Twenty six male patients who had been diagnosed as PPMS according to the 2010 McDonald Diagnosis Criteria, for at least 1 year prior to the study and aged between 24-60 years were enrolled (7).

Age and gender matched 20 controls were also enrolled in this study. Healthy volunteers with normal cognitive function, aged between 32-60 years old, and having a BMI between 20 and 40 were included. Control participants did not have any diseases or medication use which affected bone metabolism.

The evaluation of the patients and the control groups were performed in Hacettepe University Faculty of Medicine, Department of Physical Medicine and Rehabilitation clinic.

All the participants' demographics, such as age, height, weight, body mass index (BMI), gender, occupation, and education status were recorded in the participant evaluation form. Smoking and alcohol consumption habits, concomitant systemic diseases, and medications were also recorded. Family history of MS, OP, or pathological/fargility fractures were questioned.

MS type, duration, and patient age at diagnosis were recorded on the participant evaluation form. For standardization, The Expanded Disability Status scale (EDSS) was performed by the same neurologist (8).

Laboratory Tests

Blood was collected from participants after a minimum of eight hours fasting and tested for complete blood count and erythrocyte sedimentation rate. Plasma levels of calcium, sodium, magnesium, phosphate, blood sugar, alanine transaminase, aspartate transaminase, alkaline phosphatase, gamma glutamyl transferase, blood urea nitrogen, thyroid stimulating hormone, parathyroid hormone, 25-hydroxy vitamin D3, sex hormone binding globulin (SHBG), testosterone, growth hormone, OC and CTX were evaluated in Hacettepe University Hospital Department of Biochemistry.

CTX levels were measured with the Human Cross Linked C-telopeptide of Type I Collagen ELISA Kit (Elabscience, Houston, TX, USA). Reference values selected were concordant with the Turkish population.

Bone Mineral Density Evaluation

BMD was evaluated by dual-energy X-ray densitometry at Hacettepe University Hospital, Clinic of Radiology with the Lunar Prodigy Advance Bone Densitometer (GE, Chicago, IL, USA). Diagnosis of OP, osteopenia, or normal BMD was accessed with T-score values. The T-scores of L1-L4 vertebra and the total femur bone is used for diagnosis. The mismatch of the measured values is evaluated as either a major or minor mismatch. According to the World Health Organization's criteria, a major mismatch is if one of the measured regions is between OP limits but the other one is in normal limits. A minor mismatch is if one region is osteopenic but the other is either normal or osteopenic (9).

As recommended by the writing group for the ISCD Position Development Conference, not only the T-scores but Z-scores were also taken into consideration (10).

Statistical Analysis

The IBM SPSS (Statistical Package for Social Sciences for Windows) 22.0 program was used for statistical analysis. A type 1 error level of 0.05 and a power level of 80% determined the number of participants to enroll. It was predicted that there would be a difference of at least 0.8 units between the MS and control groups according to T-score means (standard deviation: 1.43). Differences in the numerical variables between MS and control groups were assessed by independent sample t-test or Mann-Whitney U test. Relations between categorical variables were evaluated using the chi-square test. BMD, bone

formation and resorption markers, and SHBG relationships were evaluated using the Pearson or Spearman correlation coefficient. A p value <0.05 was considered statistically significant.

Results

The demographics and tobacco and alcohol consumption were statistically similar in both groups. Mean age of the patient group was 42.5±10.0 (24-60) years, whereas mean disease duration was 3.5±1.5 years.

A significant difference was found BMI between the patient and the control group (p<0.01). Basic characteristics of the study population are shown in Table 1.

25-hydroxy vitamin D levels were found to be 18.5±9.5 ng/mL in the patient group and 19.5±6.3 ng/mL in the control group (p>0.05). Some other laboratory results of the study population are given in Table 2.

Regarding the BMD measurements; femoral BMD (p=0.01), femoral T-scores (p=0.04), and femoral Z-scores (p=0.05) were lower in the patient group. The comparison of BMD, Vitamin D, CTX, and OC levels between PPMS patients and the control group is shown in Figure 1.

Although we found a significant difference in BMD and CTX levels between PPMS patients and control group, there were no significant correlations between SHBG levels, EDSS, BMD scores, biomarkers (CTX and OC), and other biochemical variables. However, the p values were close to the significant value. BMD scores were lower in the patient group compared to the control group. Comparison of the CTX and OC levels of the PPMS patients and control group is given in Figure 2 and comparison of the BMD results between PPMS patients and control group is given in Figure 3.

The mean EDSS score was found as: 4.6 ± 1.6 and the distribution of EDSS Scores of PPMS Patients is given in Figure 4.

Table 1. Characteristics of the study population

	MS n=26	Control group n=20	p
Mean age (years)	42.5±10.0	42.7±7.9	0.942
BMI (kg/m²)	24.05±2.98	26.47±2.83	0.008
Educational status			
Illiterate	0	1 (5%)	0.170
Literate	1 (5%)	0	
Primary education	7 (27%)	2 (10%)	
High school	8 (31%)	11 (55%)	
University	10 (39%)	6 (30%)	
Marital status			
Married	18 (69%)	20 (100%)	0.005
Single	7 (27%)	-	
Divorced	1 (4%)	-	
Occupation			
Government official	10 (39%)	13 (65%)	0.022
Retired	1 (4%)	3 (15%)	
Unemployed	4 (15%)	-	
Self-employed	11 (42%)	4 (20%)	

BMI: Body mass index, MS: Multiple sclerosis, n: Number

Discussion

Bone is a dynamic tissue that is continuously regenerated and destroyed. MS is a chronic autoimmune disease of the central nervous system that results in varying degrees of disability.

Patients with MS have multiple risk factors for osteoporotic fractures, such as progressive immobilization, long-term glucocorticoids treatment or vitamin D deficiency (11).

There may also be several other confounding factors that effect the bone metabolism in MS patients. In our study, demographics and tobacco and alcohol consumption were statistically similar in both groups. There was a significant difference of BMI between the patient and the control group. This may be important due to the relationship between low BMI, low BMD levels, and the possible risk of osteoporotic fractures in the future. Hence some studies found that increased BMI is associated with elevated BMD levels and a reduced risk of fractures due to OP (12).

Femoral BMD, femoral T-scores, and femoral Z-scores were lower in the patient group compared with the controls. SHBG levels and lumbar BMD scores were negatively correlated in the patient group. This may be an important confounding factor. But there was no significant correlation between SHBG levels, EDSS scores, BMD, biomarkers, and other biochemical variables. However, p values were close to the significant value.

In young adults, MS is a leading cause of disability and triggers

Table 2. Some laboratory results of the study population

	PPMS n=26	Control n=20	p*
ALT	25.6 (±12.8)	25.2 (±11.5)	0.7
GGT	39.5 (±32.5)	29.4 (±23.2)	0.8
Creatinine	1.3 (±2)	0.8 (±0.1)	0.7
GH	0.15 (±0.3)	0.09 (±0.08)	0.5
SHBG	35.5 (±19.7)	30.4 (±18.1)	0.1
TSH	1.4 (±0.8)	1.2 (±0.4)	0.1
Testosteron	309.2 (±73.4)	330.8 (±109)	0.4
PTH	39.1 (±14.7)	41.3 (±14.8)	0.6
CTX	0.261 (±0.23)	0.398 (±1.75)	0.1
Osteocalcin	2.8 (±3.9)	2.1 (±0.2)	0.8

*PPMS and Control group p<0.05 is significant, **Standart daviation, Mann-Whitney U test, PPMS: Primary progressive multiple sclerosis, ALT: Alanine transaminase, GGT: Gamma glutamyl transferase, GH: Growth hormone, SHBG: Sex hormone binding globulin, TSH: Thyroid stimulating hormone, PTH: Parathormone, CTX: Carboxy-terminal telopeptide

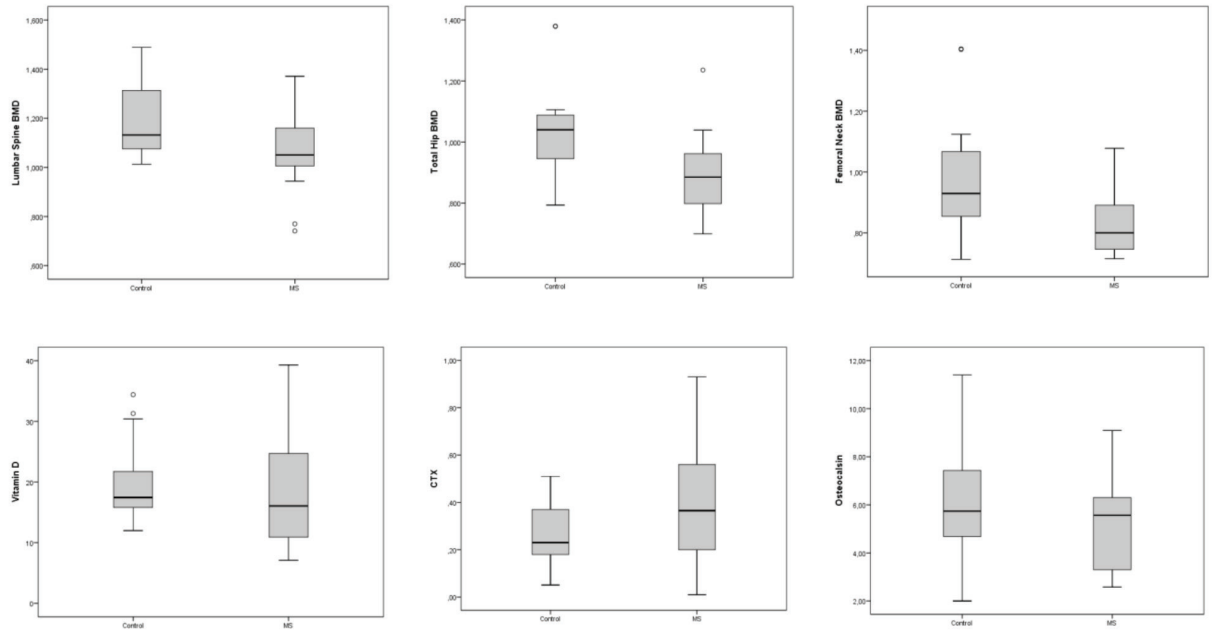

Figure 1. Comparison of the BMD, Vitamin D, OC and CTX of PPMS patients and control group
BMD: Bone mineral density, OC: Osteocalcin, CTX: Carboxyterminal telopeptide of collagen I, PPMS: Primary progressive multiple sclerosis

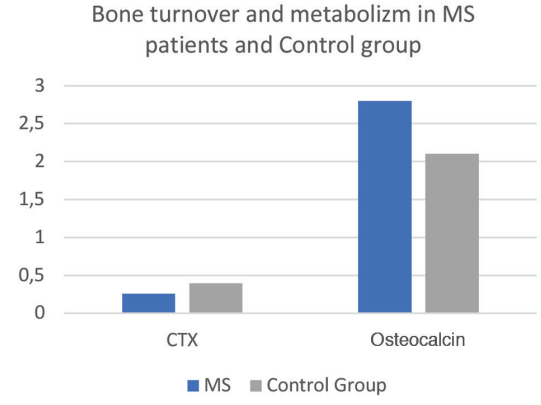

Figure 2. Comparison of the CTX and OC levels of the PPMS patients and control group
CTX: Carboxyterminal telopeptide of collagen I, OC: Osteocalcin, PPMS: Primary progressive multiple sclerosis

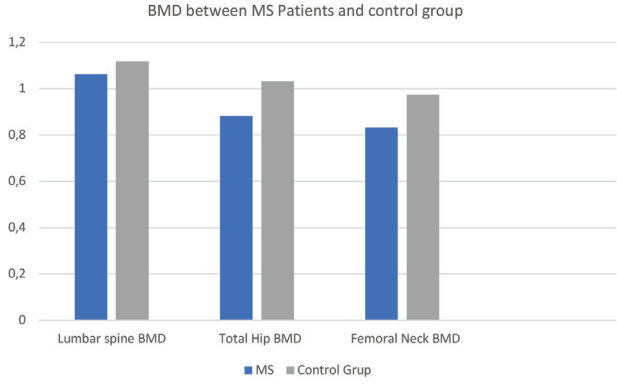

Figure 3. Comparison of the BMD results between PPMS patients and control group
BMD: Bone mineral density, PPMS: Primary progressive multiple sclerosis

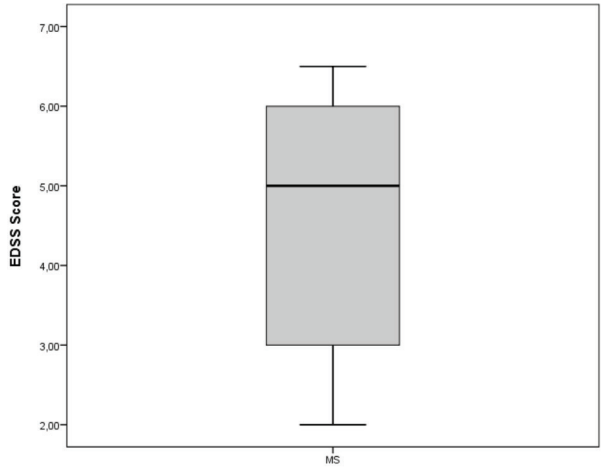

Figure 4. EDSS score distribution of PPMS patients
EDSS: Expanded disability status scale, PPMS: Primary progressive multiple sclerosis

bone mineral deficiency by many factors, such as immobilization, steroid use, and cytokines (13,14). Thus, patients with MS have faster bone loss and suffer fractures more often than healthy adults in their age group. In the NARCOMS study, Nickersonan et al. (15) reported that 27.2% of all MS patients have osteopenia and 15.4% have OP.

In a study comparing male and female bone loss, 80% of the male MS patients (n=40) had bone loss in some level and 37.5% had OP. Whereas among the females (n=47) osteoporotic patient ratio was 16.3% and and 7.4% of the pre-menopausal women (n=27) had OP (16).

Progressive immobilization in MS causes BMD loss, OP, and

fractures. After 20-30 weeks of bed rest, healthy young adults have negative calcium balances of 150-200 mg daily. This loss is more prominent among paraplegic patients. The loss and disappearance of the biomechanical stress over the skeleton is the main cause of OP (17). Mechanical load increases bone formation in cortical and trabecular bone by decreasing bone turnover (18). In MS, there may be a decrease in BMD according to the level of ambulation, and decreased functional capacity can cause femoral BMD loss. Zikan et al. (19) indicated that femur trochanteric BMD was lower among wheelchair bound patients compared to ambulatory patients. Previously another study had also pointed out that the decrease in femoral BMD is correlated with poor ambulation (20). There are several other studies showing a positive correlation between physical activity and BMD (21,22).

Among non-ambulatory MS patients, the decrease of the axial mechanical load over the femur causes BMD loss. BMD loss due to an inadequate ambulation is more dominant in the femoral region than in the lumbar region (23). That is an important contributing factor in MS patients and we excluded this factor with including relatively mobile patients due to the EDSS score. Nevertheless we identified that the total BMDs of the lumbar and femur in the MS group were significantly lower than in the healthy controls. Whereas, there was no significant relationship between EDSS score and BMD. This may be explained by the fact that all patients were ambulatory, either assisted or independent, and the maximum EDSS score was 6.5.

Continuous or intermittent steroid use is an another factor affecting BMD in MS patients. Steroid use has reportedly caused bone mass loss, and long-term steroid use causes OP by decreasing bone formation and increasing resorption (24,25). Bone loss is observed among 30-50% of patients undergoing glucocorticoid treatment. Steroids affect bone metabolism through three mechanisms, calcium homeostasis, sex hormones, and inhibition of bone formation. They mainly inhibit bone formation directly by influencing osteoblast genes or growth factors. Eventually matrix formation is reduced (26). Some studies have shown loss of cortical bone volume and density after systemic steroid use (27).

Patients enrolled in our study had not used intravenous or oral steroid treatments within the last year, and in that way this important etyological factor was eliminated. Also we found no correlation between cumulative steroid use and BMD, but results among MS patients are controversial. Schwid et al. (28) showed that a 6-month pulse steroid treatment resulted in a significant increase in lumbar BMD but not in femoral BMD.

Vitamin D deficiency is another theory for explaining MS related OP, and has an immunomodulatory effect and its deficiency decreases BMD. Kirbas et al. (29) showed that vitamin D levels and BMD of newly diagnosed MS patients were correlated. In both groups of our study vitamin D levels were in normal ranges.

Remodeling of bone is an important determinant of bone strength. BTM are commonly used for the detection of bone turover. We measured serum CTX as a resorption marker and OC as a formation marker (6).

BMD measurements reflect a static condition of bone tissue. On the other hand, bone markers reveal the dynamic state. Studies showed no correlation between bone turnover markers and lower BMD measurements in early MS patients. We also did not find a relationship between either formation or resorption markers and BMD. These results are compatible with other studies in the literature (6,30). However, there is limited data about bone formation markers. In conditions like MS, bone loss rate is not very prominent. Evidence regarding the bone formation markers are not sufficient yet, and therefore, bone formation markers cannot be used for diagnostic purposes (31).

Our study supports the view of MS-related OP independent of other risk factors, when excluded chronic immobilization and oral glucocorticoid use. This concept can be explained with the common etiological and pathological mechanisms of MS and OP. We would like to underlie the importance of considering bone health in male patients with PPMS. In addition to disease modifying therapies, lifestyle strategies focused on overall health and well-being should be emphasized as part of a management plan in MS patients.

Ethics

Ethics Committee Approval: This study was approved by the Hacettepe University Non-interventional Clinical Research Ethics Committee (decision no: GO 14/524-06) and carried out in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ç.A., N.P.A., Concept: A.Ç.A., Y.G.K., Design: A.Ç.A., Y.G.K., Data Collection or Processing: A.Ç.A., N.P.A., F.A., S.K., R.K., Analysis or Interpretation: S.K., A.Ç.A., F.A., Literature Search: A.Ç.A., Y.G.K. Writing: A.Ç.A., Y.G.K., N.P.A., R.K.

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The Relationship Between Iron Accumulation, Vitamin D Deficiency and Bone Mineral Density in Patients with Thalassemia Major, Thalassemia Intermedia and Sickle Cell

Talasemi Majör, İntermedya ve Orak Hücreli Hastalarda Demir Birikimi ve D Vitamini Eksikliği ile Kemik Mineral Yoğunluğu İlişkisi

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Abstract

Objective: Osteopenia and osteoporosis are important causes of morbidity in patients with hemoglobinopathies. This study investigates the association between iron accumulation, vitamin D and bone mineral density (BMD) in patients with thalassemia major, thalassemia intermedia and sickle cell.

Materials and Methods: Serum samples collected from 102 patients with hemoglobinopathy were used; the relationship between ferritin, vitamin D levels and BMD, which was performed with dual energy X-ray absorptiometry (DEXA), was investigated.

Results: The ratio of thalassemia intermedia, thalassemia major and sickle cell patients with normal BMD according to the DEXA Femoral T-score was 56.25%, 35% and 39%, respectively. The ratio of thalassemia intermedia, thalassemia major and sickle cell patients with normal BMD according to the DEXA lumbar T-score was 31.25%, 7.5% and 41.25%, respectively. When the patients' ferritin values and DEXA scores were compared, femur T-score, lumbar T-score, femur Z-score and lumbar Z-score were significantly lower in those with high ferritin values (p values were respectively: 0.0005, 0.0002, <0.0001, 0.0002). When the femur T-score, lumbar T-score, femur Z-score and lumbar Z-score were compared in patients with normal and low vitamin D levels, a statistically significant change was observed in the severe deficiency patients (p values were respectively: 0.001, 0.001, 0.0027, 0.0003).

Conclusion: Patients with hemoglobinopathy should be screened through DEXA at an early age. The efforts to provide appropriate vitamin D replacement and to restore the ferritin levels to the normal range may be effective in reducing the morbidity associated with osteoporosis.

Keywords: Hemoglobinopathies, osteoporosis, iron accumulation, vitamin D

Öz

Amaç: Osteopeni ve osteoporoz hemoglobinopatili hastalarda önemli bir morbidite nedenidir. Bu çalışmanın amacı talasemi majör, talasemi intermedya ve orak hücreli anemi hastalarında demir birikimi, D vitamini ve kemik mineral yoğunluğu (KMY) arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Hemoglobinopatili 102 hastadan serum örnekleri toplandı ve ferritin ve D vitamini düzeyleri ile çift enerjili X-ışını absorpsiyometrisiyle (DEXA) ölçülen KMY arasındaki ilişki araştırıldı.

Bulgular: DEXA femoral T-skoruna göre normal KMY olan talasemi intermedya, talasemi majör ve orak hücreli anemi hasta oranı sırasıyla %56,25, %35 ve %39 idi. DEXA lomber T-skoruna göre normal KMY olan talasemi intermedya, talasemi majör ve orak hücreli anemi hasta oranı sırasıyla %31,25, %7,5 ve %41,25 idi. Hastaların ferritin değerleri ve DEXA skorları karşılaştırıldığında, femur T-skoru, lomber T-skoru, femur Z-skoru ve lomber Z-skoru, ferritin değeri yüksek olanlarda istatistiksel olarak anlamlı derecede düşüktü (p değerleri sırasıyla: 0,0005, 0,0002, <0,0001, 0,0002). Femur T-skoru, lomber T-skoru, femur Z-skoru ve lomber Z-skoru normal ve düşük D vitamini seviyesine sahip hastalarda karşılaştırıldığında, ciddi eksikliği olan hastalarda istatistiksel olarak anlamlı bir değişiklik gözlendi (p değerleri sırasıyla: 0,001, 0,001, 0,0027, 0,0003).

Sonuç: Hemoglobinopatili hastalar DEXA ile erken yaşta taranmalıdır. Uygun D vitamini replasmanının sağlanması ve ferritin seviyelerinin normal aralığa getirilmesi çabaları osteoporoz ile ilişkili morbiditeyi azaltmada etkili olabilir.

Anahtar kelimeler: Hemoglobinopatiler, osteoporoz, demir birikimi, vitamin D

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Introduction

Osteopenia and osteoporosis is an important cause of morbidity in patients with hemoglobinopathy across all genders and ages. Many genetic and acquired factors are inculpated for the pathogenesis of osteoporosis in these patients. Some of the acquired factors for osteoporosis in these patients include thinning of cortical and trabecular bone due to bone marrow expansion caused by increased ineffective erythropoiesis, calcium and phosphorus metabolism disorders, hypogonadotropic hypogonadism, growth hormone and IGF-1 deficiency, delayed puberty, increased osteoclast activity and decreased osteoblast activity, toxic effect of desferrioxamine chelation treatment and physical inactivity (1-4). In recent years, developments in transfusion management and chelation treatment improved the skeletal development and cosmetic bone appearance. However, these patients are still reported to have low bone density despite the optimal conventional treatment and reduction of endocrinal complications (5). Vitamin D is a basic hormone for the control of normal calcium and phosphate homeostasis, and also an important factor required for bone development and the continuity of bone mass (6). Elevated serum ferritin level points to iron storage in the organs including bones especially in patients with transfusion-dependent thalassemia major. Excessive iron deposition in bones impairs the number and activation of osteoid and bone mineralization, leading to osteoporosis (7). In our region, thalassemia major, intermedia and sickle cell disease are quite common and for these patient groups, osteoporosis causes frequent morbidity in early ages. In this study we wanted to investigate the association between the iron accumulation, vitamin D and bone mineral density (BMD) in thalassemia major, intermedia and sickle cell patients.

Materials and Methods

In this cross-sectional observational study, the approval of the Çukurova University Faculty of Medicine of Local Ethics Committee (decision no: 2014/27) was obtained and 102 patients with thalassemia major, intermedia and sickle cell who admitted to Çukurova University Hematology Outpatient Clinic from 2013 to 2015 were analyzed. Written consent form was obtained from all patients before enrollment in the study. The patients were divided into three groups: patients with thalassemia intermedia, thalassemia major and sickle cell. Patients who received regular transfusion and chelation therapy were included in the study. The patients who did not receive osteoporosis treatment before, did not use any medication that could affect the calcium and vitamin D metabolism (anticonvulsants, gonadotropin releasing hormone analogues, cyclosporine, estrogen preparations, calcium and vitamin D-containing medications), did not have any known renal or hepatic disease, did not have any known metabolic bone disease, did not have any health problem except hemoglobinopathy that might lead to secondary osteoporosis (hyperthyroidism, use of steroid etc) were included in the study. Therefore, 50 patients were excluded from the study for these reasons. Fasting blood test was performed for the eligible patients included in the study and their dual energy X-ray absorptiometry (DEXA) measurements were performed. Ferritin and vitamin D levels were examined in the blood sample. Serum vitamin D levels were measured using a Chromosystem test kit (Chromosystem, Munich, Germany) using high performance liquid chromatography method. Ferritin was measured by electro chemiluminescence method, by using BIO Diagnostic Products Corporation (DPC), Los Angeles, USA test kit and by ImmuliteONE instrument. The DEXA method was used for the diagnosis of osteoporosis. The BMD of the patients was measured on anterio-posterior and lateral lumbar vertebrae (L1-L4) and left femur neck. Fractured sites or prosthetic sites were not measured. The measurements were performed with DEXA (Norland, XR 46, USA) at radiology department. Measurements were completed in as short as 7-20 minutes, depending on the region where the shots were taken, and BMD results were expressed in g/cm^2, as T- and Z-score. T- and Z-scores were used in evaluating DEXA results. T-score is the standard deviation (SD) of BMD according to a person's young age group. The Z-score is the SD of BMD according to the individual's age group, used in the diagnosis of secondary osteoporosis. We evaluated both T- and Z-scores for our patient groups. The results of the BMD were divided into 3 groups as osteoporosis, osteopenia and normal according to T-score in line with the criteria proposed by the World Health Organization. Patients with a vertebral and/or femoral T-score of ≤-2.5 were assigned to the osteoporosis group, those with a T-score of -2.5< to ≤-1.0 were assigned to the osteopenia group, and those with a T-score of >-1.0 were assigned to the normal group. The patients' Z-scores were also evaluated. Those patients with a Z-score of -2 SD and below were considered to have a lower bone mass than expected based on their chronological age, while those with a Z-score above -2 SD considered to have a normal bone mass according to their chronological age.

Biochemical Analysis

The normal range was considered as 23.9-336.2 ng/mL for ferritin. The normal range of vitamin D was taken as 30-120 ng/mL. 20-29.9 ng/mL was considered as mild vitamin D deficiency, 10-19.9 ng/mL was considered as medium vitamin D deficiency, and a value lower than 10 ng/mL was considered as severe vitamin D deficiency.

Statistical Analysis

The statistical analysis of the data was performed using Microsoft Windows compatible SPSS 21.0 package software. The descriptive statistics were expressed as numbers and percentage (%) for categorical variables, and as means and SD (and as median and minimum-maximum when required) for continuous variables. For the comparison of continuous variables between the groups, the distribution was analyzed. One-Way ANOVA test was performed for the parameters with a normal distribution depending on the number of variables One-Way. For the comparison of the categorical variables, chi-square test was

used. The effects of ferritin and vitamin D levels on BMD were compared using cox multi regression analysis. P value of 0.05 was considered to be statistically significant in all tests.

Results

Sixteen patients had thalassemia intermedia (15.7%), 40 had thalassemia major (39.2%), 46 had sickle cell disease (45.1%). Demographic and laboratory data of patients are presented in Table 1. Patients with thalassemia intermedia were diagnosed at a mean age of 8 years and the mean follow-up was 19 years; patients with thalassemia major were diagnosed at a mean age of 1 year and the mean follow-up was 24 years; patients with sickle cell disease were diagnosed at a mean age of 6 years and the mean follow-up was 22 years. In patients with thalassemia intermedia and major, lomber T- and Z-scores were significantly lower than femur T- and Z-scores (p=0.028, p=0.015, p=0.035, p=0.03 respectively). There was no statistically difference between lumbar and femur regions in sickle cell patients (p=0.87, p=0.9). The classification of the patients according to their ferritin levels is indicated in Table 2. The classification of the patients according to their vitamin D levels is shown in Table 3. The mean vitamin D levels, in the group of very high ferritin levels (>=1.000 ng/mL) and in the group of whose ferritin levels <1.000 ng/mL, were 13.7 and 14.8, respectively and this was not statistically significant (p=0.08). The ratio of patients with thalassemia intermedia, thalassemia major and sickle cell with normal BMD according to DEXA femoral T-score was 56.25%, 35% and 39%, respectively. The ratio of patients with thalassemia intermedia, thalassemia major and sickle cell with normal BMD according to DEXA lumbar T-score was 31.25%, 7.5% and 41.25%, respectively. Table 4 presents the comparison between the vitamin D levels and BMD of all patients. When the femur- T-score, lomber T-score, femur Z-score and lomber Z-score were compared in patients with normal and low

Table 1. Demographic and laboratory data of patients

Parameter	Thalassemia intermedia mean ± SD (n=16)	Thalassemia major mean ± SD (n=40)	Sickle cell patients mean ± SD (n=46)
Mean age	29±11	25±7	31±10
Gender			
Female **Male**	9 7	18 22	23 23
Ferritin	782.08±880.39 ng/mL	1386.75±1264.94 ng/mL	921.05±996.62 ng/mL
Vitamin D	17.87±10.09 ng/mL	15.70±11.19 ng/mL	15.84±10.98 ng/mL
Femoral T-score	-0.97±1.33	-1.41±1.05	-0.88±1.98
Lumbar T-score	-1.89±1.61 p=0.028	-2.36±1.07 p=0.035	-0.80±2.31 p=0.87
Femoral Z-score	-0.5±1.43	-1.39±1.05	-0.73±2.02
Lumbar Z-score	-1.42±1.57 p=0.015	-2.31±1.08 p=0.03	-0.58±2.29 p=0.9

SD: Standard deviation

Table 2. Classification of the patients based on their ferritin levels

	Ferritin		
	Low	**Normal**	**High**
Thalassemia intermedia (n=16)	1 (6.2%)	2 (12.5%)	13 (81.2%)
Thalassemia major (n=40)	0 (0%)	2 (5%)	38 (95%)
Sickle cell patients (n=46)	1 (2.2%)	18 (39.1%)	27 (58.7%)

Low: ≤23.9 ng/mL, Normal: 23.9-336.2 ng/mL High: ≥336.2 ng/mL

Table 3. Classification of the patients based on their vitamin D levels

	Vitamin D			
	Mild deficiency	**Medium deficiency**	**Severe deficiency**	**Normal**
Thalassemia intermedia (n=16)	4 (25%)	4 (25%)	4 (25%)	4 (25%)
Thalassemia major (n=40)	5 (12.5%)	19 (47.5%)	12 (30%)	4 (10%)
Sickle cell patie nts (n=46)	3 (6.5%)	20 (43.5%)	16 (34.8%)	7 (15.2%)

Mild deficiency: 20-29.9 ng/mL, Medium deficiency: 10-19.9 ng/mL, Severe deficiency: <10 ng/mL, Normal: 30-120 ng/mL

Table 4. Comparison between vitamin D levels and bone mineral densitometry of all patients

Vitamin D	DEXA femoral T-score mean ± SD	DEXA lumbar T-score mean ± SD	DEXA femoral Z-score mean ± SD	DEXA lumbar Z-score mean ± SD
Severe deficiency (n=32)	-1.82±0.88 p=0.001	-2.5±0.94 p=0.001	-1.66±1.0 p=0.0027	-2.23±1.02 p=0.0003
Medium deficiency (n=43)	-0.84±1.88 p=0.66	-1.26±2.21 p=0.42	-0.73±1.92 p=0.62	-1.14±2.3 p=0.37
Mild deficiency (n=12)	-0.76±1.39 p=0.78	-1.35±2.14 p=0.44	-0.52±1.5 p=0.92	-1.05±1.98 p=0.53
Normal (n=15)	-0.6±1.58	-0.74±1.92	-0.46±1.57	-0.58±1.86

Mild deficiency: 20-29.9 ng/mL, Medium deficiency: 10-19.9 ng/mL, Severe deficiency: <10 ng/mL Normal: 30-120 ng/mL
SD: Standard deviation, DEXA: Dual energy X-ray absorptiometry

vitamin D levels, a statistically significant change was observed in severe deficiency patients (p=0.001, 0.001, 0.0027, 0.0003 respectively) and this was shown in Figure 1. BMD of patients with severe vitamin D deficiency was very low. There was no statistically significant change in BMD when moderate and mild vitamin D deficiency was compared with normal vitamin D levels. Table 5 shows the comparison between the ferritin levels and BMD. When the patients' ferritin values and DEXA scores were compared with high ferritin values and low and normal ferritin values, femur T-score, lomber T-score, femur Z-score, and lomber Z-score were significantly lower in those with high ferritin values (p=0.0005, 0.0002, <0.0001, 0.0002 respectively). In patients with a high level of ferritin, vitamin D levels decrease but this is not statistically significant (p=0.436).

Discussion

Previous studies reported that decreasing vertebral and femoral BMD are a major health problem in patients with thalassemia and sickle cell and more than 2/3 of these patients are affected (8,9). Nakamura et al. (10), Vupputuri et al. (11), Pirinççioğlu et al. (12) and Frisk et al. (13) reported that the prevalence of osteoporosis was 40-62% in well-managed thalassemia major; our study is consistent with these studies and we found that more than 65% of the patients with thalassemia major who underwent regular transfusion and chelation treatment had osteopenia and osteoporosis. In addition, more than half of the patients with thalassemia intermedia were affected by

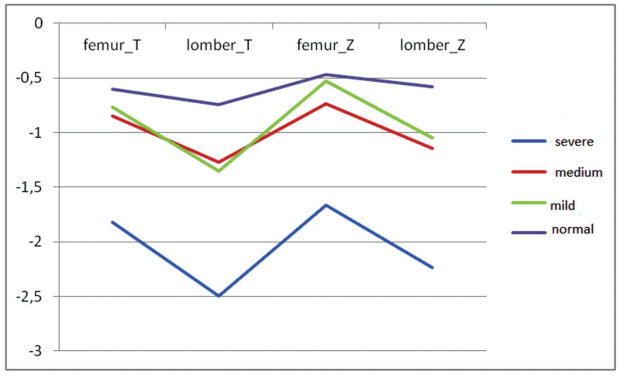

Figure 1. Association between vitamin D deficiency and bone mineral densitometry

osteopenia and osteoporosis. Osteopenia and osteoporosis defined by BMD are reported to be common in patients with sickle cell (53%-86%) (14). In our study, approximately 60% of the patients with sickle cell had osteopenia and osteoporosis.

In studies about the patients with thalassemia major, no significant association was found between vitamin D levels and BMD and there is insufficient data on this issue in patients with sickle cell (15,16). In this study, we found that vitamin D deficiency was quite common in our 3 patient groups and severe vitamin D deficiency and high ferritin levels were significantly associated with low BMD. But mild and moderate vitamin D deficiency was not significantly associated with low BMD. We think that vitamin D plays a key role in bone metabolism disorders in patients with hemoglobinopathy and this should be clarified with further studies.

The lumbar vertebrae BMD values of the patients with thalassemia were significantly lower than the femoral BMD values, which was consistent with the literature. It was argued that this was caused by bone marrow expansion due to the ineffective erythropoiesis resulting in thinning of trabecular bones such as lumbar vertebra more than the cortical bone (17). However, there was no statistically significant difference between femur and lumbar vertebrae BMD in patients with sickle cell anemia. In our study, 95% of the patients had a high ferritin level, while there was a significant association between the ferritin levels and femoral and lumbar BMD values. Ferritin levels, and the BMD were negatively correlated. There are studies in the literature reporting that there is no correlation between the serum ferritin level and BMD (18-20) while contrary to these findings, there are other studies reporting a negative relationship between the serum ferritin level and BMD (21-23). Napoli et al. (24) found that there was a negative correlation between vitamin D level, age and serum ferritin level. They made a comparison between the patients with thalassemia with low vitamin D levels and those with normal vitamin D levels and showed that patients with low vitamin D levels had higher serum ferritin and parathormon levels. Bisbocci et al. (25) found a significant reduction in the vitamin D level in parallel to the elevated ferritin. In our study, we found a negative correlation between high ferritin level and vitamin D but it was not statistically significant. In patients with sickle cell, bone loss is attributed partly to bone marrow hyperplasia and inflammation secondary to chronic anemia or bone marrow ischemia. However, recent

Table 5. Comparison between ferritin levels and bone mineral densitometry of all patients

Ferritin	Femoral T-score mean ± SD	p	Lumbar T-score mean ± SD	p	Femoral Z-score mean ± SD	p	Lumbar Z-score mean ± SD	p
Normal and low (n=24)	-0.16±2.13	**0.0005**	-0.32±2.77	**0.0002**	-0.04±2.19	**<0.0001**	-0.14±2.78	**0.0002**
High (n=78)	-1.41±1.24	-	-1.99±1.44	-	-1.26±1.31	-	-1.79±1.46	-

SD: Standard deviation

studies argue that children and adults usually have undetected severe vitamin D deficiency (26,27). Therefore, our study will shed a guiding light in this field. Our findings show that vitamin D deficiency is very common in this group and affect 84.8% of the patients with sickle cell. Moreover, four studies found very low vitamin D levels in adults with sickle cell disease and only one of these studies was a controlled study and demonstrated that the serum concentrations of vitamin D was significantly lower in adult patients with sickle cell disease than in the control group (12.6±8.7 vs 36±3.4 ng/mL) in Saudi Arabia (28). Deep vitamin D deficiency was also demonstrated in children with sickle cell disease. In a controlled study, Afro-American children with sickle cell disease in the USA had higher rates of vitamin D deficiency than the healthy Afro-American children living in the same geographical region. Malnutrition associated with low socio-economic status could not explain the prevalence of vitamin D deficiency in these children. They demonstrated the evidence that vitamin D deficiency could be a unique complication of sickle cell disease (29). Serum concentrations of vitamin D reflect the total vitamin D reservoir depending on exposure to sunlight (nearly 90% of vitamin D), diet and conversion to vitamin D from the fat storages in the liver (30). Very low concentrations of vitamin D that is common in patients with sickle cell may be associated with a few mechanisms: low synthesis on the skin (given that vitamin D was found to be low in patients with sickle cell disease compared to the healthy controls with the same skin phenotype in some studies, this is not associated only with dark skin pigmentation), decreased absorption in the intestines and impaired fat tissue metabolism. Accumulation of bilirubin on the skin due to chronic hemolysis may possibly decrease the synthesis of vitamin D from the ultraviolet B rays of the sun. Vitamin D deficiency in patients with sickle cell may also be associated with the malabsorption of this fat-soluble vitamin as also demonstrated in chronic cholestasis patients (31). In fact, black-pigmented biliary calculi caused by increased bilirubin expression and leading to low-grade biliary canal obstruction are common in these patients despite cholecystectomy (32).

Recent studies have shown that vitamin D deficiency is present in the majority of the patients with thalassemia and many factors have been suggested to explain the low serum vitamin D levels in this patient group. Potential reasons are; intestinal malabsorption of vitamin D, impaired synthesis of vitamin D by the skin because of jaundice and impaired 25 hydroxylation of vitamin D due to decreased enzyme function because of parenchymal iron deposition in liver (33,34).

In a study, although some patients were on treatment with oral vitamin D and calcium supplements at the time of measurement, only 12.4% of thalassemia major patients had normal vitamin D levels (35).

In our study, the patients who were using vitamin D or calcium supplements were excluded and only 10% of patients with thalassemia major and 25% of patients with thalassemia intermedia had normal vitamin D levels.

Study Limitations

The limitation of our study was the fact that our study was single-centered and the number of patients was not distributed homogenously between the groups. The other limitation was that vitamin D and ferritin levels could not be compared with BMD in the subgroups due to the limited number of patients. However, contrary to many studies in the literature, the significant association of severe vitamin D deficiency with BMD increases the importance of our study.

Conclusion

Severe deficiency of vitamin D and high ferritin levels may be associated with a decrease in BMD in patients with thalassemia major, intermedia and sickle cell. These patients should be screened through bone densitometry at an early age, and their bone parameters should be investigated. The efforts to provide appropriate vitamin D replacement and restore the ferritin levels to the normal range may be effective in reducing the morbidity associated with osteoporosis.

Ethics

Ethics Committee Approval: The study was approved by the Çukurova University Faculty of Medicine of Local Ethics Committee (decision no: 2014/27). All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B., İ.F.B., Concept: M.B., İ.F.B., Design: M.B., Data Collection or Processing: M.B., İ.F.B., Analysis or Interpretation: M.B., Literature Search: M.B., Writing: M.B.

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The Relationship Between Postmenopausal Osteoporosis and Autophagic Gene Polymorphisms

Postmenopozal Osteoporoz ve Otofajik Gen Polimorfizmleri Arasındaki İlişki

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Abstract

Objective: This study investigates the role of *ATG16L1* rs2241880, *ATG10* rs1864183 and *ATG5* rs2245214 gene polymorphisms, which are involved in autophagosome formation, in the susceptibility to postmenopausal osteoporosis (PMO) disease.
Materials and Methods: Hundred PMO patients and 100 healthy controls without PMO were included into the study. The distribution of the genotypes of *ATG16L1* rs2241880, *ATG10* rs1864183 and *ATG5* rs2245214 polymorphisms in these subjects were analyzed using the TaqMan 5´-exonuclease allelic discrimination assay.
Results: The T allele was detected more frequent among patients with osteoporosis (53%) of the *ATG10* rs1864183 polymorphism. C allele in *ATG16L1* rs2241880 polymorphism in the group of patients with osteoporosis was observed more frequent (56.5%). Besides, the G allele of the *ATG5* rs2245214 polymorphism was identified more common in PMO (34%) than in control group. However, no significant difference were detected in genotype and allele frequencies in terms of these polymorphisms between the patient and the control groups (p>0.05).
Conclusion: In summary, the results of our study do not support the hypothesis that *ATG16L1* rs2241880, *ATG10* rs1864183 and *ATG5* rs2245214 polymorphisms influence the predisposition for osteoporosis in postmenopausal women.
Keywords: Autophagy, gene polymorphism, postmenopausal osteoporosis

Öz

Amaç: Bu çalışmada otofajik mekanizmada otofagozom oluşumunda yer alan *ATG16L1* rs2241880, *ATG10* rs1864183 ve *ATG5* rs2245214 gen polimorfizmlerinin postmenopozal osteoporoz (PMO) hastalığına yatkınlıktaki rolü incelenmiştir.
Gereç ve Yöntem: Bu çalışmaya 50 yaş ve üzeri PMO'su olan 100 hasta ve PMO gelişimi olmayan 100 kontrol grubu alınmıştır. *ATG16L1* rs2241880, *ATG10* rs1864183 ve *ATG5* rs2245214 polimorfizmlerinin genotiplendirmesi amacıyla polimorfik dizileri çoğaltmak için diziye özgü primerler ve her polimorfizmin her iki alelini saptamak için TaqMan 5´-ekzonükleaz alelik diskriminasyon yöntemi kullanılmıştır.
Bulgular: *ATG10* rs1864183 polimorfizminin osteoporozlu (%53) hastalarda T aleli daha sık saptanmıştır. Osteoporozlu hasta grubunda *ATG16L1* rs2241880 polimorfizmindeki C aleli daha sık görülmüştür (%56,5). Ayrıca, *ATG5* rs2245214 polimorfizminin G aleli, PMO'da (%34) kontrol grubuna göre daha yüksek olarak tanımlanmıştır. Ancak genotip ve alel frekanslarında hasta ve kontrol grupları arasındaki bu polimorfizmler açısından anlamlı fark saptanmamıştır (p>0,05).
Sonuç: Özetle, çalışmamızdaki sonuçlar *ATG16L1* rs2241880, *ATG10* rs1864183 ve *ATG5* rs2245214 polimorfizmlerinin postmenopozal kadınlarda osteoporoza yatkınlık sağlayabileceği hipotezini desteklememektedir.
Anahtar kelimeler: Gen polimorfizmi, postmenopozal osteoporoz, otofaji

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Introduction

According to the World Health Organization, Osteoporosis is a systemic skeletal disease that is characterized by low bone mass, decreased bone strength, leading to increased microarchitectural structure and quality of bone tissue together with an increase in the risk of fractures (1). Osteoporosis is a metabolic bone disease that causes an important public health problem in terms of the incidence of osteoporosis fractures associated with morbidity and mortality with the increase of the aging population in our country as well as all over the world (2). The disease progresses silently until a secondary disease like cardiovascular disease or fractures resulting in mortality (3). In the FRACTURK study, which examined the epidemiology of osteoporosis in Turkey in recent years, the prevalence of osteoporosis in the femoral neck was determined to be 7.5% in men over the age of 50, while the women was 33.3% (4). Hip fractures are the ones that have the highest economic burden and are mortal among other osteoporotic fractures. In the Turkish population, the probability of hip fracture in individuals aged 50 and over is 3.5% in men and 14.6% in women for the rest of their life (5).

Osteoporosis is a multifactorial disease that is affected by genetic, hormonal, nutritional factors and lifestyle (6,7). Peak bone mass is reached in adult life, and both men and women begin to lose more or less bone mass at this point depending on the combination of internal and external factors (8,9). This process can become worse with the presence of other chronic diseases like immobilization (10), long-term corticosteroid therapy (11), estrogen deficiency (12), aging (13) and diabetes, especially for postmenopausal women.

Although estrogen deficiency in postmenopausal women is considered to be the main reason for bone loss and osteoporosis, studies showed that it is one of the most important factors contributing to bone loss caused by aging and increased oxidative stress in bone tissue (14,15).

Autophagy is a catabolic process that degradation of the cellular content occurs lysomally, which is stored by a double membrane vesicle called autophagosome; thus, cells maintain homeostatic functions such as protein breakdown and organelle turnover process. Under physiological conditions, although autophagy is responsible for the removal of damaged or unnecessary organelles, under pathological conditions, it helps to redistribute the intracellular nutrients to cover the energy requirement. In this way, it controls the energy and chemical homeostasis of each cell and various types of tissues, including bones (16). Recent studies have shown that autophagy plays an important role in remodelling and differentiation of the stem cells, so that the relation between autophagy and bone metabolic disease pathogenesis has attracted a lot of interest (17).

In the literature, studies on the relation between autophagy-related gene (*ATG*) polymorphisms and osteoporosis are very limited. In this study, our purpose was to examine the effect of polymorphisms in genes involved in the formation of autophagosome in the autophagic mechanism on the risk of developing postmenopausal osteoporosis (PMO). In this context, the role of *ATG16L1* rs2241880, *ATG10* rs1864183 and *ATG5* rs2245214 gene polymorphisms in the susceptibility to PMO disease was investigated.

Materials and Methods

Subjects

A hundred postmenopausal osteoporosis patients aged 50 years and over, and 100 control individuals without the development of postmenopausal osteoporosis, who referred to SANKO University, Sani Konukoğlu Practice and Research Hospital, Clinic of Physical Medicine and Rehabilitation in the last 1 year, were included in the study. Individuals who had early menopause, malabsorption, major gastrointestinal operation, metabolic bone diseases, hyper and hypothyroidism, hormone replacement therapy, and also, individuals using antiosteoporosis and active vitamin D3 medications that could affect bone and calcium metabolism were excluded from the study.

The risk assessment of the participants for fracture risks was examined with the dual energy X-ray absorptiometry device (GE-Lunar DPX) and standard protocol was used as bone mineral density (BMD) (g/cm^2) in the femur neck and lumbar spinal area (18). SANKO University Clinical Research Ethics Committee of approved the study protocol (decision no: 05, date: 24.07.2018). Informed consents were obtained from all participants.

DNA Isolation and Polymorphism Genotyping

Genomic DNA was extracted from 5 peripheral blood samples of 200 individuals according to the protocol recommended by the manufacturer. Genotypings of *ATG2B* rs3759601, *ATG16L1* rs2241880, *ATG10* rs1864183 and *ATG5* rs2245214 polymorphisms were performed using TaqMan 5´-exonuclease allelic discrimination assays that contain sequence-specific forward and reverse primers to amplify the polymorphic sequences and two probes labeled with VIC and FAM dyes to detect both alleles of each polymorphism (19). Polymerase chain reaction (PCR) reactions were carried out using TaqMan universal PCR Master Mix following instructions in a Step-One Plus Real-time PCR system. In the application of this method, Real-time PCR device in the Department of Biology of Gaziantep University Faculty of Science was used. The autophagic gene polymorphisms and locations that were examined are given in Table 1.

Table 1. Autophagy polymorphisms analyzed in the study

SNP	SNP ID	Base change	SNP	Chromosomal location
ATG16L1	rs2241880	T>C	T300A	2
ATG10	rs1864183	C>T	T212M	5
ATG5	rs2245214	C>G	Intronic	10

SNP: Single nucleotide polymorphism

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). Categorical data were analyzed by Pearson chi-square test and Fisher's exact test. The normality assumptions were controlled by the Shapiro-Wilk test. The differences between the two groups were evaluated with Student's t-test for normally distributed data, or with Mann-Whitney U test for non-normally distributed data. Data are expressed as n (%), mean ± standard deviation (range) or median (range), as appropriate. P values <0.05 were considered statistically significant.

Results

Demographic Characteristics and Bone Mineral Density Status of Participants

The baseline characteristics of the study population are presented in Table 2. As expected, the body mass index, BMD values of the lumbar spine (L1-L4), femoral neck and total hip showed significant differences between patient and control groups.

Table 2. Comparison of clinical characteristics between groups

	Control (n=100)	Patients (n=100)
Age	61.08±7.13 (50-76)	64.62±7.16 (50-78)*
BMI	32.46 (21.94-346.81)	28.5 (17.75-41.12)*
Habitual smoking		
Yes	5 (8.8)	14 (14.1)
No	52 (91.2)	85 (85.9)
Total L1-L4	-0.4 (-2.3-2.9)	-2.5 (-4.7-0.5)*
Total L2-l4T	-0.4 (-2.3-3.6)	-2.5 (-5.1-3.2)*
Total femur T	-0.2 (-2.4-2.8)	-1.75 (-6.9-0.7)*
Total neck T	-0.7 (-2.3-10)	-1.8 (-5-2)*
Presence of fractures		
Yes	6 (11.5)	37 (38.9)*
No	46 (88.5)	58 (61.1)

Data are presented as n (%), mean ± standard deviation (range), median (range). *Significant p-values are represented
BMI: Body mass index

ATG10, *ATG16L1* and *ATG5* Genotypes and Allele Distributions

The genotypic frequencies and the result of the association analysis of *ATG10* rs1864183, *ATG16L1* rs2241880 and *ATG5* rs2245214 polymorphisms in PMO and controls are summarized in Table 3. The distribution of allelic frequencies for *ATG10*, *ATG16L1* and *ATG5* polymorphisms are shown in Table 4.

The T allele of the *ATG10* polymorphism was more common among patients with osteoporosis (53%) than in normal controls (51%). C allele in *ATG16L1* rs2241880 polymorphism in the group of patients with osteoporosis was observed more frequent (56.5%) than in control group (55%). Besides, the G allele of the *ATG5* rs2245214 polymorphism was identified more common in PMO (34%) than in control group (29.5%). However, no significant difference was detected in genotype and allele frequencies in terms of these polymorphisms between the patient and control groups (p>0.05) (Table 4).

Moreover, among the studied groups, the effect of autophagy gene polymorphisms on the risk of developing PMO was

Table 3. Genotypic frequencies of autophagy genes polymorphisms among cases and controls

	Control	Patients	p
ATG5			
CC	42 (42%)	48 (48%)	0.599
CG	48 (48%)	45 (45)%	-
GG	10 (10%)	7 (7%)	-
ATG10			
CC	23 (23%)	25 (25%)	0.926
CT	48 (48%)	48 (48%)	-
TT	29 (29%)	27 (27%)	-
ATG16L1			
TT	22 (22%)	20 (20%)	0.604
TC	43 (43%)	50 (50%)	-
CC	35 (35%)	30 (30%)	-

Data are presented as n (%). Pearson chi-square test.

Table 4. Allele frequencies of autophagy gene polymorphisms among cases and controls and the association with postmenopausal osteoporosis

SNP	Allele	Patients	Controls	p
ATG10 rs1864183	C	94 (47%)	98 (49%)	0.764
	T	106 (53%)	102 (51%)	
ATG16L1 rs2241880	T	87 (43.5%)	90 (45%)	0.840
	C	113 (56.5%)	110 (55%)	
ATG5 rs2245214	C	132 (66%)	141 (70.5%)	0.390
	G	68 (34%)	59 (29.5%)	

Data are presented as n (%). Pearson chi-square test

evaluated and correlated with bone parameters. No significant differences were found in the analysis of the different clinical forms and the genotypic distributions of the polymorphisms included in our study.

Discussion

Autophagy is a catabolic process that is responsible for the fragmentation and recycling of cellular components like unnecessary organelles and proteins. The process begins with the formation of "autophagosome" merged with lysosomes and hydrolase that is responsible for disrupting the content of the target (20,21). At least 18 *ATG* genes (related to autophagy) were identified in the formation of autophagosome (22). It was shown in recent years that proteins that are involved in bone destruction and construction of autophagy play important roles in regulating osteoclastogenesis (23,24) but the effect of autophagic genes in osteoporosis is not yet unexplained completely. It has also been shown that autophagy plays critical roles in the onset and progression of pathological conditions that are characterized by many metabolic disorders, including both physiological process and metabolic disease (25), cancer (26), neurodegenerative diseases (27), aging (28) and bone-related diseases (29).

In vitro studies demonstrated that autophagy increases oxidative stress in osteoblast-like cells and stimulates apoptosis in these cells with pharmacological inhibition of autophagy (30). Unlike this, in osteoblast-like cell cultures, the induction of autophagy reduces oxidative stress and inhibits apoptosis (31). It was reported that estrogen inhibits osteoblast apoptosis *in vitro* and induces autophagy in these cells (32).

Studies revealed that autophagy plays an important role in osteoclast-mediated bone resorption. Gene deletions (*ATG5*, *ATG7, ATG4B* and LC3) that encode key proteins in the formation of autophagosome reduced bone resorption and increased bone volume in mice after ovariectomy (in the osteoclast brush border) (33,34). Some authors suggested that autophagy inhibition in osteoclasts might serve as a possible therapeutic mechanism against bone diseases, which means an excessive increase in bone resorption. It was observed that pharmacological and genetic inhibition of autophagy prevented bone loss in mice caused by ovariectomy or glucocorticoid treatment, reducing osteoclast genesis and bone resorption (35).

Aging is among the most closely related factors with the onset of osteoporosis with the changes in hormones and increased oxidative stress (36). Parallel to this, the autophagic activity level in many cells decreases during aging, more pronounced in osteocytes and osteoclasts. This hypothesis was supported by studies conducted on many animal models (37,38).

It was shown in previous studies that autophagy modulation has therapeutic potential in the prevention and treatment of bone-related diseases. However, the modulation of autophagic activity may not be enough alone to affect the overall remodeling process of the skeletal system. And, larger and randomized controlled clinical studies are needed to be conducted on humans to validate the possible relation between autophagic dysfunction and osteoporosis and develop potential pharmacological treatments for bone diseases.

In the literature, there are several studies in which *ATG16L1* was investigated for the effect of polymorphism on the predisposition to autoimmune diseases, and it was found that Crohn's disease, ulcerative colitis, palmoplantar pustulosis play roles in this respect (39-41). High *ATG5* levels were detected in autoimmune demyelination and multiple sclerosis in mice model and humans (42), *ATG* expression in synovial tissue, between disease activity and severity in patients with active rheumatoid arthritis relations were found to be significant (43).

In another study, it was reported that GC genotype has protective effects on the development of small-cell lung cancer in *ATG5* rs2245214 gene polymorphism (44). In a study that was conducted in Spain a relation was detected between *ATG10* rs1864183 and laryngeal cancer, *ATG16L1* rs241880 and oral carcinoma development. Also, in Spain, a study examined the effects of the same autophagic gene polymorphism in Paget's disease, which is the most common metabolic bone disease after osteoporosis. It was shown that carrying *ATG16L1* rs2241880 and *ATG5* rs2245214 polymorphisms were associated with increased risk of developing Paget's disease, and *ATG10* rs1864183 polymorphism was associated with increased Paget's disease risk, and carrying T allele of *ATG10* rs1864183 polymorphism was associated with reduced risk (45).

This study is the first that examined *ATG16L1* rs2241880, *ATG10* rs1864183 and *ATG5* rs245214 gene polymorphisms in PMO women. No significant relations were detected between PMO patients and control groups in terms of these polymorphisms. As a result, the data of this study showed that the polymorphisms might not contribute to the predisposition of PMO. A future study is planned to be conducted in different populations and larger sampling sizes.

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Ethics

Ethics Committee Approval: SANKO University Clinical Research Ethics Committee of approved the study protocol (decision no: 05, date: 24.07.2018).

Informed Consent: Informed consents were obtained from all paticipants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.T., S.G., Ö.A., A.A., Concept: T.T., E.P., F.Ö.G., Design: E.P., F.Ö.G., Data Collection or Processing: T.T., E.P., Analysis or Interpretation: E.P., Literature Search: T.T., E.P., Writing: T.T., E.P., F.Ö.G.

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Gebeliğin Tetiklediği Kalçanın Geçici Osteoporozu Tedavisinde K2 Vitamininin Etkinliği: Olgu Sunumu

The Efficacy of Vitamin K2 in the Treatment of Pregnancy-associated Transient Osteoporosis of the Hip: A Case Report

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Öz

Kalçanın geçici osteoporozu, akut başlangıçlı kalça ağrısı, antaljik yürüme ve eklem hareket kısıtlılığı ile karakterize etiyolojisi bilinmeyen, nadir görülen ve kendi kendini sınırlayan klinik bir durumdur. Sıklıkla semptomlar birkaç ay (6 ila 8 ay) içerisinde kendiliğinden geriler, dolayısıyla konservatif tedavi en iyi tedavi yaklaşımıdır. Cerrahi dekompresyon sadece konservatif tedaviye dirençli hastalar için uygulanır. Bu makalede, gebeliğin tetiklediği kalçanın geçici osteoporozu olan ve konservatif tedaviye K2 vitamini eklendiğinde tatmin edici iyileşme gösteren 32 yaşında bir hasta sunulmuştur. K2 vitamini, kalçada geçici osteoporozu olan ve daha önce tarif edilen konservatif tedavi yöntemlerine yeterince yanıt vermeyen hastalarda cerrahi müdahaleden önce bir tedavi seçeneği olarak düşünülebilir.
Anahtar kelimeler: Kalçanın geçici osteoporozu, tanı, tedavi, K2 vitamini

Abstract

Transient osteoporosis of hip is an uncommon, self-limiting clinical condition of unknown etiology characterized by an acute onset of hip pain, an antalgic gait and limited ranges of motion. Frequently this is followed by spontaneous regression of the symptoms within a few months (6 to 8 months), therefore conservative treatment is the best therapeutic strategy. Surgical decompression are performed only for the conservative therapy resistant patients. In this report, it is presented a 32-years old female who had pregnancy-associated transient osteoporosis and showed satisfactory improvement with conservative treatment via adding vitamin K2. Vitamin K2 may be considered as a treatment option before surgical intervention in the patients with transient osteoporosis of the hip who did not adequately respond to previously described conservative treatment modalities.
Keywords: Transient osteoporosis of hip, diagnosis, treatment, vitamin K2

Giriş

Kalçanın geçici osteoporozu (KGO), akut başlangıçlı kalça ağrısı, antaljik yürüme ve eklem hareket kısıtlılığı ile karakterize etiyolojisi bilinmeyen, nadir görülen ve kendi kendini sınırlayan klinik bir durumdur. Genellikle, 4. veya 5. dekattaki erkeklerde (olguların üçte ikisi) ve gebeliğin 3. trimesterindeki (ortalama görülen gebelik haftası 32 hafta) veya erken doğum sonrası dönemdeki kadınlarda (olguların üçte biri) görülür. İlgili ekleme sınırlı femur başı ve boynunun radyografik osteopenisi ile kemik veya eklem patolojisinin tanınabilir başka bir nedeninin olmamasıyla ilişkilidir (1,2). Sıklıkla semptomlar birkaç ay (6 ila 8 ay) içerisinde kendiliğinden geriler, dolayısıyla konservatif tedavi en iyi tedavi yaklaşımıdır (3). Bu makalede, daha önce tarif edilen konservatif tedavi yöntemlerine orta derecede yanıt veren ve mevcut tedavilere K2 vitamini eklendiğinde semptomları tamamen iyileşen, gebeliğin tetiklediği KGO olan bir olgu sunulmuştur.

Olgu Sunumu

Bir hafta önce sezaryen doğum ile doğum yapan 32 yaşında bir kadın hasta, şiddetli çift taraflı kalça ağrısı ve yürüme güçlüğü şikayeti ile polikliniğe başvurdu. Hastanın, ikinci gebeliğinin 24. haftasında sol tarafta başlayan, bir hafta sonra sağ tarafta da ortaya çıkan kalça ağrısının giderek arttığı ve gebeliğin 28. haftasında yürüyemez hale geldiği öğrenildi. Bu şikayet ilk hamileliği sırasında ortaya çıkmamıştı. Hastanın takip edildiği kadın hastalıkları bölümünde gebeliğinin 32. haftasında çekilen bilateral kalça manyetik rezonans (MR) incelemesinde, bilateral femur başı ve boynunun yaygın kemik iliği ödemi tespit edilmişti (Şekil 1). Hastaya KGO tanısı konulup şiddetli ağrı ve hareket kabiliyetinde

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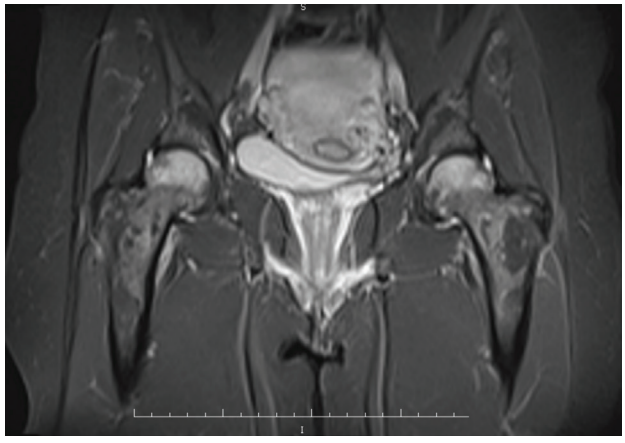


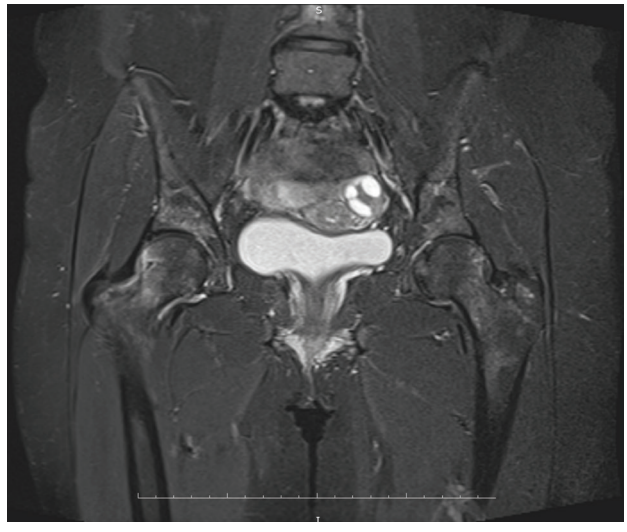
Şekil 1. Olguya ait tedavi öncesi MR görüntülemede bilateral femur başı ve boynunda diffüz kemik iliği ödemi
MR: Manyetik rezonans

azalma nedeniyle 33. gebelik haftasında sezaryen doğum yapılmıştı. Hasta buradan ortopedi bölümüne yönlendirilmiş ve hastaya sadece istirahat önerilmişti. Hasta polikliniğe başvurduğunda bilateral kalça hareketleri belirgin olarak ağrılıydı ve fizik muayenede her yöne kısıtlıydı. Düz bacak kaldırma ve Laseque testleri negatif, FABER (kalçanın fleksiyon-abdüksiyon-dış rotasyonu) ve FADIR (kalçanın fleksiyon-addüksiyon-iç rotasyonu) testleri pozitifti. Nörolojik muayenesinde özellik yoktu. Hastanın ambülasyonu çok kısıtlanmıştı ve kişi desteği ile ayakta durabiliyor ve yürüyebiliyordu. Hastanın ağrısı yüklenme ve yürümekle artarken dinlenmekle azalıyordu. Travma, enfeksiyon, kronik hastalık, sigara ve alkol kullanım öyküsü yoktu. Vizüel Analog skala (VAS) 0 (ağrı yok) ile 10 (şiddetli ağrı) arasında değişen bir aralıkta hastanın ağrı seviyesini ölçmek için kullanılan bir anket formudur. Hastanın ağrı değerlendirmesi için kullanılan VAS skoru 10/10 idi. Laboratuvar testleri; tam kan sayımı, eritrosit sedimantasyon hızı, romatoid faktör, C-reaktif protein, Brucella Aglütinasyon testi, tiroid, böbrek ve karaciğer fonksiyon testleri, serum kalsiyum, fosfor, magnezyum, alkalen fosfataz, 25(OH) vitamin D3 ve paratiroid hormonu (PTH) normal sınırlardaydı. Ayrıca, kemik formasyon-rezorpsiyon markerleri [karboksile osteokalsin (OK), serum tartata dayanıklı asit fosfataz-5b ve idrar tip I kollajen N-terminal telopeptid] normal sınırlardaydı. Kemik mineral dansitometrisinde (BMD) femur boyun T-skoru -2,7 ve ortalama L1-L4 T-skoru -2,1 idi. Hastaya kombine medikal (haftada bir kez 70 mg/alendronat, kalsiyum 600 mg/gün, vitamin D3 880 IU/gün, sadece iki hafta boyunca asemetazin 90 mg/gün) ve fizik tedavi (hotpack, transkutanöz elektriksel sinir stimülasyonu, ultrason, ağrılı dönemde eklem hareket açıklığı egzersizleri/3 hafta ve sonrasında daha az ağrılı dönemde abdüktör güçlendirme egzersizleri (lateral bacak kaldırma: yan yatarak bacağın yukarı kaldırılıp indirilmesi ve yapabiliyorsa pelvik lift egzersizi: ayaktayken bir eliyle sandalyeye tutunarak bacağın yana doğru açılıp tekrar kapatılması/3 hafta) başlanıldı. Bunlara ek olarak, istirahat ve klinik düzelme olana kadar zorunlu mobilizasyon durumlarında destek amaçlı kullanılmak üzere bilateral koltuk değneği ile yürümesi önerildi. Ayrıca ağrısı geçene kadar koltuk değneği kullanması tavsiye edildi. Bir aylık takipte hastanın VAS skoru 5/10 idi ve hastanın şikayetleri orta derecede azalmıştı, ancak hasta sadece 15 dakika süresince ayakta durabiliyordu. Bu durumun günlük yaşam aktivitelerini olumsuz yönde etkilediğini belirtti. Bu nedenle hastanın medikal tedavisine K2 vitamini (menaquinone-7, üç ay boyunca 100 µg/gün) ilave edildi. İki aylık takipte hastanın VAS skoru 1/10 idi ve hastanın kalça ağrısı belirgin şekilde azalmıştı ve sadece uzun yürüyüşlerde ortaya çıktığını söyledi. Tedavi başlangıcından 3 ay sonra çekilen MR görüntülemesinde belirgin derecede iyileşme tespit edildi (Şekil 2). Üçüncü ve 4. aylık takiplerde hasta tamamen düzeldi ve normal yürüyüş paterni elde edildi. Altı aylık takipte BMD belirgin bir şekilde düzelmişti (femur boyun T-skoru -1 ve ortalama L1-L4 T-skoru -1,1 idi). Bir yıllık takipte hastada herhangi bir şikayet olmadı. Hastadan sözlü ve yazılı onam alınmıştır.

Tartışma

KGO, akut başlangıçlı eklem ağrısı ve takibinde lokal osteopeni ve spontan iyileşme ile karakterize nadir görülen ve kendini sınırlayan bir sendromdur. Literatürde, geçici demineralizasyon, gezici osteoliz, kalçanın refleks sempatik distrofisi ve geçici kemik iliği ödemi gibi diğer eş anlamları bildirilmiştir (1). Genellikle tek taraflı semptomların akut başlangıcı ile ortaya çıkarken, birkaç olguda bilateral ya da ikinci gebelikte rekürrens olabilir. Ayrıca primigravidalarda da yaygın olarak görülme eğilimindedir (4). Kalça en sık etkilenen eklem olmasına rağmen geçici osteoporoz diz, ayak, ayak bileği ve daha az sıklıkla omuz, bel, dirsek, el bileği ve eli de etkileyebilir (5).

Radyografik ve laboratuvar bulguları sıklıkla belirgin değildir, ancak MR görüntülemesi kemik iliği ödeminin varlığını gösterir (6). Ayrıca, MR görüntüleme hastalığın ilerlemesini izlemek ve



Şekil 2. Olguya ait tedaviden 3 ay sonraki MR görüntülemede bilateral femur başı ve boynunda diffüz kemik iliği ödeminde belirgin azalma
MR: Manyetik rezonans

diğer hastalıkları ayırt etmek için de kullanılmaktadır. KGO ayırıcı tanıları arasında avasküler nekroz (AVN), enflamatuvar eklem hastalıkları, femur boyun kırığı, refleks sempatik distrofi (RSD), osteomiyelit, septik artrit, pigmentli villonodüler sinovit, sinovyal kondromatozis ve maligniteler vardır. Erken evrede, KGO ve AVN arasında ayırıcı tanı zor olabilir, ancak KGO'da diffüz bir zonda geçici bir iskemi ile, daha kısıtlı bir bölgede daha şiddetli ve uzun süreli iskemiye sahip AVN'den ayrımı yapılabilir (7).

KGO'nun etiyolojisi ve patogenezi belirsizdir. Başlatıcı bir olay (travma, enfeksiyon, enflamasyon, dejeneratif süreç, iskemik yaralanma, neoplazi, cerrahi, ilaçlar, metabolik ve nörolojik bozukluklar gibi) süreci tetikler ve kemik dönüşümünde artışa, venöz hipertansiyona ve/veya mikrofraktürlere neden olur. Gebelik, bilinen bir risk faktörüdür (örneğin; laktasyonla PTH ile ilişkili peptit salgısının artması, fetal kemiğe ve anne sütüne kalsiyum beslemesinin artması, doğumdan sonra östrojenin azalması, hamilelikten önce mevcut osteopeni). Steroid alımı, sigara, alkolizm, hemoglobinopatiler, hipotiroidizm, hipofosfatazi, osteogenezis imperfekta, fiziksel hareketsizlik, düşük testosteron, yetersiz kalsiyum ve düşük D vitamini (25-OH kolekalsiferol) gibi diğer risk faktörleri de kabul edilmiştir (8). Genetik yatkınlık, obturator sinirin sıkışması, travmatik olmayan refleks sempatik distrofi, kemik medüller hipertansiyonu ve küçük damar iskemisi, viral enfeksiyon ve metabolik, kimyasal veya hormonal faktörler de dahil olmak üzere çeşitli lokal ve sistemik teorilerin bu duruma katkıda bulunduğu öne sürülmüştür (3). Kısaca, geçici iskemik bir olaydan kaynaklanan KGO, geçici ve geri dönüşümlü kemik yaralanmasından (spontan rezolüsyon) geniş avasküler kemik ölümüne kadar değişen bir klinik spektrumda bulunabilir (9).

Sıklıkla semptomlar birkaç ay (6 ila 8 ay) içerisinde kendiliğinden geriler, dolayısıyla konservatif tedavi (örneğin; analjezikler non-steroid anti-enflamatuvar ilaçlar (NSAİİ), kortikosteroidler, kalsitonin, bifosfanatlar, iloprost, uzun süreli istirahat, kısıtlı ağırlık taşıma, eklem hareket açıklığı ve kalça abdüktör güçlendirme egzersizleri) en iyi tedavi yaklaşımıdır. Cerrahi dekompresyon sadece konservatif tedaviye dirençli hastalar için uygulanır (10,11).

Tedavide amaç, ağrının hemen giderilmesi, etkilenen eklemin fonksiyonel iyileşmesinin hızlandırılması, mikrofraktürlerin azaltılması ve patolojik stres kırıklarının önlenmesidir. Ağrıyı gidermede basit analjezikler, NSAİİ'ler ve tramadol kullanılmaktadır. Kortikosteroidler hastalığın süresini ve ilerlemesini değiştirmez (12). Kalsitonin ve bifosfonatların faydalı etkileri olduğu bildirilmiştir. Ağrının hızla giderilmesi ve kemik iliği ödeminin azaltılması için bifosfonatlar (alendronat, zoledronat, ibandronat, pamidronat, klodronat ve neridronat gibi) önerilmektedir (13). Antiresorptif ajanların KGO içindeki etki mekanizması bilinmemektedir, ancak bu ajanlar, örneğin aktif T hücreleri tarafından pro-enflamatuvar sitokin üretiminin azaltılması gibi anti-enflamatuvar özellikleri sayesinde etkili olabilirler. Alternatif olarak, osteoblast apopitozunu önleyerek ve böylece kemik oluşumunu teşvik ederek etki edebilirler (3,14,15). Bir *in vitro* çalışmada, alendronatın kemik kaybını ve mekanik hiperaljeziyi önlediği (16), bu nedenle hastaların tedavisinde alendronatın tercih edilebileceği önerilmiştir. Öte yandan, BMD'de bifosfonatlarla iyileşme tedavinin ilk yılında sağlanmış olmasına rağmen, uzun vadede BMD artışı plato göstermektedir (17). Bu nedenle bu makalede, bifosfonat tedavisi ile yeterli bir yanıt alınamadığı için hastanın tedavisine K2 vitamini eklenmiştir. İnsan müdahale çalışmalarında K2 vitamininin kemik metabolizmasını değiştirebileceği gösterilmiştir. Osteoblastların ürettiği OK, kalsiyumun kan dolaşımından alınmasına ve kemik matriksine bağlanmasına yardımcı olur, kemiğin mineral bileşenine bağlanma kabiliyeti sayesinde kemik mineralizasyonunu etkiler, bu da iskeleti daha güçlü ve kırılmaya daha dayanıklı hale getirir. Yeni yapılan OK etkin değildir ve tamamen aktif hale gelmesi ve kalsiyumu bağlaması için K2 vitaminine ihtiyaç duyar. OK'nin molekülünde glutamik kalıntıları vardır ve bunlar K2 vitaminine bağlı bir karboksilazın aracılık ettiği translasyon sonrası modifikasyon ile γ-karboksiglutamik aside dönüştürülür (18). Çift kör, randomize kontrollü bir çalışmada, kemik sağlığının artmasına neden olan OK-γ-karboksilasyonu artırmak için günlük ≥100 µg günlük K2 vitamini alımının yeterli olacağı önerilmiştir (19), bu nedenle hastanın tedavisinde günlük 100 µg K2 vitamin dozu kullanıldı ve bu doz hastanın şikayetlerini iyileştirmek için yeterli olmuştur. Ayrıca, daha önceki bir olgu sunumunda, K2 vitamini multiple vertebra fraktürü olan gebeliğin tetiklediği KGO tedavisinde kullanılmış ve K2 vitamininin BMD'yi artırmada ve de novo fraktürleri önlemede etkili olabileceği belirtilmiştir (20). Diğer bir olgu sunumunda, D3 ve K2 vitaminlerinin kombinasyon tedavisinin, gebelik ve laktasyonla ilişkili osteoporoz hastalarında BMD'de iyileşme sağladığı bulunmuştur (21). Bu makalenin sonucuna göre (sadece patolojik stres kırığı olan hastaların tedavisinde değil), daha önce tarif edilen konservatif tedavi yöntemlerine tam olarak yanıt vermeyen KGO'lu hastalarda K2 vitamini cerrahi girişimden önce bir tedavi seçeneği olarak düşünülebilir.

Sonuç olarak, KGO ile K2 vitamini arasındaki korelasyonu destekleyecek yeterli kanıt bulunmamasına rağmen, K2 vitamini ile osteoporoz ve patolojik fraktür arasındaki ilişkiye dayanarak, iyileşme süresini kısaltmak ve gereksiz cerrahi girişimleri azaltmak için K2 vitamini potansiyel bir terapötik seçenek olarak göz önünde bulundurulabilir.

Etik

Hasta Onayı: Hastadan sözlü ve yazılı onam alınmıştır.

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Paget's Disease Diagnosed on Cranial and Sacroiliac Involvement in Contrast to Normal Alkaline Phosphatase Levels

Kraniyal ve Sakroiliak Tutulum ile Tanı Konulan Alkalen Fosfatazın Normal Olduğu Paget Hastalığı

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Abstract

Paget's disease of bone is characterized by a chronic focal bone remodelling disorder, which is usually detected incidentally during routine imagining examinations. Although the measurement of total serum alkaline phosphatase usually provides a general indication of bone turnover in Paget's disease, about 10-15% of patients present with alkaline phosphatase levels within the normal range. The treatment of symptomatic forms relies on bisphosphonates that are efficient in reducing the bone turnover. Here, I present the case of an 80-year-old man suffering from chronic low back pain, and diagnosed as Paget's disease, with normal serum alkaline phosphatase and bone-specific alkaline phosphatase levels.

Keywords: Paget's disease, alkaline phosphatase, bone scintigraphy

Öz

Kemiğin Paget hastalığı, genellikle radyolojik incelemelerde tesadüfen tespit edilen kronik fokal kemik yapılanma bozukluğu ile karakterizedir. Her ne kadar serum total alkalen fosfataz Paget hastalığında genel bir kemik döngüsü belirteci olsa da, hastaların yaklaşık %10-15'inde referans aralığında bulunur. Semptomatik formların tedavisi, kemik döngüsündeki yükselmeleri azaltmakta etkili olan bifosfonatlar ile sağlanır. Burada kronik bel ağrısı olan ve normal serum alkalen fosfataz ve kemik spesifik alkalen fosfataz düzeyleri ile Paget hastalığı tanısı alan 80 yaşında bir olgu sunulmaktadır.

Anahtar kelimeler: Paget hastalığı, alkalen fosfataz, kemik sintigrafisi

Introduction

Paget's disease of bone (PDB) is a nonmalignant, chronic and focal skeletal disorder that mainly presents in elderly population and is the second most common metabolic bone disease after osteoporosis affecting individuals. Although the etiology of Paget's disease is enigmatic, the role of viruses (paramyxovirus and measles) and genetics remain debated in the literature. It is more common in European ancestry and man is affected more as compared to woman (1-3).

Paget's disease begins with an increase in osteoclastic bone resorption, followed by an increase in osteoblastic activity and consequently lamellar bone formation in the mosaic structure. Normal bone structure is replaced by disorganized, hypertrophic and weak bone nature that is more fibrous and less dense with irregular trabecular pattern. It usually effects the bones focal (monostotic), but diffuse involvement (polyostotic) can also be seen depending on the number of bone involved. There may be involvement of almost every bone but there is a predilection for some skeletal sites (pelvis, spine, sacrum, skull, femur and tibia) (4,5).

Case Report

An 80-year-old male patient complained of a low back pain for the last 4 years and 8 weight loss in the last 3 months. His pain did not change with the movement and continued at night. No fever was detected while sweating accompanied by night pain. He had hypertension for 20 years and memory loss for a year. There was no history of diabetes, tuberculosis, malignancy, inflamatory arthritis or any other significant diseases. He also stated that he had taken calcium and vitamin D for a few months. On physical examination, the patient had kyphosis of the back, movements in the spine were limited

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and painful. Direct compression of the sacroiliac joint on the left was positive while other joint evaluations were normal. Some of her blood tests were: serum alkaline phosphatase (ALP): 78 (40-150)) U/L, 25-hydroxy-vitamin D3: 156.5 (10-60) µg/L, bone-specific ALP: 21.0 (3.10- 22.40) µg/L, urinary deoxypyridinoline: 8.05 nM/mM creatinine ratio and brucella agglutination test was negative. Other laboratory evaluations, parathyroid and thyroid hormone levels, calcium and tumor marker levels were normal but blood urea and creatinine levels were slightly elevated.

Cranial X-rays showed diffuse sclerosis and calvarial thickening while pelvic radiography revealed sclerosis of the left sacroiliac joint (Figure 1). No pathology was observed on chest X-ray.

Magnetic resonance imaging showed sacroiliac involvement as signal changes resembling degeneration on the iliac side. The patient's bone scintigraphy was performed by administering 20 milliCurie of Technetium 99m-methylene diphosphonate intravenously and demonstrated involvement in the left hemipelvic region and left area of the cranium. Screening for possible malignancy with positron emission tomography and abdominal tomography did not revealed any primaly tumor.

Although serum ALP and bone-specific ALP levels were normal, imaging studies of the patient were mainly compatible with PDB. Since urea and creatinine levels were slightly elevated, the patient's treatment started with hydration and renal functions improved during follow-up. The patient underwent zoledronic acid 5 mg/100 mL/year single dose infusion therapy with creatine clearance of 32. The patient's complaints regressed and he was discharged with recommendations. The pagetic lesions achieved marked improvement after 6 months and outpatient follow-up was uneventful for a year. Written informed consent was obtained from the patient for publication of this case report.

Discussion

Paget's disease of the bone is seen in 3-3.7% of patients over 40 years of age, which can cause complications such as chronic bone pain, skeletal deformities, heart failure and cranial nerve compressions, so early diagnosis is prominent. While the majority of patients are asymptomatic, the most common symptom is bone pain in Paget's disease which is typically worse at rest (6). Depending on the involvement, patients mostly complain of low back and hip pain. Sacroiliac joint involvement can be seen rarely in PDB and differantial diagnosis of spondyloarthritis should be considered in these cases (7). Possible complications include hearing loss, basilar invagination of skull, obstructive hydrocephalus, spinal canal stenosis and paraplegia. The presenting complaint was spinal pain in our patient. Pathological fractures, neurological or auditory problems were not detected.

ALP is an enzyme which is synthesized by osteoblasts and made mostly in liver and bone. It is associated with mineralization of bone and represents an effective biochemical marker of bone formation. Compared with various bone derivied diseses, the highest serum ALP level is observed in Paget's disease. which is caused by osteoblasts action following bone destruction by the uncontrolled activity of osteoclasts (8). It is also a sensitive screening marker for PDB and is helpful in monitoring the treatment response. Although blood test for ALP is usually elevated in people with PDB which is very important for diagnosis, ALP can be detected in normal levels in 10-15% of patients as in our case (9). In case of normal serum ALP levels, bone-specific ALP levels are elevated in 60% and urinary pyridinoline is increased in 40% of the patients in PDB (10). The fact that other markers of bone formation and destruction are within normal limits can be explained by disease of limited extend in two regions and the previous use of bisphosphonate in our patient (11).

In our case, sacroiliac joint sclerosis and cortical thickening of the skull which were observed on radiographs were important in diagnosis. Our patient did not meet the clinic or radiographic criteria of spondyloarthritis or other disease that may lead to sacroiliitis.

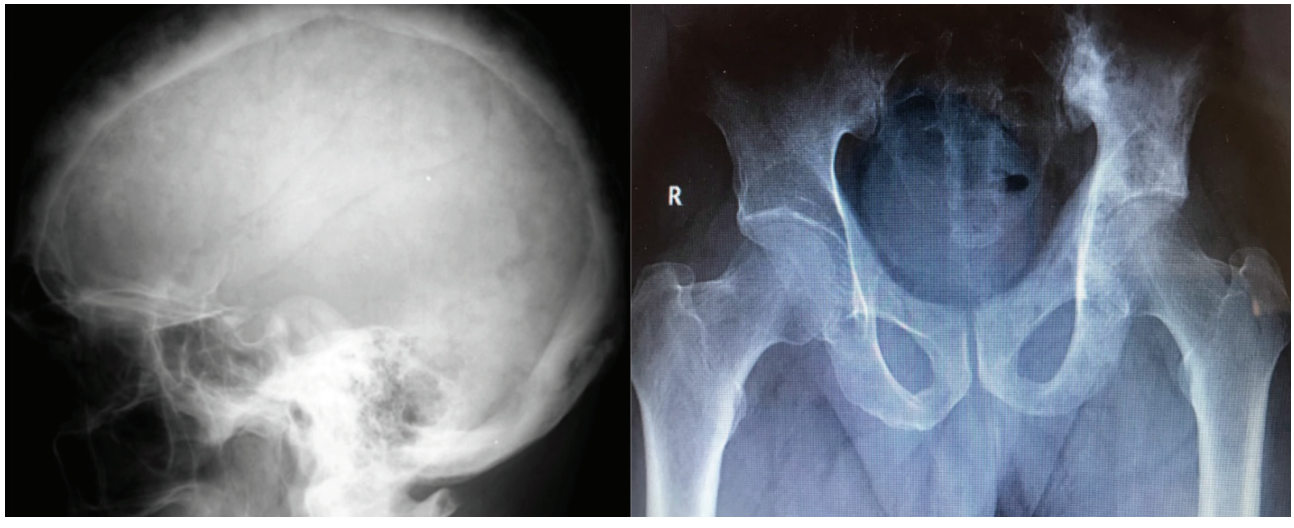

Figure 1. X-rays of cranium and pelvis

PDB and bone metastases share many common features in terms of pathophysiological changes in bone. Prostate, breast, stomach, bladder and lung cancers may develop osteosclerotic involvement similar to those of PDB. In addition, osteosarcoma, multiple myeloma and lymphoma of primary bone cancers may have osteosclerotic appearance (12).

Therefore, malignancy should be ruled out in the elderly patients with sclerotic lesions. In our patient, tumor markers and imaging methods were screened and no signs of malignancy were detected. Bone scintigraphy is recommended to all patients for differential diagnosis. It showed diffuse increased uptake of isotope by parietal bone of skull and left sacroiliac joint suggestive of PDB in our patient. While bone scintigraphy is widely considered to be the most sensitive method for determining the extend of skeleteal damage and evaluating the scope, X-rays should be taken in all symptomatic areas and it should be kept in mind that osteosarcomatous transformation may ocur which constitutes the most dreaded complication of the disease (13).

Before treatment, the presence of Paget's symptoms and secondary complications should be evaluated. The most common indication for treatment is symptomatic disease that can be featured with bone pain, radiculopathy or arthropathy due to PDB, or other complications. The purpose of medications are supressing the accelerated bone turnover and improving bone pain. The mainstay of medical management involves the use of bisphosphonates since decades which are given after vitamin D replacement (14,15). Oral alendronate or risedronate, intravenous pamidronate or zoledronic acid may be given as they inhibit exaggerated bone turnover and reduces bone loss (13). The recommended treatment by the guideline published by the Endocrine Society is a single dose of intravenous infusion of 5 mg zoledronic acid (16). In literature, zoledronic acid is found to be the most potent agent in decreasing ALP blood level, improving quality of life and preventing relapse. The response to zoledronic acid is also more rapid when compared to oral bisphosphonates and the response is sustained for years (17,18).

Calcitonin also reduces bone resorption by inhibiting osteoclastic activity and provides timely pain relief. It was used for the treatment of PDB previously but is not used anymore due to the relapses and resistances after treatment. Denosumab have also been reported to improve bone pain and decrease total ALP levels but is not licensed for PDB yet. Some studies revealed that denosumab rapidly decrease ALP levels compared to bisphosphonates (19,20).

In addition to bisphosphonate therapy, analgesics can be added for pain management. Non-steroidal anti-inflammatory drugs and anti-neuropathic agents can be useful for pain control. In cases with skeletal deformities, cranial nerve involvement or severe osteoarthritis, surgical intervention is required that includes osteotomy for progressive deformity, fixation of impending fracture, joint arthroplasty and spinal decompression (21).

In this case report, I aimed to emphasize the importance of scintigraphy in early diagnosis of Paget's disease and to indicate that Paget's disease should not be excluded in patients with normal ALP levels in chronic skeletal pain.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Internally peer-reviewed.

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Sacral Stress Fracture in Pregnancy: Case Report and Review of Literature

Gebelikte Sakral Stres Kırığı: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Abstract

Sacral stress fractures (SSF) are one of the rare causes of lumbar and hip pain during pregnancy. The purpose of this report is to present a case of SSF diagnosed in the second trimester of pregnancy along with its diagnosis and treatment as wells as the type of birth. A 27-year-old primigravid patient presented with lumbar and hip pain at 25 weeks of gestation. Magnetic resonance imaging revealed SSF. The patient was followed up with conservative treatment. She gave birth by caesarean section at 38 weeks of gestation. Bone mineral density analysis revealed pregnancy-related osteoporosis in the postpartum period. Two months later, the patient's symptoms were completely resolved. SSF should be considered in the differential diagnosis of lumbar and hip pain during pregnancy, and it should be kept in mind that these fractures may also occur in the prepartum period. Pregnancy-related osteoporosis is a risk factor for SSF. Caesarean section can be recommended as the type of birth in the women with SSF while considering the possible displacement risk for the fracture.
Keywords: Sacral stress fracture, pregnancy-related osteoporosis, lumbar, hip, pain

Öz

Sakral stres kırıkları (SSF), hamilelikte bel ve kalça ağrısının nadir sebeplerinden biridir. Bu raporun amacı, gebeliğin ikinci trimesterinde tanı konan bir SSF olgusuna tanı, tedavi ve doğum şekli sunmaktır. Yirmi yedi yaşında primigravid hasta, 25 haftalık gebelikte bel ve kalça ağrısı şikayeti ile başvurdu. SSF, manyetik rezonans görüntüleme kullanılarak tanı konuldu. Hasta konservatif tedavi ile takip edildi. Otuz sekizinci haftada sezaryen ile doğum yaptırıldı. Kemik mineral yoğunluğu analizi doğum sonrası dönemde gebeliğe bağlı osteoporozu ortaya çıkardı. İki ay sonra, hastanın semptomları tamamen düzeldi. Gebelikte bel ve kalça ağrısının ayırıcı tanısında SSF düşünülmeli ve bu kırıkların da doğum öncesi dönemde ortaya çıkabileceği akılda tutulmalıdır. Gebelikle ilişkili osteoporoz, SSF için bir risk faktörüdür. Sezaryen, bu kadınlarda, kırılma için olası yer değiştirme riskini göz önüne alarak, doğum tipi olarak önerilebilir.
Anahtar kelimeler: Sakral stres kırığı, gebelikle ilişkili osteoporoz, bel, kalça, ağrı

Introduction

There are two types of stress fractures, which are insufficiency and fatigue fractures. Insufficiency fractures occur when normal stress is applied to the weakened bone, whereas fatigue fractures occur when excessive stress is applied to normal bone (1-5). These fractures, more common in the elderly, patients with weakened bones (neoplasic, metabolic, etc), and athletes (runners), are increasingly reported in recent years during the peripartum period (6,7). Peripartum sacral stress fractures (SSF) are reported in literature as fatigue and insufficiency fractures (1-5). Pregnancy-related SSF is frequently reported during the postpartum period; however, to the best of our knowledge, only three cases are reported during the prepartum period (1,4,8).

SSF diagnosis can be delayed due to its rarity and unknown etiology and is included in the differential diagnosis of lumbar and hip pain in pregnant women. It is diagnosed via a vertical fracture line in the sacrum and edema in the surrounding bone as revealed by magnetic resonance imaging (MRI) (4,9). Difficulties may be experienced in prepartum SSF treatment due to pregnancy; the question of which type of birth should be performed in these patients remains controversial (1,4). Herein, we present a case of prepartum SSF and discuss these patients with their treatment and type of birth.

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Case Report

A 27-year-old primigravid patient presented to our clinic with complaints of lumbar pain, left hip pain and antalgic gait at 25 weeks of gestation. The patient stated that she felt mild hip pain for 2 days that spontaneously occurred and then had difficulty walking due to a sudden aggravating pain. There was no known comorbidity, who did not smoke, drink alcohol, or use drugs. Obstetrics examination and abdominal ultrasonography revealed no pregnancy-related problems. In physical examination, the patient with antalgic gait had marked tenderness in the palpation of the left sacrum region. Left hip movements were free in all directions but painful. The Gaenslen and Patrick tests were positive. Neurological examination were normal. Radiography could not be performed due to pregnancy, and pelvic MRI showed nondisplaced oblique and vertically fractured line in the left sacral region and edema in the surrounding bone (Figure 1a). Laboratory tests performed to investigate the etiology of the fracture revealed that parathormone, 25-OH vitamin D, calcium, phosphorus, and alkaline phosphatase levels were normal. The patient was conservatively treated with SSF diagnosis. Rest, sacroiliac pregnancy belt, and paracetamol [1-2 gram (g) daily] as analgesic were recommended. Additionally, oral vitamin D (880 international units daily) and calcium (1 g daily) supplementation was given. Patient follow-up at 38 weeks of gestation showed that the pain was almost completed relieved and that the patient was able to walk with ease. Considering the risks that normal vaginal delivery (NVD) may enlarge and displace the sacral fracture, the fetus was delivered by cesarean section. The patient delivered a healthy girl weighing 3.340 g, and pelvic MRI taken on the 10th postpartum day revealed that the fracture line in the left sacral area had become less clear and bone marrow edema had diminished (Figure 1b). Bone mineral density (BMD) of the patient was measured using dual-energy X-ray absorptiometry at postpartum month 1, and osteoporosis diagnosed was made (Table 1) (10). The patient had no other risk factors for osteoporosis other than pregnancy and was diagnosed with pregnancy-related osteoporosis (PrO). Her treatment was continued with vitamin D and calcium replacement. The patient continued to breastfeed. Postpartum month 2 follow-up revealed that the patient's complaints and examination findings had completely resolved. Written informed consent was obtained from the patient for this article.

Discussion

Definition and Epidemiology

First reported by Lourie in 1982, SSF are insufficiency and fatigue fractures of unknown etiology (6). Although the exact incidence of these fractures is unknown because they can be overlooked during diagnosis, their incidence is reported to be between 1% and 1.8% in the patient population at risk (11,12). Lumbar and hip pain is common during the peripartum period; however, SSF

Table 1. Results of dual-energy X-ray absorptiometry

Skeletal region	BMD[a] (g/cm^2)	*Z-score (SD[b])	T-score (SD[b])
Spine (L1-4)	0.914	-1.4	-1.8
Femur total	0.695	-2.2	-2.5
Femur neck	0.756	-1.5	-1.7

[a]BMD: Bone mineral density, [b]SD: Standard deviation, *Z-score: Recommended in premenopausal women (The International Society for Clinical Densitometry recommends the use of BMD Z-scores in premenopausal women, where a Z-score of lower than -2.0 should be interpreted as "below the expected range forage") (10)

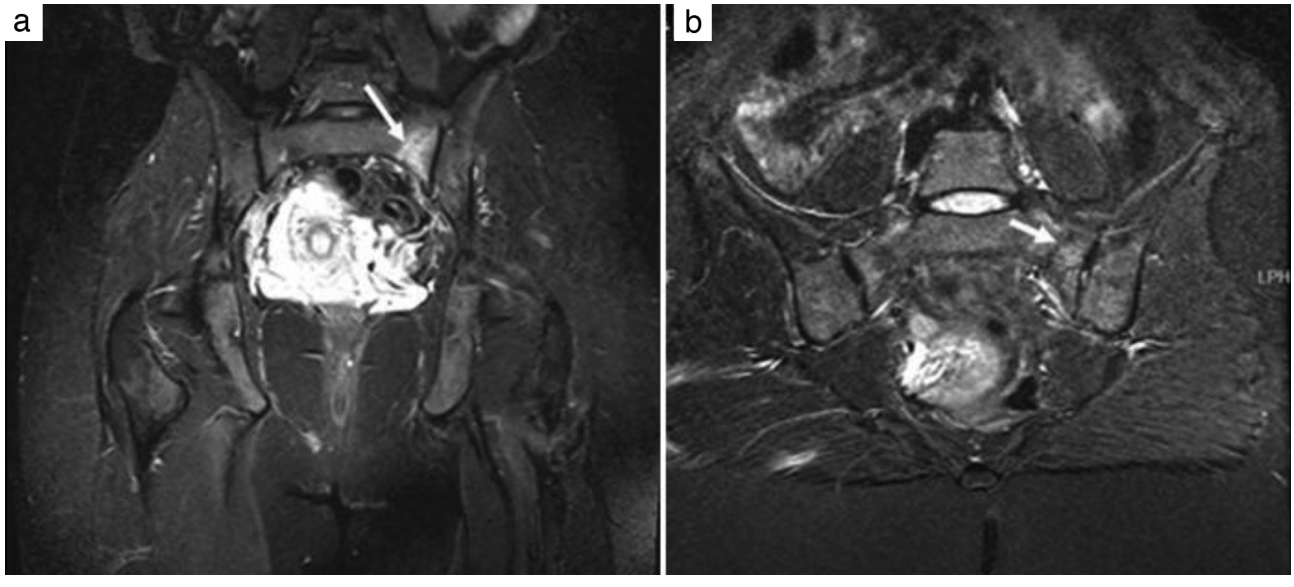

Figure 1. (a) In the prepartum period, magnetic resonance imaging (MRI) of the pelvis demonstrated bone fracture in the left sacral ala. On T2 coronal sequence the fracture line was seen as an oblique and vertically, high signal line surrounded by an area of edema. (b) In the postpartum period, coronal short-tau inversion-recovery sequences of sacroiliac MRI; it was seen that the fracture line in the left sacral area had become less clear and bone marrow edema had diminished

diagnosis is overlooked during pregnancy due to the relief of pain after birth and imaging methods being rarely used during prepartum period; therefore, the actual incidence is thought to be higher than what is reported (6,13). Although cases during pregnancy are reported especially during postpartum period, our case of sacral insufficiency fracture is one of the few cases reported during prepartum period (1,4,8).

Clinical Features

Patients are usually admitted with spontaneous lumbar and hip pain. Gaenslen and Patrick tests can be positive during examination. Pain and tenderness can be localized by palpation, especially on the sacrum. Antalgic gait and functional limitation may occur. However, none of the examination findings are specific (1,4,14).

Risk Factors

Patients with conditions that impair bone quality, like osteoporosis, neoplasm (multiple myeloma), bone diseases (osteomalacia, Paget's disease), and hyperparathyroidism, in addition to elderly people and athletes are at risk for stress fractures (6,7,15).

SSF risk factors during pregnancy include forced or rapid vaginal delivery, excess weight gain during pregnancy, hyperlordosis, pelvic ligament relaxation, vitamin D deficiency, decreased maternal calcium intake, heparin use, and PrO (3,9,14-17). The only risk factor in our patient was PrO.

Diagnosis

SSF diagnosis can be confirmed by radiological imaging. Plain radiography and computed tomography (CT) are not preferred in pregnant women due to radiation effects. Plain radiographs and CT have low sensitivity in SSF diagnosis between 20%-30% and 60%-75%, respectively (11). Therefore, MRI is the first choice for diagnosis. MRI can detect SSF with approximately 100% sensitivity (11,12). MRI can be safely used during peripartum period, and SSF has the appearance of a vertical or oblique fracture line in the sacrum and edema in the surrounding bone, as described in our case and in other reported cases (1,4).

Treatment and Prognosis

Treatment options for SSF are limited due to pregnancy. Treatment is conservative, and pain control is the first priority (4,14). Rest, activity modification and analgesics are generally recommended (4). Oral paracetamol is the most common analgesic that can be safely used in all pregnancy trimesters. Intravenous paracetamol and morphine may be rarely administered in some cases (1). Bed rest is recommended during the early period until adequate pain control is achieved. In patients with decreasing pain, early mobilization (partial loading, gradual ambulation with walking aids) may be initiated to accelerate bone healing and reduce the complications of immobilization (1,6,14). Moreover, osteoporosis treatment should be included in the treatment of patients with PrO (15). SSF is mostly stable, none of the peripartum SSF cases required surgical treatment (1,14). With conservative treatment, these patients returned to their daily living activities in approximately 6weeks (1,4). Complete recovery of the fracture line was observed on MRI after 4-9 months (4,14). Our patient regained her daily living activities with 12 weeks of conservative treatment before birth.

PrO and Bone Mineral Density

Four types of PrO have been identified: idiopathic osteoporosis of pregnancy, transient osteoporosis of the hip, post-pregnancy vertebral osteoporosis, and lactation-related osteoporosis (18). Because PrO is a risk factor for SSF, postnatal BMD measurement is recommended for these patients (1,4,13). BMD decreases by an average of 3.5% during pregnancy; BMD measurement results may vary (15). BMD may be normal, osteopenic, or osteoporotic due to the time between fracture formation and measurement (13). BMD returns to normal in most PrO patients within 5-10 years after birth. Persistent osteoporosis can be described if BMD does not return to normal within this period (19).

Most of the postpartum SSF patients whose BMD was measured did not have PrO, and only one of the three prepartum cases had PrO. Femoral BMD measurements were low in these patients with PrO (3,5,8). Our patient had PrO (idiopathic type) with low femoral BMD values.

PrO treatment can be continued with calcium and vitamin D replacement because bisphosphonates and calcitonin are not recommended during pregnancy and lactation (15). Furthermore, early mobilization and walking are beneficial for osteoporosis (15).

Type of Birth

According to literature review, the type of birth was not reported in the first case (8); the second case had NVD at term, despite being recommended with cesarean section (1); and cesarean section was performed in the third case (4). Ozturk et al. (5), presented intrapartum SSF developed in NVD. Although pain starts during pregnancy, NVD is frequently reported in patients with postpartum SSF (3,9,14). Giannoulis et al. (4) recommended cesarean section due to the increased risk of displacement of the sacral fracture, which is associated with the increased tension in the pelvis during NVD. In another patient with PrO who had transient osteoporosis of the hip, femoral fracture was reported during NVD (20). Our patient preferred cesarean section in line with our recommendation.

Conclusion

SSFs must be considered in the differential diagnosis of lumbar pain, hip pain, and antalgic gait during pregnancy. Considering that these fractures may occur during the prepartum period, early diagnosis using MRI will increase the success of pain control. Moreover, PrO should be considered as a risk factor for SSFs. In pregnant women with SSFs, cesarean section may be recommended as the type of birth considering the possible displacement risk of fracture.

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Ethics

Informed Consent: Written informed consent was obtained from the patient.
Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.S., A.A., Concept: H.S., Design: H.S., Data Collection or Processing: H.S., A.A., Analysis or Interpretation: H.S., A.A., Literature Search: H.S., Writing: H.S., A.A.
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Osteomalacia due to Vitamin D Deficiency: A Case Report

D Vitamini Eksikliğine Bağlı Osteomalazi: Olgu Sunumu

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Abstract

Osteomalacia is a metabolic bone disease characterized by demineralization of the newly formed osteoid in adults. Vitamin D deficiency due to insufficient vitamin D intake, inadequate exposure to sunlight, and malabsorption of vitamin D are the most widespread cause of osteomalacia. Here,we present the case of 18 year old female patient who presented to our hospital with complaints of low back pain. Sacral bone pseudofracture was detected by magnetic resonance imaging due to osteomalacia. Patient was treated with vitamin D.
Keywords: Osteomalacia, vitamin D deficiency, pseudofracture

Öz

Osteomalazi, yetişkinlerde yeni oluşan osteoidin mineralleşmesinde azalma ile karakterize metabolik bir kemik hastalığıdır. Yetersiz D vitamini alımı, güneş ışığına yetersiz maruz kalma ve D vitamini malabsorpsiyonu nedeniyle D vitamini eksikliği, osteomalazinin en sık nedenidir. Bu yazıda, bel ağrısı şikayeti ile hastaneye başvuran 18 yaşında kadın hastayı sunduk. Osteomalazi nedeniyle manyetik rezonans görüntüleme ile sakral kemik psödofraktürü saptandı. Hasta D vitamini ile tedavi edildi.
Anahtar kelimeler: Osteomalazi, D vitamini eksikliği, psödofraktür

Introduction

Osteomalacia is a metabolic bone disease identify by a decrease in the mineralization of the newly formed osteoid in adults. Mechanisms that result in hypocalcemia, hypophosphatemia, vitamin D metabolism disorders, or direct inhibition of the mineralization process cause osteomalacia (1).

Osteomalacia should be suspected in cases of malabsorption, gastric bypass surgery, celiac disease, chronic liver disease, or bone pain due to chronic kidney disease.

The diagnosis is based on a combination of clinical features (bone pain and tenderness, fractures and/or muscle weakness), laboratory results, radiologic findings, and rarely,transiliac bone histomorphometry (1-3). Vitamin D deficiency due to insufficient vitamin D intake, inadequate exposure to sunlight, and malabsorption of vitamin D is the most widespread cause of osteomalacia (1-3).

Case Report

An 18-year-old female refugee patient presented to our outpatient clinic with low back pain and legs pain. The patient, who was seen by the neurosurgery department because of low back pain, was diagnosed as having spondylolisthesis at the L5-S1 level and was given a lumbosacral steel corset. There was no regression in the patient's pain. The patient described having difficulty in walking with low back pain and legs pain, and difficulty in walking up and down stairs. On physical examination, the range of motion of the lumbar joint was complete, deep tendon reflexes were normoactive, there was no sensory defect and pathologic reflex. Trendelenburg gait was markedly observed. Lumbosacral radiography revealed no spondylolisthesis. In laboratory tests, the hemogram was normal; glucose, urea, creatinine, aspartate transaminase, and alanine transaminase were normal; alkaline phosphatase (ALP) was 1479 U/l, calcium (Ca) was 8.88 g/dL, phosphorous (P) was 1.95 mg/dL, parathyroidhormone (PTH) was 449 pg/mL, 25-hydroxy vitamin D [25(OH)D] was 3 ng/mL, and the 24-hour urine Ca was 25 mg. There were multiple stress fractures in the magnetic resonance imaging (MRI) of the sacral region of the pelvis (Figures 1a, 1b, 1c).

The patient was diagnosed as having osteomalacia as a result of the detection of common pain, typical Trendelenburg gait pattern, low Ca, P, and 25(OH)D, high ALP, low 24-hour urinary

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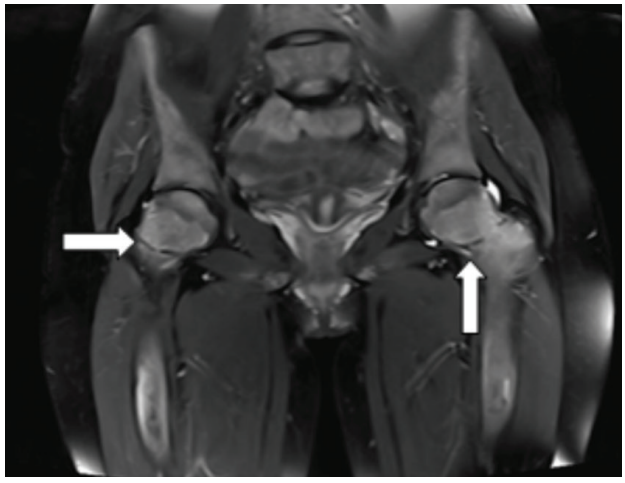

Figure 1a. Magnetic resonance coronal T2- weighted Fat-Sat image

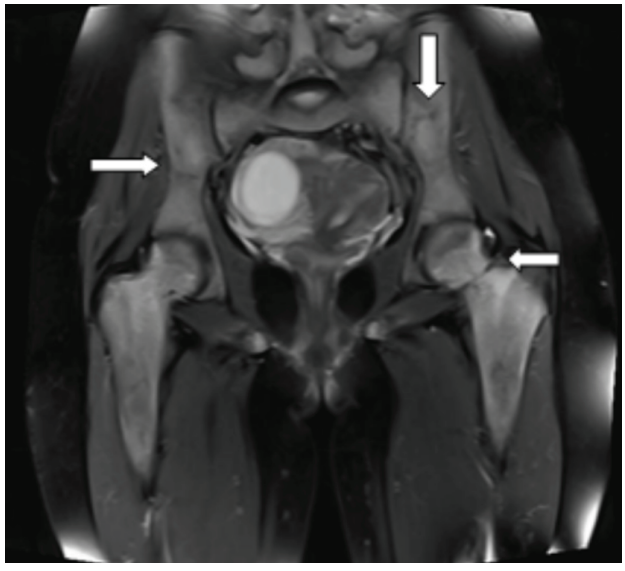

Figure 1b. Magnetic resonance coronal T2- weighted Fat-Sat image

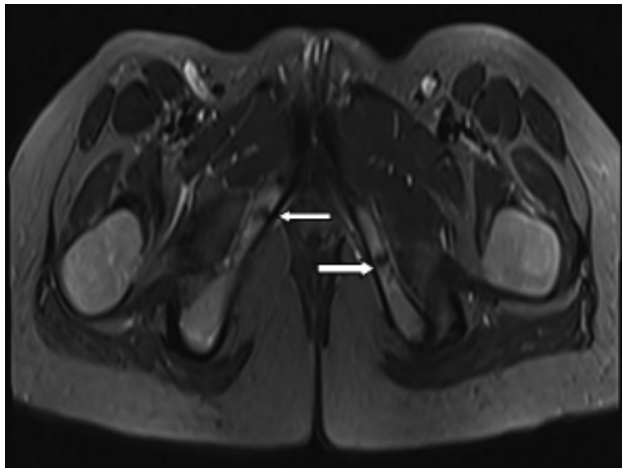

Figure 1c. Magnetic resonance axial T2- weighted image

Ca, and secondary PTH elevation, and detection of multiple stress fractures in sacral MRI. one thousand two hundred milligrams of Ca and 50,000 IU of oral vitamin D per week were started for eight weeks. The patient was advised to have exposure to the sun, and nutrition and exercise recommendation were made.

Discussion

The diagnosis of osteomalacia is depends on the clinical, laboratory,and radiologic findings of the patient. Osteomalacia can be asymptomatic or radiologically appear as osteopenia. It may also cause typical symptoms, regardless of underlying causes such as extensive joint and bone pain, muscle weakness, and walking difficulty (1-4).

It was reported that among 17 patients who were diagnosed as having osteomalacia via bone biopsy, bone pain and muscle weakness was present in 16 (94%), bone tenderness in 15 (88%), fracture in 13 (76%), walking difficulty and Trendelenburg gait (24%), muscles pasms, cramps and positive Chvostek sign (12%), and prickling sensation, drowsiness and difficulty in movement was present in (6%) (5).

Bone pain is generally evident in the lower spine, pelvis and lower extremities with fractures, and palpation reveals severe tenderness. Pain can be increased by activity and weightbearing. Fractures can typically arise without mild trauma or no trauma, includin gribs, vertebrae and longbones. Muscle weakness is characteristic of the proximal muscles of the extremities and muscle loss may be accompanied by hypotonia (1,6).

In retrospective analyses of patients with definite nutritional osteomalacia diagnosed through biopsy, elevated ALP (95-100%), decreased in serum Ca and P concentrations (27-38%), decreased urinary Ca (87%), and 25(OH)D concentrations at 15 ng (100%), and increased PTH concentrations (100%) were observed (1,4). Vitamin D deficiency due to insufficient vitamin D intake, insufficient exposure to sunlight and malabsorption of vitamin D is the most widespread cause of osteomalacia (1-3).

Clinical evaluations such as gastrointestinal system diseases, sun exposure, dietary habits,and duration of initial symptoms (insidious or acute) may help to determine the etiology of osteomalacia (1-3). Vitamin D deficiency causes secondary hyperparathyroidism by reducing the absorption of Ca and phosphate in the intestine. Bone destruction, renal phosphate excretion,and renal tubular Ca reabsorption increase (1,2,7).

Vitamin D support results in a dramatic improvement in muscle strength and bone sensitivity with in weeks. The effect of vitamin D is usually most pronounced when there is sufficient Ca intake at the same time. Bone mineral density (BMD) may improve with in three to six months (7). Ca concentrations and urinary Ca excretion should be monitored at 1 month and 3 months in the treatment of osteomalacia. It should then be monitored less frequently (every 6 to 12 months) until the 24-hour urinary excretion is normal. Serum Ca concentrations should be monitored for the early detection of hypercalcemia.

Serum 25(OH)D should be measured nearly 3 to 4 months after starting treatment. The doses hould be adjusted to prevent hypercalciuria or hypercalcemia. In most cases, serum Ca and phosphate are normal after a few weeks of treatment, but ALP may remain high for several months. Urinary Ca excretion and an increase in BMD are thought to improve osteomalacia. Osteomalacia may take a year or more to cure.The recovery time depends on the degree and duration of the deficiency (8).

For patients with severe vitamin D deficiency [25(OH)D <10 ng/mL (25 nmol/L)], a common approach is to treat with oral 50,000 IU D2 or D3 weekly for 6 to 8 weeks, and then it is recommended to maintain with 800 IUof vitamin D3 daily (9).

Patients with gastric bypass or malabsorption may require a dosage of 10,000 to 50,000 IU/day of vitamin D.

In liver-related diseases, vitamin D metabolite calcidiol should be used because it does not require 25-hydroxylation. The onset of action is faster. In this case, th edose is 50 to 200 micrograms/day (1,2,5,9).

Osteomalacia should be kept in mind in patients with generalized pain, Trendelenburg gait, and vitamin D deficiency.

Ethics

Informed Consent: Informed consent form was obtained from all patients included in our study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.O., Concept: B.O., Design: B.O., Data Collection or Processing: B.O., K.U., Analysis or Interpretation: B.O., K.U., H.U., Literature Search: B.O., K.U., H.U., Writing: B.O.

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

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Case Report / Olgu Sunumu

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A Rare Presentation of Primary Hyperparathyroidism: Generalized Brown Tumors

Primer Hiperparatiroidizmin Nadir Bir Sunumu: Yaygınlaşmış Kahverengi Tümörler

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Abstract

Primary hyperparathyroidism is a common and easily diagnosed disease at present. However, its complicated presentation as a brown tumour is rare. Here, we present the case of a patient with knee pain and common asymmetrically located brown tumours. The parathyroid adenoma was radiologically detected, followed by successful minimally invasive parathyroidectomy. However, the brown tumours regressed after surgery. Primary hyperparathyroidism can still present with common bone involvements and can be clinically and radiologically improved with appropriate treatment.

Keywords: Primary hyperparathyroidism, bone, brown tumour, parathyroidectomy

Öz

Primer hiperparatiroidizm, günümüzde yaygın ve kolay teşhis edilebilen bir hastalıktır. Neyse ki, kahverengi tümör şeklinde komplikasyonla karşılaşılması nadirdir. Aşağıda, diz ağrısı ile başvuran ve asimetrik yerleşimli kahverengi tümörleri olan primer hiperparatiroidizmli bir olgu sunduk. Paratiroid adenomu radyolojik olarak tespit edildi, ardından minimal invaziv paratiroidektomi ile başarıyla ameliyat edildi. Kahverengi tümörler ameliyattan sonra geriledi. Primer hiperparatiroidizmin hala yaygın kemik tutulumu ile ortaya çıkabildiği ve uygun tedavi ile klinik ve radyolojik olarak iyileştirilebileceği anlaşılmaktadır.

Anahtar kelimeler: Primer hiperparatiroidizm, kemik, kahverengi tümör, paratiroidektomi

Introduction

Primary hyperparathyroidism (PH) is one of the commonest endocrinological disorders in the whole world (1). It presents with hypercalcemia, hypo or normophosphatemia and high or mid-to-high parathyroid hormone level (2). Its target organs are kidney, bone and intestine, main signs and symptoms are artralgia, bone pain, urinal stones, bone fractures, cysts and/or brown tumors (3). Brown tumor, also called osteoclastoma, is a focal, benign lytic bone lesion of primary or secondary hyperparathyroidism. Today, PH can be diagnosed earlier and the incidence of this lesion has decreased (4). We present a case with brown tumors involving whole skeleton.

Case Report

A 39-year-old woman admitted to orthopedics with left knee pain. A hypoechoic lesion was detected on X-ray. Laboratory evaluation revealed mild hypercalcemia with calcium of 11.6 mg/dL. A whole-body bone scintigraphy was taken on suspicion of cancer, multiple similar lesions with increased activity were determined on right and left knees, 4th thoracal spine, left iliac crest, right symphysis pubis and between left femur's head and neck (Figure 1). An excisional biopsy was made and reported as brown tumor. After that she was directed to our endocrinology policlinic because of hypercalcemia and hyperparathyroidism. We detected that calcium: 13 mg/dL, phosphorus: 2.4 mg/dL, parathyroid hormone: 625 pg/mL, 25 hidroksi vitamin D: 8 ng/mL and we hospitalized her with the diagnosis of PH. We started intensive hydration with 0.9% NaCl and followed urine output, then gived intravenous furosemide infusion. In the one daily urine, calcium excretion was 461 mg/day. On the ultrasound, we detected a single, smooth edged, non-vascularized, hypoechoik lesion, size in 8x10x15 millimeters, under the right thyroid lobe and two thyroid nodules more than 15 millimeters. Parathyroid scintigraphy showed same lesion. Thyroid fine needle aspirations were resulted as benign thyroid nodule. We also researched multiple endocrine neoplasia (MEN) type

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1 because of young age of the patient and we did not detect any other components of this syndrome. We also excluded other reasons for hypercalcemia like malignancy. Although we used hydration and loop diuretic threapy, serum calcium did not fall enough, so we had to use calcitonin and succeeded that calcium falled under 11 mg/dL. We applied vitamin D to protect from hungry bone syndrome (HBS) and transfered the patient to general surgery for operation. Minimally invasive parathyroid adenomectomy was performed successfully and calcium and parathyroid hormone levels decreased quickly. The pathology was resulted as parathyroid adenoma. By the way, vitamin D had been replaced preoperativelly, nevertheless the patient developed HBS and she was given medication. After 6 months, the bone scintigraphy was repeated and reported that the previous lesions were regressed (Figure 2). Informed consent was obtained from the patient.

Discussion

Brown tumor or osteitis fibrosa cystic is the result of increased osteolitic activity and fibroblastic proliferation due to uncontrolled primary or secondary hyperparathyroidism (5). Its brown colour arises from bleeding and hemosiderin deposition (6). The incidence is nearly 5% of PH (7) and this has decreased because of the earlier diagnosis and therapy of the disease (8). In the case report of 100 patients from Poland, brown tumors were identified in 10 cases, the authors noted that they did not expect so high result (9). Because of the radiological view, it should be differentiated from giant cell granuloma, aneurysmal bone cyst and similar lesions. Biopsy and elevated parathyroid hormon level can help in this instance (10).

Brown tumor often occurs in pelvis, long bones and ribs. Additionally, it can be seen on face and so any part of skeleton (11). It can cause paraplegia, fracture, movement limitation, bleeding and pain according to its site (4,12). Rarely, PH can cause brown tumor with extensive parenchymal calcification in kidneys, it calls as 'putty kidney' (radiological name) (13). It can mimic other diseases like malignancy and so the diagnosis delays (14). Vaishya et al. (15) reported a brown tumor of tibial diaphyses in a young female patient. She had severe pain, tenderness and immobilization due to lesion. The radiograph showed a geographical lytic lesion like malignancy. But she had secondary hyperparathyroidism according to severe Vitamin D deficiency. After vitamin D replacement, the lesion was disappeared, so it was diagnosed as brown tumor clinically and she was prevented unnecessary surgery. In our patient, it was considered as malignancy, so whole body bone scintigraphy was performed. It showed a great number of similar lesions spreading all over the skeleton asymmetrically and move from here the pathological diagnosis was made.

Because of reporting as brown tumor, she referred our clinic and the diagnosis and treatment came step by step. During this time, we researched MEN type 1 owing to the patient's age. Because, PH is the most common component of this syndrome and MEN-1 is seen in 1-3% of PH (16). Shortly after surgery, HBS occurred despite of vitamin D replacement preoperatively so she was administered intravenous and oral therapy and she improved quickly. HBS is an uncommon complication of parathyroidectomy for severe PH. Patients with preoperative

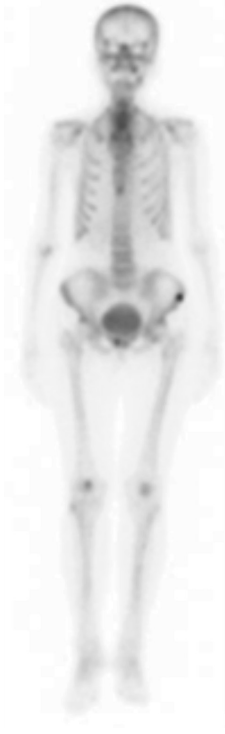

Figure 1. The wholebody bone scintigraphy

Figure 2. The whole body bone scintigraphy after 6 months from the surgery

high bone turn over-like our patient- have this risk highly. Long duration of PH is also important. The therapy and follow of this syndrome must be done quickly and carefully (17).

Conclusion

Despite of developing in diagnostic methods, formerly seen lesions like brown tumor can occur any time. It comes in front of us with a lot of symptoms. Both of clinicians and surgeons must be alert for this lesion. If it is not considered, the diagnosis delays and it can cause inappropriate medical interventions and irreversible damages to patients.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

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Primary Hydatid Cyst of the Musculoskeletal System Involving the Femur and Vastus Lateralis

Femur ve Vastus Lateralis Tutulumu Olan Primer Kas İskelet Sistemi Kist Hidatiği

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Dear Editor;

Thirty-six-years-old female patient applied to physical therapy clinic due to local swelling on left anterior femoral area. The patient stated she had accompanying pain, and had no neuropathic pain complaints such as numbness and tingling. She had no known history of trauma, she was not diagnosed with a chronic and rheumatic disease. She did not spend time abroad and she had no close contact with dogs. In physical examination, a mobile, sensitive mass was observed in anterior femoral area. No accompanying ecchymosis, erythema or lymphadenopathy was determined. Muscle strength and sensory examinations was normal. Routine laboratory tests were normal. Direct X-ray of this area revealed a lytic lesion in left femur neck and proximal metaphysodiaphysis with narrow zone of transition. Pathologies such as fibrous dysplasia and aneurysmal bone cyst were considered for differential diagnosis. Patient was evaluated with scintigraphy which showed a photopenic appearance in phase 3 in the proximal of left femur. On magnetic resonance imaging, thin-walled cystic lesion with multicystic appearance were observed in left vastus lateralis muscle with hyperintense signal on T2w series, and hypointense signal on T1w series (Figure 1). Also, a lesion was observed in T2w series with heterogeneous hyperintense signal in the femur neck at proximal diaphyseal level with medullary location, which caused slight expansion of the bone (Figure 2). The indirect hemagglutination test that was performed due to suspicious appearance was determined to be positive (+1/640), and the diagnosis was determined as hydatid cyst with both muscle and bone involvement. Total joint prosthesis operation was planned for the patient. Lamellar membrane of hydatid cyst, mixed inflammatory cells, hystiocytes and necrosis were observed in histopatological examination. After the operation, albendazole 400 mg/day pharmacological treatment was applied for weeks. No signs of local relapse were observed in the last examination of patient at post-operative follow-up year 1. Hydatid cyst is a zoonosis caused by the larval form of *Echinococcus Granulosus*, which

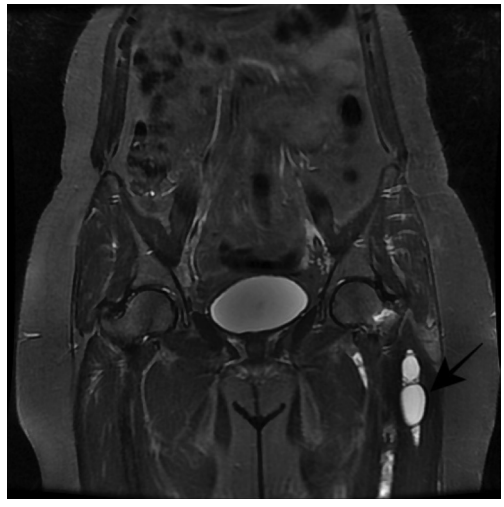

Figure 1. Cystic lesion with multicystic appearance were observed in left vastus lateralis muscle with hyperintense signal in T2w series

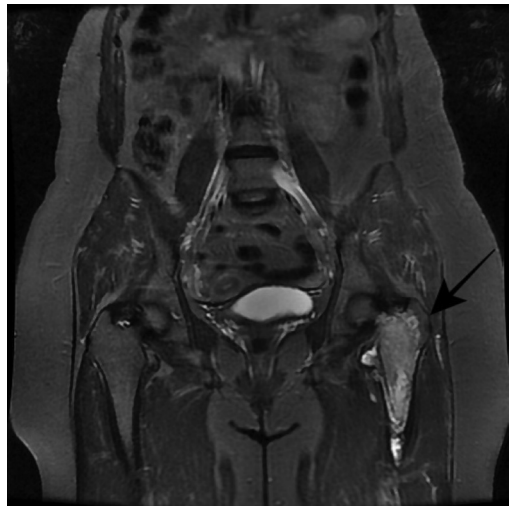

Figure 2. Heterogeneous-hyperintense signal lesion in the femur neck at proximal diaphyseal level with medullary location, which caused slight expansion of the bone

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is transmitted to humans by the consumption of infected food and direct contact with infected animal. It may cause morbidity with effect of pressure, being located at areas that may result in functional loss such as bones, and with complications such as opening to bile ducts, anaphylaxis. Liver is its most common area of residence (1). It has been reported in literature that it is observed in musculoskeletal system at 1%-5.4% rate (2). The reason why it is observed rarely in muscles is suggested to be that lactic acid formed in skeletal muscle contractions prevents the Hydatid cyst from settling in. It was reported in literature that it most commonly settles in psoas muscle. Cases with involvement of pectoralis major, biceps brachii, latissimus dorsi, adductor, gluteus maximus, quadriceps, gastro-soleus muscles were also observed (3). The main symptom of hydatid muscle cysts is local swelling felt by touch. Similar to literature, our case has applied complaining from local swelling, however, it was rare and atypical because bone tissue was also affected. Although isolated femoral bone involvement has also been reported, bone involvement generally shows asymptomatic course. Secondary infection gives symptoms after fractures or pressure on neighboring neuromuscular structures (4). While the diagnosis may be determined with medical history, clinical findings, laboratory tests and radiological examinations, surgical excision and histopathological examination are required for definitive diagnosis. Hematoma, abscess and tumor should be considered for differential diagnosis. AAspirations for diagnostic purposes may result in anaphylaxis and local spreading due to rupture hence it is important to be recognized before intervention. Surgery, interventional radiological methods (PAIR) and medical therapy (albendazole) may be used for treatment (5). In conclusion, differential diagnosis of hydatid cyst should be kept in mind in patients with local soft tissue swelling, it should be considered that adjacent bone tissue may be affected along with soft tissue involvement, and treatment planning should be performed accordingly.

Keywords: Vastus lateralis, hydatid cyst, femur
Anahtar kelimeler: Vastus lateralis, kist hidatik, femur

Peer-review: Externally and internally peer-reviewed.
Financial Disclosure: The author declared that this study received no financial support.

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